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Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende venetoclax i kombination med rituximab som mulig standardbehandling til kronisk lymfatisk leukæmi

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om anbefalingen

Anbefalingen er Medicinrådets vurdering af, om lægemidlets samlede pris er rimelig, når man sammenligner den med lægemidlets værdi for patienterne.

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
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Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Venclyxto®
Generisk navn	Venetoclax
Firma	AbbVie
ATC-kode	L01XX52
Virkningsmekanisme	Venetoclax hæmmer det antiapoptotiske protein BCL-2, som er overudtrykt i B-cellerne hos patienter med kronisk lymfatisk leukæmi.
Administration/dosis	Venetoclax p.o. 20 mg dagligt i uge 1, 50 mg dagligt i uge 2, 100 mg dagligt i uge 3, 200 mg dagligt i uge 4, 400 mg dagligt i uge 5 og herefter 400 mg dagligt fra uge 6 og 24 måneder frem. Fra uge 6 i 6 serier a 28 dage rituximab 375 mg/m^2 i.v. på dag 1 i serie 1, 500 mg/m^2 på dag 1 i serie 2-6.
EMA-indikation	Venetoclax i kombination med rituximab til voksne patienter med kronisk lymfatisk leukæmi der har modtaget mindst én tidligere behandling.

2 Medicinrådets anbefaling

Medicinrådet **anbefaler** venetoclax i kombination med rituximab som mulig standardbehandling til voksne patienter med kronisk lymfatisk leukæmi, der har modtaget mindst én tidligere behandling. Medicinrådet bemærker, at effekten af ibrutinib efter venetoclax i kombination med rituximab såvel som effekten af venetoclax i kombination med rituximab efter ibrutinib er ubelyst.

De kliniske spørgsmål, som ligger til grund for anbefalingen, er som følger:

Hvilken værdi har venetoclax i kombination med rituximab sammenlignet med venetoclax monoterapi til behandling af patienter med deletion17p/TP53-mutation, som oplever relaps eller behandlingssvigt efter behandling med ibrutinib?

Hvilken værdi har venetoclax i kombination med rituximab sammenlignet med ibrutinib til 2.-linjebehandling af patienter, der er behandlet med kemoterapi i kombination med et CD20-antistof i 1. linje?

Hvilken værdi har venetoclax i kombination med rituximab sammenlignet med kemoterapi i kombination med CD20-antistof til behandling af patienter uden deletion17p/TP53-mutation, der har behandlingskrævende relaps mere end 3 år efter deres første behandling?

3 Formål

Formålet med Baggrund for Medicinrådets anbefaling vedrørende venetoclax i kombination med rituximab som mulig standardbehandling til kronisk lymfatisk leukæmi er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

Kronisk lymfatisk leukæmi er en hæmatologisk kræftsygdom, som opstår i kroppens B-lymfocytter. Både sygdomsstadie, patientens symptomer og risikoprofil har indflydelse på igangsættelse og valg af behandling, ligesom de har betydning for patienternes prognose. Medianoverlevelse fra diagnosetidspunktet varierer fra 4 til > 12 år afhængig af sygdomsstadie og risikoprofil.

Incidensen er i Danmark ca. 6-7 pr. 100.000 indbyggere pr. år, og der registreres ca. 450-500 nye tilfælde om året i Danmark. Det estimeres, at ca. 4.000 patienter lever med sygdommen i Danmark.

Yderligere information findes i "Medicinrådets vurdering af klinisk merværdi for venetoclax i kombination med rituximab til behandling af kronisk lymfatisk leukæmi".

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den foreløbige ansøgning den 24. september 2018. Protokollen blev godkendt af Medicinrådet og sendt til ansøger den 16. maj 2019.

Det endelige datagrundlag for Medicinrådets vurdering blev modtaget den 15. august 2019. Medicinrådet vurderede den kliniske merværdi på rådsmødet den 25. september 2019. Anbefalingen blev drøftet på rådsmødet den 23. oktober, men denne drøftelse førte til, at Medicinrådet havde behov for yderligere kvalificering af vurderingsrapporten for at træffe endelig beslutning. Der var således udvidet clock-stop fra den 23. oktober til den 2. november 2019 og betød i sidste ende også en væsentlig forsinkelse af selve anbefalingen. Rådet genbehandlende vurderingsrapporten med den kliniske merværdi på rådsmødet den 20. november 2019.

Medicinrådet har gennemført vurderingen på 15 uger og 3 dage (108 dage).

5 Medicinrådets vurdering af samlet værdi

Medicinrådet finder, at den samlede værdi af venetoclax i kombination med rituximab sammenlignet med venetoclax monoterapi **ikke kan kategoriseres** til patienter med deletion17p/TP53-mutation, som oplever behandlingssvigt under behandling med ibrutinib i 1. linje. Medicinrådet vurderer dog, at venetoclax i kombination med rituximab ikke er en dårligere behandling end venetoclax monoterapi. Behandling med venetoclax i kombination med rituximab foretrækkes, fordi den er tidsbegrænset og giver patienterne mulighed for en behandlingsfri periode.

Medicinrådet finder, at den samlede værdi af venetoclax i kombination med rituximab sammenlignet med ibrutinib **ikke kan kategoriseres for patienter**, der oplever behandlingskrævende relaps eller behandlingssvigt mindre end 3 år efter behandling med kemoterapi i kombination med CD20-antistof og/eller patienter med sent relaps og nytilkommen deletion17p/TP53-mutation. Lægemidlerne vurderes dog som klinisk ligeværdige behandlingsvalg.

Medicinrådet finder, at den samlede værdi af venetoclax i kombination med rituximab sammenlignet med chlorambucil i kombination med obinutuzumab **ikke kan kategoriseres** for patienter med kronisk lymfatisk

leukæmi uden deletion17p/TP53-mutation, der oplever behandlingskrævende relaps mere end 3 år efter deres første behandling med kemoterapi i kombination med CD20-antistof. Medicinrådet vurderer dog, at effektforholdet mellem behandlingerne vil være i overensstemmelse med sammenligningen af venetoclax i kombination med rituximab med bendamustin i kombination med rituximab.

Medicinrådet vurderer, at venetoclax i kombination med rituximab til patienter med kronisk lymfatisk leukæmi uden deletion17p/TP53-mutation, der oplever behandlingskrævende relaps mere end 3 år efter deres første behandling med kemoterapi i kombination med CD20-antistof, giver en **moderat merværdi** sammenlignet med bendamustin i kombination med rituximab. Evidensens kvalitet vurderes at være moderat.

6 Høring

Ansøger har den 26. november 2019 indsendt et høringssvar, som ikke gav anledning til at ændre Medicinrådets vurdering af lægemidlets værdi. Høringssvaret er vedlagt som bilag 3.

7 Resumé af økonomisk beslutningsgrundlag

Amgros vurderer, at behandling med venetoclax i kombination med rituximab er forbundet med besparelser sammenlignet med venetoclax monoterapi. Amgros vurderer, at der er et rimeligt forhold mellem den kliniske merværdi og de inkrementelle omkostninger, selvom lægemidlets værdi ikke kan kategoriseres, da venetoclax i kombination med rituximab er vurderet som ikke værende et dårligere behandlingsalternativ end venetoclax monoterapi.

Amgros vurderer, at behandling med venetoclax i kombination med rituximab er forbundet med besparelser sammenlignet med ibrutinib. Amgros vurderer, at der er et rimeligt forhold mellem lægemidlets værdi og de inkrementelle omkostninger, selvom værdien ikke kan kategoriseres, da fagudvalget for kronisk lymfatisk leukæmi har vurderet venetoclax i kombination med rituximab som et klinisk ligeværdigt behandlingsvalg med ibrutinib.

Amgros vurderer, at behandling med venetoclax i kombination med rituximab er forbundet med høje meromkostninger sammenlignet med chlorambucil i kombination med obinutuzumab, men Amgros vurderer, at der er et rimeligt forhold mellem den kliniske merværdi og de inkrementelle omkostninger.

Amgros vurderer, at behandling med venetoclax i kombination med rituximab er forbundet med meget høje meromkostninger sammenlignet med bendamustin i kombination med rituximab. Amgros vurderer, at der ikke er et rimeligt forhold mellem de inkrementelle omkostningerne og lægemidlets værdi for venetoclax i kombination med rituximab sammenlignet med bendamustin i kombination med rituximab til voksne patienter med kronisk lymfatisk leukæmi, som har modtaget mindst én anden behandling.

Hvis Medicinrådet anbefaler venetoclax i kombination med rituximab til patienter i klinisk spørgsmål 2, betyder det dog, at patienterne i klinisk spørgsmål 3, som er kandidater til genbehandling med kemoterapi og CD20-antistof som følge af sent relaps (> 3 år efter seneste behandling), vil blive kandidater til venetoclax i kombination med rituximab i den efterfølgende linje. I det tilfælde vil meromkostningerne ved at anbefale venetoclax i kombination med rituximab til patienter, der i dag genbehandles med kemoterapi, blive væsentligt reduceret. Dette er ikke belyst i Amgros' analyse.

Amgros har indgået en aftale om indkøb af venetoclax i kombination med rituximab til en reduceret pris i forhold til AIP. Konklusionen er baseret på denne aftalepris.

Amgros' beslutningsgrundlag og Amgros' sundhedsøkonomiske analyse er vedlagt som bilag 1 og 2.

8 Overvejelser omkring alvorlighed/forsigtighed

Medicinrådet har ikke fundet anledning til at inddrage forhold vedrørende alvorlighed eller forsigtighed i anbefalingen.

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kronisk lymfatisk leukæmi (CLL)

Formand	**Indstillet af**
Robert Schou Pedersen Overlæge	Lægevidenskabelige Selskaber og udpeget af Region Midtjylland
Medlemmer	**Udpeget af**
Thor Høyer Afdelingslæge	Region Nordjylland
Annika Rewes Afdelingslæge	Region Syddanmark
Kan ikke opfylde Medicinrådets habilitetskrav	Region Sjælland
Kan ikke opfylde Medicinrådets habilitetskrav	Region Hovedstaden
Stine Trolle Poulsen Farmaceut	Dansk Selskab for Sygehusapoteksledelse
Jakob Henriksen Læge	Dansk Selskab for Klinisk Farmakologi
To patienter/patientrepræsentanter	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. th. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Thomas Linemann (projekt- og metodeansvarlig) Heidi Møller Johnsen (projektdeltager) Jan Odgaard-Jensen (biostatistiker) Anette Pultera Nielsen (fagudvalgskoordinator) Annemette Anker Nielsen (teamleder)

10 Versionslog

Version	Dato	Ændring
1.0	11. decemeber 2019	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

- Amgros' beslutningsgrundlag
- Amgros' sundhedsøkonomiske analyse
- Høringssvar fra ansøger
- Vurdering af venetoclax i kombination med rituximab til behandling af kronisk lymfatisk leukæmi
- Ansøgers endelige ansøgning
- Protokol for vurdering af venetoclax i kombination med rituximab til behandling af kronisk lymfatisk leukæmi

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Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af venetoclax (Venclyxto) i kombination med rituximab som mulig standardbehandling til voksne patienter med kronisk lymfatisk leukæmi, som tidligere har modtaget mindst én anden behandling. Vurderingen er baseret på lægemidlets gennemsnitlige inkrementelle omkostninger (baseret på SAIP) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	11-12-2019
Firma	Abbvie (ansøger)
Lægemiddel	Venetoclax (Venclyxto)
Indikation	Venetoclax (Venclyxto) i kombination med rituximab (R) til voksne patienter med kronisk lymfatisk leukæmi, som har modtaget mindst én anden behandling

Overordnet konklusion

Medicinrådet har vurderet, at venetoclax (Venclyxto) i kombination med rituximab sammenlignet med venetoclax monoterapi giver merværdien **kan ikke kategoriseres.** Behandling med venetoclax (Venclyxto) i kombination med rituximab er forbundet med besparelser sammenlignet med venetoclax monoterapi. Amgros vurderer, at der **er** et rimeligt forhold mellem den kliniske merværdi og de inkrementelle omkostninger selvom merværdien ikke kan kategoriseres, da venetoclax (Venclyxto) i kombination med rituximab er vurderet, som ikke værende et dårligere behandlingsalternativ til venetoclax monoterapi.

Medicinrådet har vurderet, at venetoclax (Venclyxto) i kombination med rituximab sammenlignet med ibrutinib giver merværdien **kan ikke kategoriseres.** Behandling med venetoclax (Venclyxto) i kombination med rituximab er forbundet med besparelser sammenlignet med ibrutinib. Amgros vurderer, at der **er** et rimeligt forhold mellem den kliniske merværdi og de inkrementelle omkostninger selvom merværdien ikke kan kategoriseres, da venetoclax (Venclyxto) i kombination med rituximab er vurderet som et klinisk ligeværdigt behandlingsvalg med ibrutinib.

Medicinrådet har vurderet, at venetoclax (Venclyxto) i kombination med rituximab sammenlignet med chlorambucil i kombination med obinutuzumab giver merværdien **kan ikke kategoriseres.** Behandling med venetoclax (Venclyxto) i kombination med rituximab er forbundet med høje meromkostninger sammenlignet med chlorambucil i kombination med obinutuzumab, men at effektforholdet mellem behandlingerne vil være i overensstemmelse med P3b. Amgros vurderer, at der **er** et rimeligt forhold mellem den kliniske merværdi og de inkrementelle omkostninger.

Medicinrådet har vurderet, at venetoclax (Venclyxto) i kombination med rituximab sammenlignet med bendamustin i kombination med rituximab giver en **moderat klinisk merværdi.** Behandling med venetoclax (Venclyxto) i kombination med rituximab er forbundet med meget høje meromkostninger sammenlignet med bendamustin i kombination med rituximab. Amgros vurderer, at der **ikke er** et rimeligt forhold mellem den kliniske merværdi og de inkrementelle omkostninger.

Amgros' sundhedsøkonomiske vurdering

- Amgros vurderer, at der **er** et rimeligt forhold mellem de inkrementelle omkostningerne og den kliniske merværdi for venetoclax (Venclyxto) i kombination med rituximab sammenlignet med venetoclax monoterapi til voksne patienter med kronisk lymfatisk leukæmi, som har modtaget mindst én anden behandling (P1)

- Amgros vurderer, at der **er** et rimeligt forhold mellem de inkrementelle omkostningerne og den kliniske merværdi for venetoclax (Venclyxto) i kombination med rituximab sammenlignet med ibrutinib til voksne patienter med kronisk lymfatisk leukæmi, som har modtaget mindst én anden behandling (P2)

- Amgros vurderer, at der **er** et rimeligt forhold mellem de inkrementelle omkostningerne og den kliniske merværdi for venetoclax (Venclyxto) i kombination med rituximab sammenlignet med chlorambucil i kombination med obinutuzumab til voksne patienter med kronisk lymfatisk leukæmi, som har modtaget mindst én anden behandling (P3a)

- Amgros vurderer, at der **ikke er** et rimeligt forhold mellem de inkrementelle omkostningerne og den kliniske merværdi for venetoclax (Venclyxto) i kombination med rituximab sammenlignet med bendamustin i kombination med rituximab til voksne patienter med kronisk lymfatisk leukæmi, som har modtaget mindst én anden behandling (P3b)

Andre overvejelser

Amgros har en kontrakt med Orifarm om indkøb af venetoclax (Venclyxto), 100 mg, 112 stk. til en SAIP, som er lavere end AIP. Kontrakten er gældende indtil [redacted].

Der er store usikkerheder forbundet med forløbet af efterfølgende behandlinger, da der ikke findes data der

sammenligner venetoclax (Venclyxto) i kombination rituximab og komparatorerne venetoclax monoterapi, ibrutinib og chlorambucil i kombination med obinutuzumab. En følsomhedsanalyse der ekskluderer efterfølgende behandling er derfor præsenteret i afrapporteringen.

Sundhedsøkonomisk vurdering

Tabel 1 Merværdi, meromkostninger og Amgros' vurdering (baseret på SAIP)

Population	Komparator	Merværdi	Usikkerhed for klinisk merværdi	Amgros' konklusion om forholdet mellem meromkostninger og merværdi
P1: Patienter med kronisk lymfatisk leukæmi med deletion 17p/TP53-mutation, som oplever behandlingssvigt under behandling med ibrutinib 1. linje.	Venetoclax monoterapi	Kan ikke kategoriseres*	Meget lav evidenskvalitet	Rimeligt
P2: Patienter med kronisk lymfatisk leukæmi der oplever behandlingskrævende relaps eller behandlingssvigt mindre end 3 år efter behandling med kemoterapi i kombination med CD20-antistof og/eller patienter med sent relaps og nytilkommen deletion 17p/TP53-mutation.	Ibrutinib	Kan ikke kategoriseres**	Meget lav evidenskvalitet	Rimeligt
P3: Patienter med kronisk lymfatisk leukæmi uden deletion 17p/TP53-mutation, der oplever behandlingskrævende relaps mere end 3 år efter deres første behandling med kemoterapi i kombination med CD20-antistof.	A: Chlorambucil i kombination med obinutuzumab	Kan ikke kategoriseres***	Meget lav evidenskvalitet	Rimeligt
	B: Bendamustin i kombination med rituximab	Moderat klinisk merværdi	Moderat evidenskvalitet	Ikke rimeligt

For P1 er vurderingen baseret på, at Medicinrådet har vurderet venetoclax + rituximab som ikke værende et dårligere behandlingsalternativ end komparator venetoclax som monoterapi, og vurderingen af meromkostninger og klinisk værdi beror på denne.

For P2 er vurderingen baseret på, at Medicinrådet har vurderet venetoclax + rituximab som værende klinisk ligeværdig behandling med komparator ibrutinib, og vurderingen af meromkostninger og klinisk værdi beror på denne.

For P3a er vurderingen baseret på, at Medicinrådet har vurderet venetoclax + rituximab sammenlignet med komparator chlorambucil + obinutuzumab som havende samme effektforhold mellem behandlingerne som for P3b, og vurderingen af meromkostninger og klinisk værdi beror på denne.

For P3b er vurderingen baseret på, at Medicinrådet har valgt bendamustin + rituximab som komparator for patientpopulationen, og vurderingen af meromkostninger og klinisk værdi beror på denne.

Resumé af resultaterne fra Amgros' afrapportering

Konklusion på omkostnings- og budgetkonsekvensanalyserne

Resultatet fra Amgros' afrapportering på omkostningsanalyserne er gengivet i det følgende. For uddybende gennemgang af analyse og resultater henvises til afrapporteringen på http://www.amgros.dk.

Inkrementelle omkostninger per patient

Behandling med venetoclax (Venclyxto) i kombination med rituximab er forbundet med besparelser og høje meromkostninger alt efter hvilken komparator der sammenlignes med.
I tabel 2, 3, 4 og 5 ses de inkrementelle omkostninger for venetoclax (Venclyxto) og komparatorne.

Ansøger estimerer i analysen de inkrementelle omkostninger per patient for venetoclax (Venclyxto) + R sammenlignet med venetoclax (Venclyxto) monoterapi (P1) til at være ca. [redacted], sammenlignet med ibrutinib (P2) til at være ca. [redacted], sammenlignet med chlorambucil + obinutuzumab (P3a) til at være ca. [redacted] og sammenlignet med bendamustin + R (P3b) til at være ca. [redacted].

Tabel 2: Resultat af Amgros hovedanalyse for P1, DKK, SAIP

	Venetoclax (Venclyxto)+R [DKK]	Venetoclax (Venclyxto) [DKK]	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	96.397	82.577	13.820
Patientomkostninger	35.850	36.496	-645
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 3: Resultat af Amgros hovedanalyse for P2, DKK, SAIP

	Venetoclax (Venclyxto)+R [DKK]	Ibrutinib [DKK]	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	102.566	58.518	17.975
Patientomkostninger	35.399	17.424	44.047
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 4: Resultat af Amgros hovedanalyse for P3a, DKK, SAIP

	Venetoclax (Venclyxto)+R [DKK]	Chlorambucil + obinutuzumab [DKK]	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	102.566	77.903	24.662
Patientomkostninger	35.399	34.209	1.191
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 5: Resultat af Amgros hovedanalyse for P3b, DKK, SAIP

	Venetoclax (Venclyxto)+R [DKK]	Bendamustin + R [DKK]	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	102.566	71.709	30.857
Patientomkostninger	35.399	34.209	1.191
Totale omkostninger	[redacted]	[redacted]	[redacted]

Hvis analysen udføres med AIP bliver de inkrementelle omkostninger til sammenligning hhv. ca. - 620.000 DKK for P1, ca. -1,9 mio. DKK for P2, ca. 275.000 DKK og ca. 400.000 DKK for de to komparatorer i P3 (hhv. chlorambucil i kombination med obinutuzumab og bendamustin i kombination med rituximab).

Hvis efterfølgende behandlingslinjer inkluderes i analysen, øges besparelserne for P1 og P2 til ca. [redacted] DKK for P1 til ca. [redacted] DKK for P2. De inkrementelle omkostninger stiger til ca. [redacted] for P3a og til ca. [redacted] DKK for P3b.

I disse analyser drives meromkostninger i høj grad af lægemiddelomkostningerne for venetoclax (Venclyxto) og komparatorerne.

Budgetkonsekvenser

Amgros vurderer, at anbefaling af venetoclax (Venclyxto) + R som mulig standardbehandling, vil resultere i følgende budgetkonsekvenser i år 1 til år 5:

- P1 på ca. [redacted] DKK
- P2 ca. [redacted] DKK
- P3a ca. [redacted] DKK
- P3b ca. [redacted] DKK

Angives analysen i AIP bliver budgetkonsekvenserne i år 5 ca. -13,5 mio. DKK for P1, ca. -70,4 mio. DKK for P2, ca. 400.000 DKK for P3a og ca. 3,2 mio. DKK for P3b.

Amgros påpeger også usikkerheden omkring markedsoptaget, der ligger til grund for budgetkonsekvenserne. Amgros vurderer, at de reelle budgetkonsekvenser for P3a og P3b populationen vil ligge imellem hovedanalysens estimat og følsomhedsanalysens estimat på ca. [redacted] DKK for P3a og ca. [redacted] DKK for P3b.

VENETOCLAX (VENCLYXTO) I KOMBINATION MED RITUXIMAB

KRONISK LYMFATISK LEUKÆMI

AMGROS 30. september 2019

AMGROS

OPSUMMERING

Baggrund

Venetoclax (Venclyxto) i kombination med rituximab er indiceret til voksne patienter med kronisk lymfatisk leukæmi, som tidligere har modtaget mindst én anden behandling. I Danmark kandiderer omkring 150 patienter til den ansøgte indikation. Amgros' vurdering tager udgangspunkt i dokumentation indsendt af Abbvie.

Analyse

I analysen estimeres de inkrementelle omkostninger forbundet med behandling med venetoclax (Venclyxto) i kombination med rituximab, sammenlignet med venetoclax (Venclyxto) monoterapi (P1), ibrutinib (P2), chlorambucil i kombination med obinutuzumab (P3a) samt bendamustin kombination med rituximab (P3b).

Inkrementelle omkostninger og budgetkonsekvenser

Amgros har vurderet de gennemsnitlige meromkostninger per patient ved brug af venetoclax i kombination med rituximab. De følgende inkrementelle omkostninger er angivet i SAIP.

- P1: De gennemsnitlige meromkostninger for venetoclax i kombination med rituximab sammenlignet med venetoclax monoterapi til den nævnte indikation er ca. [redacted].
- P2: De gennemsnitlige meromkostninger for venetoclax i kombination med rituximab sammenlignet med ibrutinib til den nævnte indikation er ca. [redacted]
- P3a: De gennemsnitlige meromkostninger for venetoclax i kombination med rituximab sammenlignet med chlorambucil i kombination med obinutuzumab, til den nævnte indikation er ca. [redacted]
- P3b: De gennemsnitlige meromkostninger for venetoclax (Venclyxto) i kombination med rituximab sammenlignet med bendamustin i kombination med rituximab, til den nævnte indikation er ca. [redacted]

Hvis analysen udføres med AIP bliver de inkrementelle omkostninger til sammenligning hhv. ca. - 620.000 DKK for P1, ca. -1,9 mio. DKK for P2, ca. 275.000 DKK for P3a og ca. 400.000 DKK for P3b.

Amgros vurderer, at budgetkonsekvenserne for regionerne ved anbefaling venetoclax (Venclyxto) i kombination med rituximab som standardbehandling vil være ca. [redacted] for P1, ca. [redacted] for P2, samt hhv. ca. [redacted] for P3a og [redacted] for P3b i år 1-5. Hvis analysen udføres med AIP, er budgetkonsekvenser ca. -13,5 mio. DKK år 5 for P1 i år 5, Ca. -70,4 mio. DKK for P2 i år 5, ca. 400.000 DKK for P3a i år 5 og 3,2 mio. DKK for P3b år 5.

Konklusion

Behandling med venetoclax (Venclyxto) i kombination med rituximab er forbundet med besparelser sammenlignet med P1 og P2 og med høje meromkostninger for P3. Analysens resultat drives af lægemiddelomkostningerne samt behandlingslængden.

Liste over forkortelser

AIP	Apotekernes indkøbspris
BSC	Best supportive care
CIRS	Cumulative illness rating scale
CLL	Kronisk lymfatisk leukæmi
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
IGHV	Immunoglobulin heavy-chain variable region
MAIC	Matched adjusted therapy comparison
OS	Samlet Overlevelse
PFS	Progressionsfri overlevelse
R	RituximabX
SAIP	Sygehusapotekernes indkøbspriser
SPC	Produktresumé

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	Abbvie
Handelsnavn:	Venclyxto
Generisk navn:	Venetoclax
Indikation:	Voksne patienter med kronisk lymfatisk leukæmi der har modtaget mindst én tidligere behandling (2. linjebehandling)
ATC-kode:	L01XX52

Proces	
Ansøgning modtaget hos Amgros:	21-08-2019
Endelig rapport færdig:	30-09-2019
Sagsbehandlingstid fra endelig ansøgning:	35 dage
Arbejdsgruppe:	**Louise Greve Dal** Line Brøns Jensen Mark Friborg Pernille Winther Johansen

Priser
Denne rapport bygger på analyser udført på baggrund sygehusapotekernes indkøbspriser (SAIP). Enkelte steder er analysens resultat yderligere angivet på baggrund af listepriser (AIP).

1 BAGGRUND

Venetoclax (Venclyxto) i kombination med rituximab (R) er indiceret til behandling af voksne patienter med kronisk lymfatisk leukæmi (CLL), som har modtaget mindst én tidligere behandling (2. linjebehandling). Abbvie (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af venetoclax (Venclyxto) og har den 15.08.2019 indsendt en ansøgning til Medicinrådet om anbefaling af venetoclax (Venclyxto) i kombination med rituximab, som standardbehandling på danske hospitaler af den nævnte indikation. Som et led i denne ansøgning vurderer Amgros, på vegne af Medicinrådet, de økonomiske analyser, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Den økonomiske analyse blev godkendt 21.08.2019. Denne rapport er Amgros' vurdering af de fremsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger per patient og de samlede budgetkonsekvenser for regionerne, ved anbefaling af venetoclax (Venclyxto)+ R, som standardbehandling på danske hospitaler af den nævnte indikation. I analyserne sammenlignes behandling med venetoclax (Venclyxto) + R med behandling med venetoclax monoterapi (P1), ibrutinib (P2), chlorambucil + obinutuzumab (P3a) og bendamustin + R (P3b).

1.2 Patientpopulation

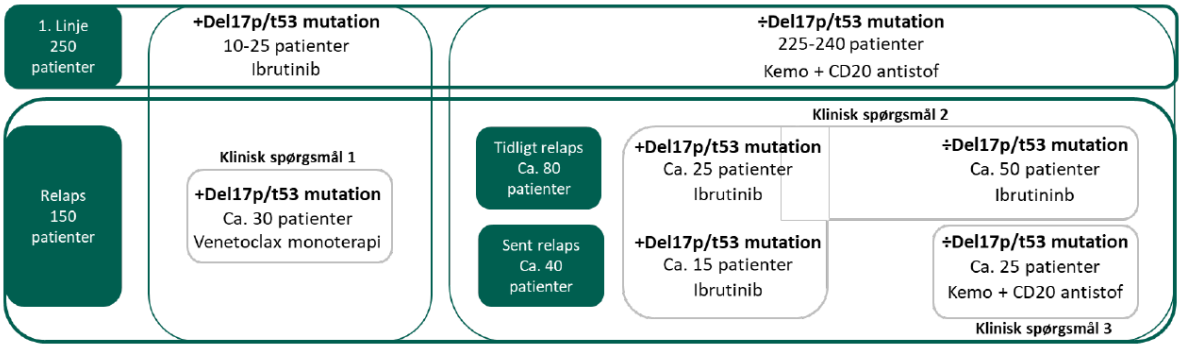
Kronisk lymfatisk leukæmi er en hæmatologisk kræftsygdom, som opstår i kroppens B-lymfocytter og påvirker cellernes regulering af celledeling og celledød. Det fører til en ophobning af B-lymfocytter bl.a. i knoglemarv, lymfeknuder, milt og blod. B-cellernes normale funktioner svækkes, ligesom funktionen af knoglemarvens andre celler kan være påvirket. Symptomerne hos patienter med kronisk lymfatisk leukæmi er relaterede hertil og omfatter typisk hævede lymfeknuder, forstørret milt, blodmangel, træthed, uforklarlig feber, vægttab og øget infektionstendens(1).
Kronisk lymfatisk leukæmi er den mest almindelige type leukæmi i de vestlige lande, og diagnosen udgør her ca. 30 % af samtlige leukæmier. Incidensen er i Danmark ca. 6-7 pr. 100.000 indbyggere pr. år, og der registreres ca. 450-500 nye tilfælde om året i Danmark. Det estimeres, at ca. 4.000 patienter lever med sygdommen i Danmark og medianalderen er ved diagnose 70 år, og dobbelt så mange mænd som kvinder får diagnosen(2–4).
Kronisk lymfatisk leukæmi er ofte asymptomatisk på diagnosetidspunktet og kan blive opdaget tilfældigt efter en blodprøve. Diagnosen stilles ved konstatering af persisterende lymfocytose, dvs. > 5 mia. monoklonale B-celler pr. liter blod i tre måneder eller derover. På diagnosetidspunktet foretages en vurdering af sygdomsstadie og sygdommens aggressivitet (risikoprofil på baggrund af cytogenetiske forandringer, immunoglobulin heavy-chain variable region (IGHV)-mutationsstatus). Både sygdomsstadie, patientens symptomer og risikoprofil har indflydelse på igangsættelse og valg af behandling, ligesom de har betydning for patienternes prognose. Kronisk lymfatisk leukæmi har ofte et indolent forløb, hvor patienterne med tidlige stadier og langsomt progredierende sygdom følges ved årlige kontroller eller afsluttes til egen læge. Median overlevelse fra diagnosetidspunktet varierer fra 4 til > 12 år afhængig af sygdomsstadie og risikoprofil(1).

1.3 Nuværende behandling

Patientpopulationen opdeles i behandlingsøjemed efter, hvorvidt de har deletion 17p/p53-mutation eller ej, og behandlingsstrategien afhænger af patientspecifikke faktorer (performancestatus, komorbiditet (cumulative illnes rating scale (CIRS)), alder, præferencer), sygdomskarakteristika (tumorbyrde, stadie, risikoprofil (FISH), mutationsstatus) og behandlingsmuligheder(1).
Hvorvidt patienterne har deletion17p/p53-mutation eller ej er afgørende for, om de i 1. linje er kandidater til cytostatika i form af enten chlorambucil, fluradabin og cyclofosfamid, eller bendamustin i kombination med et CD20-antistof. Patienter med deletion17p/p53-mutation er ikke følsomme for behandling med cytostatika og behandles i stedet med proteinkinasehæmmeren ibrutinib(1).
For patienter uden deletion17p/p53-mutation afgøres valget af cytostatika og CD20-antistof af patientens alder, performancestatus og mængden af komorbiditet(5). Traditionelt har man anvendt cytostatika i 1. linje, når det

var muligt, fordi de medicinske behandlingsmuligheder har været få, og fordi højere alder og deletion17p/p53-mutation senere i sygdomsforløbet kan udelukke behandling med cytostatika. Desuden har man god dokumentation for effekt og bivirkninger ved de velkendte kemoterapier, mens viden om den langsigtede effekt af nyere behandlinger er sparsom. I takt med nye og mere målrettede behandlingsmuligheder er der en tendens til at bevæge sig væk fra anvendelse af cytostatika, blandt andet fordi cytostatika er forbundet med langvarig immundepletion(1).

Figur 1 viser nuværende behandlingsalgoritme. Der er ca. 150 patienter om året med behandlingsbehov i 2. linje(5). Ved tidlig relaps behandles både patienter uden og patienter med nytilkommen deletion17p/p53-mutation med ibrutinib (ca. 90 patienter)(5). Patienter, der i 1. linje blev behandlet med ibrutinib, behandles hovedsageligt med venetoclax monoterapi (ca. 30 patienter). Hos patienter uden deletion17p/p53-mutation med sen relaps (senere end 3 år efter sidste behandling) kan kemoterapi i kombination med et CD20-antistof gentages (ca. 25 patienter)(1).



Figur 1: Behandlingsalgoritme med angivelse af fagudvalgets estimater af populationsstørrelser og mest anvendte behandling.

Fagudvalget vedr. kronisk lymfatisk leukæmi's angivelse af antallet af patienter i de forskellige grupper er baseret på estimater fra tidligere RADS-behandlingsvejledning, viden om tid til første relaps, og forekomsten af deletion17p/p53-mutation på forskellige tidspunkter i behandlingsforløbet(6–9).

I nuværende dansk klinisk praksis skelnes der i behandlingsøjemed ikke imellem, hvorvidt patienterne har IGHV-mutation eller ej, selvom det er af betydning for patienternes prognose. Patienter med non-muteret sygdom har en dårligere prognose end patienter med muteret sygdom. Studier viser, at en opdeling af patienterne i forhold til IGHV-mutation er relevant for effekten af nogle behandlinger, og fagudvalget forventer, at den praksis på sigt vil blive gældende i dansk sammenhæng(10–12).

1.4 Behandling med venetoclax (Venclyxto) + rituximab

Indikation

Voksne patienter med kronisk lymfatisk leukæmi, som har modtaget mindst én tidligere behandling.

Virkningsmekanisme

Venetoclax (Venclyxto)hæmmer det antiapoptotiske protein BCL-2, som er overudtrykt i B-cellerne hos patienter med kronisk lymfatisk leukæmi. Forøget BCL-2 øger tumorcellernes overlevelse og er associeret med resistens mod kemoterapi.

Dosering

Venetoclax (Venclyxto) i kombination med rituximab skal til den ansøgte indikation doseres som følger:

- Venetoclax (Venclyxto) p.o. 20 mg dagligt i uge 1, 50 mg dagligt i uge 2, 100 mg dagligt i uge 3, 200 mg dagligt i uge 4, 400 mg dagligt i uge 5 og herefter 400 mg dagligt fra uge 6 og 24 måneder frem
- Fra uge 6, i 6 serier a 28 dage rituximab 375 mg/m2 i.v. på dag 1 i serie 1, 500 mg/m2 på dag 1 i serie 2-6

1.4.1 Komparator

Medicinrådet har defineret følgende komparatorer til følgende populationer(1):

Tabel 1: Definerede populationer og komparatorer.

Population	Komparator
P1: Patienter med deletion17p/p53-mutation, som oplever behandlingssvigt under behandling med ibrutinib i 1. linje	Venetoclax monoterapi, doseret som følger: Venetoclax p.o. 20 mg dagligt i uge 1, 50 mg dagligt i uge 2, 100 mg dagligt i uge 3, 200 mg dagligt i uge 4, 400 mg dagligt i uge 5 og herefter 400 mg dagligt fra uge 6 og frem til progression
P2: Patienter med kronisk lymfatisk leukæmi, der oplever behandlingskrævende relaps eller behandlingssvigt mindre end 3 år efter behandling med kemoterapi i kombination med CD20-antistof og/eller patienter med sen relaps og nytilkommen deletion17p/p53-mutation.	Ibrutinib p.o. 420 mg dagligt indtil progression
P3: Patienter med kronisk lymfatisk leukæmi uden deletion17p/p53-mutation, der oplever behandlingskrævende relaps mere end 3 år efter deres første behandling med kemoterapi i kombination med CD20-antistof	**P3a:** Chlorambucil i kombination med obinutuzumab doseret som følger i 6 serier a 28 dage: Chlorambucil p.o. 0,5 mg/kg på dag 1 og 15 Obinutuzumab s.c. 100 mg på dag 1, 900 mg på dag 2 og 1000 mg på dag 8 og 15 i 1. serie, herefter 1000 mg på dag 1 i serie 2-6. **P3b:** Bendamustin i kombination med rituximab doseret som følger i op til 6 serier a 28 dage: Bendamustin i.v. 70-90 mg/m2 på dag 1 og 2 Rituximab i.v. 375 mg/m2 på dag 1 i første serie, herefter i.v. 500 mg/m2 på dag 1 i efterfølgende serier.

1.5 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi af venetoclax (Venclyxto) + rituximab til voksne patienter med kronisk lymfatisk leukæmi:

Kliniske spørgsmål:

- **P1:** Hvilken værdi har venetoclax i kombination med rituximab sammenlignet med venetoclax monoterapi til behandling af patienter med deletion17p/p53-mutation, som oplever relaps eller behandlingssvigt efter behandling med ibrutinib?
- **P2**: Hvilken værdi har venetoclax i kombination med rituximab sammenlignet med ibrutinib til 2.-linjebehandling af patienter, der er behandlet med kemoterapi i kombination med et CD20-antistof i 1. linje?
- **P3:** Hvilken værdi har venetoclax i kombination med rituximab sammenlignet med kemoterapi i kombination med CD20-antistof til behandling af patienter uden deletion17p/p53-mutation, der har behandlingskrævende relaps mere end 3 år efter deres første behandling?

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I analysen af inkrementelle omkostninger per patient sammenlignes behandling med venetoclax (Venclyxto) + R med behandling med venetoclax (Venclyxto) monoterapi (P1), Ibrutinib (P2), chlorambucil + obinutuzumab (P3a) og bendamustin + R (P3b) til voksne patienter med CLL, der har modtaget mindst en tidligere behandling. Analysen inkluderer omkostninger til lægemidler, monitorering, bivirkninger, patienttid og transport samt omkostninger til efterfølgende behandlinger og best supportive care (BSC).

Amgros' havde flere indvendinger mod første indsendte model. Det er kun den seneste model der præsenteres i følgende afsnit.

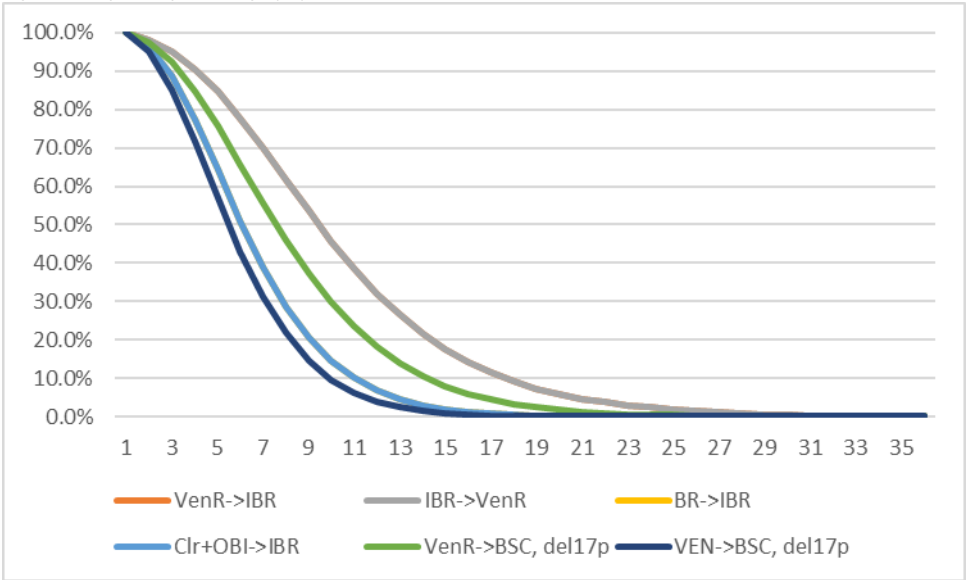
2.1 Model, metode og forudsætninger

2.1.1 Modelbeskrivelse

Ansøger har indsendt 4 økonomiske modeller for de 3 kliniske spørgsmål og 4 komparatorer. Modellerne er alle en partioned survival model, der inkluderer stadierne overlevelse (OS), progressionsfri overlevelse (PFS) og progression (PD). Ansøger har ekstrapoleret studiedata fra MURANO-studiet, og anvendt Weibull distribution, der viser det bedste statistiske fit (AIC/BIC) til Kaplan-Meier PFS-kurven og OS-kurven. Da behandlingen med venetoclax (Venclyxto) + R gives 24 måneder efter indkørselsfasen, stopper behandlingen for venetoclax (Venclyxto) + R efter denne behandlingsperiode.

Ansøger inkluderer desuden omkostninger ud fra behandlingssekvenser. Efterfølgende behandling efter progression er beregnet ud fra PFS og OS, hvor OS justeres ud fra hhv. 2. linjebehandling og 3. linjebehandling. Se figur 2. X aksen er tid vist i antal år og y aksen er overlevelse i procent.

Figur 2: OS for de forskellige populationer



*Da frekvenserne VenR->IBR og BR->IBR er ens med overlevelseskurven IBR->VenR, er det kun denne kurve som illustreres

Tiden patienten befinder sig i hver af sygdomsstadierne relaterer sig til hvilken behandling patienten modtager, og omkostningerne er relateret til behandlingen. Patienterne behandles når de befinder sig i PFS og PD stadierne.

Der foreligger ingen studier, der direkte sammenligner venetoclax (Venclyxto) + R med venetoclax (Venclyxto) monoterapi (P1), ibrutinib (P2), chlorambucil + obinutuzumab (P3a). Disse er derfor baseret på narrative sammenligninger.

Den økonomiske analyse, for behandling med venetoclax (Venclyxto) + R sammenlignet med venetoclax (Venclyxto) monoterapi (P1), er baseret på 3 kliniske studier (13–15) og en matched adjusted indirect comparison (MAIC). Ansøger anvender forskellen i Hazard Ratio (HR) mellem studierne til at beregne forskellen mellem behandlingerne, og anvender HR på de kliniske forløbsdata i MURANO-studiet(16,17). Patienten modtager enten venetoclax (Venclyxto) + R, og modtager BSC efter progression, eller starter behandling med venetoclax (Venclyxto) monoterapi, og modtager BSC efter progression.

I den økonomiske analyse for behandling med venetoclax (Venclyxto) + R sammenlignet med ibrutinib (P2), antages ibrutinib at have samme PFS og OS som venetoclax (Venclyxto) + R(17). Patienten modtager enten venetoclax (Venclyxto) + R, og derefter ibrutinib ved progression, eller patienten modtager ibrutinib, derefter venetoclax (Venclyxto) + R. Patienten modtager herefter BSC i begge behandlingsfrekvenser indtil død.

I den økonomiske analyse, for behandling med venetoclax (Venclyxto) + R sammenlignet med bendamustin + R (P3b), er venetoclax (Venclyxto) + R blevet direkte sammenlignet i MURANO-studiet(17). Patienten modtager enten venetoclax (Venclyxto) + R, og derefter ibrutinib ved progression, eller patienten modtager bendamustin + R, derefter ibrutinib. Patienten modtager herefter BSC i begge behandlingsfrekvenser indtil død.

Den økonomiske analyse for behandling med venetoclax (Venclyxto) + R sammenlignet med chlorambucil + obinutuzumab (P3a), antages chlorambucil + obinutuzumab at have samme behandlingseffekt som bendamustin + R på baggrund af 2 studier der viste samme relative effekt som bendamustin + R (18,19). Behandlingslængden for chlorambucil + obinutuzumab er således sat til den samme som bendamustin + R(P3b), som er beregnet i MURANO-studiet(17). Patienten modtager enten venetoclax (Venclyxto) + R, og derefter ibrutinib ved progression, eller patienten modtager chlorambucil + obinutuzumab, derefter ibrutinib. Patienten modtager herefter BSC i begge behandlingsfrekvenser indtil død.

Amgros' vurdering

Amgros vurderer der er stor usikkerhed for OS- og PFS-estimaterne beregnet for venetoclax (Venclyxto) monoterapi, ibrutinib og chlorambucil + obinutuzumab, da disse ikke er baseret på en direkte sammenligning, men accepterer ansøgers metoder, da der ikke eksisterer andre data.
Da der ikke forefindes data til ekstrapolering mellem alle komparatorer er forløbsdataene håndteret ud fra HR, der er forbundet med usikkerheder.
Amgros vurderer der er stor usikkerhed ved at inkludere efterfølgende behandlinger, da studierne kun rapporterer overlevelsesdata, og ikke tager højde for effekten af efterfølgende behandlinger. Der findes ikke flere mulige valg af efterfølgende behandling, og inkludering af efterfølgende behandling beror sig derfor i dette tilfælde på et skift i behandlingsfrekvens mellem ansøgte indikation og i forvejen anvendte behandling (komparator) eller ens efterfølgende behandling.

Amgros accepterer ansøgers model tilgang.
Amgros udarbejder en følsomhedsanalyse der ekskluderer efterfølgende behandlinger, for at belyse usikkerheden omkring disse.

2.1.2 Analyseperspektiv

Ansøger har indsendt en omkostningsanalyse med et begrænset samfundsperspektiv. Analysen har en tidshorisont på 600 cyklusser af 28 dage, svarende til 46 år hvor alle patienter er døde. Omkostninger der ligger efter det første år, er diskonteret med en rate på 4 % jf. Amgros' metodevejledning.

Amgros' vurdering

Analysens begrænsede samfundsperspektiv og diskonteringsrate er i tråd med Amgros' retningslinjer og accepteres.

2.1.3 Omkostninger

Følgende afsnit redegør for omkostninger inkluderet i ansøgers analyse.

Lægemiddelomkostninger

Ansøger har inkluderet omkostninger til lægemidler.

I tabel 2 ses lægemiddelpriserne for venetoclax (Venclyxto), rituximab og komparatorer.

Tabel 2: Anvendte lægemiddelpriser, SAIP, (september 2019).

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Venetoclax (Venclyxto)	10 mg	14 stk.	[redacted]	Amgros
	50 mg	7 stk.	[redacted]	Amgros
	100 mg	7 stk.	[redacted]	Amgros
	100 mg	14 stk.	[redacted]	Amgros
	100 mg	112 stk.	[redacted]	Amgros
Rituximab	500 mg	1 stk.	[redacted]	Amgros
Ibrutinib	420 mg	28 stk.	[redacted]	Amgros
Chlorambucil	2 mg	25 stk.	[redacted]	Amgros
Obinutuzumab	1000 mg	1 stk.	[redacted]	Amgros
Bendamustin	2,5 mg/ml	5 stk.	[redacted]	Amgros

Den anvendte dosering af lægemidlerne er baseret på lægemidlernes SPC'er(20–24). Ansøger antager at en gennemsnitlig patient vejer 70 kg og har et overfladeareal på 1.89 m^2.

Amgros' vurdering

Amgros har udskiftet de indsendte lægemiddelpriser fra AIP til SAIP.

Amgros vurderer, at ansøgers tilgang til lægemiddelomkostninger er acceptabel.

Hospitalsomkostninger

Ansøger har inkluderet omkostninger til monitorering af lægemidlerne. Dette inkluderer omkostninger til indlæggelse ved opstart, ambulante besøg, både opstartsbesøg og årlige besøg.

Ansøger antager at patienten indlægges i 24 timer i de 5 uger hvor patienten er i optitreringsfasen af venetoclax (Venclyxto) på baggrund af SPC'et. Behandling med chlorambucil + obinutuzumab antages et ambulant besøg per cyklus. Der er antaget samme monitorering for bendamustin + R.
Behandling med ibrutinib antages at gives indenfor 3 årlige ambulante besøg. For BSC antager ansøger at patienten indlægges 30 dage, da patienterne her progredierer fra 3. linjebehandling og har opbrugt alle relevante medicinske behandlingsmuligheder.

Tabel 3 viser monitoreringsfrekvenser estimeret af ansøger år 1 og efterfølgende år i behandling for hvert behandlingsregime.

Tabel 3: Monitoreringsfrekvenser for behandlingerne.

Behandling	Indlæggelse ved behandlingsstart	Ambulatoriebesøg opstart	Ambulatoriebesøg Per år
Venetoclax (Venclyxto) + R	5	0	3
Venetoclax (Venclyxto) mono	5	0	3
Ibrutinib	0	0	3
Chlorambucil + obinutuzumab	0	6	3
Bendamustin + R	0	6	3
BSC	30	0	3

Ansøger har estimeret enhedsomkostninger for monitorering ved brug af ambulante 2017 DRG-takster og Rigshospitalets priskatalog fra klinisk biokemisk afdeling. Tabel 4 viser omkostninger til monitorering.

Tabel 4: Enhedsomkostninger for DRG-takster 2017 til monitorering, fremskrevet til 2019-værier

	Enhedsomkostning [DKK]	Kilde
Indlæggelse	4.249	DAGS-takst 2017: Sengedagstakst Hæmatologisk afdeling
Ambulatoriebesøg	2.045	DAGS-takst BG50A+DG30L

Administrationsomkostninger

Ansøger antager at administrationsomkostninger er inkluderet i ambulatoriebesøgene.

Amgros' vurdering

Amgros vurderer der kan være flere omkostninger forbundet med administrationer for de forskellige lægemidler, men at dette har lille betydning for analysens resultat.

Amgros accepterer ansøgers tilgang.

Omkostninger til bivirkninger

Ansøger har i deres hovedanalyse inkluderet omkostninger til bivirkninger. Bivirkninger større end grad 3 samt med forekomst ≥5% er inkluderet, og er baseret på studierne anvendt for den kliniske merværdi (13–17). Bivirkningsomkostningerne antages at forekomme det første år, efter behandlingsstart.

Se tabel 5 og tabel 6 for bivirkningsfrekvenserne og omkostninger forbundet med bivirkninger.

Tabel 5: Bivirkningsfrekvens per behandling, %

	P1	P2	P3a	P3b	VEN
Anæmi	10.82	4.62	11.70	13.83	13.83
Anæmi (autoimmun)	2.58			1.60	5.33
Febril neutropeni	3.61		7.9	9.57	4.44
Infusionsrelaterede reaktioner	2.06			5.32	
Neutropeni	58.76	16.41	52.50	39.89	39.11
Pneumoni	6.19	6.67	14	7.98	6.67
Trombocytæmi	6.19	5.64	19.6	10.11	13.33

Tabel 6: Enhedsomkostning for bivirkning, DRG-takster fra 2017, fremskrevet til 2019

Bivirkning	Enhedsomkostning [DKK]	Kilde
Anæmi	32.747,60	DRG-takst 2017: Hæmalytiske anæmier og anæmier forårsaget af enzymatiske forstyrrelser m.m
Anæmi (autoimmun)	32.747,60	DRG-takst 2017: Hæmalytiske anæmier og anæmier forårsaget af enzymatiske forstyrrelser m.m
Febril neutropeni	46.417,95	DRG-takst 2017: Granulo- og trombocytopeni
Infusionsrelaterede reaktioner	522,41	DRG-takst 2017: Småskader
Neutropeni	46.417,95	DRG-takst: Granulo- og trombocytopeni
Pneumoni	25.271,58	DRG-takst: Lungebetændelse og pleurit, pat. 18-59 år
Trombocytæmi	16.896,76	DRG-takst: Koagulationsforstyrrelser

Amgros' vurdering

Amgros vurderer der kunne være flere omkostninger forbundet med bivirkninger, hvis omkostningerne relaterede sig til behandlingscyklus. Omkostninger har dog mindre betydning for analysens resultat.

Amgros accepterer ansøgers fremgangsmåde.

Patientomkostninger

Ansøger har valgt at inkludere omkostninger til patienttid. Dette er gjort ud fra lægemiddelmonitorerings besøg på hospitalet og inkluderer tiden på hospitalet og transporttid. Ansøger antager patienter bruger 24 timer per indlæggelse og 1,5 time per ambulant besøg inkl. transportomkostninger frem og tilbage. Ansøger anvender Amgros' enhedsomkostning for patienttid, som er 182,72 kr. per time, og patienttransportomkostninger på 100 kr. per besøg.

Estimerede patienttid og transportomkostninger kan ses i tabel 7.

Tabel 7: Transport- og patienttid baseret på behandlingsregime

Behandling	Patienttid 1. år [Timer]	Patienttid efterfølgende år [Timer]	Transport 1. år [Antal]	Transport efterfølgende år [Antal]
Venetoclax (Venclyxto) + R	126	6	16	6
Venetoclax (Venclyxto) mono	30	6	6	6
Ibrutinib	150	6	18	6
Chlorambucil + obinutuzumab	126	6	16	6
Bendamustin + R	150	6	18	6
BSC	726	6	66	6

Amgros' vurdering

Amgros mener at omkostninger for 24 timers patienttid for en indlæggelse er en overestimering. Dette har lille betydning for analysens resultat.

Amgros accepterer ansøgers estimater.

2.2 Følsomhedsanalyser

Ansøger har ikke udarbejdet nogle følsomhedsanalyser.

Amgros' vurdering

Amgros vurderer der er usikkerheder forbundet med estimaterne for hospitalsomkostninger og patienttid. Amgros har selv undersøgt betydningen af usikkerheden ved disse estimater.
Amgros vurderer det er relevant at se på omkostningernes betydning uden efterfølgende behandlingsregime, og udarbejder en følsomhedsanalyse der undersøger de inkrementelle omkostninger herved.

Amgros har selv undersøgt usikkerhederne forbundet med estimaterne for monitorering og patienttid. De har mindre betydning for analysens resultat. Amgros præsenterer derfor ikke disse følsomhedsanalyser.

Amgros udarbejder selv en følsomhedsanalyse der belyser betydningen af ekskludering af efterfølgende behandlingsregimer. Resultatet kan ses i afsnit 3.2.

3 RESULTATER

3.1 Ansøgers hovedanalyse

Resultaterne fra ansøgers hovedanalyse præsenteres i tabel 8, 9, 10 og 11.

Ansøger estimerer i analysen de inkrementelle omkostninger per patient for venetoclax (Venclyxto) + R sammenlignet med venetoclax (Venclyxto) monoterapi (P1) til at være ca. [redacted]. Besparelserne i P1 populationen skyldes en længere behandlingstid i komparator armen, da denne ikke er tidsbegrænset som ansøgte indikation. 2. Linje er BSC for interventionsarmenX

Tabel 8: Resultatet af ansøgers hovedanalyse for P1, DKK, SAIP

	Venetoclax (Venclyxto)+R [DKK]	Venetoclax (Venclyxto) [DKK]	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	96.397	82.577	13.820
Patientomkostninger	35.850	36.496	-645
Totale omkostninger	[redacted]	[redacted]	[redacted]

Ansøger estimerer i analysen de inkrementelle omkostninger per patient for venetoclax (Venclyxto) + R sammenlignet med ibrutinib (P2) til at være ca. [redacted]. Ibrutinib behandles med indtil progression. Venetoclax (Venclyxto) behandles maksimalt med i 24 måneder. 2. linje i interventionen er ibrutinib i interventionsarmen og for komparator er det venetoclax (Venclyxto). I interventionsarmen modtager patienten ingenting efter 24 måneders behandling indtil progression, som kan være op 6 år. For ibrutinib får patienten behandling indtil progression, hvorefter der gives venetoclax (Venclyxto) i 24 måneder.

Tabel 9: Resultatet af ansøgers hovedanalyse for P2, DKK, SAIP

	Venetoclax (Venclyxto)+R [DKK]	Ibrutinib [DKK]	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	102.566	58.518	17.975
Patientomkostninger	35.399	17.424	44.047
Totale omkostninger	[redacted]	[redacted]	[redacted]

Ansøger estimerer i analysen de inkrementelle omkostninger per patient for venetoclax (Venclyxto) + R sammenlignet med chlorambucil + obinutuzumab (P3a) til at være ca. [redacted].

Tabel 10: Resultatet af ansøgers hovedanalyse for P3a, DKK, SAIP

	Venetoclax (Venclyxto)+R [DKK]	Chlorambucil + obinutuzumab [DKK]	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	102.566	77.903	24.662
Patientomkostninger	35.399	34.209	1.191
Totale omkostninger	[redacted]	[redacted]	[redacted]

Ansøger estimerer i analysen de inkrementelle omkostninger per patient for venetoclax (Venclyxto) + R sammenlignet med bendamustin + R (P3b) til at være ca. [redacted].

Tabel 11: Resultatet af ansøgers hovedanalyse for P3b, DKK, SAIP

	Venetoclax (Venclyxto)+R [DKK]	Bendamustin + R [DKK]	Inkrementelle omkostninger [DKK]
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	102.566	71.709	30.857
Patientomkostninger	35.399	34.209	1.191
Totale omkostninger	[redacted]	[redacted]	[redacted]

Hvis analysen udføres med AIP bliver de inkrementelle omkostninger til sammenligning hhv. ca. - 620.000 DKK for P1, ca. -1,9 mio. DKK for P2, ca. 275.000 DKK og ca. 400.000 DKK for de to komparatorer i P3 (hhv. chlorambucil i kombination med obinutuzumab og bendamustin i kombination med rituximab).

Amgros' vurdering

Amgros vurderer, at ansøgers analyse er tilstrækkelig og anvender derfor ansøgers analyse som Amgros' egen hovedanalyse.

3.2 Amgros' følsomhedsanalyse

Jf. afsnit 2.2 vurderer Amgros det er relevant at se på betydningen af ekskludering af efterfølgende behandlingsregimer, da der er stor usikkerhed forbundet med ekstrapoleringerne for progression til 3. linjebehandling og fra progredierende stadier til død, da disse ikke beror sig på forløbsdata.

- Amgros udarbejder en følsomhedsanalyse der præsenterer de inkrementelle omkostninger hvor efterfølgende behandlingsregimer ikke er inkluderet

Resultaterne fra Amgros' følsomhedsanalyse præsenteres i tabel 12.

Tabel 12: Amgros' følsomhedsanalyser, inkrementelle omkostninger, DKK, SAIP

Population	Base case [DKK]	Ekskl. efterfølgende behandling [DKK]
P1	[redacted]	[redacted]
P2	[redacted]	[redacted]
P3a	[redacted]	[redacted]
P3b	[redacted]	[redacted]

4 BUDGETKONSEKVENSER

Budgetkonsekvenserne per år er baseret på antagelsen om, at venetoclax (Venclyxto) + R vil blive anbefalet som standardbehandling. Man ser derfor på to scenarier:

- Venetoclax (Venclyxto) + R bliver anbefalet som standardbehandling af Medicinrådet til omtalte indikationer
- Venetoclax (Venclyxto) + R bliver ikke anbefalet som standardbehandling

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimater

4.1.1 Patientpopulation og markedsandel

Ansøger har estimeret patientantallet til at være:

- 30 patienter om året, baseret på Medicinrådet protokol for venetoclax (Venclyxto) + R til P1
- 95 patienter om året, baseret på Medicinrådet protokol for venetoclax (Venclyxto) + R til P2
- 25 patienter om året, baseret på Medicinrådet protokol for venetoclax (Venclyxto) + R til P3

Ansøger estimerer såfremt venetoclax (Venclyxto) + R anbefales, at markedsoptaget vil se ud som følgende, ud for hver population, se tabel 13.

Tabel 13 viser ansøgers estimat af markedsoptag årligt ud fra hver population.

Tabel 13: Ansøgers estimat af markedsoptaget

	År 1	År 2	År 3	År 4	År 5
P1 (sammenlignet med venetoclax (Venclyxto) monoterapi)	80 %	85 %	90 %	90 %	90 %
P2 (sammenlignet med ibrutinib)	80 %	85 %	90 %	90 %	90 %
P3a (sammenlignet med chlorambucil + obinutuzumab)	20 %	20 %	20 %	20 %	20 %
P3b (sammenlignet med bendamustin + R)	10 %	15 %	20 %	25 %	30 %

Amgros' vurdering af estimeret antal patienter

Ansøger anvender det estimerede patientantal der er defineret i protokollen(1). Der er usikkerheder forbundet med markedsoptaget. Ved større markedsoptag i P3 populationen vil dette resultere i højere budgetkonsekvenser.
Ansøger har ikke udarbejdet følsomhedsanalyser omkring markedsoptaget. Amgros udarbejder en følsomhedsanalyse af budgetkonsekvenser der viser et højt markedsoptag hvis venetoclax (Venclyxto) + R anbefales til P3.

Amgros accepterer ansøgers estimat af patientantal og markedsoptaget, men udarbejder en følsomhedsanalyse der belyser et højt markedsoptag af venetoclax (Venclyxto) + R, hvis denne anbefales til P3.

4.1.2 Estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen.

Amgros' vurdering

Ansøger har inkluderet patientomkostninger i budgetkonsekvensanalyse. Dette er ikke i overensstemmelse med Amgros' metoder, jf. Amgros' Metodevejledning. Amgros udarbejder derfor budgetkonsekvenser baseret på ansøgers hovedanalyse eksklusiv patientomkostninger. Amgros anvender ligeledes ansøgers estimater af patientantal og markedsoptag.

Amgros udarbejder nye budgetkonsekvenser baseret på ansøgers hovedanalyse, uden patientomkostninger.

4.2 Amgros' estimater af budgetkonsekvenserne

Resultaterne af budgetkonsekvenserne, baseret på ansøgers hovedanalyse uden patientomkostninger, ses i tabel 14, 15, 16 og 17.

Tabel 14: Amgros' hovedanalyse for totale budgetkonsekvenser for P1, mio. SAIP, DKK

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Med de indlagte antagelser vil anvendelse af venetoclax (Venclyxto) + R for P1 vil resultere i budgetkonsekvenser på ca. [redacted] i år 1 til år 5.

Tabel 15: Amgros' hovedanalyse for totale budgetkonsekvenser for P2, mio. SAIP, DKK

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Med de indlagte antagelser vil anvendelse af venetoclax (Venclyxto) + R for P2 vil resultere i budgetkonsekvenser på ca. [redacted] i år 1 til år 5.

Tabel 16: Amgros' hovedanalyse for totale budgetkonsekvenser for P3a, mio. SAIP, DKK

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Med de indlagte antagelser vil anvendelse af venetoclax (Venclyxto) + R for P3a vil resultere i budgetkonsekvenser på ca. [redacted] i år 1 til år 5.

Tabel 17: Amgros' hovedanalyse for totale budgetkonsekvenser for P3b, mio. SAIP, DKK

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Med de indlagte antagelser vil anvendelse af venetoclax (Venclyxto) + R til P3b vil resultere i budgetkonsekvenser på ca. [redacted] i år 1 til år 5.

Hvis analysen udføres med AIP, er budgetkonsekvenser ca. -13,5 mio. DKK for P1 i år 5, ca. -70,4 mio. DKK for P2 i år 5, ca. 400.000 DKK for P3a år 5 og ca. 3,2 mio. DKK for P3b år 5.

4.3 Amgros' følsomhedsanalyse af budgetkonsekvenserne

Amgros har udarbejdet en følsomhedsanalyse på budgetkonsekvenserne med højere markedsoptag for P3 på 80% per år, såfremt venetoclax (Venclyxto) + R anbefales.
Resultaterne for Amgros' følsomhedsanalyse af budgetkonsekvenser ses i tabel 18 (P3a: chlorambucil + obinutuzumab) og i tabel 19 (P3b: bendamustin + R).

Tabel 18: Amgros' følsomhedsanalyse for totale budgetkonsekvenser med højt markedsoptag, P3a, mio., SAIP, DKK

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 19: Amgros' følsomhedsanalyse for totale budgetkonsekvenser med højt markedsoptag, P3b, mio., SAIP, DKK

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5 DISKUSSION

Behandling med venetoclax (Venclyxto) + R er forbundet med besparelser sammenlignet med komparatorer i P1 og P2 og meromkostninger sammenlignet med komparatorer i P3. Besparelser og meromkostningerne er drevet af lægemiddelomkostningerne samt behandlingslængderne.

Behandlingslængden for den ansøgte indikation er indiceret til en begrænset behandlingstid på 24 måneder efter titreringsperioden. Derfor har PFS (behandlingstiden) for de forskellige komparatorer stor betydning for resultatet, da behandlingstiden for disse ikke er tidsbegrænset.

Resultaterne skal ses isoleret set i forhold til de kliniske spørgsmål.

Hovedanalysen indeholder flere behandlingslinjer, hvilket er udregnet ved at regne på omkostninger ud fra behandlingssekvenser. Efterfølgende behandling efter progression er beregnet ud fra PFS og OS, hvor OS justeres ud fra hhv. 2. linjebehandling og 3. linjebehandling. Behandlingsfrekvenserne vil ikke differentiere mellem flere valg i efterfølgende behandling efter patienten er progredieret, og den økonomiske analyse afspejler dette. Der er justeret for OS alt efter om patienten er progredieret.

Der er stor usikkerhed for OS- og PFS-estimaterne beregnet for venetoclax (Venclyxto) monoterapi, ibrutinib og chlorambucil + obinutuzumab, da disse ikke er baseret på en direkte sammenligning. Men Amgros mener, at den anvendte metode giver det mest pålidelige resultat.

Amgros påpeger også usikkerheden omkring markedsoptaget, der ligger til grund for Amgros' følsomhedsanalyse for budgetkonsekvenserne. Amgros vurderer, at de reelle budgetkonsekvenser for P3a og P3b populationen vil ligge imellem hovedanalysen og følsomhedsanalysen.

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Fra: Eskildsen, Lars <lars.eskildsen@abbvie.com>
Sendt: 26. november 2019 13:16
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Cc: Heidi Møller Johnsen <HJO@medicinraadet.dk>
Emne: RE: Høring venetoclax i kombination med rituximab til behandling af kronisk lymfatisk leukæmi

Kære Thomas,

Tak for det tilsendte udkast til vurdering af klinisk merværdi for venetoclax i kombination med rituximab. Abbvie har taget udkastet til efterretning og har ikke yderligere kommentarer hertil.
Jeg vil gerne benytte lejligheden til at takke for et godt og konstruktivt sammenarbejde med Medicinrådet om evalueringen af venetoclax i kombination med rituximab.

Med venlig hilsen,
Lars

LARS ESKILDSEN
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Medicinrådet

Medicinrådets vurdering af venetoclax i kombination med rituximab til behandling af kronisk lymfatisk leukæmi

Version 1.1

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler og indikationsudvidelser vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om vurderingen

Vurderingen af et nyt lægemiddel er Medicinrådets vurdering af, hvor effektiv og sikkert lægemidlet er i forhold til andre lægemidler til den samme gruppe patienter.

Vurderingen indgår, når Medicinrådet skal beslutte, om lægemidlet anbefales som mulig standardbehandling.

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
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Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Venclyxto®
Generisk navn	Venetoclax
Firma	AbbVie
ATC-kode	L01XX52
Virkningsmekanisme	Venetoclax hæmmer det antiapoptotiske protein BCL-2, som er overudtrykt i B-cellerne hos patienter med kronisk lymfatisk leukæmi.
Administration/dosis	Venetoclax p.o. 20 mg dagligt i uge 1, 50 mg dagligt i uge 2, 100 mg dagligt i uge 3, 200 mg dagligt i uge 4, 400 mg dagligt i uge 5 og herefter 400 mg dagligt fra uge 6 og 24 måneder frem. Fra uge 6, i 6 serier a 28 dage rituximab 375 mg/m^2 i.v. på dag 1 i serie 1, 500 mg/m^2 på dag 1 i serie 2-6.
EMA-indikation	Venetoclax i kombination med rituximab til voksne patienter med kronisk lymfatisk leukæmi der har modtaget mindst én tidligere behandling.

2 Medicinrådets konklusion

Medicinrådet finder, at den samlede værdi af venetoclax i kombination med rituximab sammenlignet med venetoclax monoterapi **ikke kan kategoriseres** til patienter med deletion17p/TP53-mutation, som oplever behandlingssvigt under behandling med ibrutinib i 1. linje. Medicinrådet vurderer dog, at venetoclax i kombination med rituximab ikke er en dårligere behandling end venetoclax monoterapi. Behandling med venetoclax i kombination med rituximab foretrækkes, fordi den er tidsbegrænset og giver patienterne mulighed for en behandlingsfri periode.

Medicinrådet finder, at den samlede værdi af venetoclax i kombination med rituximab sammenlignet med ibrutinib **ikke kan kategoriseres** for patienter, der oplever behandlingskrævende relaps eller behandlingssvigt mindre end 3 år efter behandling med kemoterapi i kombination med CD20-antistof og/eller patienter med sent relaps og nytilkommen deletion17p/TP53-mutation. Lægemidlerne vurderes dog som klinisk ligeværdige behandlingsvalg.

Medicinrådet finder, at den samlede værdi af venetoclax i kombination med rituximab sammenlignet med chlorambucil i kombination med obinutuzumab **ikke kan kategoriseres** for patienter med kronisk lymfatisk leukæmi uden deletion17p/TP53-mutation, der oplever behandlingskrævende relaps mere end 3 år efter deres første behandling med kemoterapi i kombination med CD20-antistof. Medicinrådet vurderer dog, at effektforholdet mellem behandlingerne vil være i overensstemmelse med sammenligningen af venetoclax i kombination med rituximab med bendamustin i kombination med rituximab.

Medicinrådet vurderer, at venetoclax i kombination med rituximab til patienter med kronisk lymfatisk leukæmi uden deletion17p/TP53-mutation, der oplever behandlingskrævende relaps mere end 3 år efter deres første behandling med kemoterapi i kombination med CD20-antistof, giver en **moderat merværdi** sammenlignet med bendamustin i kombination med rituximab. Evidensens kvalitet vurderes at være moderat.

Medicinrådet kategoriserer lægemidlers værdi i en af følgende kategorier:

• **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.

• **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.

• **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.

• **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.

• **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.

• **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

• **Samlet værdi kan ikke kategoriseres:** På grund af usikkerheder omkring effektforhold er det ikke muligt at kategorisere lægemidlets samlede værdi.

3 Forkortelser

BCL-2:	B-cellelymfom 2
BR:	Bendamustin i kombination med rituximab
CI:	Konfidensinterval
CIRS:	*Cummulative illness rating scale*
CLL:	Kronisk lymfatisk leukæmi
Clr-obi:	Chlorambucil i kombination med obinutuzumab
EMA:	*European Medicines Agency*
EORTC:	*European Organisation for Research and Treatment of Cancer*
FISH:	Flourescens in-situ hybridisering
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
IGHV:	*Immunoglobulin heavy chain variable region*
IWCLL:	*International workshop on Chronic Lymphatic Lymphoma*
OR:	*Odds ratio*
QLQ:	*Quality of life questionnaire*
RR:	Relativ risiko
VEN-R:	Venetoclax i kombination med rituximab

4 Formål

Formålet med Medicinrådets vurdering af venetoclax i kombination med rituximab til kronisk lymfatisk leukæmi er at vurdere den værdi, lægemidlet har i forhold til andre lægemidler (komparatorer) til samme patientgruppe.

Med udgangspunkt i vurderingen og en omkostningsanalyse udarbejdet af Amgros beslutter Medicinrådet, om venetoclax i kombination med rituximab kan anbefales som mulig standardbehandling.

5 Baggrund

Kronisk lymfatisk leukæmi er en hæmatologisk kræftsygdom, som opstår i kroppens B-lymfocytter og påvirker cellernes regulering af celledeling og celledød. Det fører til en ophobning af B-lymfocytter bl.a. i knoglemarv, lymfeknuder, milt og blod. B-cellernes normale funktioner svækkes, ligesom funktionen af knoglemarvens andre celler kan være påvirket. Symptomerne hos patienter med kronisk lymfatisk leukæmi er relaterede hertil og omfatter typisk hævede lymfeknuder, forstørret milt, blodmangel, træthed, uforklarlig feber, vægttab og øget infektionstendens.

Kronisk lymfatisk leukæmi er den mest almindelige type leukæmi i de vestlige lande, og diagnosen udgør her ca. 30 % af samtlige leukæmier [1]. Incidensen er i Danmark ca. 6-7 pr. 100.000 indbyggere pr. år, og der registreres ca. 450-500 nye tilfælde om året i Danmark. Det estimeres, at ca. 4.000 patienter lever med sygdommen i Danmark [2]. Medianalderen er ved diagnose 70 år, og dobbelt så mange mænd som kvinder får diagnosen [1,3].

Kronisk lymfatisk leukæmi er ofte asymptomatisk på diagnosetidspunktet og kan blive opdaget tilfældigt efter en blodprøve. Diagnosen stilles ved konstatering af persisterende lymfocytose, dvs. > 5 mia. monoklonale B-celler pr. liter blod i tre måneder eller derover. På diagnosetidspunktet foretages en vurdering af sygdomsstadie (baseret på sygdomsudbredelse, Binet-stadieinddeling) og sygdommens aggressivitet (risikoprofil på baggrund af cytogenetiske forandringer og *immunoglobulin heavy-chain variable region* (IGHV)-mutationsstatus). Både sygdomsstadie, patientens symptomer og risikoprofil har indflydelse på igangsættelse og valg af behandling, ligesom de har betydning for patienternes prognose. Kronisk lymfatisk leukæmi har ofte et indolent forløb, hvor patienterne med tidlige stadier og langsomt progredierende sygdom følges ved årlige kontroller eller afsluttes til egen læge. Medianoverlevelse fra diagnosetidspunktet varierer fra 4 til > 12 år afhængig af sygdomsstadie og risikoprofil.

Nuværende behandling

Behandlingen af kronisk lymfatisk leukæmi varetages af de hæmatologiske afdelinger. På diagnosetidspunktet skelnes mellem behandlingskrævende og ikkebehandlingskrævende sygdom. Ikkebehandlingskrævende sygdom følges med watch and wait, indtil sygdommen bliver behandlingskrævende ifølge kriterier defineret af IWCLL.

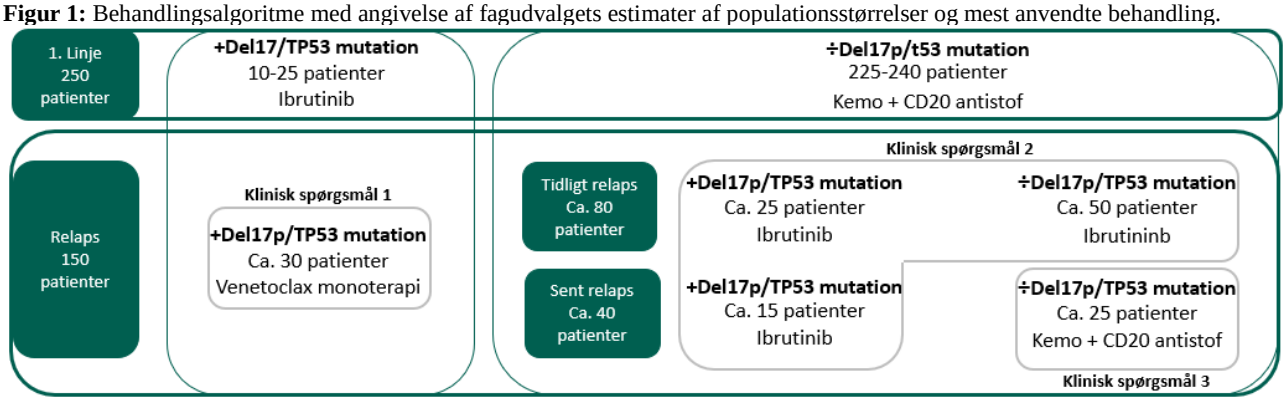
Behandlingsstrategien afhænger af patientspecifikke faktorer (performancestatus, komorbiditet (cumulative illnes rating scale (CIRS)), alder, præferencer), sygdomskarakteristika (tumorbyrde, stadie, risikoprofil (FISH), mutationsstatus).

I behandlingsøjemed opdeles patientpopulationen efter, hvorvidt de har deletion17p/TP53-mutation eller ej og efter performancestatus, alder og komorbiditeter.

Hvorvidt patienterne har deletion17p/TP53-mutation eller ej er afgørende for, om de i 1. linje er kandidater til cytostatika i form af enten chlorambucil, fluradabin og cyclofosfamid eller bendamustin i kombination med et CD20-antistof. Patienter med deletion17p/TP53-mutation er ikke følsomme for behandling med cytostatika og behandles i stedet med proteinkinasehæmmeren ibrutinib. For patienter uden deletion17p/TP53-mutation afgøres valget af cytostatika og CD20-antistof af patientens alder, performancestatus og mængden af komorbiditet [4]. Traditionelt har man anvendt cytostatika i 1.-linje, når det var muligt, fordi de medicinske behandlingsmuligheder har været få, og fordi højere alder og deletion17p/TP53-mutation senere i sygdomsforløbet kan udelukke behandling med cytostatika. Desuden har man god, langvarig dokumentation for effekt og bivirkninger ved de velkendte kemoterapier, mens viden om den langsigtede effekt af nyere behandlinger er sparsom. I takt med nye og mere målrettede behandlingsmuligheder er der dog påbegyndt en bevægelse væk fra anvendelse af cytostatika, blandt andet fordi cytostatika er forbundet med langvarig immundepletion, sekundær malignitet og terapiinduceret myelodysplastisk syndrom.

Figur 1 viser nuværende behandlingsalgoritme. Der er ca. 150 patienter om året med behandlingsbehov i 2. linje [4]. Patienter, der i 1. linje blev behandlet med ibrutinib, behandles hovedsageligt med venetoclax monoterapi. Ibrutinib i 2. linje anvendes til patienter med tidligt relaps uden deletion17p/TP53-mutation og patienter med nytilkommen deletion17p/TP53-mutation (ca. 80 patienter i alt) samt til patienter med sent relaps og nytilkommet deletion17p/TP53 (ca. 15 patienter) [4]. Hos patienter uden deletion17p/TP53-mutation med sent relaps (senere end 3 år efter sidste behandling) kan kemoterapi i kombination med et CD20-antistof gentages (ca. 25 patienter).

Figur 1: Behandlingsalgoritme med angivelse af fagudvalgets estimater af populationsstørrelser og mest anvendte behandling.



Fagudvalgets angivelse af antallet af patienter i de forskellige grupper er baseret på estimater fra tidligere RADS-behandlingsvejledning, viden om tid til første relaps og forekomsten af deletion17p/TP53-mutation på forskellige tidspunkter i behandlingsforløbet [5–8].

I nuværende dansk klinisk praksis skelnes der i behandlingsøjemed ikke imellem, hvorvidt patienterne har IGHV-mutation eller ej, selvom det er af betydning for patienternes prognose. Patienter med non-muteret sygdom har en dårligere prognose end patienter med muteret sygdom. Studier viser, at en opdeling af patienterne i forhold til IGHV-mutation er relevant for effekten af nogle behandlinger, og fagudvalget forventer, at den praksis på sigt vil blive aktuel i dansk sammenhæng [9–11].

Anvendelse af det nye lægemiddel

Venetoclax hæmmer det antiapoptotiske protein BCL-2, som er overudtrykt i B-cellerne hos patienter med kronisk lymfatisk leukæmi. Forøget BCL-2 øger tumorcellernes overlevelse og er associeret med resistens mod kemoterapi.

Venetoclax er allerede godkendt som monoterapi til en del af den ansøgte indikation for venetoclax i kombination med rituximab.

Venetoclax i kombination med rituximab (VEN-R) skal til den ansøgte indikation doseres som følger:

- Venetoclax p.o. 20 mg dagligt i uge 1, 50 mg dagligt i uge 2, 100 mg dagligt i uge 3, 200 mg dagligt i uge 4, 400 mg dagligt i uge 5 og herefter 400 mg dagligt fra uge 6 og 24 måneder frem.
- Fra uge 6, i 6 serier a 28 dage rituximab 375 mg/m^2 i.v. på dag 1 i serie 1, 500 mg/m^2 på dag 1 i serie 2-6.

6 Metode

De præspecificerede metoder i protokollen er udarbejdet af Medicinrådet. Ansøgningen er valideret af Medicinrådet.

Den endelige ansøgning blev modtaget den 15. august 2019. Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokol som blev godkendt i Medicinrådet den 15. maj 2019.

Ansøgningen indeholder sammenligninger mellem venetoclax i kombination med rituximab (VEN-R) og komparatorerne, som defineret i protokollen; hhv. venetoclax monoterapi (VEN-monoterapi) i klinisk spørgsmål 1, ibrutinib i klinisk spørgsmål 2, og to komparatorer i klinisk spørgsmål 3 hhv. chlorambucil i kombination med obinutuzumab (Clr-obi) og bendamustin i kombination med rituximab (BR) i klinisk spørgsmål 3.

Metode til besvarelse af klinisk spørgsmål 1 – VEN-R versus VEN-monoterapi

VEN-R er sammenlignet med VEN-monoterapi ved en narrativ sammenligning. Dette er begrundet med, at der ikke findes et studie med direkte sammenligning. Ligeledes er der ingen fælles komparator i studierne, hvorfor der ikke kan udføres en indirekte analyse.

Metode til besvarelse af klinisk spørgsmål 2 – VEN-R versus ibrutinib

VEN-R er sammenlignet med ibrutinib ved en narrativ sammenligning. Dette er begrundet med, at der ikke findes et studie med direkte sammenligning. Ligeledes er der ingen fælles komparator i studierne, hvorfor der ikke kan udføres en indirekte analyse.

Metode til besvarelse af klinisk spørgsmål 3 – VEN-R versus Clr-obi

VEN-R og chlorambucil i kombination med obinutuzumab (Clr-obi) (herefter omtalt som klinisk spørgsmål 3a) er sammenlignet narrativt, da der ikke er nogen direkte sammenlignende studier og ej heller studier, der tillader en indirekte statistisk sammenligning (ingen fælles komparatorarm).

VEN-R og BR (herefter omtalt som klinisk spørgsmål 3b) er sammenlignet direkte i et randomiseret fase 3-studie.

Medicinrådets sekretariat og fagudvalget accepterer ansøgers valg af analysemetoder og vurderer, at kategoriseringen kan basere sig på de indsendte analyser med følgende bemærkninger:

- Studiepopulationen i MURANO adskiller sig væsentligt fra studiepopulationerne i komparatorstudierne. Dette vanskeliggør direkte sammenligning af effektestimater på tværs af studier. Fagudvalget vil for hvert klinisk spørgsmål foretage en vurdering af betydningen af dette.
- Ansøger har leveret data for progressionsfri overlevelse (PFS) og minimal residual disease negativitet (MRD-negativitet) for alle sammenligninger, uanset om der findes modne data for overlevelse. I protokollen er det specificeret, at data for surrogateffektmålene PFS og MRD-negativitet kun medtages, hvis der ikke er data for 3-års overlevelse. Fagudvalget vil således ikke anvende data for PFS og MRD, hvor overlevelsesdata er tilgængelige, og opfølgningstiden er tilstrækkelig.
- Ansøger har ikke leveret data på den relevante intervention (VEN-R) for effektmålet livskvalitet. Ansøger har fremsendt data vedrørende effekten af VEN-monoterapi på effektmålet livskvalitet opgjort på EORTC-QLC-C30 subskalaer. Fagudvalget vurderer, at livskvalitetsdata for monoterapi, som udgangspunkt ikke er overførbart i vurdering af kombinationsbehandling med rituximab, da denne er forbundet med betydeligt flere bivirkninger. Derudover er der ikke sammenlignelige livskvalitetsdata tilgængelig for komparatorerne, hvorfor det ikke er muligt at foretage nogen sammenligning.
- Ansøger har for klinisk spørgsmål 2 summeret de individuelle forekomster af grad 3-4 hændelser pr. hændelsestype ved 19 måneders median opfølgningstid, delt på antallet af patienter for at opnå en rate af grad 3-4 hændelser [12]. Det medfører en overestimering, da én enkelt patient antages at have én hændelse, men de enkelte patienter kan have oplevet flere forskellige grad 3-4 hændelser. Derudover er det kun grad 3-4 hændelser, der forekommer i mindst 15 % af patienterne, der medtages. Dette vil omvendt lede til en underestimering af antal af grad 3-4 hændelser. Dette medfører, at de ikke er noget relevant estimat for grad 3-4 hændelser for ibrutinib.
- Ansøger har leveret supplerende information i form af to netværksmetaanalyser for klinisk spørgsmål 2. Fagudvalget har valgt at se bort fra disse analyser, idet netværkene lukkes vha. en indirekte analyse af ibrutinib, ibrutinib + bendamustin i kombination med rituximab (BR) og BR fra behandlingsarme i RESONATE- og HELIOS-studierne [13]. Analysen er behæftet med en række begrænsninger, herunder betydelige forskelle i patientsammensætningen i studierne. Det bemærkes desuden, at resultaterne fra netværksanalysen ikke muliggør kategorisering af værdien af VEN-R som følge af stor usikkerhed omkring effektestimaterne. De supplerende analyser er derfor ikke yderligere omtalt i denne vurderingsrapport.

Vurdering af evidensens kvalitet

Vurderingen af evidensens kvalitet er udført ved brug af GRADE-systemet for spørgsmål 3b – VEN-R versus BR. For øvrige kliniske spørgsmål er der tale om narrative sammenligninger, og der er derfor ikke lavet en stringent evidensvurdering, idet kvaliteten i disse tilfælde altid vil være meget lav.

Fra evidens til kategori. Medicinrådet vurderer værdien af et lægemiddel ud fra den indsendte endelige ansøgning, evt. suppleret med andet materiale. I protokollen blev effektmålene angivet som "kritiske", "vigtige" og "mindre vigtige". I vurderingen vægter de kritiske højest, de vigtige næsthøjest og de mindre vigtige indgår ikke.

Både den relative og absolutte effekt indgår i kategoriseringen af et lægemiddel. Dette foregår i en trinvis proces. Fagudvalget kategoriserer først den relative foreløbige kategori på baggrund af væsentlighedskriterierne og den absolutte foreløbige kategori på baggrund af de præspecificerede mindste klinisk relevante forskelle. Her er der tale om en ren kvantitativ proces. Herefter fastlægger fagudvalget den aggregerede kategori for hvert effektmål ved at sammenholde de foreløbige kategorier. Her kan fagudvalget inddrage deres kliniske indsigt. Når den samlede kategori for lægemidlets værdi skal fastlægges, sammenvejer fagudvalget alle effektmål. Effektmålenes kategorier kombineres med effektmålenes vægt, og eventuelle kliniske overvejelser inddrages. Den samlede kategorisering af lægemidlets værdi er således delvis en kvantitativ og delvis en kvalitativ proces, hvor der foretages en klinisk vurdering af det foreliggende datagrundlag. Vurdering af evidensens kvalitet foretages med udgangspunkt i GRADE og udtrykker tiltroen til evidensgrundlaget for de enkelte effektstørrelser og den endelige kategori for klinisk værdi. Evidensens kvalitet inddeles i fire niveauer: høj, moderat, lav og meget lav. GRADE-metoden er et internationalt anerkendt redskab til systematisk vurdering af evidens og udarbejdelse af anbefalinger. I denne vurdering er metoden anvendt til at vurdere evidensens kvalitet.

7 Litteratursøgning

Ansøger har foretaget litteratursøgning efter publicerede, randomiserede studier med data på sammenligningen mellem VEN-R og de fire komparatorer som angivet i protokollen. Der blev identificeret 124 referencer, som blev screenet på titel-abstract-niveau. 23 artikler blev screenet på fuldtekstniveau, og heraf blev 10 referencer fra 5 kliniske studier inkluderet. Derudover udførte ansøger en ikkesystematisk søgning for at finde data på livskvalitet, der identificerede 23 referencer, hvoraf ansøger inkluderede fire referencer fra tre kliniske studier.

MURANO-studiet anvendes til at belyse effekten af VEN-R på tværs af alle kliniske spørgsmål. De studier, der er anvendt til at belyse effekt af komparatorer for hvert af de kliniske spørgsmål, er listet herunder:

Klinisk spørgsmål 1 (VEN-R versus VEN-monoterapi):

- M13-982 (NCT01889186), VEN-monoterapi single arm [14,15]
- M14-032 (NCT02141282), VEN-monoterapi single arm [16]

Klinisk spørgsmål 2 (VEN-R versus ibrutinib):

- RESONATE (NCT01578707), Ibrutinib versus ofatumumab

Klinisk spørgsmål 3a (VEN-R versus Clr-obi):

- GREEN (NCT01905943), non-komparativt (Clr-obi anvendt her) [19]
- MABLE NCT01056510), chlorambucil i kombination med rituximab versus bendamustin i kombination med rituximab [23]

Klinisk spørgsmål 3b (VEN-R versus BR):

- MURANO (NCT02005471), komparativt RCT med VEN-R versus bendamustin i kombination med rituximab (BR) [20,21]

Ansøger har desuden beskrevet data fra studierne HELIOS [22] og VENICE II. HELIOS-studiet udgår af vurderingen, da det alene er anvendt i forbindelse med de netværksmetaanalyser, som fagudvalget har valgt at se bort fra. For VENICE II rapporteres livskvalitetsdata for VEN-monoterapi, idet der ikke foreligger livskvalitetsdata for VEN-R. Data for VEN-monoterapi vurderes ikke at være overførbare som beskrevet i

afsnit 6, og studiet er derfor ikke omtalt yderligere i denne vurdering.

8 Databehandling

Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

9 Lægemidlets værdi

9.1 Konklusion klinisk spørgsmål 1

Hvilken værdi har venetoclax i kombination med rituximab sammenlignet med venetoclax monoterapi til behandling af patienter med deletion17p/TP53-mutation, som oplever relaps eller behandlingssvigt efter behandling med ibrutinib?

Fagudvalget finder, at den samlede værdi af venetoclax i kombination med rituximab sammenlignet med venetoclax monoterapi **ikke kan kategoriseres,** idet de tilgængelige data ikke er sammenlignelige.

Fagudvalget vurderer, at VEN-R ikke er en dårligere behandling end VEN-monoterapi. Behandling med venetoclax i kombination med rituximab foretrækkes, fordi den er tidsbegrænset og giver patienterne mulighed for en behandlingsfri periode.

9.1.1 Gennemgang af studier

Studiekarakteristika

Tabel 1: Studiekarakteristika for MURANO-, M13- og M14-studiet

Studie, NCT	Studiekarakteristika	Inklusions/eksklusionskriterier
MURANO NCT02005471	Design: Ublindet, randomiseret studie fase 3-studie. Patienter: 389 patienter randomiseret til enten VEN-R (n = 194) eller BR (n = 195). Stratifikationsfaktorer: del17p, hvorvidt de havde respons på tidligere behandling og geografisk region. Opfølgningstid (median): 23,9 måneder og 36 måneder. Primært effektmål: investigatorbedømt PFS. Sekundære effektmål: PFS bedømt af uafhængig review-komité samt overall survival (OS), MRD-negativitet alle bedømt af både en uafhængig review-komité og investigator, grad 3-4 uønskede hændelser.	Inklusion**:** -Behandlingskrævende CLL jf. iwCLL-kriterier - op til 3 tidligere behandlinger - ECOG 0-1 Eksklusion Bendamustin intolerance eller responsvarighed på < 24 måneder
M13-982 NCT01889186	Design: Ublindet, ikke randomiseret fase II-studie. Patienter: 153 tidligere behandlede CLL-patienter og 5 behandlingsnaive patienter fik venetoclax monoterapi til progression. Opfølgningstid (median): 26,6 måneder. Primært effektmål: Overall response rate (ORR). Sekundære effektmål: PFS og OS samt grad 3-4 hændelser.	-Behandlingskrævende CLL jf. iwCLL-kriterier -ingen restriktion på antal af tidligere behandlinger positiv for del17p-mutation

M14-032 NCT02141282	Design: Ublindet, ikke randomiseret fase II-studie. Patienter: 91 patienter med R/R CLL blev behandlet med venetoclax monoterapi. Patienterne havde tidligere fået ibrutinib. Opfølgningstid (median): 14 måneder. Primært effektmål: ORR. Sekundære effektmål: Sekundære effektmål: PFS og OS samt grad 3-4 hændelser.	-Behandlingskrævende CLL jf. iwCLL-kriterier -Tidligere behandlet med B-celle-receptor-inhibitor (BCRi) - ingen restriktion på antal af tidligere behandlinger -ECOG 0-2

Baselinekarakteristika

Tabel 2: Baselinekarakteristika for patienter der indgik i MURANO-, M13- og M14-studiet

Karakteristika	**MURANO** [21]	**M13-982 (del17p)** [14]	**M14-032 (BCRi-erfarne)** [14]
Alder (median, range)	64,5 (22-83)	67,0 (29-85)	72,0 (45-87)
ECOG	0: 57,2 % 1: 42,3 % 2: 0,5 %	0: 44 % 1: 49 % 2: 7 %	0: 32 % 1: 59 % 2: 9 %
Del17p-mutation	26,6 %	100 %	47 %
TP53-mutation	25 %	71 %	33 %
IGHV-mutation - Hypermuteret - Umuteret - Ukendt	 29,4 % 68,3 % 2,3 %	 22 % 78 %	 25 % 75 %
Antal tidligere behandlinger	Median: 1 1: 57,2 % 2: 29,4 % 3: 11,3 % > 3: 2,1 %	Median: 2 (0-10)	Median: 4 (1-15)
Type af tidligere behandling	Anti-CD20: 78,5 % BCRi: 2,6 %	Anti-CD20: fremgår ikke BCRi: 5 %	Anti-CD20: 78 % BCRi: 100 %

Fagudvalget vurderer, at studierne ikke giver mulighed for at sammenligne effekten af VEN-monoterapi og VEN-R pga. af væsentlige forskelle i følgende prognostiske patientkarakteristika, herunder ECOG-status, alder, mutationsstatus (del17p/TP53/IGHV) og antal tidligere behandlinger [7,24].

Til trods for at effektestimaterne fra studierne ikke er sammenlignelige, har fagudvalget nedenstående redegjort for, hvorfor VEN-R ikke forventes at være en dårligere behandling end VEN-monoterapi.

9.1.2 Fagudvalgets konklusion for klinisk spørgsmål 1

Fagudvalget finder, at den samlede værdi af venetoclax i kombination med rituximab sammenlignet med venetoclax monoterapi til patienter med deletion17p/p53-mutation, som oplever behandlingssvigt under behandling med ibrutinib i 1. linje, **ikke kan kategoriseres**. Fagudvalget vurderer dog, at VEN-R ikke er en dårligere behandling end VEN-monoterapi. Behandling med venetoclax i kombination med rituximab foretrækkes, fordi den er tidsbegrænset og giver patienterne mulighed for en behandlingsfri periode.

For effektmålet overlevelse er det bedst sammenlignelige effektestimat 2-års overlevelse. Dette er opgjort i M13-studiet for VEN-monoterapi til 73 % af patienterne med del17p. Patienter med del17p-mutation har en væsentligt ringere prognose end patienter uden, hvorfor effektestimaterne ikke er sammenlignelige med MURANO, hvori kun 26,6 % har en del17p-mutation. Derudover har patienter behandlet med VEN-monoterapi i M13-studiet fået flere tidligere behandlinger (mellem 1-10 tidligere linjer, median 2) end patienterne i MURANO (mellem 1-4 tidligere linjer, median på 1). Dette forventes ligeledes at forværre

patienternes prognose i M13. I MURANO var 2-års overlevelse 91,9 % og 3-års overlevelse 87,9 % for patienter behandlet med VEN-R. På denne baggrund er der intet, der indikerer, at VEN-R er en dårligere behandling, men det er ikke muligt at konkludere, at lægemidlerne er ligeværdige, eller at det er bedre end det andet, da det er uvist, hvor stor indflydelsen af de prognostiske faktorer er på effektestimatet.

Derudover ønsker fagudvalget at fremhæve et retrospektivt kohortestudie, hvori det er vist, at patienter med sammenlignelige baselinekarakteristika behandlet med hhv. VEN-R og VEN-monoterapi har samme risiko for at dø (HR for overlevelse på 1,0) [25]. Dette er i et sparsomt patientgrundlag og med kort opfølgningstid, hvorfor det kun kan understøtte fagudvalgets vurdering af, at VEN-R ikke er en dårligere behandling end VEN-monoterapi.

Fagudvalget bemærker, at VEN-monoterapi er en kontinuert behandling, som fortsættes til progression, mens behandling med VEN-R afsluttes efter to år (R i 6 måneder, VEN i 24 måneder). Fagudvalget forventer, at hovedparten af patienterne vil foretrække den tidsbegrænsede behandling med VEN-R. Fagudvalget estimerer, at nogle patienter kan opnå en behandlingsfri periode på optil flere år ved at vælge VEN-R. Baseret på data fra M13 vurderes det, at over halvdelen af patienterne vil opnå en gevinst i form af en behandlingsfri periode. I M13 er 54 % af patienterne fortsat i live og i behandling efter 24 måneder. Disse patienter skal fortsat behandles med VEN-monoterapi, hvorimod de kunne afslutte deres behandlingsforløb på VEN-R.

Fagudvalget vurderer på baggrund af klinisk erfaring, at sikkerheden af de to behandlinger er sammenlignelig.

9.2 Konklusion klinisk spørgsmål 2

Hvilken værdi har venetoclax i kombination med rituximab sammenlignet med ibrutinib til 2.-linjebehandling af patienter, der er behandlet med kemoterapi i kombination med et CD20-antistof i 1. linje?

Fagudvalget finder, at den samlede værdi af venetoclax i kombination med rituximab sammenlignet med ibrutinib ikke kan kategoriseres. Fagudvalget vurderer dog, at venetoclax i kombination med rituximab samlet set ikke har dårligere effekt eller sikkerhedsprofil end ibrutinib. Fagudvalget vurderer, at ibrutinib og venetoclax i kombination med rituximab er klinisk ligeværdige behandlingsvalg.

I tabellen herunder fremgår den samlede kategori for lægemidlet og kvaliteten af en samlede evidens. Man kan også se både absolutte og relative effektforskelle samt foreløbige og aggregerede værdier.

Tabel 3. Kategorier og resultater for venetoclax i kombination med rituximab i sammenligning med komparatoren ibrutinib.

Effektmål	**Målenhed**	**Vigtighed**	**Absolut effektestimat** *Estimaterne er ikke direkte sammenlignelige*	**Foreløbig værdi**	**Aggeregeret kategori**
Overlevelse*	Overlevelsesrate ved 3 år Retningsgivende MKRF: 5 %-point	Kritisk	VEN-R: 87,9 % Ibrutinib: 74 %	Kan ikke kategoriseres*	Kan ikke kategoriseres*
Livskvalitet	Ændring i point målt med EORTC QLQ-C30 Retningsgivende MKRF: 10-point	Vigtigt	Ingen data	Kan ikke kategoriseres**	Kan ikke kategoriseres*
Bivirkninger	Andel der oplever grad 3-4 uønskede hændelser (+ kvalitativ gennemgang**) Retningsgivende MKRF: 10 %-point	Vigtigt	VEN-R: 82 % Ibrutinib: ikke tilgængelig	Kan ikke kategoriseres*	Kan ikke kategoriseres*
Samlet kategori for lægemidlets værdi sammenlignet med ibrutinib				Kan ikke kategoriseres*	
Kvalitet af den samlede evidens				Meget lav	

Effektestimater i tabellen kan ikke sammenlignes direkte, da der er væsentlige forskelle patientkarakteristika for Herudover synes prognosen for patienter i MURANO-studiet generelt bedre baseret på patientkarakteristika
*narrativ sammenligning hvorfor den foreløbige værdi ikke kan kategoriseres.
** Se afsnit 9.2.2 for kvalitativ gennemgang.

9.2.1 Gennemgang af studier

Studiekarakteristika

Tabel 4: Studiekarakteristika for MURANO- og RESONATE-studiet

Studie, NCT	**Studiekarakteristika**	**Inklusion/eksklusionskriterier**
MURANO, NCT02005471	Design: Ublindet, randomiseret studie fase 3-studie. Patienter: 389 patienter randomiseret til enten VEN-R (n = 194) eller BR (n = 195). Stratifikationsfaktorer: del17p, hvorvidt de havde respons på tidligere behandling og geografisk region. Opfølgningstid (median): 23,9 måneder og 36 måneder. Primært effektmål: investigatorbedømt PFS. Sekundære effektmål: PFS bedømt af uafhængig review-komité samt overall survival (OS), MRD-negativitet alle bedømt af både en uafhængig review-komité og investigator, grad 3-4 uønskede hændelser.	Inklusion: -Behandlingskrævende R/R CLL jf. iwCLL-kriterier - op til 3 tidligere behandlinger - ECOG 0-1 Eksklusion: Bendamustin intolerance eller responsvarighed på < 24 måneder
RESONATE, NCT01578707	Design: Ublindet randomiseret kontrolleret fase III-forsøg. Patienter: 391 patienter blev randomiseret 1:1 til oral ibrutinib 420 mg dagligt til progression (n = 195) eller ofatumumab i.v. 300 mg initialt, efterfulgt af 2 g x 11 doser i 24 uger (n = 196). Stratifikationsfaktorer: del17p13.1 og hvorvidt de havde resistens mod purinanalog. Opfølgningstid (median): 44 måneder (længst tilgængelige opfølgningstid). Primært effektmål: PFS bedømt af uafhængig review-komité. Sekundære effektmål: overall survival (OS). Eksploratoriske effektmål: EORTC QLQ-C30, CTCAE, grad 3-4 uønskede hændelser.	**Inklusion**: SLL og CLL (5 % med SLL) Alder: 18-65 år ECOG 0-1 Mindst én tidligere behandling Ikke kandidater til purinanalogbaseret behandling **Eksklusion**: Tidligere behandling med ofatumumab eller ibrutinib

Baselinekarakteristika

Tabel 5: Baselinekarakteristika for patienter der indgik i MURANO- og RESONATE-studiet

Karakteristika	**MURANO** [21]	**RESONATE** [18]
Alder (median, range)	64,5 (22-83)	67,0 (30-86)
ECOG	0: 57,2 % 1: 42,3 % 2: 0,5 %	0: 41 % 1: 59 %
Del17p	26,6 %	32 %
IGHV-mutation - Hypermuteret - Umuteret - Ukendt	 29,4 % 68,3 % 2,3 %	 19 % 50 % 31 %
Antal tidligere behandlinger	Median (range): 1 (1-4) 1: 57,2 % 2: 29,4 % 3: 11,3 % > 3: 2,1 % (≥ 3: 13,4)	Median (range): 3 (1-15) 1: 18 % 2: 29 % ≥ 3: 53 %
Type af tidligere behandling	Anti-CD20: 78,5 % BCRi: 2,6 %	Anti-CD20: 94 % BCRi: 0 %

Antallet af tidligere behandlinger varierer blandt patienter i studierne, hvor hhv. 13,4 % har fået ≥ 3 tidligere behandlinger i MURANO mod 53 % i RESONATE. Herudover synes prognosen for patienter i MURANO-studiet generelt bedre baseret på patientkarakteristika præsenteret i tabel 5. Dette medfører en risiko for at favorisere VEN-R, når estimater fra de to studier sammenlignes. Fagudvalget inddrager disse forskelle i besvarelsen af det kliniske spørgsmål nedenfor. Fagudvalget vurderer, at studiepopulationerne er sammenlignelige med den forventede danske population.

9.2.2 Resultater og vurdering

Det kliniske spørgsmål som besvares nedenfor er:

Hvilken værdi har venetoclax i kombination med rituximab sammenlignet med ibrutinib til 2.-linjebehandling af patienter, der er behandlet med kemoterapi i kombination med et CD20-antistof i 1. linje?

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som hhv. kritiske og vigtige, følger nedenfor.

Overlevelse (kritisk)

3-årsoverlevelsen var 87,9 % blandt patienter behandlet med VEN-R i MURANO-studiet og 74 % blandt patienter behandlet med ibrutinib i RESONATE-studiet.

Effekten af VEN-R sammenlignet med ibrutinib på 3-årsoverlevelsen **kan ikke kategoriseres**, da der er tale om en narrativ sammenligning. Fagudvalget vurderer, at forskellen i naive estimater kan være drevet af forskelle i prognostiske faktorer mellem patientpopulationerne.

Livskvalitet

Der er ikke leveret relevante data vedr. effekten af VEN-R på livskvalitet. Effekten af VEN-R på livskvalitet **kan ikke kategoriseres**.

Bivirkninger (vigtigt)

Grad 3-4 uønskede hændelser

Andelen af patienter, der oplevede uønskede hændelser af grad 3-4, var 82 % blandt patienter behandlet med VEN-R i MURANO-studiet, og der er ikke opgjort nogle sammenlignelige effektestimater for ibrutinib i RESONATE-studiet (se afsnit 6).

Kvalitativ gennemgang af bivirkninger

Der er flere hæmatologiske bivirkninger ved behandling med VEN-R (særligt neutropeni og tumorlyse-syndrom under optitreringsperioden) end med ibrutinib. Patienter i behandling med ibrutinib kan opleve hjerteflimmer medførende behov for antikoagulationsbehandling. Dette kan kompliceres af en generelt øget tendens til blødninger blandt disse patienter. Herudover er ibrutinib forbundet med generende bivirkninger i form af diarré og hududslæt.

Effekten af VEN-R sammenlignet med ibrutinib på andelen af patienter, der oplever grad 3-4 uønskede hændelser, **kan ikke kategoriseres**, da der er tale om en narrativ sammenligning. Fagudvalget vurderer, at sikkerheden af lægemidlerne er sammenlignelig, men at der er væsentlige forskelle i bivirkningsprofilerne, og dette kan have betydning for den enkelte patients præference og egnethed.

9.2.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 2 er samlet set vurderet som værende **meget lav**. Da der er tale om en narrativ sammenligning, er evidensens kvalitet ikke vurderet vha. GRADE.

9.2.4 Fagudvalgets konklusion for klinisk spørgsmål 2

Fagudvalget finder, at den samlede værdi af venetoclax i kombination med rituximab sammenlignet med ibrutinib som 2.-linjebehandling af patienter, der er behandlet med kemoterapi i kombination med et CD20-antistof i 1. linje, **ikke kan kategoriseres**. Fagudvalget vurderer, at ibrutinib og VEN-R er klinisk ligeværdige behandlingsvalg.

Patientpopulationerne, som indgår i den narrative sammenligning, stammer fra hhv. RESONATE og MURANO. Grupperne adskiller sig fra hinanden på prognostiske faktorer, som kan betyde, at effekten af VEN-R på effektmålet overlevelse overestimeres i forhold til ibrutinib i denne sammenligning. Fagudvalget vurderer, at sikkerheden af lægemidlerne er sammenlignelig, men forskelle i bivirkningsprofilerne kan have betydning for individuelle patienters præference i valget mellem de to lægemidler.

Fagudvalget bemærker, at ibrutinib er en kontinuert behandling, som fortsættes til progression, mens behandling med VEN-R afsluttes efter to år (R i 6 mdr., VEN i 24 mdr.). Dette kan have betydning for patienternes behandlingspræference.

9.3 Konklusion klinisk spørgsmål 3a (chlorambucil i kombination med obinutuzumab)

Hvilken værdi har venetoclax i kombination med rituximab sammenlignet med kemoterapi i kombination med CD20-antistof til behandling af patienter uden deletion17p/TP53-mutation, der har behandlingskrævende relaps mere end 3 år efter deres første behandling?

Fagudvalget finder, at den samlede værdi af venetoclax i kombination med rituximab sammenlignet med chlorambucil i kombination med obinutuzumab (Clr-Obi) **ikke kan kategoriseres**, idet de tilgængelige data ikke er sammenlignelige.

Da det tilgængelige datagrundlag ikke er sammenligneligt og der ikke er opgjort relevante effektmål for Clr-obi, har fagudvalget ikke fundet det muligt at vurdere, hvorvidt VEN-R samlet set har en bedre effekt eller sikkerhedsprofil end Clr-obi. Fagudvalget forventer dog, at effektforholdet mellem behandlingerne vil være i overensstemmelse med sammenligningen af VEN-R med BR.

9.3.1 Gennemgang af studier

Studiekarakteristika

Tabel 6: Studiekarakteristika for MURANO- og GREEN-studiet

Studie, NCT	Studiekarakteristika	Inklusions/eksklusionskriterier
MURANO NCT02005471	Design: Ublindet, randomiseret studie fase 3-studie. Population: 389 patienter randomiseret til enten VEN-R (n = 194) eller BR (n = 195). Stratifikationsfaktorer: Del17p, hvorvidt de havde respons på tidligere behandling og geografisk region. Opfølgningstid: 23,9 måneder og 36 måneder. Primært effektmål: investigatorbedømt PFS. Sekundære effektmål: PFS bedømt af uafhængig review-komité samt overall survival (OS), MRD-negativitet alle bedømt af både en uafhængig review-komité og investigator.	Inklusion**:** -Behandlingskrævende CLL jf. iwCLL-kriterier - op til 3 tidligere behandlinger - ECOG 0-1 Eksklusion Bendamustin intolerance eller responsvarighed på < 24 måneder
GREEN NCT02005471	Design: Ublindet, ikke randomiseret, fase-IIIb studie Population: Flere behandlingsarme. Den relevante er 114 patienter med væsentlig komorbiditet CIRS > 6, der fik Clr-obi, heraf 68 patienter i 1.-linjebehandling og 46 der var enten refraktære eller havde relaps (R/R). Opfølgningstid: ikke opgivet specifikt for patienter i behandlingsarmen der fik Clr-obi (opgivet til median 20,8-28,8 måneder afhængig af behandlingsarm). Primært effektmål: uønskede hændelser grad ≥ 3. Sekundære effektmål: ORR, CR. Tid til event analyser (PFS og OS) er ikke udført pga. utilstrækkelig opfølgningstid.	-Behandlingskrævende CLL jf. iwCLL-kriterier -op til 3 tidligere behandlinger -ECOG 0-2

Baselinekarakteristika

Det er ikke muligt at finde baselinekarakteristika specifikt for de patienter, der modtog Clr-obi, da patientkarakteristika ikke er opgjort pr. studiearm, men pr. patientgruppe, f.eks. patienter i 1.-linje-behandling eller relaps og refraktære patienter. Patienterne behandlet med Clr-obi stammer fra de to grupper i studiet, der er refraktære eller har relaps og for 1.-linjepatienter, der er *unfit* (har betydelig komorbiditet og høj performancestatus). Valget af behandlingsarm er i GREEN-studiet skete efter investigators valg, dvs. uden randomisering. Patienterne behandlet med Clr-obi kan derfor adskille sig fra de samlede grupper, som er præsenteret i tabellen.

Tabel 7: Baselinekarakteristika for patienter der indgik i MURANO- [21] **og GREEN-studiet**

Baseline karakteristika for udvalgte studier			
Karakteristika	MURANO, n = 194	GREEN, n = 341 Relaps/refraktær	GREEN, n = 292 1. linje, unfit
Alder (median, range)	64,5 (22-83)	68,0 (33-90)	72,0 (45-87)
ECOG	0: 57,2 % 1: 42,3 % 2: 0,5%	0: 55,1 % 1: 39,3 % 2: 5,6 %	0: 62 % 1: 35,7% 2: 2,4 %
Del17p mutation	26,6 %	13,5 %	6,8 %
TP53 mutation	25 %	Ikke opgjort	Ikke opgjort
IGHV mutation - Hypermuteret - Umuteret - Ukendt	 29,4 % 68,3 % 2,3 %	 18,8 % 55,1 % 26,1 %	 30,8 50,0 19,2
Antal tidligere behandlinger	Median: 1 1: 57,2 % 2: 29,4 % 3: 11,3 % > 3: 2,1 % (≥ 3: 13,3 %)	Median: 1 - yderligere detaljer ikke oplyst	Median: 1 - yderligere detaljer ikke oplyst
Type af tidligere behandling	Anti-CD20: 78,5 %	Rituximab: 45 %	Ikke relevant, 1. linje

Fagudvalget vurderer, at studierne ikke giver mulighed for at sammenligne effekten af Clr-obi og VEN-R pga. af væsentlige forskelle i prognostiske patientkarakteristika, herunder alder, mutationsstatus (del17p/TP53/IGHV) og antal tidligere behandlinger. Derudover vanskeliggøres sammenligningen yderligere af, at patientkarakteristika for den specifikke gruppe behandlet med Clr-obi ikke er tilgængelige. Ud fra de tilgængelige baselinedata vil forskelle i del17p og andel med 1.-linjebehandling være til fordel for Clr-obi, mens alder og grad af komorbiditet (CIRS) være til fordel for VEN-R. Endeligt er der i GREEN-studiet kun leveret data på overall response-rater samt komplet respons-rater, der ikke er præspecificerede effektmål i protokollen.

Fagudvalget vurderer derfor, at det kliniske spørgsmål ikke kan besvares, og data fremgår derfor ikke af vurderingsrapporten. Til trods for at studierne ikke kan belyse effektforholdet, så kan der drages paralleller fra MABLE-studiet af chlorambucil-rituximab (Clr-R) overfor BR i forhold til, om der kan forventes en bedre overlevelse ved behandling med VEN-R overfor Clr-obi. I MABLE-studiet er det vist, at BR giver anledning til bedre komplette remissionsrater, overall respons-rater samt PFS, men ingen forskel i overlevelse. Dette tyder på, at effekten på overlevelse er ens. Her skal det dog nævnes, at der er anvendt et andet CD20-antistof, rituximab i stedet for obinutuzumab i tillæg til Clr, og at der fortrinsvis er tale om førstelinjepatienter. På denne baggrund forventer fagudvalget, at effektforholdet mellem behandlingerne VEN-R og Clr-obi vil være i overensstemmelse med sammenligningen af VEN-R med BR.

9.4 Konklusion klinisk spørgsmål 3b (bendamustin i kombination med rituximab)

Hvilken værdi har venetoclax i kombination med rituximab sammenlignet med kemoterapi i kombination med CD20-antistof til behandling af patienter uden deletion17p/TP53-mutation, der har behandlingskrævende relaps mere end 3 år efter deres første behandling?

Fagudvalget vurderer, at venetoclax i kombination med rituximab til patienter med kronisk lymfatisk leukæmi uden deletion17p/TP53-mutation, der oplever behandlingskrævende relaps mere end 3 år efter deres første behandling med kemoterapi i kombination med CD20-antistof, giver en **moderat merværdi**

sammenlignet med bendamustin i kombination med rituximab. Evidensens kvalitet vurderes at være **moderat**.

I tabellen herunder fremgår den samlede kategori for lægemidlet og kvaliteten af en samlede evidens. Man kan også se både absolutte og relative effektforskelle samt foreløbige og aggregerede værdier.

Tabel 8. Kategorier og resultater for venetoclax i kombination med rituximab i sammenligning med komparatoren bendamustin i kombination med rituximab.

Effektmål	Måleenhed	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi pr. effektmål
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Overlevelse	Forskel i overlevelsesrate ved 3 år Justerede MKRF: 2,5%-point	Kritisk	8,4 %- point	Kan ikke kategoriseres	HR: 0,5 (0,30-0,85)	Moderat merværdi	Moderat merværdi
Livskvalitet	Ændring i point målt med EORTC QLQ-C30 Justerede MKRF: 5-point	Vigtigt	Ingen data	Kan ikke kategoriseres**	Ingen data	Kan ikke kategoriseres**	Kan ikke kategoriseres**
Bivirkninger	Andel der oplever grad 3-4 uønskede hændelser (+ kvalitativ gennemgang*) Justerede MKRF: 5%-point	Vigtigt	11,9 %- point (2,8-21,8)	Kan ikke kategoriseres	RR: 1,17 (1,04-1,31)	Negativ merværdi	Ingen dokumenteret merværdi
Samlet kategori for lægemidlets værdi sammenlignet med bendamustin i kombination med rituximab		Moderat merværdi					
Kvalitet af den samlede evidens		Moderat					

Overlevelse tilhører effektmålsgruppen dødelighed. Den absolutte forskel overstiger den retningsgivende mindste klinisk relevante forskel på 5 %-point for 3-årsoverlevelse, men da der ikke er nogen konfidensintervaller, kan den foreløbige værdi ikke kategoriseres. Den relative effektforskel giver en foreløbigt en moderat merværdi jf. væsentlighedskriterierne 0,85 ≤ UL < 0,95.

Bivirkninger opgjort som andel, der oplever grad 3-4 uønskede hændelser, tilhører effektmålsgruppen livskvalitet samt alvorlige symptomer og bivirkninger. Den foreløbige kategori for den absolutte forskel kan ikke kategoriseres, idet den nedre grænse er mindre end den justerede mindste klinisk relevante forskel på 5-point og den øvre grænse i konfidensintervallet er større end den justerede mindste klinisk relevante forskel. Negativ værdi for den relative effektforskel har jf. væsentlighedskriterierne nedre grænse > 1.

* Se afsnit 9.4.2 for kvalitativ gennemgang
**da der ikke findes data for effektmålet kan værdien ikke kategoriseres.

9.4.1 Gennemgang af studier

MURANO-studiets (NCT02005471) karakteristika og population er beskrevet i afsnit 9.3.1. Her beskrives derfor kun, hvorvidt studieresultaterne kan anvendes i besvarelsen af det kliniske spørgsmål baseret på, om der er overensstemmelse mellem studiepopulation og den danske population.

Der er flere afvigelser i forhold til det kliniske spørgsmål. I MURANO har 26,6 % % af patienterne del17p-mutation. Disse patienter vil i dansk kontekst blive behandlet med ibrutinib i 1. linje og evt. idelalisib/ venetoclax monoterapi i 2. linje, men der er ganske få patienterne i studiet (< 3 % i hver studiearm), der tidligere er behandlet med b-cellereceptorinhibitor (ibrutinib/idelalisib). 40 % af patienterne i studiet har modtaget mere end én tidligere behandling, mens det kliniske spørgsmål går på patienter, der tidligere kun har modtaget én tidligere behandling. Derudover er nogle af patienterne tidligere behandlet med bendamustin, men ansøger har ikke oplyst, hvor stor en andel, det drejer sig om. Det er et inklusionskriterie i studiet, at patienter tidligere behandlet med bendamustin skal have haft et respons på mindst 24 måneder, mens der i dansk kontekst sigtes mod et behandlingsrespons på mindst 36 måneder, før genbehandling med kemoterapi anbefales. Fagudvalget vurderer ikke, at effekten af genbehandling med bendamustin er væsentlig afhængig af, hvorvidt responsvarigheden er 24 eller 36 måneder.

Overordnet vurderes ovenstående forhold ikke at have betydning for anvendelse af de relative effektestimater fra den samlede population i studiet til besvarelse af det kliniske spørgsmål. Fagudvalget lægger her vægt på, at subgruppeanalyser af PFS viser, at behandlingseffekten er konsistent på tværs af alle subgrupper, herunder del17p/TP53, samt uafhængigt af hvor mange tidligere behandlinger patienterne har fået.

Fagudvalget vurderer, at overførbarheden af resultaterne fra MURANO-studiet er tilstrækkelig i forhold danske forhold og kan anvendes til besvarelse af klinisk spørgsmål 3b.

9.4.2 Resultater og vurdering

Det kliniske spørgsmål, som besvares nedenfor, er:

Hvilken værdi har venetoclax i kombination med rituximab sammenlignet med kemoterapi i kombination med CD20-antistof til behandling af patienter uden deletion17p/TP53-mutation, der har behandlingskrævende relaps mere end 3 år efter deres første behandling?

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som hhv. kritiske og vigtige, følger nedenfor.

Overlevelse (kritisk)

Den mediane overlevelse er ikke tilgængelig ved godkendelsen af nye lægemidler til behandling af CLL, fordi overlevelsen med nuværende behandlingsmuligheder er mellem 4 og 12 år afhængig af patienternes prognose. Fagudvalget har derfor valgt 3-årsoverlevelsesrater som effektmål. Data for 3-årsoverlevelse er tilgængelige, og derfor vil data for PFS og MRD ikke blive anvendt i kategoriseringen.

<u>Vurdering af data for 3-årsoverlevelse</u>

Efter 3-års opfølgning var der hhv. 87,9 % af patienter behandlet med VEN-R i live, mens der var 79,5 % i live i gruppen behandlet med BR, svarende til en absolut effektforskel på 8,4 %-point [20]. Da der ikke kan beregnes konfidensintervaller for det absolutte effektestimat, kan den foreløbige værdi af effekten på 3-årsoverlevelse ikke kategoriseres.

Baseret på den relative effektforskel (HR: 0,5 (0,30-0,85)) har VEN-R foreløbigt en **moderat merværdi** vedr. overlevelse [20].

På aggregeret niveau vurderer fagudvalget, at VEN-R har en **moderat merværdi** på effektmålet overlevelse (moderat evidenskvalitet), idet det relative effektestimat giver en foreløbig moderat merværdi, mens merværdien ikke kan kategoriseres på det absoluteffektestimat. Det bemærkes, at punktestimatet for den absolutte forskel er højere end den mindste klinisk relevante forskel, dog uden kendskab til usikkerheden omkring dette estimat (ingen konfidensintervaller).

Bivirkninger (vigtig)

Grad 3-4 uønskede hændelser

Fagudvalget ønsker bivirkninger opgjort som andel af patienter, der oplever grad 3-4 uønskede hændelser, og en forskel mellem grupperne på 10 %-point anses som klinisk relevant. Data for grad 3-4 uønskede hændelser stammer fra det tidlige data-cut med 23,9 måneders median opfølgningstid, hvor hhv. 60 % havde afsluttet hele deres behandlingsforløb med VEN-R, og 80 % havde afsluttet BR [21]. Dette giver anledning til en vis underestimering af andelen, der oplever grad 3-4 uønskede hændelser i VEN-R-gruppen, da flere af patienterne ikke har afsluttet deres behandlingsforløb. Da bivirkninger ved VEN-R særligt falder tidligt i behandlingen, vurderes det ikke at være af væsentlig betydning.

I VEN-R-gruppen oplevede 82 % af patienterne grad 3-4 uønskede hændelser, mens det tilsvarende tal i kontrolgruppen var 70,2 % [21]. Baseret på disse tal var er den absolutte effektforskel en øgning på 11,9 %-point [2,8-21,8] i andelen, der oplevende grad 3-4 uønskede hændelser.

Baseret på den absolutte effektforskel kan **merværdien ikke kategoriseres** for VEN-R foreløbigt, da den mindste klinisk relevante forskel ikke er opnået. Dette baseres på, at den nedre grænse er mindre end den justerede mindste klinisk relevante forskel på 5 %-point, og den øvre grænse er større end den justerede mindste klinisk relevante forskel. Retningen af effekten er dog konsistent med, at VEN-R giver flere grad 3-4 hændelser end komparator, men det er muligt, at størrelsen af effekten ikke er klinisk relevant baseret på den nedre grænse for konfidensintervallet. Effektestimatet fra studiet er større end den retningsgivende mindste klinisk relevante forskel på 10 %-point.

Baseret på den relative effektforskel på 1,17 (1,04-1,31) har VEN-R foreløbigt en **negativ værdi** vedr. andel, der oplever grad 3-4 hændelser.

Kvalitativ gennemgang af bivirkninger

Ved gennemgang af grad 3-4 uønskede hændelser konstateres det, at forskellen mellem grupperne især er drevet af grad 3-4 neutropeni, der er mere hyppigt i VEN-R-gruppen med 57,7 % mod 38,8 % for BR.

Her skal det fremhæves, at selvom der var flere neutropenier, gav de ikke anledning til flere infektioner i VEN-R-gruppen med hhv. 17,5 % mod 21,8 % for BR. Neutropeni er en velkendt bivirkning ved alle nuværende behandlinger og vurderes at være håndterbar i klinisk praksis ved at give hæmatopoietiske vækstfaktorer, dosisafbrydelse eller dosisreduktion af behandling. Derudover bemærkes det, at den mere alvorlige type af febril neutropeni er mere udbredt i BR-gruppen hhv. 9,6 % mod 3,6 % i VEN-R-gruppen, samt at der er flere infektioner 17,5 % mod 21,8 %.

Fagudvalget ønsker endeligt at inddrage den viden, der er opnået om bendamustin udenfor MURANO-studiet. Her er det velkendt, at lægemidlet bidrager til en øget risiko for udvikling af sekundær malignitet i form af myelodysplastisk syndrom samt akut myeloid leukæmi. Derudover er det dokumenteret, at bendamustin øger risikoen for særligt alvorlige opportunistiske infektioner af typen bakteriel pneumoni, cytomegalovirus, varicella zoster virus samt pneumocystis jirovecii, der kan give anledning til alvorlige komplikationer samt lange indlæggelser. I denne sammenhæng er det dokumenteret, at det er patienter, der modtager bendamustin i anden eller tredje linje, der har særlig høj risiko for at udvikle disse infektioner [26].

På aggregeret niveau vurderer fagudvalget, at VEN-R har **ingen dokumenteret merværdi** for effektmålet bivirkninger (moderat evidenskvalitet). Dette skyldes, at VEN-R medfører flere grad 3-4 uønskede hændelser end komparator BR, men fagudvalget vurderer dog, at de bivirkninger, der er forbundet med BR, er mere alvorlige og komplicerede. Den kvantitative forskel i grad 3-4 hændelser i MURANO-studiet er derfor ikke klinisk betydende, og på baggrund af alvorligheden af bivirkninger ved BR foretrækkes bivirkningsprofilen for VEN-R.

Livskvalitet (vigtig)

Effektmålet livskvalitet **kan ikke kategoriseres,** da der ikke findes relevante data.

9.4.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 3b vedrørende patienter med kronisk lymfatisk leukæmi uden deletion17p/TP53-mutation, der oplever behandlingskrævende relaps mere end 3 år efter deres første behandling med kemoterapi i kombination med CD20-antistof, er samlet set vurderet som værende **moderat**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 1.

9.4.4 Fagudvalgets konklusion for klinisk spørgsmål 3b

Fagudvalget vurderer, at VEN-R samlet giver en **moderat merværdi** sammenlignet med BR til behandling af patienter med kronisk lymfatisk leukæmi uden deletion17p/TP53-mutation, der har behandlingskrævende relaps mere end 3 år efter deres første behandling. Evidensens samlede kvalitet er vurderet til moderat.

For effektmålet overlevelse er 3-års overlevelsesrater hhv. 87,9 % for patienter behandlet med VEN-R og 79,5% for patienter behandlet med BR, svarende til en absolut effektforskel på 8,4 %-point. Da der ikke er konfidensintervaller for det absolutte effektestimat, kan den foreløbige værdi af effekten på 3-årsoverlevelse ikke kategoriseres, men punktestimatet er højere end den mindste kliniske relevante forskel. I forhold til den absolutte dødelighed i opfølgningsperioden er den absolutte effektforskel et udtryk for en markant reduktion, hvilket også reflekteres i, at den relative effektforskel er HR: 0,5 (0,30-0,85). Det bemærkes, at den relative effektforskel ligger præcis på grænsen til en stor merværdi. Samlet betyder dette, at VEN-R får en **moderat merværdi** for effektmålet overlevelse.

For effektmålet bivirkninger oplevede 82 % af patienterne i VEN-R-gruppen grad 3-4 uønskede hændelser, mens der tilsvarende er 70,2 % i kontrolgruppen svarende til en forskel på 11,9 %-point [2,8-21,8]. Den relative risiko er 1,17 (1,04-1,31). Ved gennemgang af hændelseslisterne fra MURANO-studiet fremgår det, at forskellen primært er drevet af hyppigere neutropeni i VEN-R-gruppen, mens mere alvorlig febril neutropeni samt infektioner er mere hyppigt i BR-gruppen. Ligeledes er det udenfor MURANO-studiet dokumenteret, at bendamustin giver anledning til opportunistiske infektioner og sekundær malignitet. Den kvantitative forskel i grad 3-4 hændelser i MURANO-studiet er derfor ikke klinisk betydende, og på baggrund af alvorligheden af bivirkninger ved BR foretrækkes bivirkningsprofilen for VEN-R.

På denne baggrund vurderer fagudvalget, at VEN-R har **ingen dokumenteret merværdi** for effektmålet bivirkninger.

Det kritiske effektmål overlevelse bliver dermed bærende for en samlet **moderat merværdi** for VEN-R sammenlignet med BR.

10 Fagudvalgets vurdering af samlet værdi og samlet evidensniveau

Fagudvalget vurderer værdien af venetoclax i kombination med rituximab til kronisk lymfatisk leukæmi som følger:

- **Samlet værdi kan ikke kategoriseres** sammenlignet med venetoclax monoterapi til patienter med deletion17p/TP53-mutation, som oplever behandlingssvigt under behandling med ibrutinib i 1. linje. Fagudvalget vurderer, at VEN-R ikke er en dårligere behandling end VEN-monoterapi. Behandling med venetoclax i kombination med rituximab foretrækkes, fordi den er tidsbegrænset og giver patienterne mulighed for en behandlingsfri periode.
- **Samlet værdi kan ikke kategoriseres** sammenlignet med ibrutinib til patienter med kronisk lymfatisk leukæmi, der oplever behandlingskrævende relaps eller behandlingssvigt mindre end 3 år efter behandling med kemoterapi i kombination med CD20-antistof og/eller patienter med sent relaps og nytilkommen deletion17p/TP53-mutation. Lægemidlerne vurderes dog som klinisk ligeværdige behandlingsvalg.
- **Samlet værdi kan ikke kategoriseres** sammenlignet med chlorambucil i kombination med obinutuzumab til patienter med kronisk lymfatisk leukæmi uden deletion17p/TP53-mutation, der oplever behandlingskrævende relaps mere end 3 år efter deres første behandling med kemoterapi i kombination med CD20-antistof. Fagudvalget vurderer, at effektforholdet mellem behandlingerne vil være i overensstemmelse med sammenligningen af VEN-R med BR.
- **Moderat merværdi** sammenlignet med bendamustin-rituximab til patienter med kronisk lymfatisk leukæmi uden deletion17p/TP53-mutation, der oplever behandlingskrævende relaps mere end 3 år efter deres første behandling med kemoterapi i kombination med CD20-antistof (**moderat evidens**).

11 Rådets vurdering af samlet værdi og samlet evidensniveau

- **Samlet værdi kan ikke kategoriseres** sammenlignet med venetoclax monoterapi til patienter med deletion17p/TP53-mutation, som oplever behandlingssvigt under behandling med ibrutinib i 1. linje. Medicinrådet vurderer dog, at venetoclax i kombination med rituximab ikke er en dårligere behandling end venetoclax monoterapi. Behandling med venetoclax i kombination med rituximab foretrækkes, fordi den er tidsbegrænset og giver patienterne mulighed for en behandlingsfri periode.
- **Samlet værdi kan ikke kategoriseres** sammenlignet med ibrutinib til patienter med kronisk lymfatisk leukæmi, der oplever behandlingskrævende relaps eller behandlingssvigt mindre end 3 år efter behandling med kemoterapi i kombination med CD20-antistof og/eller patienter med sent relaps og nytilkommen deletion17p/TP53-mutation. Lægemidlerne vurderes dog som klinisk ligeværdige behandlingsvalg.
- **Samlet værdi kan ikke kategoriseres** sammenlignet med chlorambucil i kombination med obinutuzumab til patienter med kronisk lymfatisk leukæmi uden deletion17p/TP53-mutation, der oplever behandlingskrævende relaps mere end 3 år efter deres første behandling med kemoterapi i kombination med CD20-antistof. Medicinrådet vurderer dog, at effektforholdet mellem behandlingerne vil være i overensstemmelse med sammenligningen af venetoclax i kombination med rituximab med bendamustin i kombination med rituximab.

- **Moderat merværdi** sammenlignet med bendamustin-rituximab til patienter med kronisk lymfatisk leukæmi uden deletion17p/TP53-mutation, der oplever behandlingskrævende relaps mere end 3 år efter deres første behandling med kemoterapi i kombination med CD20-antistof (moderat evidens).

12 Relation til eksisterende behandlingsvejledning

Der eksisterer en behandlingsvejledning fra RADS, senest opdateret i 2016. Hvis VEN-R anbefales, har det konsekvenser for denne behandlingsvejledning.

13 Referencer

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14 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kronisk lymfatisk leukæmi (CLL)

Formand	**Indstillet af**
Robert Schou Pedersen Overlæge	Lægevidenskabelige Selskaber og udpeget af Region Midtjylland
Medlemmer	**Udpeget af**
Thor Høyer Afdelingslæge	Region Nordjylland
Annika Rewes Afdelingslæge	Region Syddanmark
Kan ikke opfylde Medicinrådets habilitetskrav	Region Sjælland
Kan ikke opfylde Medicinrådets habilitetskrav	Region Hovedstaden
Stine Trolle Poulsen Farmaceut	Dansk Selskab for Sygehusapoteksledelse
Jakob Henriksen Læge	Dansk Selskab for Klinisk Farmakologi
To patienter/patientrepræsentanter	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. th. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Thomas Linemann (projekt- og metodeansvarlig) Heidi Møller Johnsen (projektdeltager) Jan Odgaard-Jensen (biostatistiker) Anette Pultera Nielsen (fagudvalgskoordinator) Annemette Anker Nielsen (teamleder)

15 Versionslog

Version	Dato	Ændring
1.0	25. september 2019	Godkendt af Medicinrådet.
1.1	20. november 2019	Yderligere kvalificering af kategoriseringen af lægemidlets værdi. Godkendt af Medicinrådet.

16 Bilag 1: GRADE-evidensprofiler

16.1 Cochrane Risk of Bias – MURANO-studiet

Studiets risiko for bias er vurderet ved brug af tjeklisten Cochrane Risk of Bias tool (Cochrane handbook version 5.1, del 2.8, se http://handbook-5-1.cochrane.org/

Bias	**Risk for bias**	**Uddybning**
Selection bias		
Random sequence generation	**Low**	Central webbaseret tilordning.
Allocation concealment	**Low**	Central webbaseret tilordning.
Deviations from intended interventions	**Low**	Der er ikke noget, der indikerer nogen afvigelse.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes (livskvalitet og bivirkninger)	**Unclear**	Ikkeblindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager. Det kan ikke udelukkes eller bekræftes, at patientens og personalets kendskab til behandlingsallokering kan påvirke udfaldet for effektmålene.
Objective outcomes (overlevelse)	**Low**	Patienter og personale har kendskab til, hvilken behandling patienterne modtager, men det vurderes ikke at have betydning for effektmålet overlevelse.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes (livskvalitet og bivirkninger)	**Unclear**	Ikkeblindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager. Det kan ikke udelukkes eller bekræftes, at patientens og personalets kendskab til behandlingsallokering kan påvirke udfaldet for effektmålene.
Objective outcomes (overlevelse)	**Low**	Patienter og personale har kendskab til, hvilken behandling patienterne modtager, men det vurderes ikke at have betydning for effektmålet overlevelse.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Unclear**	Data analyseret på ITT- eller safety-populationerne, men der er forskel mellem grupperne på antallet af patienter, der udgår af studiet.
Reporting bias: selective reporting outcome data.	**Low**	Der er ikke noget, der indikerer selektiv rapportering af resultater.
Other bias	**Low**	No other concern regarding potential risk of bias.
Overall bias	Low	

16.2 GRADE-evaluering af evidenskvaliteten til vurdering af den kliniske merværdi af venetoclax i kombination med rituximab

Klinisk spørgsmål 3b – VEN-R versus BR

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	**Studiedesign**	**Risk of bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**VEN-R**	**BR**	**Relativ**	**Absolut**		
3-års overlevelse (median opfølgningstid 36 måneder)												
1	Randomiseret forsøg	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Ikke alvorlig	Ingen	195	194	HR 0,50 [0,30;0,85]	8,4 %-point	⊕⊕⊕◯ MODERAT	KRITISK
Grad 3-4 hændelser (medianopfølgningstid 23,9 måneder)												
1	Randomiseret forsøg	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Ikke alvorlig	Ingen	194	188	RR: 1,17 [1,04-1,31]	11,9 %-point [2,8-21,8]	⊕⊕⊕◯ MODERAT	VIGTIGT
Livskvalitet												
0											⊕◯◯◯ MEGET LAV	VIGTIGT

HR: Hazard ration; RR: Risk ratio
a. Der er kun ét studie, og der vil derfor altid være usikkerhed omkring, hvorvidt resultaterne er repræsentative.

Application for the assessment of clinically added value of Venclyxto® in combination with rituximab for relapsed or refractory chronic lymphocytic leukemia

Contents

1 Basic information

Table 1 Contact information

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Area of responsibility	Market Access
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Table 2 Overview of the pharmaceutical

Proprietary name	Venclyxto®	
Generic name	Venetoclax + rituximab	
Marketing authorization holder in Denmark	AbbVie Deutschland GmbH & Co. KG Knollstrasse 67061 Ludwigshafen Germany	
ATC code	L01XX52	
Pharmacotherapeutic group	Other antineoplastic agents	
Active substance(s)	venetoclax	
Pharmaceutical form(s)	Film-coated tablet (10mg, 50 mg and 100mg)	
Mechanism of action	Venetoclax is a potent, selective inhibitor of B cell lymphoma (BCL)-2, an anti-apoptotic protein.	
Dosage regimen	The starting dose is 20 mg of venetoclax once daily for 7 days. The dose must be gradually increased over a period of 5 weeks up to the daily dose of 400 mg. Rituximab should be administered after the patient has completed the dose-titration schedule and has received the recommended daily dose of 400 mg venetoclax for 7 days. Venetoclax should be taken for 24 months from Cycle 1 Day 1 (C1D1) of rituximab	
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Venclyxto in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.	
Other approved therapeutic indications	Venclyxto® as monotherapy is indicated for treatment of CLL: - in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B cell receptor pathway inhibitor, or - in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B cell receptor pathway inhibitor.	
Patient population	Incidence: From 2011-2015, an average 398 persons were diagnosed each year (www.cancer.dk)	Prevalence: By the end of 2015, there was a total of 3.677 patients in Denmark
Will dispensing be restricted to hospitals?	Yes	
Combination therapy and/or co-medication	Rituximab	
Packaging – types, sizes/number of units, and concentrations	Carton, film-coated tablets, 7-day pack, 10 mg, 14 film-coated tablets Carton, film-coated tablets, 7-day pack, 50 mg, 7 film-coated tablets	

	Carton, film-coated tablets, 7-day pack, 100 mg, 7 film-coated tablets Carton, film-coated tablets, 7-day pack, 100 mg, 14 film-coated tablets Carton multipack, 100 mg film-coated tablets, 112 (4 x 28) film-coated tablets
Orphan drug designation	No

2 Abbreviations

BL: baseline

BSA: Body surface area

CI: Confidence Interval

CI_low: Lower confidence Interval

CI_high: Higher confidence Interval

EMA: European Medicines Agency

EOT: End of therapy in the MURANO trial

EOCT: End of combination therapy in the MURANO trial

EPAR: European public assessment report

LOCF: Last observation carried forward

NRI: Non-responder imputation

OLE: Open label extension

PBO: Placebo

PD: Pharmacodynamics

PK: Pharmacokinetics

PY: Person years

RCT: Randomized controlled trial

SAE: Serious Adverse Event

SD: Standard Deviation

SE: Standard Error

SmPC: Summary of product Characteristics

3 Summary

Venetoclax® is a first-in-class targeted medicine that selectively binds and inhibits the B-cell lymphoma-2 (BCL-2) protein. In chronic lymphocytic leukemia (CLL), BCL-2 prevents cancer cells from undergoing their natural death or self-destruction process, called apoptosis. Venetoclax targets and inhibits the BCL-2 protein and works to help restore the process of apoptosis. In 24 months fixed duration therapy Venetoclax has, in combination with 6 cycles of rituximab, demonstrated first in class efficacy, with the achievement of unparalleled deep response as measured by minimal residual disease negativity at similar and manageable safety profile to competitors.

On 29th October 2018, venetoclax in combination with 6 cycles rituximab received EMA approval as the first fixed duration, targeted, chemotherapy-free, combination for the treatment of adult patients with CLL who have received at least one prior therapy. The approval was based on the MURANO Phase 3 clinical trial, in which venetoclax plus rituximab reduced the risk of disease progression or death by 83 percent and overall survival was prolonged compared to bendamustine in combination with rituximab. Most patients (62.4 percent) treated with venetoclax plus rituximab achieved MRD negativity in peripheral blood compared to 13.3 percent of patients who received bendamustine plus rituximab.

Current treatment options in second line treatment of CLL entails either fixed duration with chemoimmunotherapy or continuous indefinite targeted therapy. Venetoclax plus rituximab is the first and only approved fixed duration targeted therapy with a favorable safety profile and substantial clinical benefit.

Venetoclax plus rituximab has achieved the highest rate of MRD negative responses observed so far in a randomized prospective study in second line CLL, correlating as a surrogate for a longer OS. Even if a proportion of patients are ultimately destined to develop PD by iwCLL criteria and require treatment, a number of years off drug, would have quality-of-life, toxicity, and societal economic benefit.

The Medicines council outlined 3 clinical questions to be answered in this application for recommendation to be used as standard of care in Danish hospitals:

Clinical question 1: *What is the clinically added value of venetoclax in combination with rituximab compared to venetoclax mono therapy for patients with deletion17p/p53-mutation, in R/R CLL patients after ibrutinib?*

- In R/R CLL patients with del17p, fixed treatment duration with venetoclax in combination with 6 cycles of rituximab, has in the MURANO study achieved better results on OS, PFS and significantly deeper response through higher rates of MRD negativity compared to continuous infinite venetoclax monotherapy. Recorded rates of AE grade 3-4 were similar for VEN+R study compared VEN monotherapy and the safety profile of VEN+R was consistent with the known safety profiles of venetoclax and rituximab as single agents.

Clinical question 2: *What is the clinically added value of venetoclax in combination with rituximab compared to ibrutinib in 2nd line therapy for patients treated with chemoimmunotherapy in 1st line.?*

- In a recently published indirect therapy comparison fixed treatment duration with venetoclax in combination with rituximab was found to have numerically better but not statistically significant OS rates to continuous infinite therapy with ibrutinib. PFS was numerically similar to ibrutinib but not statistically significant. MRD negativity rates with VEN+R are substantially higher compared to ibrutinib, while rates of grade 3-4 AEs are slightly higher. However, the safety profile

of venetoclax monotherapy period of MURANO was comparable to Ibrutinib and the safety profile of VEN+R was consistent with the known safety profiles of venetoclax and rituximab as single agents.

Clinical question 3: *What is the clinically added value of venetoclax in combination with rituximab compared to chemoimmunotherapy for patients without deletion17p/p53-mutation, who have relapsed more than 3 years after first treatment?*

- Narrative analysis of venetoclax plus rituximab compared to chlorambucil plus obinutuzumab, demonstrated large scale improvements in overall response rates, and especially complete response rates, at similar rates of grade 3-4 AEs.
- In direct comparison to bendamustine plus rituximab venetoclax in combination with rituximab efficacy in terms of OS, PFS and MRD would meet the threshold for absolute differences set out in the Medicines Council protocol and with hazard ratio estimates implying moderate added value on OS and large added value for PFS and MRD. Comparing AE grade 3-4 after EOCT, the difference in proportion of patients with AE grade 3-4 was statistically insignificant for VEN+R vs BR. Comparing at EOT, after active treatment of 24 months vs 6 months in the BR arm, VEN+R had slightly higher rates of AEs grade 3-4.

Data on health-related quality of life for venetoclax in combination with rituximab has not been published, but large amounts of data was found for venetoclax monotherapy. Assessment of the data supporting venetoclax demonstrated clinically meaningful improvements as measured by EORTC QLQ-C30 both in short- and long-term data. One study reporting data on EORTC QLQ-C30 for ibrutinib was found and showed that across all dimensions of the EORTC QLQ-C30 patients did experience improvements, but in no dimension were these observed improvements clinically relevant.

4 Literature search

A systematic literature search was conducted on May 28th 2019 according to the criteria set out by the Medicines Council protocol of May 16th 2019 to reveal data to answer the 3 clinical questions. Details of the searches, including in- and exclusion criteria, search terms and strategy can be found in Appendix A.

The PRISMA flow diagram is shown in appendix 7.1.2. A total of 171 potentially relevant references were identified through searching MEDLINE and CENTRAL (see Appendix 7.1). A total of 47 reference duplicates were identified and 124 references were subsequently screened, 101 records were excluded based on titles and abstracts and 23 published full-text papers were subsequently assessed for eligibility. Of these, 13 references were excluded in full text review. In total, 10 references reporting results of 5 studies were included.

Furthermore, in order to answer the clinical questions, especially on EORTC-C30, a hand search including conference abstracts and early phase studies was performed. This hand search included 23 references, adding 3 studies (M13-982, M14-032 and VENICE II):

1. M13-982 study, NCT01889186
2. MURANO study, NCT02005471
3. M14-032 study, NCT02141282
4. RESONATE study, NCT01578707
5. HELIOS study, NCT01611090
6. GREEN study, NCT01905943
7. MABLE study, NCT01056510
8. VENICE II, NCT02980731

4.1 Relevant studies

Clinical question 1: Venetoclax + rituximab vs venetoclax monotherapy in R/R del17p/TP53 subpopulation

Table 4.1: Relevant studies included in the assessment of VR vs. Ven

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Stilgenbauer et al, 2016.(1) Stilgenbauer et al, 2018 (2)	M13-982 study	NCT01889186	June 27, 2013 - May 12, 2020	Q1
Kater et. al(3), Seymour, J. F.(4)	MURANO study	NCT02005471	31 March 2014 – May 8 2017 (Primary analysis), estimated study completion June 30, 2022	Q1
Jones et al.(5)	M14-032	NCT02141282	September 10, 2014 Estimated study completion December 8, 2021	Q1

Clinical question 2: Venetoclax + rituximab vs ibrutinib in R/R CD20 experienced patients

Table 4.2: Relevant studies included in the assessment of V+R vs. IBR

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Kater et. al(3), Seymour, J. F.(4)	MURANO study	NCT02005471	31 March 2014 – May 8 2017 (Primary analysis), estimated study completion June 30, 2022	Q2
Barrientos, J. C.(6), Brown, J. R.(7), Byrd JC(8), Byrd JC (9)	RESONATE study	NCT01578707	June 2012-October 25, 2018	Q2
Chanan-Khan, A.(10), Fraser, G.(11)	HELIOS study	NCT01611090	September 19, 2012- January 23, 2019	Q2

Clinical question 3: Venetoclax + rituximab vs chemoimmunotherapy with CD20 in non del17p/TP53 patients experiencing relapse after more than 3 years after 1st line chemoimmunotherapy with CD20

Table 4.3: Relevant studies included in the assessment of VR vs. Clr+OBI

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Leblond, V.(12)	GREEN	NCT01905943	November 4, 2013 - October 8, 2018	Q3.a (vs Clr. +OBI)
Michallet, A. S.(13)	MABLE	NCT01056510	March 2010 - March 2014	Q3.a (vs Clr. +OBI)

Table 4.4: Relevant studies included in the assessment of VR vs. BR

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Kater et. al(3), Seymour et al.(4)	MURANO study	NCT02005471	31 March 2014 – May 8 2017 (Primary analysis), estimated study completion June 30, 2022	Q3.b (vs BR)

Further, the EMA Venclyxto® Product information was included when relevant to ensure consistency with the latest approved indication and data. This information could be accessed through https://www.ema.europa.eu/en/documents/product-information/venclyxto-epar-product-information_en.pdf

4.2 Main characteristics of included studies

Please see sections for each clinical question and Appendix 7.1.4. for details on study characteristics.

5 Clinical questions

The Medicines Council protocol posed 3 questions. The only identified direct comparative study was the MURANO study where VEN+R was directly compared with BR. Thus, only clinical question 3b was answered using direct comparison from this study. All other Clinical questions would have to rely on network meta-analysis or narrative analysis in accordance with the *Handbook of the Medicines Council's process and methodologies for new pharmaceuticals and indication expansions version 2.2(14)*. The only active comparator in the MURANO study was BR. Clr+OBI (Q3a), IBR monotherapy (Q2) and VEN monotherapy (Q1) have not been studied directly vs BR and no common arms exist in any of the studies found in the systematic literature review. Consequently, all other comparative analyses will rely on the narrative approach.

The systematic literature review revealed only data on the outcome EORTC-C30 from the RESONATE study of IBR vs OFA. A hand search was conducted to retrieve data on EORTC-C30 for all other comparators in the protocol. The hand search only retrieved data on EORTC for VEN mono therapy. Therefore, a specific section on EORTC-C30 has been added and the relative added value in terms of EORTC-C30 is not addressed for each clinical question separately.

5.1 Clinical question 1

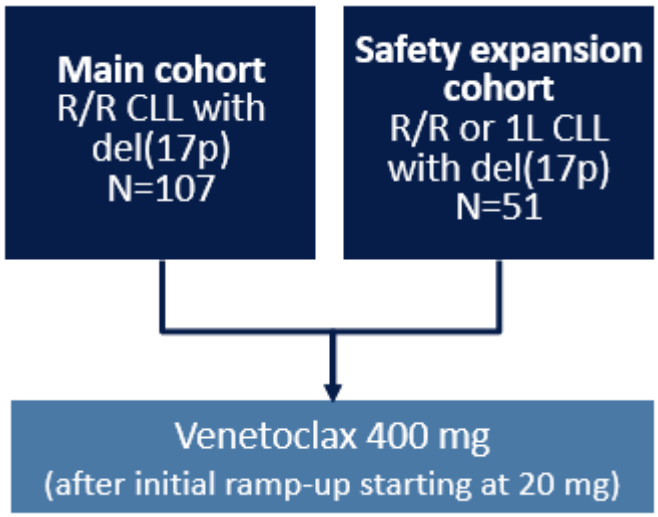
What is the clinically added value of venetoclax in combination with rituximab compared to venetoclax mono therapy for patients with deletion17p/p53-mutation, in R/R CLL patients after ibrutinib?

5.1.1 Presentation of relevant studies

1. M13-982 study

phase II, open-label, M13-982 study started in June 2013 and completed enrollment of patients with relapsed/refractory or previously untreated del(17p) CLL, with follow-up ongoing. Venetoclax monotherapy was administered orally, once daily, until disease progression or study discontinuation. Based on the results of the M12-175 phase 1, venetoclax monotherapy dose-finding study, a stepwise weekly dose ramp-up to the final 400 mg daily dose was employed to mitigate the risk for TLS. Tumor lysis syndrome (TLS) prophylaxis and initial management guidelines were specified. Follow-up is ongoing, and patients are still receiving treatment.

Figure 5.1: M13-982 study design

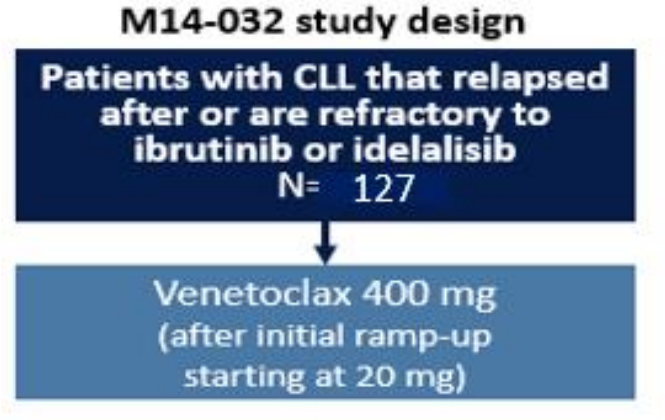


For further details, please see appendix 7.1.4.

2. M14-032study

The M14-032. study is a multicenter, open-label, non-randomized, phase 2 trial of patients with R/R CLL. 15 Patients were initially enrolled in the main cohort of the study, although a protocol amendment (on Sept 13, 2016), approved by the US Food and Drug Administration (FDA) and all institutional review boards, permitted enrolment to an expansion cohort to further establish the activity of venetoclax in patients with R/RCLL previously on BCR inhibitor therapy. The washout period for a previous BCR inhibitor was 7 days in the main cohort and 3 days in the expansion cohort. Patients were recruited to the study groups based on the last BCR inhibitor they received before enrolment. At the time of data cut-off (26 July 2017), 127 patients were enrolled and treated with venetoclax. Of these, 91 patients had received prior ibrutinib therapy and 36 had received prior idelalisib therapy. Study still active for follow-up, but not recruiting patients.

Figure 5.2:M14-032 study design

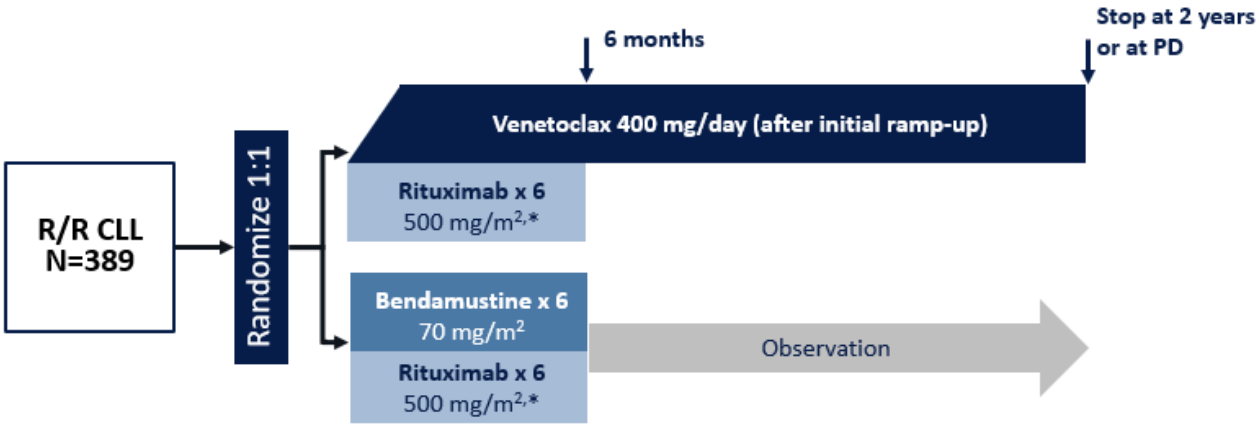


For further details, please see appendix 7.1.4.

3. MURANO study

Multicenter, phase III, open-label, randomized study. Participants were randomly assigned in 1:1 ratio to receive either venetoclax + rituximab (Arm A) or bendamustine + rituximab (Arm B). Randomization was stratified according to the presence or absence of chromosome 17p deletion, responsiveness to previous therapy and geographic region. Study still active for follow-up, but not recruiting patients. Denmark have participated in this study.

Figure 5.3: MURANO study design



For further details, please see appendix 7.1.4.

5.1.2 Results per study

Table 5.1: Relevant results from the M13-982 study, VEN in patients with 17p deletion

OUTCOMES in MR protocol	VEN (N=107)	CI
OS, 12 md	86.7%	[78.6;91.9]
OS, 24 md	73%	(65%-79%)
PFS, 12 md	72.0%	[61.8;79.8]
PFS , 24 md	54%	(45%-62%)
Best MRD status	30%	
EORTC QLQ-C30, Global Health Status, improvement 24 weeks*	9.4	
AE grade 3-4	75%	

Source: Stilgenbauer et al. 2016(1), Stilgenbauer et al. 2018(2) and *Wierda et al(15)

Table 5.2: Relevant results from the M14-032, VEN in BCRi experienced patients

OUTCOMES in MR protocol	VEN (N=127)	CI
OS, 12 md	92.0%	[85.6%;95.6%]
PFS, 12 md	75.0%	[64.0%;83.0%]
PFS, 24 md	54.0%	[41.8%, 64.6%]
Best MRD status	25%	
EORTC QLQ-C30, Global Health Status (BL=68.8), improvement 48 weeks*	6.5	
SAE , 12 md	50%	

Source: Jones et al. 2018(5), *Wierda et al. 2017(16)

The M14-032 study did not report a specific PFS or any other included outcome specifically for the del17p population, but the proportion of patients achieving a response was similar for patients with high-risk chromosomal abnormalities compared to patients without these factors(5). Of 46 patients with known del(17) or TP53 mutations 28 (61%, 95% CI 45–75) had an overall response, including four patients who had a complete response or a complete response with incomplete bone marrow recovery and 24 patients who had a nodular partial response or a partial response. Of 45 patients without del(17)(p13.1) and TP53 mutations, 30 (67%, 51–80) had an overall response, including four patients who had a complete response and 26 patients who had a nodular partial response or a partial response(5). These response rates suggest similar efficacy across these subgroups.

Table 5.3: Relevant results from the MURANO study, VEN+R vs BR

OUTCOMES in MR protocol	VEN+R	CI	BR	CI	HR	CI
OS 24 md*	91.9%		86.6%		0.48	[0.25;0.9]
OS, 36 md	87.9%		79.5%		0.5	[0.3;0.85]
PFS, 24 md*	84.9%	[79.1%;90.6%]	36.3%	[28.5%;44%]	0.17	[0.11;0.25]
PFS, 24 md, del17p*	81.5%		27.8%		0.13	[0.05;0.29]
uMRD at EOCT (9 md)	62.4%		13.3%			
uMRD at EOCT (9 md), del17p/TP53	56.9%		5.3%			
uMRD, 24 md EOT	64.0%		13.3%			
uMRD, 24 md EOT, 17p/TP53	56.9%		5.3%			
AE grade 3-4, EOCT, 7 md	74.7%					
AE grade 3-4, EOT 24 md	34.5%					
AE grade 3-4, 24 md*	82.0%		70.2%			

Note: VEN=venetoclax, R=rituximab, B=bendamustine
Source: Kater et. al.(3) and *Seymour et al.(4)

5.1.3 Comparative analysis

In the M13-982 study of VEN monotherapy, patients with 17p deletion had estimated OS after 12 md of 86.7% (95% CI: 78.6;91.9) and after 24 md of 73% (95% CI: 65%-79%) and estimated PFS after 12 months of 72% (95%CI:61.8;79.8) and 54% (95% CI: 45%-62%) after 24 md. These results seem comparable with the results from the M14-032 of VEN monotherapy, in BCRi experienced patients (46 of 127 patients harboring the de17p or TP53 mutations) where estimated OS after 12 months was 92% (95%CI: 85.6%;95.6%) and PFS 77% (95%CI: 68.1%;83.4%) after 12 months and PFS 54% (95%CI: 41.8%;64.6%). Comparing this to the estimated 24 months PFS in the MURANO fixed duration combination therapy study for the subpopulation with del17p mutation where PFS 81%, shows the relative efficacy of the VEN+R combination. OS is not available for the del17p subpopulation, but the estimated 24-month OS of 91.9% in the overall study population, suggests substantially improved OS with combination therapy.

Simply comparing these data unadjusted across the studies, suggest that VEN+R is superior compared to VEN monotherapy in the R/R CLL population with del17p.

Freise et al.(17) published a paper on the relative effects of VEN+R and VEN monotherapy in the R/R CLL population with or without 17p deletion. A total of 323 patients from 3 clinical studies of venetoclax, with and without rituximab coadministration, were pooled for the analyses. More than half (62.2%) of the patients were confirmed to have 17p deletion(17). A time-variant relative risk survival model was used to relate plasma venetoclax concentrations and rituximab administration to PFS. Demographics and baseline disease characteristics were evaluated for their effect on PFS. A concentration-dependent effect of venetoclax on PFS and a prolonged synergistic effect of 6 cycles of concomitant rituximab were identified. The 17p deletion

chromosomal aberration was not identified to affect the PFS of patients treated with venetoclax. A venetoclax dose of 400 mg daily was estimated to result in a substantial median PFS of 1.8 years (95% confidence interval [CI], 1.7-2.1), whereas the addition of 6 cycles of rituximab was estimated to increase the median PFS to 3.9 years (95% CI, 2.8-5.6). The analysis demonstrated the synergistic effect between venetoclax and rituximab, suggested to be explained by mediating the responsiveness to venetoclax through the rituximab therapy–induced upregulation of BCL-2 in the CLL cells not killed by rituximab(17).

In the M13-982 study of VEN monotherapy, in patients with 17p deletion and the M14-032 study of VEN monotherapy, in BCRi experienced patients, Best MRD negativity status was observed for 30% and 25% respectively, compared to 56.9% in the del17p subpopulation were MRD negative after end of combination therapy with venetoclax and rituximab. These data suggest that VEN+R is superior in terms of achieving a deep response through significantly higher MRD negativity which correlate to prolonged OS.

Adverse events grade 3-4/SAE was recorded for 75% and 50% of patients respectively in the two VEN monotherapy studies compared to 74.7% patients had a grade 3/4 AE during combination treatment and 34.5% during monotherapy period. These data suggest similar rates of grade 3-4 AEs with combination therapy with venetoclax and rituximab compared to venetoclax monotherapy. Overall, in patients with R/R CLL, including patients with del(17p), VEN+R was well tolerated by patients, with the majority of patients who had an AE able to continue study treatment. The safety profile of VEN+R was acceptable, predictable and generally consistent with the known safety profiles of venetoclax and rituximab as single agents(18). No new safety signals were observed in the Murano study(3, 4).

No available data for EORTC-C30 from the MURANO study deems it unfeasible to compare on this important outcome between VEN monotherapy and VEN+R please see section 5.4.

In R/R CLL patients with del17p, fixed treatment duration with venetoclax in combination with 6 cycles of rituximab, has in the MURANO study achieved better results on OS, PFS and significantly higher rates of MRD negativity compared to two studies of continuous infinite venetoclax monotherapy. Recorded rates of AE grade 3-4 were similar in the VEN+R study compared to both VEN monotherapy studies and the safety profile of VEN+R was consistent with the known safety profiles of venetoclax and rituximab as single agents.

5.2 Clinical question 2

What is the clinically added value of venetoclax in combination with rituximab compared to ibrutinib in 2nd line therapy for patients treated with chemoimmunotherapy in 1st line.?

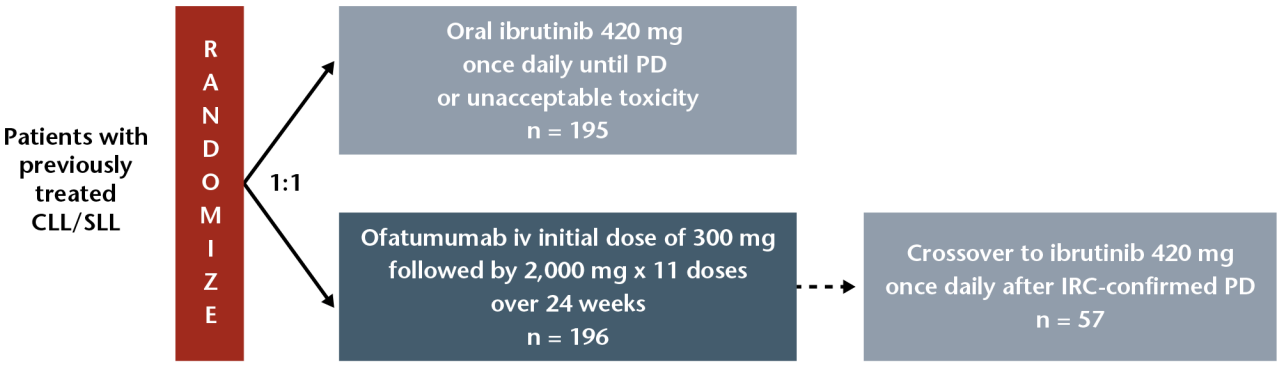
Ibrutinib has been studied in one monotherapy study, RESONATE (IBR vs OFA) and in one study in combination with bendamustine + rituximab, the HELIOS (IBR+BR vs BR). Venetoclax in combination with rituximab has been studied in the single arm study NCT01682616 and in the MURANO study (VEN+R vs BR).

5.2.1 Presentation of relevant studies

1. RESONATE study

RESONATE was a multicenter, open-label, phase 3 study. Patients were randomly assigned to receive either ibrutinib (n=195) or ofatumumab (n=196). Patients were stratified according to whether they had resistance to purine analogue chemoimmunotherapy (defined as no response or relapse within 12 months after last dose of purine analogue) and whether they had a chromosome 17p13.1 deletion. Crossover was allowed for patients who received ofatumumab and progressed to receive ibrutinib.

Figure 5.4: RESONATE study design



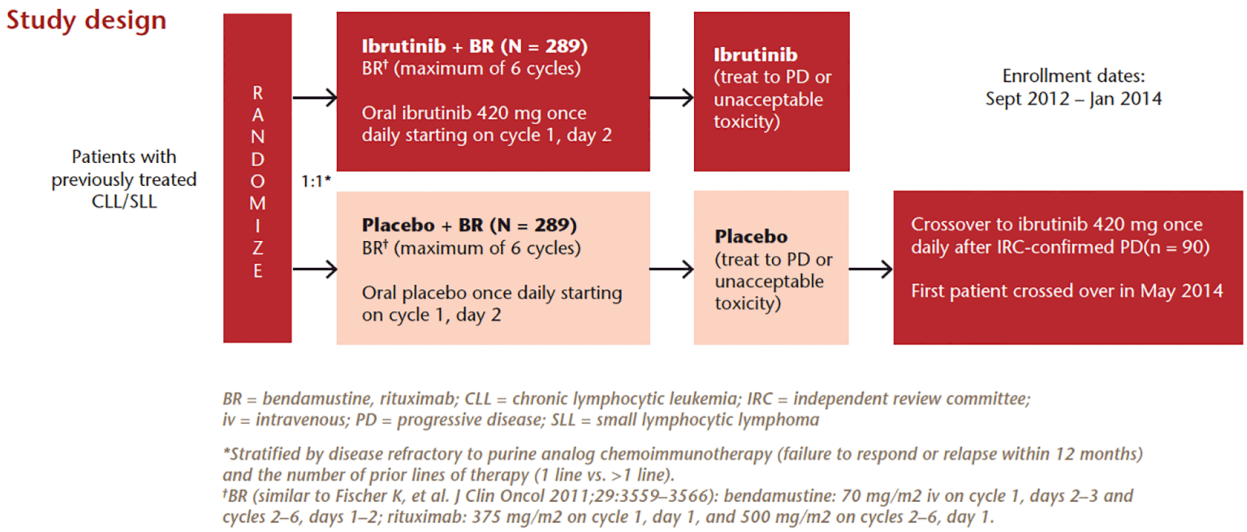
CLL = chronic lymphocytic leukemia; IRC = Independent Review Committee; iv = intravenous; PD = progressive disease; SLL = small lymphocytic lymphoma

For further details, please see appendix 7.1.4.

2. HELIOS study

The HELIOS study is a randomized, double-blind, placebo-controlled phase 3 Study of ibrutinib, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in combination with bendamustine and rituximab in subjects with R/R CLL/SLL. Patients were randomized in a 1:1 ratio on the basis of a computer-generated randomization schedule. Patients were stratified by purine analogue refractory status and number of previous lines of therapy (1 vs. > 1). Crossover to ibrutinib was permitted for patients in the placebo group with IRC-confirmed disease progression. Investigators, patients and study personnel were all blinded to the actual treatment assignment. Study is active on follow-up, not recruiting.

Figure 5.5: HELIOS patient flow



BR = bendamustine, rituximab; CLL = chronic lymphocytic leukemia; IRC = independent review committee; iv = intravenous; PD = progressive disease; SLL = small lymphocytic lymphoma

**Stratified by disease refractory to purine analog chemoimmunotherapy (failure to respond or relapse within 12 months) and the number of prior lines of therapy (1 line vs. >1 line).*
†BR (similar to Fischer K, et al. J Clin Oncol 2011;29:3559–3566): bendamustine: 70 mg/m2 iv on cycle 1, days 2–3 and cycles 2–6, days 1–2; rituximab: 375 mg/m2 on cycle 1, day 1, and 500 mg/m2 on cycles 2–6, day 1.

For further details, please see appendix 7.1.4.

5.2.2 Results per study

Table 5.4: Selected outcomes from 2 studies of ibrutinib and 1 study of venetoclax in combination with rituximab in R/R CLL patients.

OUTCOMES in MR protocol	IBR, RESONATE (N=195)	IBR +BR HELIOS (N= 289)	VEN+R MURANO (N= 194)
OS, all, 36 md	74%	81.6%	87.9%
OS, all, 24 md	86%(18 md)		91.9%
PFS, all, 36 md	59%	68.0%	71%
PFS, 2nd line, 36 md		70.0%	
PFS, all, 24 md			84.9%
PFS, all, 18 md	76.0%	79.0%	
MRD, 12 md			62.4% (9md)
MRD, 18 md		13.0%	
MRD, 24 md			83.5%
MRD, 36 md		26.3%	
EORTC - C30 (improvement in global health status after 24 weeks)	9 +/ 24.1		
AE grade 3-4		77.0%	82.0%
AE grade 3-4, 9.4 md	50.8%		

Source, Fraser et al(11), Chanan-Khan et al(10), Byrd et al.(9), Barrientos et al.(6), Byrd et al.(8), Kater et. al.(3), Seymour et al.(4)

5.2.3 Comparative analysis

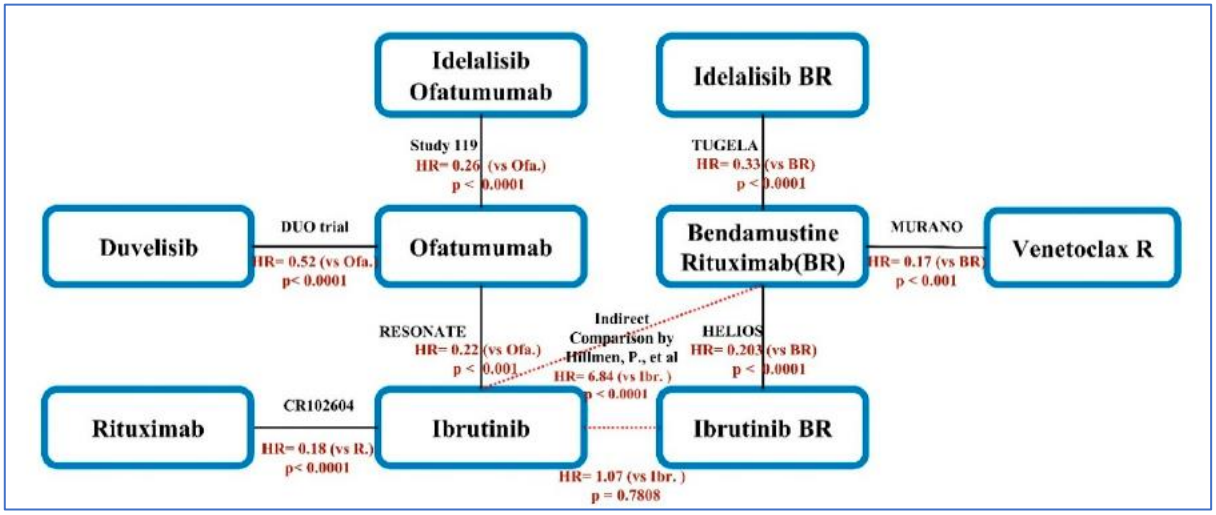
For both PFS and OS, VEN+R seems on par with IBR and IBR+BR in RESONATE and HELIOS respectively. MRD rates are substantially higher for VEN+R compared to IBR+/-BR across all trials. Safety as represented by grade 3-4 AEs, is comparable between IBR+BR and VEN+R, however numerically lower for IBR compared to VEN+R, suggesting that the addition of i.v. rituximab adds AEs. Comparing single agent VEN grade 3-4 AEs from the M13-982 and M14-032 studies and during monotherapy period of MURANO study to Resonate study, suggests that VEN and IBR have a comparable safety profile. Overall, in patients with R/R CLL, VEN+R was well tolerated by patients, with the majority of patients who had an AE able to continue study treatment. The safety profile of VEN+R was acceptable, predictable and generally consistent with the known safety profiles of venetoclax and rituximab as single agents(18). No new safety signals were observed in the Murano study(3, 4).

Relative efficacy between ibrutinib and venetoclax in combination with rituximab has been the subject of many indirect therapy comparisons (ITC). All the published ITCs rely on an ITC between ibrutinib and ibrutinib in combination with bendamustine and rituximab published by Hillmen and colleagues. Hillmen and colleagues published an ITC between the RESONATE and HELIOS studies in 2015(19). In this ITC, patient level data from the two studies were used after a median follow-up of 19 and 17 months respectively for RESONATE and HELIOS patients(19). As the HELIOS study excluded patients with del17p, all patients with del17p were deleted in the RESONATE study(19), making the ITC population comparable to the R/R CLL population without 17p deletion. Separate multivariate Cox proportional hazards models were produced for PFS and OS. In order to adjust for differences in included patients in the studies, the following covariates were included; age, gender, Rai staging, ECOG score, del11q status, refractory status, number of prior lines of therapy, bulky disease and IgVH status. Estimated adjusted HRs and 95% CIs found for CLL were; PFS (IBR + BR vs single-agent IBR: 1.03 [0.61-1.75], p = 0.9042; BR vs single-agent IBR: 7.52 [4.72-11.99], p < 0.0001) and OS (IBR + BR vs single-agent IBR: 1.20 [0.59-2.43], p = 0.6197; BR vs single-agent IBR: 2.24 [1.14-4.40], p = 0.0197). These results led Hillmen and colleagues to conclude that the addition of BR to IBR did not improve PFS or OS compared with single-agent IBR and that single-agent IBR was superior to BR in R/R CLL.

In "The *Single Technology Appraisal, Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia" [ID1097]* published 27th February 2019 by The National Institute for Health and Care Excellence (NICE), the Evidence Review Group (ERG) responsible for developing the guidance on the use of VEN+R in clinical practice in the UK, used the ITC published by Hillman et al.(19) as a basis for a network meta-analysis of VEN+R vs single-agent IBR(18). The HRs and 95%CIs estimated by the NICE ERG were: PFS (VEN+R vs single-agent IBR: 1.43 [0.78-2.61]) and OS (VEN+R vs single-agent IBR: 1.08 [0.42-2.73]) leading the ERG to the conclusion that VEN+R and single-agent IBR were on par in terms of PFS and OS in R/R CLL.

In May 2019, Chen and colleagues published a large systematic review and network metanalysis of novel, targeted agents in R/R CLL(20). This ITC uses the Hillmen ITC to close a large network including idelalisib, ibrutinib and venetoclax therapy.

Figure 5.7: Network meta-analysis from Chen et al. 2019



Source: Chen et al 2019(20)

The ITC was done for all therapies vs ofatumumab in terms of OS and PFS. Regarding PFS Chen et al. concludes that; "*With the exception of conventional BR and R, all newly developed novel-targeted-agent–based therapies were significantly more effective than Ofa and reduced the risk of progression or death by more than 48%. In the analysis of overall PFS, Ibr and VR were more effective than the other treatments for patients with R/R CLL. Both of these treatments resulted in a more favorable HR than did Ofa (Ibr: HR, 0.10; 95% CI, 0.07–0.14; VR: HR, 0.10; 95% CI, 0.05–0.21). In other words, treatments with Ibr or VR reduced the risk of disease progression or death by 90% compared to conventional Ofa.*"(20).

Figure 5.8: Network meta-analysis regarding PFS, HR vs OFA (95%CI)

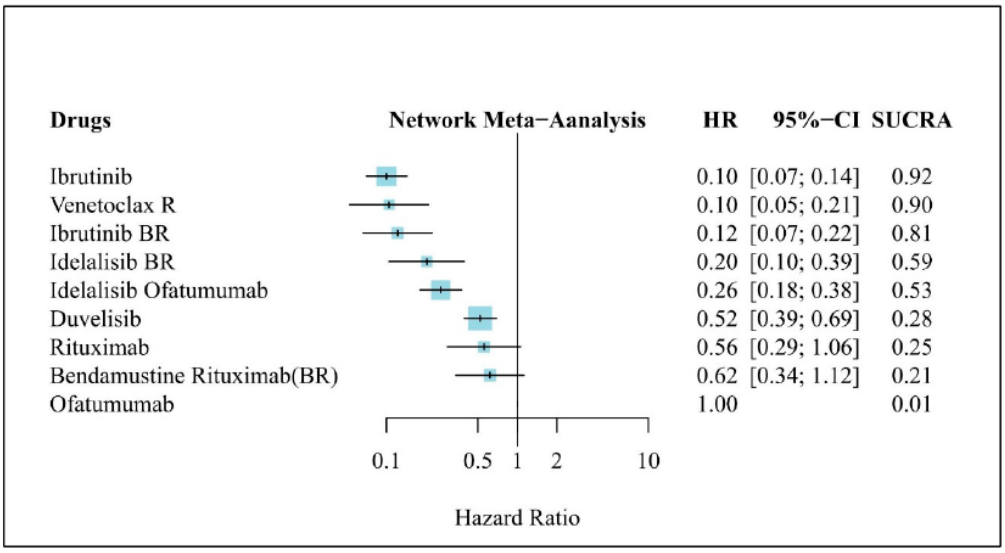


Figure 3. Network meta-analysis results of treatment efficacy in refractory/relapse (R/R) chronic lymphocytic leukemia (CLL): Forest plot of PFS in R/R CLL. HR: Hazard ratio; CI: Confidence interval, SUCRA: Surface under the cumulative ranking curve, BR: Bendamustine + Rituximab, R: Rituximab.

Source: Chen et al 2019(20)

Regarding OS Chen et al. concludes that; *"Only VR (HR, 0.335; 95% CI, 0.112–0.997) and Ibr (HR, 0.361; 95% CI, 0.208–0.627) were significantly more effective than the comparator. VR and Ibr were ranked as the most effective treatments, with similar SUCRA values of 0.85 and 0.84, respectively. The other treatments did not significantly differ from that of Ofa but had a trend toward a greater effectiveness of novel targeted agents, with the median HR ranging from 0.335 to 0.99. However, the median OS among most of the included trials had not yet been reached."*

Figure 5.9: Network meta-analysis regarding OS, HR vs OFA (95%CI)

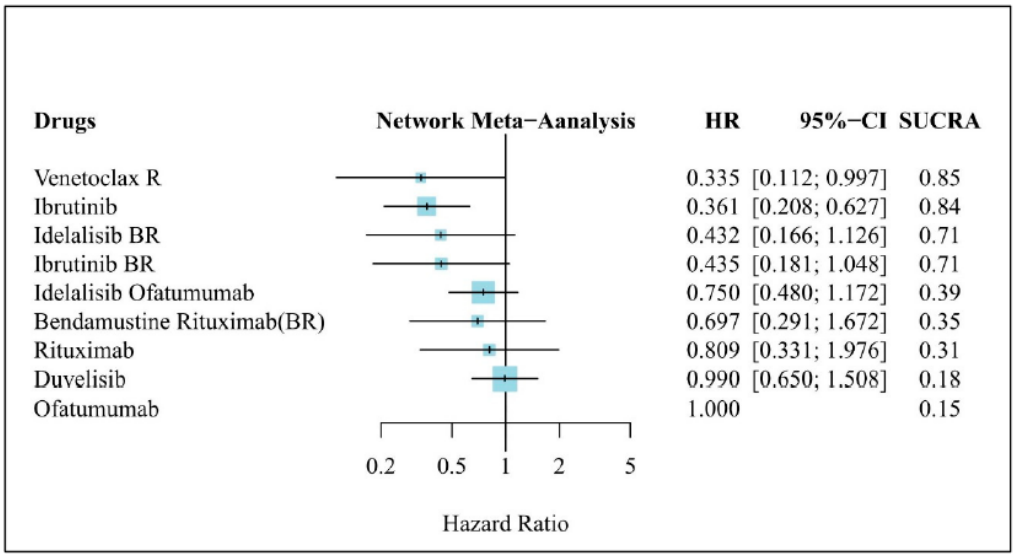


Figure 4. Network meta-analysis results of treatment efficacy in refractory/relapse (R/R) chronic lymphocytic leukemia (CLL): Forest plot of OS in R/R CLL. HR: Hazard ratio, CI: Confidence interval, SUCRA: Surface under the cumulative ranking curve, BR: Bendamustine + Rituximab, R: Rituximab.

Source: Chen et al 2019(20)

Thus, in this recently published ITC, VEN+R was found to have numerically better but not statistically significant OS while PFS was numerically similar and not statistically significant PFS compared to Ibrutinib.

In 2nd line therapy for CLL patients treated with chemoimmunotherapy in 1st line, fixed treatment duration with venetoclax in combination with 6 cycles of rituximab, has similar PFS and OS rates to infinite continuous treatment with Ibrutinib. In NICE's ITC VEN+R was found to have numerically better but not statistically significant PFS and OS compared to Ibrutinib. In a recently published ITC, VEN+R was found to have numerically better but not statistically significant OS while PFS was numerically similar and not statistically significant PFS compared to Ibrutinib. Further, substantially deeper response through higher rates of MRD negativity with VEN+R was achieved compared to ibrutinib. Rates of AE grade 3-4 are numerically higher for VEN+R compared to IBR, whereas VEN+R has similar rates of AE grade 3-4 compared to IBR+BR, and VEN monotherapy has similar rates of AE grade 3-4 compared to IBR monotherapy.

5.3 Clinical question 3

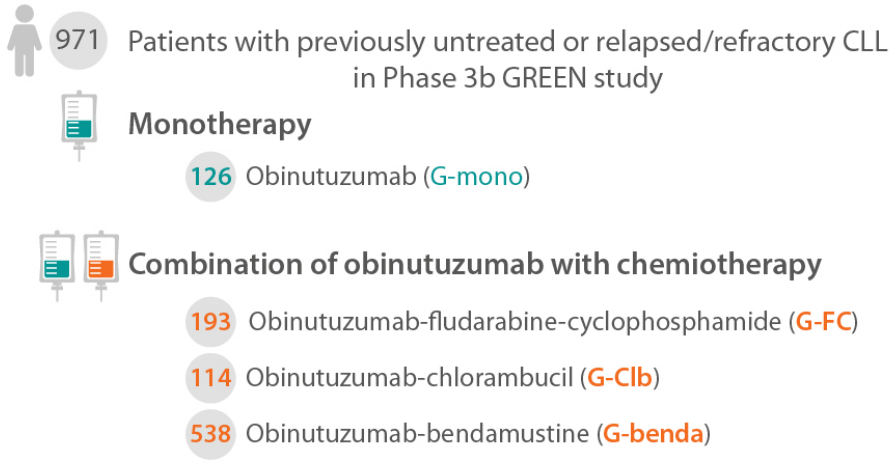
***Clinical question 3a**: What is the clinically added value of venetoclax in combination with rituximab compared to chemoimmunotherapy for patients without deletion17p/p53-mutation, who have relapsed more than 3 years after first treatment? VEN+R vs Clr+OBI*

5.3.1 Presentation of relevant studies

3. GREEN study

The GREEN study was a non-randomized, open-label, non-comparative, phase IIIb study in previously untreated or relapsed/refractory chronic lymphocytic leukemia. Patients received obinutuzumab 1000 mg alone or with chemotherapy (investigator's choice of fludarabine-cyclophosphamide for fit patients, chlorambucil for unfit patients, or bendamustine for any patient) on days 1, 8 and 15 of cycle 1, and day 1 of cycles 2-6 (28-day cycles), with the cycle 1/day 1 dose administered over two days. The primary end point was safety/tolerability. Between October 2013 and March 2016, 972 patients were enrolled and 971 treated (126 with obinutuzumab monotherapy, 193 with obinutuzumab-fludarabine-cyclophosphamide, 114 with obinutuzumab-chlorambucil, and 538 with obinutuzumab-bendamustine).

Figure 5.10: study arms in GREEN study



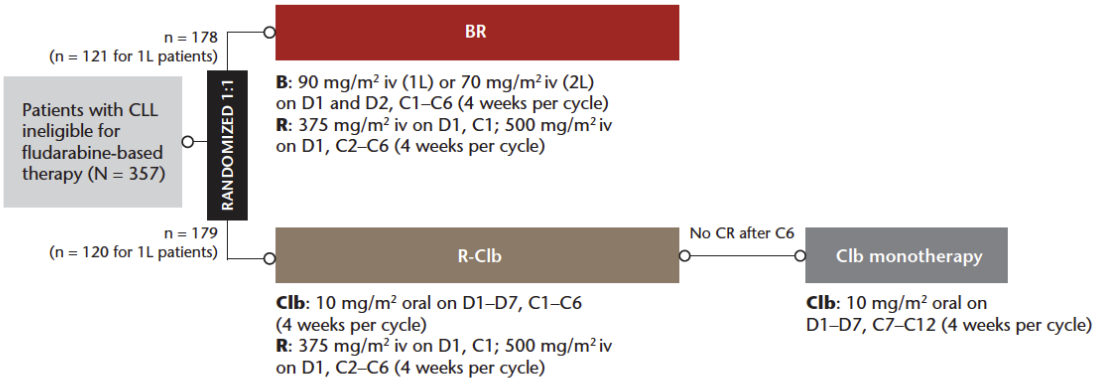
For further details, please see appendix 7.1.4.

4. MABLE study

MABLE investigated the efficacy and safety of rituximab plus bendamustine or rituximab plus chlorambucil in fludarabine-ineligible patients with chronic lymphocytic leukemia. Patients received rituximab plus bendamustine or rituximab plus chlorambucil every four weeks for six cycles. Rituximab plus chlorambucil-treated patients without a complete response after Cycle 6 received chlorambucil monotherapy for at least six additional cycles or until complete response. The primary endpoint was complete response rate (confirmed by bone marrow biopsy) after Cycle 6 in first-line patients. Secondary endpoints included progression-free survival, overall survival, minimal residual disease, and safety. The study was conducted

between 23 February 2010 and 31 March 2014. Of the 357 patients in the ITT population, comprising 241 1st line patients (R-B, n=121; R-Clb, n=120) and 116 2nd line patients (R-B, n=57; R-Clb, n=59), 355 patients received treatment (R-B, n=177; R-Clb, n=178).

Figure 5.11: Study design MABLE study



1L = first-line; 2L = second-line; B = bendamustine; BR = bendamustine plus rituximab; C = cycle; Clb = chlorambucil; CLL = chronic lymphocytic leukemia; CR = complete response; D = day; iv = intravenous; R = rituximab; R-Clb = chlorambucil plus rituximab

For further details, please see appendix 7.1.4.

5.3.2 Results per study

Table 5.5: Relevant results from the GREEN study (Clr + OBI in R/R patients), MURANO study (VEN+R) and NCT01682616, 6 md

OUTCOMES	Clr + OBI, R/R (N=46), %, [CI]	Comment	VEN+R (N=194), %	Comment
ORR	54.3% [39%;69.1%]	At 6 months	93.3%	Best response in 24 months
CR	6.5%	At 6 months	26.8%	Best response in 24 months
AE grade 3-4	68.4%	AE grade 3-4 calculated as; >=3 - Grade =5 (all R/R patients in all study arms, N=341)	74.7%	At EOCT, 7 md

Source: Leblond et al.(12), Seymour et al.(4)

Table 5.6: Relevant results from the MABLE study (Clr + R vs BR in R/R patients), MURANO study (VEN+R vs BR in R/R patients), HR vs BR, 36 md estimates

OUTCOMES in MR protocol	MABLE (Clr+R)	MURANO (VEN+R)	Comment
PFS, 36 md, HR vs BR	0.70 [0.43;1.14]	0.16 [0.12;0.23]	Follow up 36 months for MURANO (median PFS not reached for VEN+R), 23.5 months BR and 23.3 months Clr+R in MABLE
OS, 36 md, HR vs BR	0.68 [0.32;1.46]	0.5 [0.3;0.85]	Median OS not reached for VEN+R in MURANO, median OS reached for Clr+R patients in MABLE

MRD at confirmation of response visit (6-9 md)	9.0%	62.4%	Confirmation of response in MURANO at 9 months, confirmation of response after 6 cycles in MABLE
AE grade 3-4, full study	64.0%	82.0%	Active treatment in MABLE study was 6 cycles and for 10% of Clr+R patients 12 cycles as compared to 2 years in the MURANO study

Source: Michallet et al.(13), Kater et. al.(3), Seymour et al.(4)

5.3.3 Comparative analysis 3a

The Medicines Council protocol of May 16th 2019 specifies that the comparators for clinical question 3 is Clr+OBI and BR respectively. As the systematic literature review revealed that no controlled studies could be found for the efficacy and safety of Clr+OBI in R/R CLL patients. Thus, due to lack of evidence the MABLE and the Green study were included(12, 13).

In the Green study, non-comparative study, ORR was the only efficacy outcome reported for Clr+OBI in R/R CLL patients (12) . Thus, ORR is compared even though, ORR was not included in the Medicines Council protocol of May 16th 2019 Judged by ORR after 6 months, VEN+R has nearly the double efficacy compared to Clr+OBI in R/R CLL patients. Complete response in the GREEN study for R/R CLL was found in 6.5% of patients compared to 26.8 for VEN+R – a factor 4 difference.

Safety seems to be on par between Clr+OBI and VEN+R, but the AEs reported for the GREEN study includes all R/R patients (N=341) with different treatments i.e. investigator's choice of fludarabine-cyclophosphamide for fit patients, chlorambucil for unfit patients, or bendamustine for any patient. The AE grade 3-4 reported for VEN+R from the MURANO study was recorded after end of combination therapy (EOCT) that occurred after 7 months of active therapy with venetoclax, Interpretation should thus take into account, that observation time is 7 months for VEN+R and 6 months for Clr+OBI in table 5.5 above. Further, significantly lower rates of grade 3/4 AE were observed (34.5%) during monotherapy period of the MURANO study. This data suggests similar to slightly higher rates of grade 3-4 AEs during the combination therapy period with venetoclax and rituximab could possibly be due to the addition of i.v. rituximab which could sometimes add more AEs.

In the MABLE study, chlorambucil was given in combination with rituximab (Clr+R) in 59 2nd line CLL patients. Moreover, the MABLE study includes a BR arm and hazard ratios including confidence intervals are available, providing some reference when comparing to results found in the MURANO study. It should be noted that a growing number of studies conclude that Clr+R is inferior to Clr+OBI in first line CLL i.e. a network metanalysis by Städler et al.(21) and the phase III CLL11 trial(22), however no suggestions exist for the 2nd line setting.

PFS at a median follow up of 36 months for VEN+R and after median follow-up of 23.5 months for BR and 23.3 months for Clr+R in the MABLE study, demonstrated an insignificant Hazard Ratio of 0.7 (95%CI 0.43;1.14) for Clr+R vs BR in the MABLE study, while significant HR of 0.16 (95%CI 0.12;0.23) for VEN+R vs BR in the MURANO study. In the MABLE study median PFS for 2nd line CLL patients on Clr+R was reached at 16.9 months, whereas median PFS was not reached for VEN+R R/R patients in the MURANO study after median 36 months follow up. Similarly for overall survival where the MABLE study found insignificant HR: 0.68 (95%CI 0.32;1.46) for Clr+R vs BR and the MURANO study found HR: 0.5 (95%CI 0.3;0.85) for VEN+R vs BR. MRD was measured in connection to confirmation of response at 9 months in MURANO and after 6 cycles in MABLE and found 9% vs 62% for Clr+R and VEN+R respectively. Grade 3-4 AEs were reported for all Clr+R (n=178) patients receiving active treatment in the MABLE study across 1st and 2nd line patients and 64% had grade ≥3

compared to grade 3-4 AEs in 82% of VEN+R treated patients over 2 years in the MURANO study. As duration on active treatment for the MABLE study (6 cycles) and the MURANO study (2 years) differs, it is noted that grade 3-4 AEs were recorded in 74.7% of VEN+R treated patients at EOCT(4).

Clinical question 3b*: What is the clinically added value of venetoclax in combination with rituximab compared to chemoimmunotherapy for patients without deletion17p/p53-mutation, who have relapsed more than 3 years after first treatment? VEN+R vs BR*

5.3.4 Presentation of relevant studies

Please see the description in section 5.1.1

5.3.5 Results per study

Table 5.7: Relevant results from the MURANO study, VEN+R vs BR

OUTCOMES in MR protocol	VEN+R	CI	BR	CI	HR	CI
OS 24 md*	91.9%		86.6%		0.48	[0.25;0.9]
OS, 36 md	87.9%		79.5%		0.5	[0.3;0.85]
PFS, 24 md*	84.9%	[79.1%;90.6%]	36.3%	[28.5%;44%]	0.17	[0.11;0.25]
PFS, 36 md	71%	[0.65;0.78]	15%	[0.09;0.21]	0.16	[0.12;0.23]
Median PFS, 36 md	NR	NR	17	NR		
MRD at 9 months*	62.4%		13.3%			
MRD, best responce, 24 md*	83.5%		23.1%			
uMRD, 24 md EOT	64.0%		13.3%			
uMRD, 17p/TP53, 24 md EOT	56.9%		5.3%			
AE grade 3-4, EOCT, 7 md	74.7%					
AE grade 3-4, EOT 24 md	34.5%					
AE grade 3-4, 24 md*	82.0%		0.702			

Note: VEN=venetoclax, R=rituximab, B=bendamustine
Source: Kater et. al.(3) and *Seymour et al.(4)

5.3.6 Comparative analysis 3b

The MURANO study is an ongoing global, phase III, open-label, randomized study investigating the efficacy and safety of venetoclax-rituximab therapy compared with bendamustine-rituximab in patients with R/R CLL. The study enrolled 389 patients globally—194 patients in the venetoclax-rituximab arm and 195 in the bendamustine-rituximab arm. Kater et al.(3) reported the results as of the 8th of May 2018 data cutoff, with 36 months median follow up and thus 12 months after EOT.

Overall survival in the MURANO after 36 months was 87.9% vs 79.5% for VEN+R and BR respectively, with a HR at: 0.5 (95%CI 0.3;0.85) for VEN+R vs BR.

PFS at a median follow up of 36 months for VEN+R was 71% and 15% and the related HR of 0.16 (95%CI 0.12;0.23) for VEN+R vs BR. Median PFS was not reached for VEN+R R/R patients in the MURANO study after median 36 months follow up, but was 17 months for the BR arm.

MRD was measured in connection to confirmation of response at 9 months. At 9 months 13.3% vs 62% of patients were MRD negative for BR and VEN+R respectively, after 24 months at EOT 13% and 64%.

Grade 3-4 AEs were reported after end of active therapy EOT (82% VEN+R and 70.2% BR), EOCT (74.7% VEN+R) and for the period on VEN monotherapy (34.5% VEN+R). Overall, in patients with R/R CLL, VEN+R was well tolerated by patients, with the majority of patients who had an AE able to continue study treatment. The safety profile of VEN+R was acceptable, predictable and generally consistent with the known safety profiles of venetoclax and rituximab as single agents(18). No new safety signals were observed in the Murano study(3, 4). Higher rates of grade 3 or 4 AEs in the VEN+R group (82%) compared to the BR group (70.2%) were observed. The difference was mainly driven by a higher rate of grade 3 or 4 neutropenia (57.7% vs. 38.8%), notwithstanding the higher rate of neutropenia, the rates of grade 3 infections and infestations (17.5% vs. 21.8%) and febrile neutropenia (3.6% vs. 9.6%) were lower in patients in the VEN+R treatment group compared to those in the BR treatment group(3, 4). Neutropenia was manageable with standard of care measures including growth factor support, dose interruptions and dose reductions(3, 4). The rate of grade 3 or 4 TLS was higher in the VEN+R treatment group compared to the BR treatment group. TLS was reported in 3.1% of patients in the VEN+R group compared with 1.1% in the BR group(3, 4). No laboratory or clinical TLS was observed after addition of rituximab to venetoclax(3, 4).

Table 5.8: Risk ratios and absolute difference between VEN+R and BR, PFS, MRD and AE grade 3-4

Outcome	Ven+R/BR RR			Estimated absolute difference (AD) assuming event rate BR from Murano study			Observed AD	Event rate BR
	HR/RR	CI_low	CI_high	AD	CI_low	CI_high		
OS	0.50	0.30	0.85	9.7%	13.8%	2.8%	8.4%	79.5%
PFS	0.16	0.12	0.23	58.8%	64.6%	49.6%	56.2%	15.2%
MRD	4.68	3.22	6.8	48.9%	29.5%	77.1%	49.0%	13.3%
AE grade 3-4, EOCT	1.06	0.94	1.2	4.2%	-4.2%	14.0%	4.5%	70.2%
AE grade 3-4, EOT	1.17	1.04	1.31	11.9%	2.8%	21.8%	11.7%	70.2%

Note: OS and PFS, computed based on HR from Seymor et al(4), * based on RR computed using RevMan 5.3(23) on frequencies. see appendix 7.3 on Forest plots

For the efficacy outcomes, OS, PFS and MRD, the adjusted least clinically important absolute differences are meet by the outcomes observed in the Murano study. Proportion of AE grade 3-4 was, as noted before, reported both after end of combination therapy EOCT, for the VEN mono therapy part of the study and after end of therapy EOT. Comparing AE grade 3-4 after EOCT, where time at risk was the same in the VEN+R and BR arm of the Murano study, the absolute difference in proportion of patients with AE grade 3-4 was numerically positive (estimated 4.2%, observed 4.5%), but statistically insignificant for VEN+R vs BR. Comparing the proportion of patients with AE grad 3-4 at EOT, where time at risk differs substantially between the two arms of the study (6 cycles vs 24 md), estimated absolute difference is 11.9% (observed 11.7%) and the high confidence interval is 21.8%, and above the adjusted least clinically important absolute difference.

The narrative analysis of VEN+R vs Clr+OBI, showed that in terms of overall response rates, and especially complete response rates, VEN+R has achieved considerably higher proportions (by a factor 2 and 4 for ORR and CR respectively), at similar safety (AE grade 3-4 68.4% and 74.7% at EOCT). These remarkable results are further underpinned when comparing to Clr+R where HRs for OS and PFS vs BR for Clr+R are insignificant and differs from VEN+R vs BR by a factor 4 for PFS. VEN+R patients in the Murano study had MRD rates of 62% compared to 9% of Clr+R, R/R CLL patients in the MABLE study, with slightly higher rates of AE grade 3-4 for VEN+R (82%) compared to Clr+R (62%) but at substantial difference in time at risk between the two therapy options (24 months vs 6 months).

The direct comparison to BR in the Murano study showed that VEN+R would meet the threshold for absolute differences set out in the Medicines Council protocol of May 16th 2019 for OS, PFS and MRD, with HR estimates implying moderate added value on OS and large added value for PFS and MRD. Comparing AE grade 3-4 after EOCT, the difference in proportion of patients with AE grade 3-4 was statistically insignificant for VEN+R vs BR. Comparing at EOT, after 24 months vs 6 months in the BR arm active treatment, VEN+R had slightly higher rates of AEs grade 3-4.

5.4 Quality of life as measured by the EORTC-QLQ-C30

Health related quality of life (HRQoL) measures are included in most studies as exploratory endpoints however are seldomly published at the same time as clinical endpoints from studies. Often HRQoL is only published as conference proceedings, in abstracts, posters and oral presentations. In order to assess the relative HRQoL as measured by the EORTC-QLQ-C30, a pragmatic literature search for conference abstracts was conducted as the systematic literature search only reviled one full text publication.

Data on EORTC-QLQ-C30 from the MURANO study on the VEN+R combination are not available and the early phase NCT01682616 study on VEN+R did not collect patient reported outcomes on HRQoL. The assessment of the HRQoL for venetoclax therapy has therefore been relying on data from studies of VEN monotherapy. This approach has been used and accepted in Sweden, Norway and the UK in the assessments in these markets of the VEN+R combination therapy.

A number of conference proceedings were found reporting on HRQoL for VEN monotherapy, whereas the pragmatic searches did not retrieve data on other therapies included in the Medicines Council protocol of May 16th 2019.

Venetoclax – data on EORTC QLQ-C30 and EORTC QLQ-CLL16

VENICE II (NCT02980731)

The primary objective of the M15-889/VENICE II (NCT02980731) study was to evaluate the impact of venetoclax monotherapy on the quality of life of patients with R/R CLL using the Global Health Status/Quality of Life (GHS/QoL) subscale of EORTC QLQ-C30, whereas the secondary objective was to evaluate the impact of venetoclax monotherapy on quality of life patients using the EORTC QLQ-CLL16(24).

VENICE II was an open-label, phase 3b, multicenter study that assessed patient-reported HRQoL at baseline and every 4 weeks until week 12, at which point they were assessed every 12 weeks. Patients were treated with venetoclax monotherapy using a 5-week dose ramp-up, starting at 20 mg once daily, then increased weekly to 50, 100, 200, and 400 mg, followed by 400 mg once daily(24).

The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Lymphocytic Leukemia Module (EORTC QLQ-CLL16) were used to assess self-reported quality of life metrics(24).

The data cut-off of April 30, 2018 was a pre-planned analysis for the data monitoring committee at which point 22 patients had reached week 48 follow-up.

Table 5.10: VENICE II Key patient enrolment criteria

Inclusion	Exclusion
▪ Age ≥ 18 years ▪ CLL that meets published IWCLL NCI-WG guidelines ▪ R/R disease (has received at least 1 prior therapy) ▪ With or without 17p deletion or TP53 mutation ▪ With or without prior BCRi treatment ▪ ECOG PS 0-2	▪ Richter's transformation or prolymphocytic leukemia ▪ Prior allogenic stem cell transplant ▪ Active or uncontrolled autoimmune cytopenia

BCRi, B cell receptor pathway inhibitor; CLL, chronic lymphocytic leukemia; IWCLL NCI-WG, 2008 modified International Workshop on CLL National Cancer Institute Working Group; ECOG PS, Eastern Cooperative Oncology Group Performance Status; R/R, relapsed/ refractory.

Source: Cochrane et al. 2018(24)

Results

Meaningful improvements in the EORTC-QLQ-C30 subscales from baseline were observed at week 48, especially for fatigue (-10.6), pain (-6.1), role function (+13.6), global health/QoL (+11.4), social function (+9.8), and cognitive function (+5.3).

Meaningful improvements in the EORTC-QLQ-CLL16 subscales from baseline were observed at week 48 for infection (-19.7), social problems (-25.8), disease effects (-17.0), treatment side effects (-6.8), and future health concerns (-21.2).

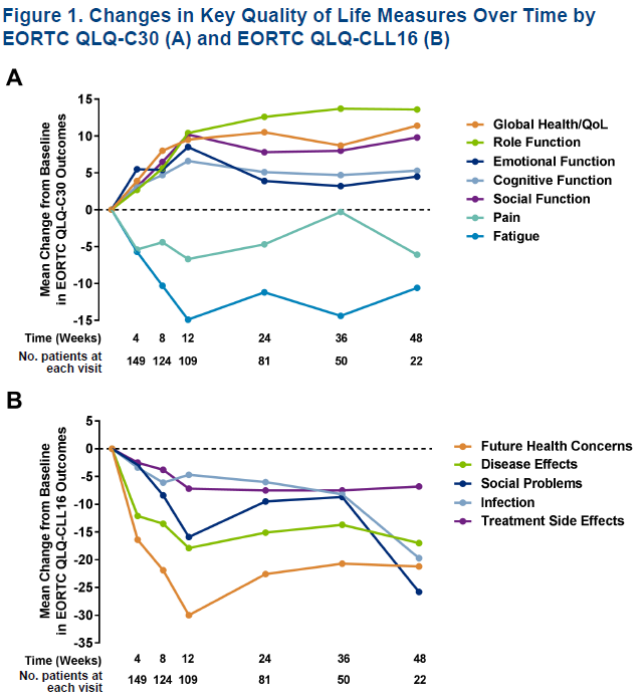
Table 5.11: EORTC QLQ-C30 and CLL16 results

	Baseline Mean (SD) Score	Mean Change (95% CI) From Baseline to Week 48
EORTC QLQ-C30 Parameter	**N=167**	**N=22**
Global Health Status/QoL	61.4 (23.2)	+11.4 (3.1, 19.6)
Role Functioning	72.5 (30.4)[a]	+13.6 (4.1, 23.2)
Emotional Functioning	79.1 (21.4)	+4.5 (-1.2, 10.3)
Cognitive Functioning	83.1 (20.9)	+5.3 (-1.3, 11.9)
Social Functioning	75.5 (28.6)	+9.8 (1.1, 18.6)
Pain[b]	20.7 (26.2)	-6.1 (-14.1, 2.0)
Fatigue[b]	38.6 (26.7)[a]	-10.6 (-20.2, -1.1)
EORTC QLQ-CLL16 Parameter	**N=168**	**N=22**
Future Health Concerns[b]	62.9 (47.9)[c]	-21.2 (-41.9, -0.5)
Disease Effects[b]	30.4 (25.7)	-17.0 (-28.0, -6.1)
Social Problems[b]	33.9 (42.9)[c]	-25.8 (-40.1, -11.4)
Infection[b]	23.4 (25.8)	-19.7 (-31.5, -7.9)
Treatment Side Effects[b]	20.3 (21.6)	-6.8 (-14.5, 0.9)

[a]N = 168; [b]Negative mean change denotes improvement; [c]N = 166.
CI, confidence interval; QoL, quality of life; SD, standard deviation.

Source: Cochrane et al. 2018(24)

Figure 5.12: Change in EORTC QLQ-C30 and CLL16



Source: Cochrane et al. 2018(24)

As with other VEN assessments of health-related quality of life, improvements were seen rapidly after initiation of therapy and already at week 12, meaningful improvements were observed in the EORTC QLQ-C30. Similar rapid onset improvements were seen for the EORTC QLQ-CLL16 rapidly after initiation of therapy and already at week 12, meaningful improvements were observed.

M13-982 study, VEN in CLL R/R 17p deleted patients

Patient-reported HRQoL measures were exploratory endpoints for the Phase 2 M13-982 VEN monotherapy study(1). EORTC QLQ-C30 and -CLL16 were included as exploratory endpoints in the M13-982 study (see section 5.1.1 and appendix 7.1.4 for further details of the M13-982 study).

Wierda and colleagues, published data on the EORTC QLQ-C30 and -CLL16 patient reported outcomes with 96 weeks follow up. Clinically relevant changes were reached as measured by EORTC QLQ-C30, Role functioning, Social and Fatigue dimensions as well as in all dimensions of the CLL16(15).

Figure 5.13: EORTC QLQ-C30 M13-982 study, 96 weeks

Figure 1. Clinically and Statistically Relevant Changes from Baseline in EORTC-QLQ-C30 with VEN Monotherapy

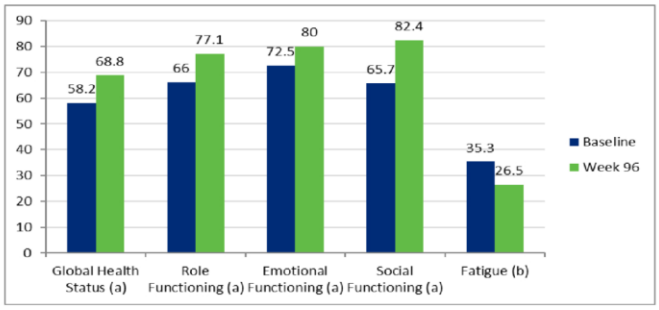
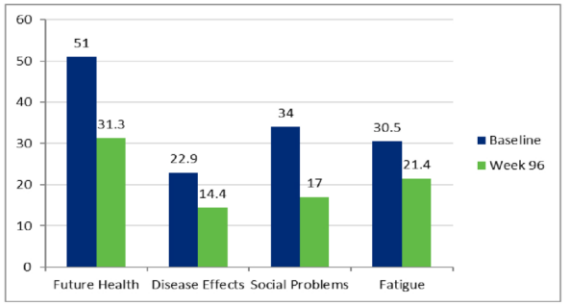


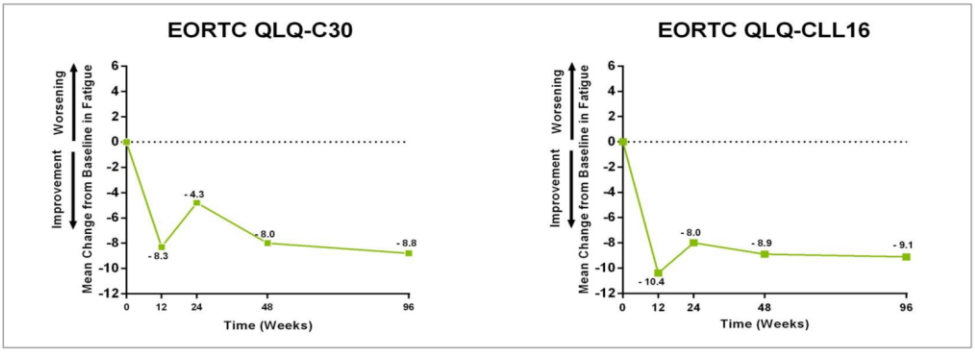
Figure 2. Clinically and Statistically Relevant Changes from Baseline in EORTC-QLQ-CLL-16 with VEN Monotherapy



(a) A positive change in score represents improvement.
(b) A negative change in score represents improvement.

- Of particular note, early and sustained statistically significant and clinically relevant improvements in fatigue were observed in both the EORTC-QLQ-C30 and the EORTC-QLQ-CLL16 (Figure 3).

Figure 3. Clinically and Statistically Relevant Changes from Baseline to Week 96 in Fatigue (EORTC-QLQ-30 and EORTC-QLQ-CLL-16) with VEN Monotherapy



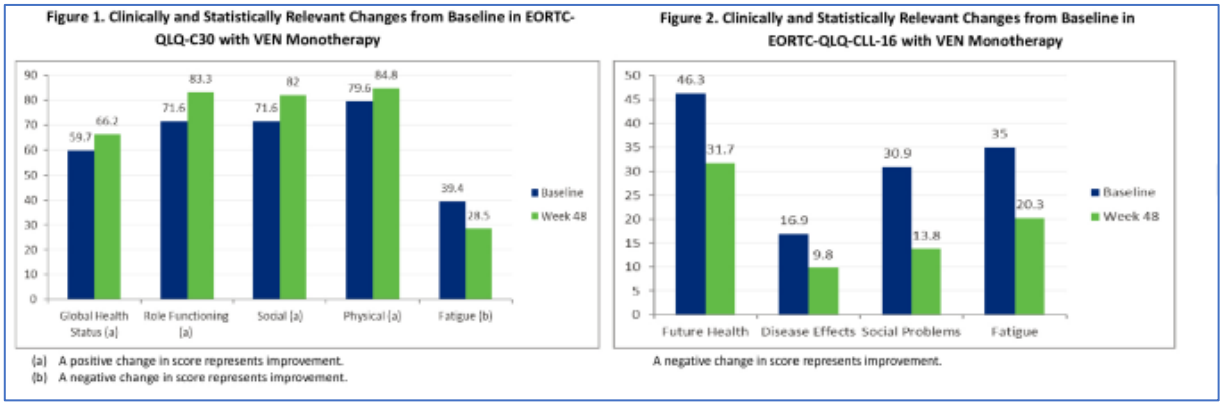
Wierda et al 2017(15)

Importantly Wierda and colleagues reported early onset of effects on fatigue after only 12 weeks active treatment with venetoclax.

M14-032 study, VEN, in CLL BCRi experienced R/R patients

Data for EORTC QLQ-C30 and EORTC QLQ-CLL16 with a follow up of 48 weeks were published by Wierda et al in 2017. After 48 weeks follow up, clinically relevant changes were observed in the EORTC QLQ-C30, Role functioning, Social and Fatigue dimensions as well as in all dimensions of the CLL16 instrument(16).

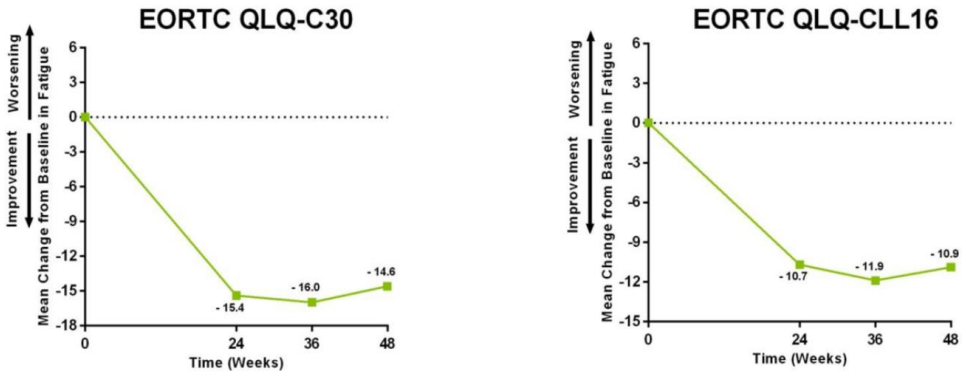
Figure 5.14: EORTC QLQ-C30 NCT02141282 study, 48 weeks



Source: Wierda et al. 2017(16)

A fast onset of improvements in the fatigue dimension of both the EORTC QLQ-C30 and EORTC QLQ-CLL16 and after 24 weeks clinical meaningful improvements of -15.4 and -10.7 points compared to baseline were observed for EORTC QLQ-C30 and EORTC QLQ-CLL16 respectively in the fatigue dimension(16).

Figure 5.15: Improvement in EORTC QLQ-C30 and CLL16 over time



Source: Wierda et al. 2017(16)

Ibrutinib EORTC QLQ-C30 and FACIT-F

In the phase 3 study RESONATE where patients were randomly assigned to receive either ibrutinib or ofatumumab, EORTC QLQ-C30 and FACIT-F was included. Ibrutinib patients across all dimensions of the EORTC QLQ-C30 did experienced improvements, but in no dimension was these observed improvements clinically relevant(6).

Table 5.12: EORTC QLQ-C30 RESONATE

Supplemental Table 2 EORTC QLQ-C30 Domains at Baseline and Week 24

	Ibrutinib (n = 195)			Ofatumumab (n = 196)		
Mean ± SD	Baseline (n = 118)[a]	Week 24 (n = 132)	Δ	Baseline (n = 89)[a]	Week 24 (n = 107)	Δ
Global health status[b]	59.8 ± 24.9	68.3 ± 21.3	9.0 ± 24.1	64.9 ± 22.7	69.5 ± 22.1	5.8 ± 21.5
Role functioning	72.9 ± 31.0	75.8 ± 26.8	4.0 ± 28.2	72.3 ± 30.4	76.3 ± 28.0	6.4 ± 27.1
Emotional functioning	76.9 ± 21.1	78.7 ± 23.9	2.4 ± 19.4	80.3 ± 19.3	81.3 ± 22.1	2.6 ± 16.2
Physical functioning	75.6 ± 23.6	80.6 ± 20.5	6.4 ± 18.0	81.4 ± 20.4	82.0 ± 20.2	1.7 ± 15.7
Cognitive functioning	82.2 ± 21.3	82.1 ± 21.0	0.6 ± 16.2	86.1 ± 20.0	82.6 ± 20.7	−3.0 ± 16.8
Social functioning	74.0 ± 28.3	80.2 ± 25.1	7.5 ± 25.4	75.7 ± 27.3	82.4 ± 21.5	8.1 ± 20.6
Fatigue[c]	35.7 ± 27.8	28.7 ± 24.7	−8.1 ± 22.8	31.2 ± 25.8	27.9 ± 24.8	−4.5 ± 23.4
Nausea/vomiting[c]	4.5 ± 12.8	6.3 ± 15.8	0.6 ± 13.4	4.5 ± 8.6	3.4 ± 8.5	−1.5 ± 9.9
Pain score[c]	19.1 ± 26.8	18.8 ± 26.2	−0.7 ± 23.7	14.0 ± 22.2	16.0 ± 24.7	0.2 ± 22.5
Dyspnea[c]	26.3 ± 29.5	15.7 ± 22.7	−11 ± 26.5	23.6 ± 28.1	15.9 ± 24.4	−9.0 ± 27.0
Insomnia[c]	26.3 ± 31.4	21.7 ± 29.7	−5.6 ± 27.7	27.7 ± 27.6	21.8 ± 26.7	−6.0 ± 23.9
Appetite loss[c]	17.2 ± 24.9	10.1 ± 22.5	−8.5 ± 27.3	22.5 ± 29.2	10.0 ± 18.4	−13.0 ± 26.8
Constipation[c]	11.9 ± 23.7	8.8 ± 22.5	−4.5 ± 25.8	8.6 ± 19.2	7.8 ± 18.6	0.4 ± 22.8
Diarrhea[c]	9.6 ± 20.0	15.2 ± 27.4	5.1 ± 29.8	10.1 ± 22.1	10.9 ± 22.8	−0.4 ± 18.5
Financial difficulties[c]	20.1 ± 30.2	18.2 ± 27.1	−3.1 ± 25.0	15.0 ± 28.4	15.6 ± 26.4	−0.7 ± 22.5

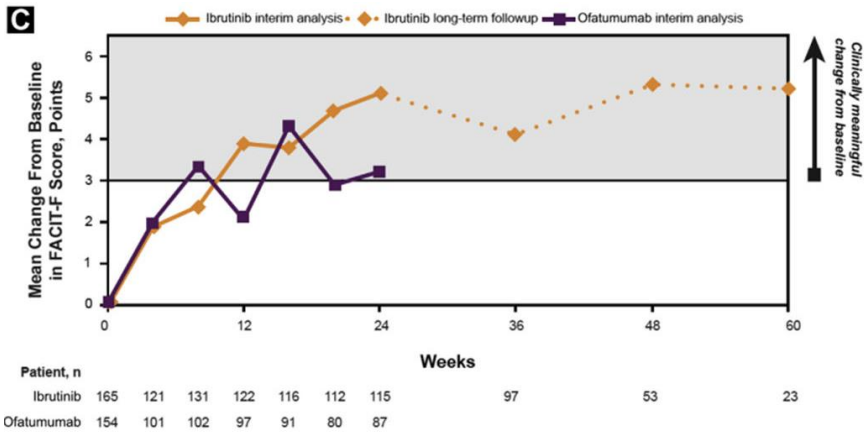
Abbreviations: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30; SD = standard deviation.
[a]Includes patients with assessment at both baseline and week 24.
[b]With ibrutinib, n = 117 at baseline and n = 131 at week 24.
[c]Negative change is an improvement, for all others a positive change is an improvement.

Source: Barrientos et al. 2018(6)

FACIT-F

Baseline FACIT-F scores for ibrutinib and ofatumumab were similar (mean, 35.7 vs. 34.5, respectively). More patients achieved clinically meaningful improvement (+3) in FACIT-F with ibrutinib versus ofatumumab (56% vs. 43%; odds ratio [OR], 1.69; P = .0101); clinically meaningful improvement with ibrutinib was sustained through 60 weeks of follow-up(6).

Figure 5.16: Improvement in FACIT-F scores over time



Source: Barrientos et al.(6)

The hand search for conference proceedings did reveal, HRQoL data for 3 trials with venetoclax monotherapy in R/R CLL patients; after BCRi therapy, with del17p and in a general population with R/R CLL. In general, venetoclax monotherapy had positive and clinically meaningful results on most dimensions of the EORTC QLQ-C30. Data for EORTC QLQ-C30 was found for ibrutinib in a full text publication(6). In the RESONATE study ibrutinib patients across all dimensions of the EORTC QLQ-C30 did experience improvements, but in no dimension were these observed improvements clinically relevant.

Data on EORTC QLQ-C30 was not found for any other comparator included in the Medicines Council protocol of May 16th 2019.

5.5 Discussion

Fixed duration, targeted therapy in CLL

Fixed-treatment duration (FTD) regimens has historically been the standard of care in CLL treatment. However, while allowing for treatment-free intervals for the patient, the termination of these treatment have been a necessity ruled by the tolerability and severe toxicity of historical FTD-treatment options. Data from the MURANO trial demonstrates, for the first time, how a non-chemo based CLL treatment can be safely terminated after a fixed number of cycles with maintained treatment effect(3, 4). Even if a proportion of patients are ultimately destined to develop PD by iwCLL criteria and require subsequent treatment such as venetoclax reintroduction, a number of years off drug would have quality-of-life, toxicity, and societal economic benefit. This would also minimize clonal selection pressure, relevant with other targeted therapies(25-27).

Minimal Residual Disease and deep response in CLL

In the MURANO trial, MRD was considered undetectable (uMRD) if the result was less than 1 CLL cell in 10,000 leukocytes (MRD value <0.0001 × 10-4). Low-MRD was defined as 10-4 to <10-2 and high-MRD was defined as ≥10-2. Higher rates of uMRD with venetoclax-rituximab were achieved at the EOCT response visit and as best MRD response compared with bendamustine-rituximab therapy. The high uMRD response rate was found in all molecular and clinical subsets, including patients with high-risk features, such as del(17p) and/or TP53 mutation. Residual H-MRD was less frequent in the venetoclax-rituximab arm than in the bendamustine-rituximab arm. Patients in each treatment arm with uMRD in PB at the EOCT response visit demonstrated prolonged PFS relative to patients who had detectable MRD. Prolonged PFS was also observed within the group with persistent MRD for those with L-MRD versus those with H-MRD(3, 4). Higher rates of PB uMRD at the EOCT response visit predicted prolonged benefit independent of clinical response, and patients with L-MRD also achieved better outcomes than did those with H-MRD. In the venetoclax-rituximab arm, high rates of uMRD were also sustained over time, and the vast majority of these patients remained PD free after drug cessation. These findings also confirm attainment of PB uMRD as a surrogate for PFS among patients who are treated with venetoclax-rituximab, which is in support of multiple studies as well as recently updated guidelines(3, 4).

MRD is an established surrogate outcome in chemo-immune therapy, multiple studies have demonstrated that achieving MRD below 10^{-4} CLL cells per leukocyte in the blood and/or bone marrow (i.e. undetectable MRD or MRD negativity) corresponds to longer PFS(28-30).

In December 2015, the European Medicines Agency (EMA) has included undetectable MRD as an intermediate endpoint in a revision document to appendix 4 to the guideline on the evaluation of anticancer medicinal products in human. EMA states that *"undetectable MRD in patients with CLL in clinical complete remission (= MRD response rate) after induction therapy may be used as an intermediate endpoint for licensure in randomised well controlled studies designed to show superiority in terms of PFS"*(31).

Furthermore, MRD is highlighted in different medical society guidelines. The CLL guidelines of the CLL group under the Danish Lymphoma society states regarding MRD negativity as the future surrogate for OS: "Det må forventes, at der fremover tilkommer MRD (minimal residual disease) negativ som surrogatmarkør for OS".

The CLL guidelines of the British Society for Haematology (BSH) present MRD as a factor which affects prognosis, based on studies reporting longer remission, improved OS and PFS for patients with undetectable MRD(32). Furthermore, the updated International Workshop on CLL (iwCLL) guidelines in March 2018, underscores the importance of MRD in CLL: According to the iwCLL update; "*Prospective clinical trials have provided substantial evidence that therapies that are able to eradicate MRD usually result in an improved clinical outcome*"(33).

Therapy-free intervals affects development of toxicity

As CLL is still an incurable disease, life-long treatment is the reality for the vast majority of CLL patients where treatment is needed. Treatment affects quality of life in many ways and in particular in terms of therapy-related toxicity(34-36). Although newer, targeted treatments have a milder toxicity-profile than CIT, they require continuous treatment until progression. Long-term safety follow-up of ibrutinib treated patients demonstrate that tolerability is a major reason for discontinuation, and higher in clinical practice compared to clinical trial setting(25, 37). Thus, treatment-free interval is an effective way of alleviating the burden of treatment-emergent toxicity and thus increase quality of life. An added benefit of FTD therapy such as venetoclax plus rituximab, is to protect the efficacy of subsequent treatments since prolonged therapy also exerts strong selective pressure, which can promote the eventual outgrowth of resistant subclones(27). As with any cancer cell, CLL cells have high intrinsic ability to adapt and find ways to survive. The most fit clones are being selected under the pressure of treatment and may result in the domination of more aggressive, or treatment-resistant clones which in turn can reduce the efficacy of subsequent treatments needed(27).

A unique combination

Current treatment options in second line treatment of CLL entails either fixed- duration CIT or continuous indefinite targeted therapy. Venetoclax plus rituximab is the first and only approved fixed-duration targeted therapy with a favorable safety profile and substantial clinical benefit. Venetoclax plus rituximab has achieved the highest rate of MRD negative responses observed so far in a randomized prospective study in second line CLL, correlating as a surrogate for a longer OS. Even if a proportion of patients are ultimately destined to develop PD by iwCLL criteria and require treatment, a number of years off drug would have quality-of-life, toxicity, and societal economic benefit.

6 Conclusion

The Medicines council outlined 3 clinical questions to be answered in this application for recommendation to be used as standard of care in Danish hospitals:

What is the clinically added value of venetoclax in combination with rituximab compared to venetoclax mono therapy for patients with deletion17p/p53-mutation, in R/R CLL patients after ibrutinib?

- In R/R CLL patients with del17p, fixed treatment duration with venetoclax in combination with 6 cycles of rituximab, has in the MURANO study achieved better results on OS, PFS and MRD negativity compared to infinite continuous venetoclax monotherapy. Recorded rates of AE grade 3-4 were similar for VEN+R study compared VEN monotherapy and the safety profile of VEN+R was consistent with the known safety profiles of venetoclax and rituximab as single agents.

What is the clinically added value of venetoclax in combination with rituximab compared to ibrutinib in 2nd line therapy for patients treated with chemoimmunotherapy in 1st line.?

- In a recently published indirect therapy comparison, fixed treatment duration with venetoclax in combination with rituximab was found to have numerically better but not statistically significant OS rates to infinite continuous treatment with ibrutinib. PFS was numerically similar to ibrutinib but not statistically significant. Deep response through MRD negativity rates with VEN+R are substantially higher compared to ibrutinib, while rates of grade 3-4 AEs are slightly higher however the safety profile of VEN+R was consistent with the known safety profiles of venetoclax and rituximab as single agents.

Clinical question 3: What is the clinically added value of venetoclax in combination with rituximab compared to chemoimmunotherapy for patients without deletion17p/p53-mutation, who have relapsed more than 3 years after first treatment?

- Narrative analysis of venetoclax plus rituximab compared to chlorambucil plus obinutuzumab, demonstrated large scale improvements in overall response rates, and especially complete response rates, at similar rates of grade 3-4 AEs.
- In direct comparison to bendamustine plus rituximab venetoclax in combination with rituximab efficacy in terms of OS, PFS and MRD would meet the threshold for absolute differences set out in the Medicines Council protocol and with hazard ratio estimates implying moderate added value on OS and large added value for PFS and MRD. Comparing AE grade 3-4 after EOCT, the difference in proportion of patients with AE grade 3-4 was statistically insignificant for VEN+R vs BR. Comparing at EOT, after active treatment of 24 months vs 6 months in the BR arm, VEN+R had slightly higher rates of AEs grade 3-4, but below the adjusted least clinically important absolute difference set out by the Medicines Council.

Data on health-related quality of life for venetoclax in combination with rituximab has not been published, but large amounts of data was found for venetoclax monotherapy. Assessment of the data supporting venetoclax demonstrated clinically meaningful improvements as measured by EORTC QLQ-C30 both in short- and long-term data. One study reporting data on EORTC QLQ-C30 for ibrutinib was found and showed that across all dimensions of the EORTC QLQ-C30 patients did experience improvements, but in no dimension were these observed improvements clinically relevant.

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7 Appendices

7.1 Literature search

Table A1: Inclusion and exclusion criteria

Inklusions- og eksklusionskriterier

De inkluderede studier skal være randomiserede kontrollerede forsøg og skal stemme overens med de kliniske spørgsmål, hvad angår de beskrevne populationer, komparatorer og indeholde minimum et relevant effektmål. Studier, som er fase I- og IIa-studier, ekskluderes.

Note: From the Medicine council protocol regarding in- and exclusion

Search strategy: MEDLINE (Pubmed) and CENTRAL (Cochrane Library) Date: 28th May, 2019

PubMed Results

Search	Query	Items found
#28	Search (#26 not #27)	87
#27	Search (case report[ti] or Case Reports[pt] or Comment[pt] or Editorial[pt] OR Review[Publication Type] OR Systematic Review[pt])	5544372
#26	Search (#24 and #25)	182
#25	Search (Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti])	1260082
#24	Search (#22 not #23)	1269
#23	Search (Animals[mh] not Humans[mh])	4583360
#22	Search (#6 and #21)	1272
#21	Search (#7 or #8 or #9 or #10 or #15 or #20)	2783
#20	Search ((#16 or #17) and (#18 or #19))	618
#19	Search (rituximab[tiab] or Mabthera*[tiab] or Rituxan*[tiab] or GP-2013[tiab] or GP2013[tiab] or IDEC-C2B8[tiab] or IDECC2B8[tiab])	18887
#18	Search Rituximab[mh]	12631
#17	Search (bendamustin*[tiab] or Levact*[tiab] or Treanda*[tiab])	1085
#16	Search Bendamustine Hydrochloride[mh]	683
#15	Search ((#11 or #12) and (#13 or #14))	99
#14	Search (obinutuzumab[tiab] or Gazyva*[tiab] or afutuzumab[tiab] or GA-101[tiab] or GA101[tiab] or RO-5072759[tiab] or RO5072759[tiab])	390
#13	Search obinutuzumab[nm]	177
#12	Search (chlorambucil[tiab] or Leukeran*[tiab] or NSC-3088[tiab] or NSC3088[tiab])	3151
#11	Search Chlorambucil[mh]	3740
#10	Search (ibrutinib[tiab] or Imbruvica*[tiab] or PCI-32765[tiab] or PCI32765[tiab])	1569
#9	Search PCI 32765[nm]	774
#8	Search (venetoclax[tiab] or Venclyxto*[tiab] or Venclexta*[tiab] or ABT-199[tiab] or ABT199[tiab] or GDC-0199[tiab] or GDC0199[tiab] or RG-7601[tiab] or RG7601[tiab])	692
#7	Search venetoclax[nm]	285
#6	Search (#1 or #2 or #3 or #4 or #5)	25479
#5	Search (chronic b-cell leukemia[tiab] or chronic b-cell leukaemia[tiab])	80
#4	Search (chronic lymphoblastic leukemia[tiab] or chronic lymphoblastic leukaemia[tiab])	71
#3	Search (chronic lymphatic leukemia[tiab] or chronic lymphatic leukaemia[tiab])	1361
#2	Search (CLL[tiab] or chronic lymphocytic leukemia[tiab] or chronic lymphocytic leukaemia[tiab])	21650
#1	Search Leukemia, Lymphocytic, Chronic, B-Cell[mh]	15304

Results from the Cochrane Central Trials

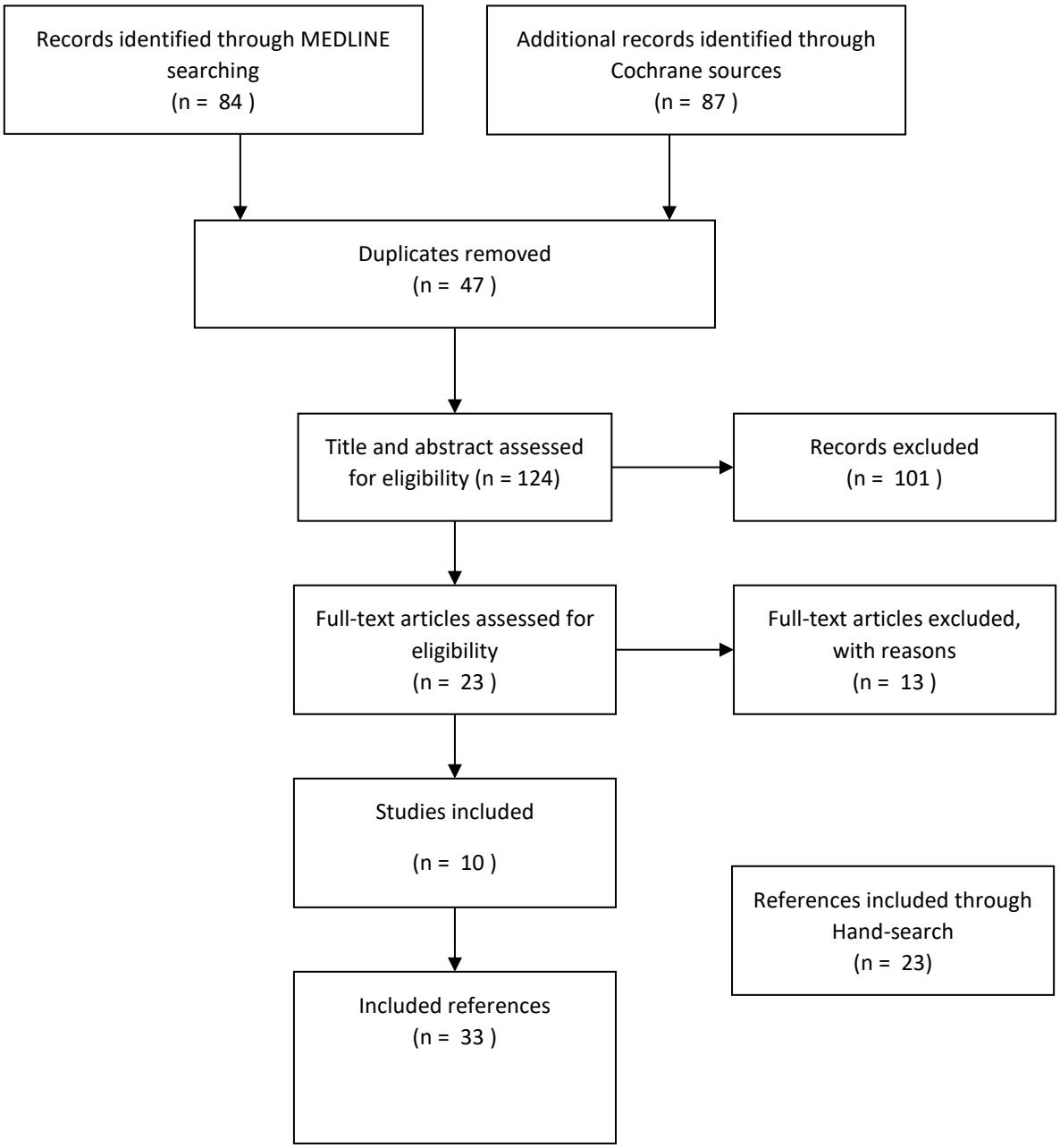
ID	Search	Hits
#1	[mh "Leukemia, Lymphocytic, Chronic, B-Cell"]	386
#2	(chronic next (lymphatic or lymphoblastic or lymphocytic or b-cell) next (leukemia or leukaemia)):ti,ab,kw or CLL:ti,ab	1767
#3	#1 or #2	1816
#4	(venetoclax or Venclyxto* or Venclexta or ABT-199 or ABT199 or GDC-0199 or GDC0199 or RG-7601 or RG7601):ti,ab,kw	167
#5	(ibrutinib or Imbruvica* or PCI-32765 or PCI32765):ti,ab,kw	425
#6	(chlorambucil or Leukeran* or NSC-3088 or NSC3088):ti,ab,kw	670
#7	(obinutuzumab or Gazyva* or afutuzumab or GA-101 or GA101 or RO-5072759 or RO5072759):ti,ab,kw	264
#8	#6 and #7	60
#9	(bendamustin* or Levact* or Treanda*):ti,ab,kw	605
#10	(rituximab or Mabthera* or Rituxan* or GP-2013 or GP2013 or IDEC-C2B8 or IDECC2B8):ti,ab,kw	4299
#11	#9 and #10	411
#12	#4 or #5 or #8 or #11	882
#13	#3 and #12	425
#14	("conference abstract" or review):pt	171315
#15	NCT*:au	136410
#16	("clinicaltrials gov" or trialsearch):so	253836
#17	#14 or #15 or #16	425211
#18	#13 NOT #17 in Trials in Trials	84

7.1.1 List of excluded articles

Title	Publication	Reason for exclusion
Bendamustine followed by obinutuzumab and venetoclax in chronic lymphocytic leukaemia (CLL2-BAG): primary endpoint analysis of a multicentre, open-label, phase 2 trial	Cramer. P et al. Lancet Oncol. Issue 9, Pages 1215-1228. 2018	Single-arm Phase 2 study. Intervention not in scope
CLL2-BIG - A novel treatment regimen of bendamustine followed by GA101 and ibrutinib followed by ibrutinib and GA101 maintenance in patients with chronic lymphocytic leukemia (CLL): results of a phase ii-trial	Tresckow et al. Blood 2015 126:4151, 2015	Single-arm Phase 2 study. Intervention not in scope
Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: a phase 2, single-arm trial	Farooqui et al. Lancet Oncol. Issue 2, Pages 169-176. 2015	Single-arm Phase 2 study
Ibrutinib versus previous standard of care: an adjusted comparison in patients with relapsed/refractory chronic lymphocytic leukaemia	Hansson L et al. Annals of Hematology. 2017	Not original data. Data from observational study and Resonate
Ibrutinib versus rituximab in relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma: a randomized, open-label phase 3 study	Huang X et al. Cancer medicine. 2018	Out of scope. Comparator not included in PICO. Populationen excluded
Long-term Follow-up of Treatment with Ibrutinib and Rituximab in Patients with High-Risk Chronic Lymphocytic Leukemia	Jain P et al. Clinical Cancer research 2016	Phase 2 study. Populationen too small.
Ofatumumab and bendamustine in previously treated chronic lymphocytic leukemia and small lymphocytic lymphoma	Ujjani C et al. Leukemia & lymphoma. 2015	Phase 2 study. Intervention not in scope.
A phase I dose-ranging study of bendamustine and rituximab in chronic lymphocytic leukemia patients with comorbidities	Danilov A.V et al. British journal of haematology. 2017	Phase 1 dose-ranging study.
Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia	Roberts A et al. N Engl J med. 2016	Phase 1 dose-escalation study
Tolerability and activity of ublituximab, umbralisib, and ibrutinib in patients with chronic lymphocytic leukaemia and non-Hodgkin lymphoma: a phase 1 dose escalation and expansion trial	Nastoupil L.J et al. Lancet Haematology. 2019	phase 1 dose escalation study
Ublituximab (TG-1101), a novel glycoengineered anti-CD20 antibody, in combination with ibrutinib is safe and highly active in patients with relapsed	Sharman J.P et al. British journal of haematology. 2017	Single arm phase 2 study. Intervention not in scope

Title	Publication	Reason for exclusion
and/or refractory chronic lymphocytic leukaemia: results of a phase 2 trial		
Minimal residual disease assessment improves prediction of outcome in patients with chronic lymphocytic Leukemia (CLL) who achieve partial response: comprehensive analysis of two phase III Studies of the German CLL Study Group	Kovac G et al. Journal of clinical oncology 2016.	Not original data
Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia	Burger J.A et al, Blood, 2019	Mixed population. Included untreated patients

7.1.2 PRISMA Flow Diagram



7.1.3 Included references

1st author and reference	Title	Study arms		Clinical Question
Barrientos, J. C.(6)	Improvement in Parameters of Hematologic and Immunologic Function and Patient Well-being in the Phase III RESONATE Study of Ibrutinib Versus Ofatumumab in Patients With Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma	IBR vs OFA	RESONATE	Q2
Brown, J. R.(7)	Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE study in patients with previously treated CLL/SLL	IBR vs OFA	RESONATE	Q2
Byrd JC(8)	Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab	IBR vs OFA	RESONATE	Q2
Chanan-Khan, A.(10)	Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study.	IBR + BR vs BR	HELIOS	Q2
Fraser, G.(11)	Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine, and rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma	IBR + BR vs BR	HELIOS	Q2
Kater, A. P.(3)	Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III Study	VEN+R vs B+R	MURANO	All questions
Leblond, V.(12)	Safety of obinutuzumab alone or combined with chemotherapy for previously untreated or relapsed/refractory chronic lymphocytic leukemia in the phase IIIb GREEN study	OBI OBI+FC OBI+B OBI+CHL	GREEN	Q3a
Michallet, A. S.(13)	Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study	B+R vs CHL+R	MABLE	Q3a
Seymour, J. F.(4)	Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia.	VEN+R vs B+R	MURANO	All questions
Byrd et al.(9)	Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia	IBR	RESONATE	Q2
Hand searched references				
Wierda et al(16)	Impact of Venetoclax on the Quality of Life of CLL patients Relapsed/refractory to B-cell Receptor (BCR) signaling Pathway inhibitor treatment.	VEN	M14-032	QoL
Freise et al.(17)	Relationship between venetoclax exposure, rituximab coadministration, and progression-free survival in patients with relapsed or refractory chronic lymphocytic leukemia: demonstration of synergy.	VEN	NA	Q1
Hillmen et al.(19)	Comparing Single-Agent Ibrutinib, Bendamustine Plus Rituximab (BR) and Ibrutinib Plus BR in Patients with Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL): An Indirect Comparison of the RESONATE and HELIOS Trials.	IBR	HELIOS and RESONATE	Q2
Chen et al.(20)	Treatment Outcomes of Novel Targeted Agents in Relapse/Refractory Chronic Lymphocytic Leukemia: A Systematic Review and Network Meta-Analysis.	VEN+R and IBR	NA	Q2
Städler et al.(21)	A Systematic Review and Network Meta-Analysis to Evaluate the Comparative Efficacy of Interventions for Unfit Patients with Chronic Lymphocytic Leukemia.	NA	NA	Q3b
Goede et al.(22)	Overall survival benefit of obinutuzumab over rituximab when combined with chlorambucil in patients with chronic	NA	CLL11	Q3a

1st author and reference	Title	Study arms		Clinical Question
	lymphocytic leukemia and comorbidities: final survival analysis of the CLL11 study.			
Cochrane et al.(24)	Venetoclax Improves Quality of Life for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia.	VEN	VENICE II	QoL
Wierda et al.(15)	Impact of Venetoclax on the Quality of Life in patients with Relapsed/refractory Chronic Lymphocytic Leukemia: Results of a Phase 2, Open-label Study of Venetoclax (ABT-199/GDC-0199) Monotherapy.	VEN	M13-982	QoL
Mato et al.(25)	Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis.	IBR	NA	Discussion
Chen et al.(26)	Economic Burden of Chronic Lymphocytic Leukemia in the Era of Oral Targeted Therapies in the United States.	NA	NA	Discussion
Landau et al.(27)	The evolutionary landscape of chronic lymphocytic leukemia treated with ibrutinib targeted therapy.	NA	NA	Discussion
Owen et al.(28)	Use of minimal residual disease assessment in the treatment of chronic lymphocytic leukemia.	NA	NA	Discussion
Kovacs et al(29)	Minimal Residual Disease Assessment Improves Prediction of Outcome in Patients With Chronic Lymphocytic Leukemia (CLL) Who Achieve Partial Response: Comprehensive Analysis of Two Phase III Studies of the German CLL Study Group.	NA	NA	Discussion
Bottcher et al.(30)	Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: a multivariate analysis from the randomized GCLLSG CLL8 trial.	NA	CLL8	Discussion
Oscier et al.(32)	Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia.	NA	NA	Discussion
Hallek et al.(33)	iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL.	NA	NA	Discussion
Molica et al.(34)	Quality of life in chronic lymphocytic leukemia: a neglected issue.	NA	NA	Discussion
Shanafelt et al.(35)	Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients.	NA	NA	Discussion
Else et al.(36)	Quality of life in chronic lymphocytic leukemia: 5-year results from the multicenter randomized LRF CLL4 trial.	NA	CLL4	Discussion
Coutre et al.(37)	Long-term safety of single-agent ibrutinib in patients with chronic lymphocytic leukemia in 3 pivotal studies.	IBR	NA	Discussion
Stilgenbauer et al.2018(2)	Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial.	VEN	M13-982	Q1
Stilgenbauer et al.(1)	Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study	VEN	M13-982	Q1
Jones, J. A.(5)	Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial	IBR->VEN IBR or IDA -> VEN IDA -> VEN	M14-032	Q1

Note: IBR=Ibrutinib, OFA=Ofatumumab, R=Rituximab, B=bendamustine, OBI= obinutuzumab, VEN=venetoclax, IDA=idealisib, FC= fludarabine-cyclophosphamide, CHL= chlorambucil

7.1.4 Main characteristics of included studies

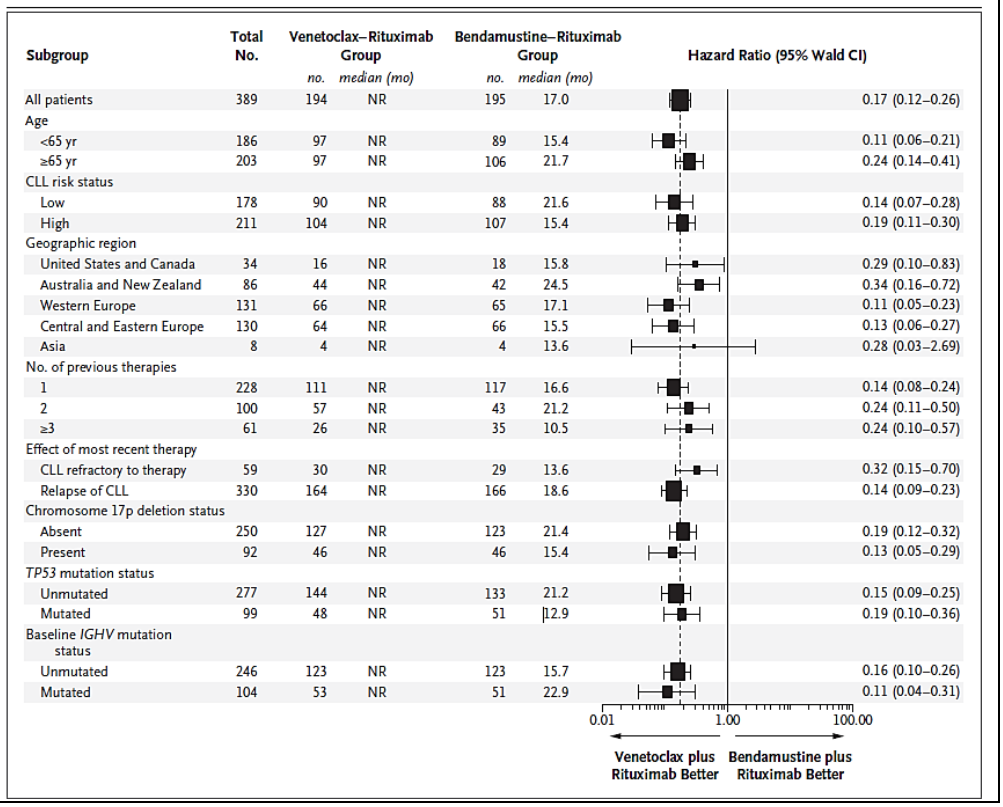
Table 2A: MURANO

Trial name	MURANO
NCT number	NCT02005471
Objective	To evaluate the benefit of venetoclax in combination with rituximab compared with bendamustine in combination with rituximab in participants with relapsed or refractory CLL.
Publications – title, author, journal, year	Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: post-treatment follow-up of the Murano phase III study. Kater PA, Seymour JF, Hillmen P, Eichhorst B, Langerak AW, Owen C, Verdugo M, Wu J, Punnoose EA, Jiang Y, Wang, J, Boyer M, Humphrey K, Mobasher M, Kipps TJ. J of Clinocal Oncology. 2019 Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. Seymour JF, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Assouline S, Owen C, Gerecitano J, Robak T, De la Serna J, Jaeger U, Cartron G, Montillo M, Humerickhouse R, Punnoose EA, Li Y, Boyer M, Humphrey K, Mobasher M, Kater AP. N Engl J Med. 2018. Jones AK, Freise KJ, Agarwal SK, Humerickhouse RA, Wong SL, Salem AH. Clinical Predictors of Venetoclax Pharmacokinetics in Chronic Lymphocytic Leukemia and Non-Hodgkin's Lymphoma Patients: a Pooled Population Pharmacokinetic Analysis. AAPS J. 2016 Sep;18(5):1192-202. Doi: 10.1208/s12248-016-9927-9. Epub 2016 May 27.
Study type and design	Multicenter, Phase III, Open-Label, Randomized Study. Participants will be randomly assigned in 1:1 ratio to receive either venetoclax + rituximab (Arm A) or bendamustine + rituximab (Arm B). Randomization was stratified according to the presence or absence of chromosome 17p deletion, responsiveness to previous therapy and geographic region. Crossover to treatment with venetoclax and rituximab was not permitted and therapy after the occurrence of disease progression was at the investigator's discretion.AbbVie and Genentech/Roche have amended the trial protocol to allow patients who have progressed after finishing treatment to be retreated with or crossed over to the venetoclax + rituximab arm (data on file). Study still active for follow-up, but not recruiting patients.
Follow-up time	Primary analysis: Median follow-up time 23.8 months (range 0.0 – 37.4) Update 36 months: Median follow-up time 36 months
Population (inclusion and exclusion criteria)	Inclusion criteria: •Diagnosis of CLL per diagnostic criteria for relapsed or refractory CLL per the international workshop on chronic lymphocytic leukemia (iwCLL) guidelines •Previously treated with 1-3 lines of therapy (example: completed greater than or equal to [>/=] 2 treatment cycles per therapy), including at least one standard chemotherapy-containing regimen •Participants previously treated with bendamustine only if their duration of response was >/= 24 months •Eastern Cooperative Oncology Group (ECOG) performance score of less than or equal to (</=) 1 •Adequate bone marrow function •Adequate renal and hepatic function •Participants must use effective birth control throughout study until at least 30 days after study treatment or 1 year after rituximab treatment, whichever is later; female participants must not be pregnant or breast-feeding •For participants with the 17p deletion, previously treated with 1-3 lines of therapy, including at least one prior standard chemotherapy-containing regimen or at least one prior alemtuzumab-containing therapy Exclusion criteria:

<table>
<tr><td>Trial name</td><td>MURANO</td></tr>
<tr><td>NCT number</td><td>NCT02005471</td></tr>
<tr><td></td><td>•Transformation of CLL to aggressive non-Hodgkin lymphoma or central nervous system (CNS) involvement by CLL
•Undergone an allogenic stem cell transplant
•A history of significant renal, neurologic, psychiatric, endocrine, metabolic, immunologic, cardiovascular or hepatic disease
•Hepatitis B or C or known human immunodeficiency virus (HIV) positive
•Receiving warfarin treatment
•Received an anti-CLL monoclonal antibody within 8 weeks prior to the first dose of study drug
•Received any anti-cancer or investigational therapy within 28 days prior to the first dose of study drug or has not recovered to less than Grade 2 clinically significant adverse effect(s)/toxicity(ies) of any previous therapy
•Received cytochrome P450 3A4 (CYP3A4) inhibitors (such as fluconazole, ketoconazole and clarithromycin) or inducers (such as rifampin, carbamazapine, phenytoin, St. John's Wort) within 7 days prior to the first dose of venetoclax
•History of prior venetoclax treatment
•Participants with another cancer, history of another cancer considered uncured on in complete remission for <5 years, or currently under treatment for another suspected cancer except non-melanoma skin cancer or carcinoma in situ of the cervix that has been treated or excised and is considered resolved
•Malabsorption syndrome or other condition that precludes enteral route of administration
•Other clinically significant uncontrolled condition(s) including, but not limited to, systemic infection (viral, bacterial or fungal)
•Vaccination with a live vaccine within 28 days prior to randomization
•Consumed grapefruit or grapefruit products, seville oranges (including marmalade containing seville oranges), or star fruit within 3 days prior to the first dose of study treatment
•A cardiovascular disability status of New York Heart Association Class >/=3. Class 3 is defined as cardiac disease in which participants are comfortable at rest but have marked limitation of physical activity due to fatigue, palpitations, dyspnea, or anginal pain
•Major surgery within 30 days prior to the first dose of study treatment
•A participant who is pregnant or breastfeeding
•Known allergy to both xanthine oxidase inhibitors and rasburicase</td></tr>
<tr><td>Intervention</td><td>Venetoclax + rituximab
Dose:
Participants will be initially placed on a venetoclax 5 weeks ramp-up period, and will receive an initial dose of 20 milligrams (mg) via tablet orally once daily (QD). Then the dose will be incremented weekly up to a maximum dose of 400 mg. Participants will then continue receiving venetoclax 400 mg QD from Week 6 (Day 1 of Cycle 1 of combination therapy) onwards, as directed by the investigator, in combination with rituximab 375 mg/m^2 via IV infusion on Day 1 of Cycle 1 followed by 500 mg/m^2 on Day 1 of Cycles 2-6.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Characteristics</th><th>Venetoclax plus rituximab n=194</th><th>Bendamustine plus rituximab n=195</th></tr>
<tr><td>Sex, n (%)</td><td></td><td></td></tr>
<tr><td>Male</td><td>136 (70.1)</td><td>151 (77.4)</td></tr>
<tr><td>Female</td><td>58 (29.9)</td><td>44 (22.6)</td></tr>
<tr><td>Age, years</td><td></td><td></td></tr>
<tr><td>Median</td><td>64.5</td><td>66.0</td></tr>
<tr><td>Min-max</td><td>28-83</td><td>22-85</td></tr>
<tr><td>ECOG score, n (%)</td><td></td><td></td></tr>
<tr><td>N</td><td>194</td><td>194</td></tr>
<tr><td>0</td><td>111 (57.2)</td><td>108 (55.7)</td></tr>
<tr><td>1</td><td>82 (42.3)</td><td>84 (43.3)</td></tr>
<tr><td>2</td><td>1 (0.5)</td><td>2 (1.0)</td></tr>
<tr><td>Rai staging at diagnosis</td><td></td><td></td></tr>
<tr><td>N</td><td>130</td><td>140</td></tr>
<tr><td>Stage 0-II</td><td>88 (67.7)</td><td>103 (73.6)</td></tr>
<tr><td>Stage III-IV</td><td>30 (23.1)</td><td>18 (12.9)</td></tr>
</table>
</td></tr>
</table>

	Fludarabine refractory, n (%)		
	N	191	194
	Yes	27 (14.1)	30 (15.5)
	No	164 (85.9)	164 (84.5)
	Creatinine clearance, n (%)		
	N	194	195
	<50 mL/min	6 (3.1)	10 (5.1)
	>50mL/min	188 (96.9)	185 (94.9)
	Baseline tumor lysis syndrome risk, n (%)	194	195
	N	54 (27.8)	55 (28.2)
	High	106 (54.6)	104 (53.3)
	Medium	34 (17.5)	36 (18.5)
	Low		
	Absolute lymphocyte count, x 10^9/L		
	<25	65 (33.5)	61 (31.3)
	Platelets, x 10^9/L		
	Median (min-max)	113.0 (13.0 – 419.0)	123.5 (11.0 – 457.0)
	<100 x 10^9/L, %	42.8	33.5
	Hemoglobin, g/dL		
	Median (min- max)	11.4 (5.5 – 16.7)	12.0 (6.8 – 16-1)
	<10 g/dL, %	31.4	19.1
	del(17p)status, n (%)		
	N	173	169
	Absent	127 (73.4)	123 (72.8)
	Present	46 (26.6)	46 (27.2)
	TP53 mutation		
	N	192	184
	Mutated	48 (25.0)	51 (27.7)
	Unmutated	144 (75.0)	133 (72.3)
	del(17p vs. TP53 mutation status, n/N (%)	171	158
		24 (14.0)	18 (11.4)
	Only del(17p)	19 (11.1)	23 (14.6)
	TP53 Mutation only	22 (12.9)	22 (13.9)
	del(17p) and TP53 mutated		
	IGHV mutational status, n (%)		
	N	180	180
	Mutated	53 (29.4)	51 (28.3)
	Unmutated	123 (68.3)	123 (68.3)
	Stratification factor: risk status (derived), n (%)	194	195
	N	109 (56.2)	118 (60.5)
	High	84 (43.3)	75 (38.5)
	Low		
	Number of prior CLL therapies, n (%)		
	N	194	195
	1	111 (57.2)	117 (60.0)
	2	57 (29.4)	43 (22.1)
	3	22 (11.3)	34 (17.4)
	>3	4 (2.1)	1 (0.5)
	Type of prior CLL therapies, n (%)		
	Alkylating agent	182 (93.3)	185 (95.4)
	Purine analogue	157 (80.5)	158 (81.4)
	Anti-CD20 antibody	153 (78.5)	148 (76.3)
	B-cell receptor inhibitors	5 (2.6)	3 (1.5)
Primary and secondary endpoints	**Primary endpoint:**		

Trial name	MURANO
NCT number	NCT02005471
	Investigator assessed progression-free survival (PFS) -PFS defined as time from randomization to the first occurrence of disease progression or relapse or death from any cause, whichever occurred first. **Secondary endpoints:** Independent-review committee (IRC) PFS Investigator and IRC assessed PFS in patients with chromosome 17p deletion Investigator and IRC assessed overall response rate (ORR), complete response (CR) rate, overall survival (OS), minimal residual disease (MRD) clearance, Investigator assessed duration of response (DOR), event-free survival (EFS), Time To Next Treatment (TTnT)
Method of analysis	Efficacy analyses were based on the intention-to-treat population (ITT). Three sensitivity analyses of investigator-assessed PFS and IRC-assessed PFS were conducted to test for the potential impact of differences in modeling or censoring approaches: 1. An unstratified log-rank test 2. PFS analyses with censoring at initiation of nonprotocol−specified anti-CLL therapy before meeting disease progression criteria to assess potential confounding of treatment effect estimates by subsequent therapy 3. PFS analyses with censoring of death or disease progression after more than one missed response assessment at the date of last adequate response assessment. To adjust for multiple testing, the prespecified hierarchical testing of three key secondary efficacy endpoints was used in the following order: IRC-assessed CR/CR with incomplete hematologic recovery (CRi); IRC-assessed ORR; and OS. Because the study met its primary endpoint, a formal statistical test of IRC-assessed CR/CRi rate between the two arms was performed at the two-sided significance level of 0.05 using a stratified Cochran–Mantel–Haenszel test. As this endpoint was not statistically significant, P-values for the subsequent hierarchically tested endpoints could only be considered descriptive. Distributions of time-to-event endpoints, including PFS, OS, EFS and TTNT were estimated by the Kaplan–Meier method. All randomized patients were included in the efficacy analyses (ITT population). All randomized patients who received at least one dose of study drug were included in the safety analyses.

Trial name	MURANO
NCT number	NCT02005471
Subgroup analyses	

Subgroup	Total No.	Venetoclax–Rituximab Group		Bendamustine–Rituximab Group		Hazard Ratio (95% Wald CI)
		no.	*median (mo)*	*no.*	*median (mo)*	
All patients	389	194	NR	195	17.0	0.17 (0.12–0.26)
Age						
<65 yr	186	97	NR	89	15.4	0.11 (0.06–0.21)
≥65 yr	203	97	NR	106	21.7	0.24 (0.14–0.41)
CLL risk status						
Low	178	90	NR	88	21.6	0.14 (0.07–0.28)
High	211	104	NR	107	15.4	0.19 (0.11–0.30)
Geographic region						
United States and Canada	34	16	NR	18	15.8	0.29 (0.10–0.83)
Australia and New Zealand	86	44	NR	42	24.5	0.34 (0.16–0.72)
Western Europe	131	66	NR	65	17.1	0.11 (0.05–0.23)
Central and Eastern Europe	130	64	NR	66	15.5	0.13 (0.06–0.27)
Asia	8	4	NR	4	13.6	0.28 (0.03–2.69)
No. of previous therapies						
1	228	111	NR	117	16.6	0.14 (0.08–0.24)
2	100	57	NR	43	21.2	0.24 (0.11–0.50)
≥3	61	26	NR	35	10.5	0.24 (0.10–0.57)
Effect of most recent therapy						
CLL refractory to therapy	59	30	NR	29	13.6	0.32 (0.15–0.70)
Relapse of CLL	330	164	NR	166	18.6	0.14 (0.09–0.23)
Chromosome 17p deletion status						
Absent	250	127	NR	123	21.4	0.19 (0.12–0.32)
Present	92	46	NR	46	15.4	0.13 (0.05–0.29)
TP53 mutation status						
Unmutated	277	144	NR	133	21.2	0.15 (0.09–0.25)
Mutated	99	48	NR	51	12.9	0.19 (0.10–0.36)
Baseline *IGHV* mutation status						
Unmutated	246	123	NR	123	15.7	0.16 (0.10–0.26)
Mutated	104	53	NR	51	22.9	0.11 (0.04–0.31)

Table 2A: M13-982

Trial name	M13-982
NCT number	NCT01889186
Objective	Primary objective was to assess the activity and safety of venetoclax monotherapy in patients with relapsed or refractory del(17p) chronic lymphocytic leukaemia
Publications – title, author, journal, year	Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial. Stephan Stilgenbauer, Barbara Eichhorst, Johannes Schetelig, Peter Hillmen, John F. Seymour, Steven Coutre, Wojciech Jurczak, Stephen P. Mulligan, Anna Schuh, Sarit Assouline, Clemens-Martin Wendtner, Andrew W. Roberts, Matthew S. Davids, Johannes Bloehdorn, Talha Munir, Sebastian Böttcher, Lang Zhou, Ahmed Hamed Salem, Monali Desai, Brenda Chyla, Jennifer Arzt, Su Young Kim, Maria Verdugo, Gary Gordon, Michael Hallek, and William G. Wierda. J of Clinical Oncology. 2018 Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Stephan Stilgenbauer, Barbara Eichhorst, Johannes Schetelig, Steven Coutre, John F Seymour, Talha Munir, Soham D Puvvada, Clemens-Martin Wendtner, Andrew W Roberts, Wojciech Jurczak, Stephen P Mulligan, Sebastian Böttcher, Mehrdad Mobasher, Ming Zhu, Monali Desai, Brenda Chyla, Maria Verdugo, Sari Heitner Enschede, Elisa Cerri, Rod Humerickhouse, Gary Gordon, Michael Hallek, William G Wierda. Lancet Oncology. 2016.
Study type and design	phase II, open-label, M13-982 study started in June 2013 and completed enrollment of patients with relapsed/refractory or previously untreated del(17p) CLL, with follow-up ongoing. At each participating site, an institutional review board approved the study protocol and amendments. Venetoclax monotherapy was administered orally, once daily, until disease progression or study discontinuation. Disease assessments were performed at screening and at each study visit starting on week 4 or 5. Responses and disease progression (PD) were evaluated according to 2008 International Workshop on Chronic Lymphocytic Leukemia criteria with clinical laboratory tests, physical examination, computed tomography (CT) scan, bone marrow aspirate, and biopsy. Peripheral blood and bone marrow assessments for MRD were conducted in patients with CR or CR with incomplete bone marrow recovery (CRi), or for patients with nodular PR (nPR) or PR and nodal masses that were , 2 cm in maximal dimension. MRD was assessed by multicolor flow cytometry per established protocols. Safety assessments were conducted from screening and up to 30 dayspost-treatment. Adverse events (AEs) and laboratory abnormalities were graded on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
Follow-up time	Interim: Median time on treatment was 12.1 months. (IQR: 10.1-14.2) Full study: Median time on study 26.6 months (range 0-44.2)

Population (inclusion and exclusion criteria)	Inclusion Criteria:
	• Subject must be greater than or equal to 18 years of age.
	• Subject must have diagnosis of CLL that meets published 2008 Modified IWCLL NCI-WG (International Workshop for Chronic Lymphocytic Leukemia National Cancer Institute-Working Group) Guidelines.
	  ○ Subject has an indication for treatment according to the 2008 Modified IWCLL NCI WG Guidelines;
	  ○ Subject has clinically measurable disease (lymphocytosis > 5 × 10^9/L and/or palpable and measurable nodes by physical exam and/or organomegaly assessed by physical exam);
	  ○ Subject must be refractory or have relapsed after receiving at least one prior line of therapy (subjects that have progressed after 1 cycle of treatment or have completed at least 2 cycles of treatment for a given line of therapy) or previously untreated CLL (previously untreated CLL subjects must have received no prior chemotherapy or immunotherapy. Subjects with a history of emergency, loco-regional radio-therapy (e.g., for relief of compressive signs or symptoms) are eligible. In addition, subjects must meet the CLL diagnostic criteria above and must have > 5 × 109/L B Lymphocytes in the peripheral blood.);
	  ○ Subjects must have 17p deletion, assessed by local laboratory (in bone marrow or peripheral blood) or assessed by central laboratory (peripheral blood).
	• Subject has an Eastern Cooperative Oncology Group (ECOG) performance score of less than or equal to 2.

Trial name	M13-982
NCT number	NCT01889186

	• Subject must have adequate bone marrow function at Screening as follows:
	  ○ Absolute Neutrophil Count (ANC) greater than or equal to 1000/µL, or
	  ○ For subjects with an ANC less than 1000/µL at Screening and bone marrow heavily infiltrated with underlying disease (unless cytopenia is clearly due to marrow involvement of CLL), growth factor support may be administered after Screening and prior to the first dose of ABT-199 to achieve the ANC eligibility criteria (greater than or equal to 1000/µL);
	  ○ Platelets greater than 30,000/mm3 (without transfusion support within 14 days of Screening, without evidence of mucosal bleeding, without known history of bleeding episode within 3 months of Screen-ing, and without history of bleeding disorder);
	  ○ Hemoglobin greater than or equal to 8.0 g/dL.
	• Subject must have adequate coagulation, renal, and hepatic function, per laboratory reference range at Screening as follows:
	  ○ Activated partial thromboplastin time (aPTT) and prothrombin time (PT) not to exceed 1.5 × the upper limit of normal;
	  ○ Calculated creatinine clearance greater than 50 mL/min using 24-hour Creatinine Clearance or modified Cockcroft-Gault equation (using Ideal Body Mass [IBM] instead of Mass). For subjects that have BMI of > 30 kg/m2 or < 19 kg/m2, 24-hour measured urine creatinine clearance is required;
	  ○ Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than or equal to 3.0 × the upper normal limit of institution's normal range; Bilirubin less than or equal to 1.5 × upper limit of normal. Subjects with Gilbert's Syndrome may have a bilirubin greater 1.5 × upper limit of normal, per correspondence between the investigator and AbbVie medical monitor.
	• For subjects at high risk of tumor lysis syndrome a pre-approval by the AbbVie medical monitor is re-quired prior to enrollment.
	
	Exclusion Criteria:
	• Subject has undergone an allogeneic stem cell transplant.
	• Subject has developed Richter's transformation confirmed by biopsy.
	• Subject has prolymphocytic leukemia.
	• Subject has active and uncontrolled autoimmune cytopenias (for 2 weeks prior to Screening), including autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura despite low dose cortico-steroids.
	• Subject has previously received ABT-199.
	• Subject has received a biologic agent for anti-neoplastic intent within 30 days prior to the first dose of study drug.
	• Subject has received any of the following within 14 days or 5 half-lives as applicable prior to the first dose of study drug, or has not recovered to less than Common Toxicity Criteria (CTC) grade 2 clinically significant adverse effect(s)/toxicity(s) of the previous therapy:
	  ○ Any anti-cancer therapy including chemotherapy, or radiotherapy;
	  ○ Investigational therapy, including targeted small molecule agents.
	• Subject has known allergy to both xanthine oxidase inhibitors and rasburicase.

Intervention	Patients received oral venetoclax once a day continuously until progression or other discontinuation criteria were met. Based on phase 1 results we used a stepwise weekly dose ramp-up from a starting dose of 20 mg to the final 400 mg daily dose (20, 50, 100, 200, 400 mg) over 4–5 weeks. Patients were then given daily 400 mg continuous dosing until disease progression or discontinuation for another reason to gradually reduce tumour bulk and thus mitigate risk of tumour lysis syndrome

Trial name	M13-982
NCT number	NCT01889186
Baseline characteristics	**Table 1.** Patients Demographics and Clinical Characteristics

Demographic and/or Characteristic	All Patients (N = 158)
Median age (range), years	67 (29-85)
Sex	
Female	59 (37)
Male	99 (63)
ECOG performance status	
0	69 (44)
1	78 (49)
2	11 (7)
CLL-IPI category*	
Low	3 (2)
Intermediate	6 (4)
High	116 (73)
Very high	33 (21)
Rai stage at screening	
0	1 (.6)
1	32 (20)
2	52 (33)
3	26 (16)
4	47 (30)
No. of prior therapies, median (range)	2 (0-10)†
Fludarabine-containing regimen	103 (65)
Fludarabine refractory	45 (28)
Cyclophosphamide-containing regimen (without fludarabine)	38 (24)
Anti-CD20 monoclonal antibody-containing regimen	123 (78)
Bendamustine-containing regimen	69 (44)
Chlorambucil-containing regimen	27 (17)
Alemtuzumab-containing regimen	24 (15)
Cladribine- or pentostatin-containing regimen	4 (3)
Steroid only	7 (4)
Other agents	7 (4)
Other chemotherapy	5 (3)
Prior B-cell pathway receptor inhibitor	16 (10)
Treatment naïve	5 (3)
TLS risk category‡	
Low	36 (23)
Medium	60 (38)
High	62 (39)
Median ALC (range), $\times 10^9$/L	25 (0.3-399)
$\geq 25 \times 10^9$/L	79 (50)
Bulky nodes	
≥ 5 cm	76 (48)
≥ 10 cm	21 (13)
Unmutated IGHV	45 of 58 (78)
TP53 mutation¶	55 of 77 (71)
Chromosome 11q deletion	38 of 157 (24)
Median serum β2-microglobulin (range), μg/mL	3.6 (1.3-31)

NOTE. Data presented as No. (%) unless otherwise noted.
Abbreviations: ALC, absolute lymphocyte count; CLL-IPI, Chronic Lymphocytic Leukemia International Prognostic Index; ECOG, Eastern Cooperative Oncology Group; IGHV, immunoglobulin heavy chain variable; TLS, tumor lysis syndrome.
*CLL-IPI categories are based on data for 17p deletion, *TP53* mutation, unmutated IGHV, β2-microglobulin, Rai or Binet stage, and age > 65 years. Missing values were imputed using Multiple Imputation.
†Includes five previously untreated patients enrolled in the safety expansion cohort.
‡TLS risk categories are defined as follows: low: all lymph nodes < 5 cm and ALC $< 25 \times 10^9$/L; medium: any lymph node ≥ 5 cm to < 10 cm or ALC $> 25 \times 10^9$/L; high: any lymph node > 10 cm or any lymph node ≥ 5 cm and ALC $> 25 \times 10^9$/L.
¶Assessed by targeted next-generation sequencing (methods described in the Data Supplement).

Primary and secondary endpoints	Primary endpoint: • IRC assessed Overall response rate

Trial name	M13-982
NCT number	NCT01889186
	Secondary endpoint: • Complete response • Partial Response • Time to first response • Time to 50% reduction in absolute lymphocyte count • Duration of overall response • Progression-free survival • Overall survival • Event-free survival • Time to progression • Proportion of patients proceeding to allogenic stem cell transplantation • Safety • Minimal residual disease • Pharmacokinetics
Method of analysis	Data cutoff for this analysis was April 4, 2017, and includes all patients who were enrolled in the main and safety expansion cohorts. Efficacy and safety analyses included all patients who received at least one dose of venetoclax. Descriptive statistics were calculated, and Kaplan- Meier methods were used for time-to-event analyses. SAS was used to generate all statistical summaries. Statistical significance was determined using two-sided $P < .05$.

Trial name	M13-982
NCT number	NCT01889186
Subgroup analyses	

Table S6. Activity by Patient Demographics

	n	ORR by IRC [95% CI]	CR/CRi rate by IRC [95% CI]	12-month PFS estimate by IRC [95% CI]
All patients	107	79.4 [70.5, 86.6]	7.5 [3.3, 14.2]	72.0 [61.8, 79.8]
Gender				
Male	70	80.0 [68.7, 88.6]	5.7 [1.6, 14.0]	69.4 [56.4, 79.2]
Female	37	78.4 [61.8, 90.2]	10.8 [3.0, 25.4]	76.8 [58.5, 87.8]
Age				
Age < 65 years	46	87.0 [73.7, 95.1]	13.0 [4.9, 26.3]	79.9 [64.9, 89.0]
Age ≥ 65 years	61	73.8 [60.9, 84.2]	3.3 [0.4, 11.3]	65.7 [51.3, 76.8]
Prior therapies				
1 prior therapy	29	93.1 [77.2, 99.2]	20.7 [8.0, 39.7]	85.9 [66.7, 94.5]
>1 prior therapy	78	74.4 [63.2, 83.6]	2.6 [0.3, 9.0]	66.4 [53.8, 76.3]
<3 prior therapies	54	85.2 [72.9, 93.4]	13.0 [5.4, 24.9]	72.6 [58.0, 82.8]
≥3 prior therapies	53	73.6 [59.7, 84.8]	1.9 [0.1, 10.1]	71.4 [56.2, 82.1]
Fludarabine refractory	34	85.3 [68.9, 95.0]	11.8 [3.3, 27.5]	76.3 [58.1, 87.4]
Not Fludarabine refractory	44	72.7 [57.2, 85.0]	4.6 [0.6, 15.5]	69.1 [52.8, 80.8]
Bendamustine refractory	38	73.7 [56.9, 86.6]	2.6 [0.1, 13.8]	69.8 [50.2, 82.8]
Not bendamustine refractory	16	81.3 [54.4, 96.0]	0 [0, 20.6]	71.1 [39.4, 88.3]
ECOG performance status				
ECOG = 0	42	85.7 [71.5, 94.6]	7.1 [1.5, 19.5]	73.6 [57.4, 84.4]
ECOG ≥ 1	65	75.4 [63.1, 85.2]	7.7 [2.5, 17.0]	70.8 [57.0, 81.0]
Bulky disease				
Nodes < 5 cm	50	82.0 [68.6, 91.4]	14.0 [5.8, 26.7]	77.5 [63.1, 86.9]
Nodes ≥ 5 cm	57	77.2 [64.2, 87.3]	1.8 [0.0, 9.4]	67.3 [52.5, 78.5]
Absolute lymphocyte count				
ALC < 25 x 10^9/L	53	81.1 [68.0, 90.6]	5.7 [1.2, 15.7]	75.9 [61.1, 85.7]
ALC ≥ 25 x 10^9/L	54	77.8 [64.4, 88.0]	9.3 [3.1, 20.3]	67.9 [52.9, 79.1]
Mutation status				
IGVH mutated	7	71.4 [29.0, 96.3]	14.3 [0.4, 57.9]	57.1 [17.2, 83.7]
IGVH unmutated	30	83.3 [65.3, 94.4]	3.3 [0.1, 17.2]	62.1 [40.1, 78.1]
TP53 mutated	60	75.0 [62.1, 85.3]	3.3 [0.4, 11.5]	69.3 [55.1, 79.8]
TP53 unmutated	17	82.4 [56.6, 96.2]	11.8 [1.5, 36.4]	70.6 [43.1, 86.6]
% of del(17p)				
≤50.25	54	83.3 [70.7, 92.1]	9.3 [3.1, 20.3]	74.4 [59.5, 84.5]
>50.25	53	75.5 [61.7, 86.3]	5.7 [1.2, 15.7]	69.0 [53.8, 80.1]
Rai Stage				
3 or 4	51	72.6 [58.3, 84.1]	3.9 [0.5, 13.5]	65.2 [49.2, 77.2]
Others	56	85.7 [73.8, 93.6]	10.7 [4.0, 21.9]	77.9 [64.3, 86.9]
Binet Stage				
C	42	73.8 [58.0, 86.1]	4.8 [0.6, 16.2]	66.0 [48.3, 78.9]
Others	65	83.1 [71.7, 91.2]	9.2 [3.5, 19.0]	75.9 [63.1, 84.8]
TLS Risk				
High	45	73.3 [58.1, 85.4]	2.2 [0.1, 11.8]	63.6 [46.6, 76.4]
Medium	43	86.1 [72.1, 94.7]	14.0 [5.3, 27.9]	78.0 [61.9, 87.9]
Low	19	79.0 [54.4, 94.0]	5.3 [0.1, 26.0]	78.9 [53.2, 91.5]

Trial name	M13-982
NCT number	NCT01889186

Supplemental Table 4. Responses by Subgroup Analyses

n (%)	ORR	CR/CRi	nPR/PR	SD	PD	NE
All Patients, N=158	122 (77)	32 (20)	90 (57)	30 (19)	3 (2)	3* (2)
***TP53* mutation, n=55**	38 (69)	10 (18)	28 (51)	16 (29)	1 (2)	0
Unmutated *IGHV*, n=45	39 (87)	7 (16)	32 (71)	4 (9)	1 (2)	1 (2)
>2 prior therapies, n=68	48 (71)	6 (9)	42 (62)	18 (27)	1 (2)	1 (2)
Fludarabine refractory, n=45	35 (78)	11 (24)	24 (53)	10 (22)	0	0
ECOG score of 0, n=69	59 (86)	16 (23)	43 (62)	10 (15)	0	0
ECOG score of 1, n=78	55 (71)	14 (18)	41 (53)	17 (22)	3 (4)	3 (4)
ECOG score of 2, n=11	8 (73)	2 (18)	6 (55)	3 (27)	0	0
Beta-2 microglobulin ≥3 at baseline, n=25	19 (76)	6 (24)	13 (52)	5 (20)	1 (4)	0
Nodes ≥5 cm at baseline, n=76	60 (79)	10 (13)	50 (66)	14 (18)	1 (1)	1 (1)
Nodes ≥10 cm at baseline, n=21	16 (76)	2 (10)	14 (67)	5 (24)	0	0
High TLS risk,† n=62	47 (76)	5 (8)	42 (68)	14 (23)	0	1 (2)

ORR, objective response rate; CR, complete remission; CRi, complete remission with incomplete marrow recovery; nPR, nodular partial remission; PR, partial remission, SD, stable disease; PD, disease progression; NE, not evaluated for response; BCRi, B-cell receptor pathway inhibitor.
*One patient discontinued after the first dose of venetoclax, one patient died after three weeks of treatment due to liver dysfunction not related to venetoclax, and one patient had pseudo obstruction of the small bowel mesentery and retroperitoneum during dose ramp up and discontinued the study.

Table 2A: M14-032

Trial name	M14-032
NCT number	NCT02141282
Objective	Primary objective was to evaluate the efficacy of ABT-199 monotherapy in subjects with chronic lymphocytic leukemia (CLL) relapsed or refractory to B-cell Receptor Signaling Pathway Inhibitors. Assessed by the investigator, based on laboratory results, physical examinations, CT scans, and bone marrow examinations
Publications – title, author, journal, year	Mato AR, Wierda WG, Davids MS, Cheson BD, Coutre SE, Choi M, Furman RR, Heffner L, Barr PM, Eradat H, Ford SM, Zhou L, Verdugo M, Humerickhouse RA, Potluri J, Byrd JC. Utility of PET-CT in patients with chronic lymphocytic leukemia following B-cell receptor pathway inhibitor therapy. Haematologica. 2019 Mar 28. pii: haematol.2018.207068. doi: 10.3324/haematol.2018.207068. [Epub ahead of print] Coutre S, Choi M, Furman RR, Eradat H, Heffner L, Jones JA, Chyla B, Zhou L, Agarwal S, Waskiewicz T, Verdugo M, Humerickhouse RA, Potluri J, Wierda WG, Davids MS. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. Blood. 2018 Apr 12;131(15):1704-1711. doi: 10.1182/blood-2017-06-788133. Epub 2018 Jan 5. Jones JA, Mato AR, Wierda WG, Davids MS, Choi M, Cheson BD, Furman RR, Lamanna N, Barr PM, Zhou L, Chyla B, Salem AH, Verdugo M, Humerickhouse RA, Potluri J, Coutre S, Woyach J, Byrd JC. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. Lancet Oncol. 2018 Jan;19(1):65-75. doi: 10.1016/S1470-2045(17)30909-9. Epub 2017 Dec 12.
Study type and design	Allocation: Non-Randomized Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment
Follow-up time	At the time of data cut-off (26 July 2017), 127 patients were enrolled and treated with venetoclax. Of these, 91 patients had received prior ibrutinib therapy and 36 had received prior idelalisib therapy
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Subject must have a diagnosis of CLL that meets 2008 Modified International Workshop on Chronic Lymphocytic Leukemia National Cancer Institute-Working Group (iwCLL NCI-WG) criteria • Subject has relapsed/refractory disease with an indication for treatment • Subject has refractory disease or developed recurrence after therapy with a BCR PI • Subject must have an Eastern Cooperative Oncology Group performance score of equal to or less than 2 • Subject must have adequate bone marrow function at Screening • Subject must have adequate coagulation profile, renal, and hepatic function, per laboratory reference range at Screening Exclusion Criteria: • Subject has undergone an allogeneic stem cell transplant within the past year • Subject has developed Richter's transformation confirmed by biopsy • Subject has active and uncontrolled autoimmune cytopenia • Subject has malabsorption syndrome or other condition that precludes enteral route of administration • Subject is human immunodeficiency virus (HIV) positive or has chronic hepatitis B or hepatitis C virus requiring treatment • Subject has known contraindication or allergy to both xanthine oxidase inhibitors and rasburicase.
Intervention	Patients received 20 mg oral venetoclax once per day for 1 week, followed by weekly ramp-up to 50 mg, 100 mg, and 200 mg per day, up to the final dose of 400 mg per day by week 5. In the expansion cohort, an accelerated dose ramp-up over 3 weeks (to 400 mg per day by week 3) was permitted for patients who had a high tumour burden with clinical signs of rapid progression during screening. Dose escalation of venetoclax to 600 mg was allowed in the expansion cohort for patients who did not respond to treatment after response assessment at week 12. Treatment continued for up to 2 years or until disease progression or discontinuation because of other reasons, and patients were removed from the study at that time.

Trial name	M14-032
NCT number	NCT02141282
Baseline characteristics	

	Main cohort (n=43)	Expansion cohort (n=48)	All patients (n=91)
Age (years)	66 (48–80)	65 (28–81)	66 (28–81)
Sex			
Male	33 (77%)	31 (65%)	64 (70%)
Female	10 (23%)	17 (35%)	27 (30%)
White*	40 (93%)	44 (92%)	84 (92%)
ECOG performance status score			
0	13 (30%)	16 (33%)	29 (32%)
1	27 (63%)	27 (56%)	54 (59%)
2	3 (7%)	5 (10%)	8 (9%)
Lymphocyte count (× 10⁹/L)	19·0 (2·5–43·2)	6·6 (1·0–32·8)	10·1 (2·5–43·6)
≥25	17 (40%)	10 (22%)	27 (30%)
≥100	7 (16%)	5 (11%)	12 (13%)
Neutrophil count (× 10⁹/L)	3·7 (2·0–11·0)	3·4 (2·3–10·4)	4·2 (2·0–11·0)
Platelet count (× 10⁹/L)	116·0 (73·0–166·0)	106·0 (73·0–151·5)	110·0 (73·0–158·0)
Haemoglobin (g/dL)	11·3 (9·6–12·4)	12·2 (10·8–13·4)	11·7 (10·4–12·9)
Creatinine clearance (mL/min)	78·2 (65·4–94·1)	75·7 (63·8–100·4)	76·0 (64·5–96·7)
Bulky nodal disease (cm)			
≥5	15 (35%)	21 (44%)	36 (40%)
≥10	7 (16%)	2 (4%)	9 (10%)
Tumour lysis syndrome risk category†			
Low	15 (35%)	19 (40%)	34 (37%)
Medium	11 (26%)	20 (41%)	31 (34%)
High	17 (39%)	9 (19%)	26 (29%)
Prognostic factors based on site-reported data‡			
Non-mutated *IGHV*	25/29 (86%)	25/38 (66%)	50/67 (75%)
del(17)(p13.1)	21/43 (49%)	21/47 (40%)	42/90 (47%)
del(11)(q22.3)	13/43 (30%)	17/48 (33%)	30/91 (33%)
TP53 mutation	15/41 (37%)	14/46 (30%)	29/87 (33%)
CD38 positive	21/42 (50%)	16/44 (36%)	37/86 (43%)
ZAP-70 positive	12/24 (50%)	17/40 (43%)	29/64 (45%)
Treatment history			
Number of previous therapies	5 (1–12)	4 (1–15)	4 (1–15)
Previous ibrutinib use	43 (100%)	48 (100%)	91 (100%)
Time on ibrutinib (months)	18 (1–56)	21 (1–61)	20 (1–61)
Relapsed during or after ibrutinib	11 (26%)	17 (35%)	28 (31%)
Refractory to ibrutinib	32 (74%)	30 (63%)	62 (68%)
Previous idelalisib use§	4 (9%)	7 (15%)	11 (12%)
Time on idelalisib (months)	16 (2–31)	9 (2–33)	9 (2–33)

Data are median (IQR), n (%), or n/N (%). ECOG=Eastern Cooperative Oncology Group. IGHV=immunoglobulin heavy-chain variable region. *Other ethnicities or races reported were black (2/43 [5%]) and Asian (1 [2%]) in the main cohort and black (4/48 [8%]) in the expansion cohort. †Low was defined as all lymph nodes smaller than 5 cm with an absolute lymphocyte count of less than 25 × 10⁹/L; medium was defined as any lymph node 5 cm or larger but smaller than 10 cm or with an absolute lymphocyte count of 25 × 10⁹/L or higher; high was defined as any lymph node 10 cm or larger or 5 cm or larger and with an absolute lymphocyte count of 25 × 10⁹/L or higher. ‡Data are presented for all patients with available data. §11 patients had previously received idelalisib followed by ibrutinib during their previous course of treatment.

Table 1: **Patient demographics and baseline clinical characteristics**

Trial name	M14-032
NCT number	NCT02141282
Primary and secondary endpoints	Primary endpoint: • IRC assessed Overall response rate Secondary endpoint: • Duration of response [Time Frame: Measured up to 2 years after the last subject has enrolled in the study.] o The number of days from the date of first response (complete response (CR) or partial response (PR)) to the earliest recurrence or disease progression (PD) • Time to progression (TTP) [Time Frame: Measured up to 5 years after the last subject has enrolled in the study.] o The number of days from the date of first dose or enrollment if not dosed to the date of earliest PD • Overall survival (OS) [Time Frame: Measured up to 5 years after the last subject has enrolled in the study.] o The number of days from the date of first dose to the date of death for all dosed subjects • Progression-free survival (PFS) [Time Frame: Measured up to 5 years after the last subject has enrolled in the study.] o The number of days from the date of first dose to the date of earliest PD or death Other Outcome Measures: • Time to Next Anti-CLL Treatment (TNT) [Time Frame: Measured up to 2 years after the last subject has enrolled in the study.] o The number of days from the date of first dose of ABT-199 to the date of first dose of new non-protocol anti-leukemia therapy (NPT) or death from any cause • Rate of minimal residual disease (MRD) negativity status [Time Frame: Measured up to 2 years after the last subject has enrolled in the study.] o The presence of less that once CLL cell per 10,000 leukocytes in either peripheral blood and/or bone marrow
Method of analysis	Activity and safety analyses included all patients who received at least one dose of venetoclax (ie, the per-protocol population). Exploratory analyses of minimal residual disease and resistance mutations included all patients within the activity and safety population with available data for these analyses. Data were analysed with SAS software version 9.4. This study is ongoing, and data for this interim analysis, as requested by regulatory agencies (FDA, European Medicines Agency, Therapeutic Goods Administration, and Swissmedic), were collected on June 30, 2017.
Subgroup analyses	NA

Tabel 2A: HELIOS

Trial name	HELIOS
NCT number	NCT01611090
Objective	To examine the safety and efficacy of Ibrutinib administered in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
Publications – title, author, journal, year	Brown JR, Moslehi J, O'Brien S, Ghia P, Hillmen P, Cymbalista F, Shanafelt TD, Fraser G, Rule S, Kipps TJ, Coutre S, Dilhuydy MS, Cramer P, Tedeschi A, Jaeger U, Dreyling M, Byrd JC, Howes A, Todd M, Vermeulen J, James DF, Clow F, Styles L, Valentino R, Wildgust M, Mahler M, Burger JA. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. Haematologica. 2017. Chanan-Khan A, Cramer P, Demirkan F, Fraser G, Silva RS, Grosicki S, Pristupa A, Janssens A, Mayer J, Bartlett NL, Dilhuydy MS, Pylypenko H, Loscertales J, Avigdor A, Rule S, Villa D, Samoilova O, Panagiotidis P, Goy A, Mato A, Pavlovsky MA, Karlsson C, Mahler M, Salman M, Sun S, Phelps C, Balasubramanian S, Howes A, Hallek M; HELIOS investigators. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. Lancet Oncol. 2016.
Study type and design	A randomized, double-blind, placebo-controlled phase 3 Study of ibrutinib, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in combination with bendamustine and rituximab in subjects with relapsed or refractory CLL/SLL. Patients were randomized in a 1:1 ratio on the basis of a computer-generated randomization schedule. Patients were stratified by purine analogue refractory status (yes, relapsed or failed within 12 months) and number of previous lines of therapy (1 vs. > 1). Crossover to ibrutinib was permitted for patients in the placebo group with IRC-confirmed disease progression. Investigators, patients and study personnel were all blinded to the actual treatment assignment. Study is active on follow-up, not recruiting. State the phase of the trial and describe the extent of crossover, method of randomization, degree of blinding, status (ongoing or completed), etc. E.g.: Double-blinded randomized placebo-controlled phase 3 study. Enrolled patients were randomly assigned 1:1 using a stratified permuted block randomization scheme via an interactive response system. No crossover was allowed. The investigators, patients, and sponsor were masked to treatment assignment.
Follow-up time	Median follow-up 17 months (range 1.7 – 20.7).
Population (inclusion and exclusion criteria)	Inclusion Criteria: •Diagnosis of chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) that meets protocol-defined criteria •Active disease meeting at least 1 of the International Workshop on Chronic Lymphocytic Leukemia 2008 criteria for requiring treatment •Measurable nodal disease by computed tomography •Relapsed or refractory CLL or SLL following at least 1 prior line of systemic therapy consisting of at least 2 cycles of a chemotherapy-containing regimen •Eastern Cooperative Oncology Group Performance Status score of 0 or 1 •Hematology and biochemical values within protocol-defined limits •Agrees to protocol-defined use of effective contraception •Women of childbearing potential must have negative blood or urine pregnancy test at screening. Exclusion Criteria: •Recent therapeutic interventions within 3 (chemotherapy/radiotherapy) to 10 weeks (immunotherapy) •Prior treatment with ibrutinib or other Bruton's tyrosine kinase inhibitors or prior randomization in any other clinical study evaluating ibrutinib

<table>
<tr><td>Trial name</td><td>HELIOS</td></tr>
<tr><td>NCT number</td><td>NCT01611090</td></tr>
<tr><td></td><td>•The presence of deletion of the short arm of chromosome 17
•Patients previously treated with a bendamustine-containing regimen who did not achieve a response or who relapsed and required treatment within 24 months of treatment with that regimen
•Patients for whom the goal of therapy is tumor debulking prior to stem cell transplant
•Received a hematopoietic stem cell transplant
•Known central nervous system leukemia/lymphoma or Richter's transformation
•Patients with uncontrolled autoimmune hemolytic anemia or autoimmune thrombocytopenia
•Chronic use of corticosteroids
•History of prior malignancy, except: malignancy treated with curative intent and with no known active disease present for >=3 years before randomization; adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease; adequately treated cervical carcinoma in situ without evidence of disease
•History of stroke or intracranial hemorrhage within 6 months prior to randomization; or clinically significant cardiovascular disease
•Requires anticoagulation with warfarin or equivalent vitamin K antagonists or treatment with strong CYP3A4/5 inhibitors
•Known history of human immunodeficiency virus or hepatitis C, or active infection with hepatitis B or C
•Any uncontrolled active systemic infection or any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the patient's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk
•A woman who is pregnant or breast feeding, or a man who plans to father a child while enrolled in this study or within 3 months after the last dose of study drug.</td></tr>
<tr><td>Intervention</td><td>289 assigned to receive ibrutinib 420 mg/daily + bendamustine 70 mg/m^2 intravenously (cycle 1, day 2-3 and days 1-2 in cycle 2-6) + rituximab 375 mg/m^2 on day 1 cycle 1 and 500 mg/m^2 on day 1 of cycles 2-6.

State the intervention including dose, dosing schedule, and number of patients receiving the intervention</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Characteristics</th><th>Ibrutinib, bendamustine and rituximab n=289</th><th>Placebo, bendamustine and rituximab n=289</th></tr>
<tr><td>Age (years)</td><td>64 (31 - 86)</td><td>63 (36 - 83)</td></tr>
<tr><td>Sex, n (%)</td><td></td><td></td></tr>
<tr><td>Male</td><td>193 (67%)</td><td>189 (65%)</td></tr>
<tr><td>Female</td><td>96 (33%)</td><td>100 (35%)</td></tr>
<tr><td>Diagnosis</td><td></td><td></td></tr>
<tr><td>CLL</td><td>257 (89%)</td><td>257 (89%)</td></tr>
<tr><td>SLL</td><td>32 (11%)</td><td>32 (11%)</td></tr>
<tr><td>ECOG score, n (%)</td><td></td><td></td></tr>
<tr><td>0</td><td>125 (43%)</td><td>126 (44%)</td></tr>
<tr><td>1</td><td>164 (57%)</td><td>163 (56%)</td></tr>
<tr><td>Rai staging at diagnosis</td><td>256</td><td>258</td></tr>
<tr><td>Stage 0-II</td><td>157 (61%)</td><td>139 (54%)</td></tr>
<tr><td>Stage III-IV</td><td>99 (39%)</td><td>119 (46%)</td></tr>
<tr><td>Binet stage</td><td>256</td><td>258</td></tr>
<tr><td>A</td><td>26 (10%)</td><td>23 (9%)</td></tr>
<tr><td>B</td><td>132 (52%)</td><td>119 (46%)</td></tr>
<tr><td>C</td><td>98 (38%)</td><td>116 (45%)</td></tr>
<tr><td>Bulky disease ≥ 5 cm</td><td>168 (68%)</td><td>156 (54%)</td></tr>
<tr><td>ZAP70 expression</td><td>271</td><td>276</td></tr>
<tr><td>Raised</td><td>204 (75%)</td><td>190 (69%)</td></tr>
<tr><td>Not raised</td><td>67 (25%)</td><td>86 (31%)</td></tr>
</table>
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Trial name	HELIOS		
NCT number	NCT01611090		
	Purine analogue refractory	75 (26%)	74 (26%)
	del(11q)	87 (30%)	65 (22%)
	IGHV mutational status, n (%)	259	260
	Mutated	49 (19%)	52 (20%)
	Unmutated	210 (81%)	208 (80%)
	Previous lines of therapy	289	288
	Mean (range)	2 (1-11)	2 (1-9)
	1	140 (48%)	138 (48%)
	2	72 (25%)	78 (27%)
	≥3	77 (27%)	72 (25%)
	Previous therapy		
	Purine analogue	206 (71%)	209 (72%)
	Alkylating agent	275 (95%)	275 (95%)
	Anti-CD20 antibody	203 (70%)	200 (69%)
	Common regimens used		
	FCR	120 (42%)	109 (38%)
	Other fludarabine-based combinations	92 (32%)	102 (35%)
	Bendamustine plus rituximab	10 (3%)	9 (3%)
	Chlorambucil plus anti-CD20 mAb	16 (6%)	15 (5%)
	Time from progression or relapse since last line of treatment to randomization (months)	2.9 (0-48)	2.6 (0-73)
	Time from last treatment to randomization (months)	24.0 (0.7 – 154.8)	20.9 (0.2 – 160.8)
Primary and secondary endpoints	IRC-assessed PFS Key secondary endpoints: - OS - IRC-assessed OR - Investigator-assessed PFS and response - MRD - Rate of sustained hemoglobin improvement - Rate of sustained platelet improvement - Patient reported outcomes (prespecified) assessed by EORTC QLQ-C20 and EORTC QLQ-CLL 16 and 'time to improvement' in FACIT-Fatigue score. State the primary and secondary outcomes of the study. E.g.: The primary endpoint was progression-free survival as assessed by the investigator, according to RECIST version 1.1. Secondary endpoints were overall survival, confirmed objective response according to RECIST version 1.1, response duration, progression-free survival assessed by an independent review facility, health-related quality of life (HRQoL) as assessed by QLQ-C30, and safety.		
Method of analysis	Efficacy analyses were ITT population. All randomized patients who received at least one dose of study drug were included in the safety analyses. PFS, OS and other time to event endpoints were estimated by the Kaplan-Meier method. E.g.: All efficacy analyses were intention-to-treat analyses. We used the Kaplan–Meier method to estimate rates of progression-free survival and overall survival, and a stratified log-rank test for treatment comparisons.		

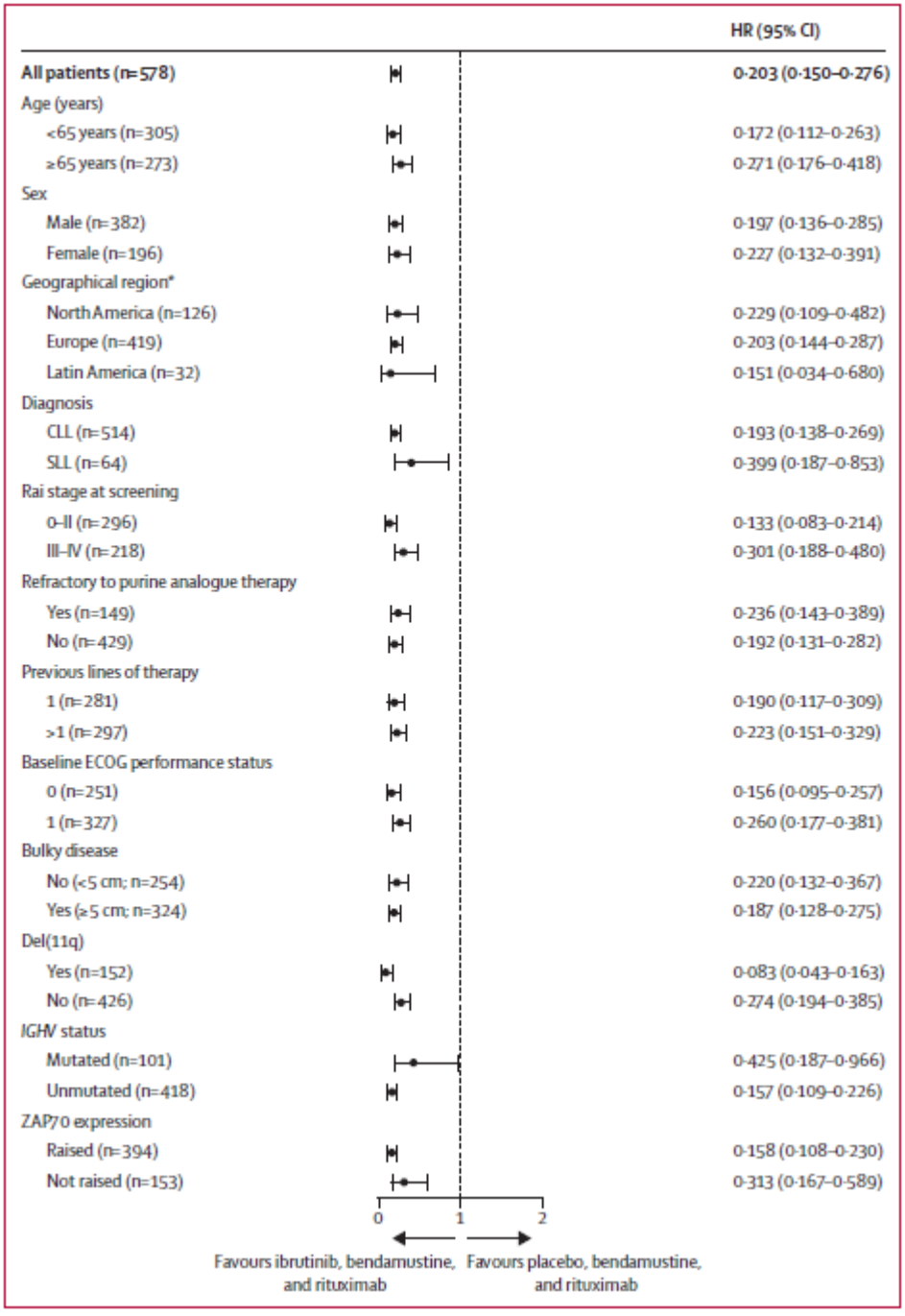
Trial name	HELIOS
NCT number	NCT01611090
Subgroup analyses	

Table 2A: RESONATE

Trial name	RESONATE
NCT number	01578707
Objective	To evaluate whether treatment with ibrutinib as a monotherapy results in a clinically significant improvement in PFS as compared to treatment with ofatumumab in patients with relapsed or refractory CLL or SLL
Publications – title, author, journal, year	Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab John C. Byrd, Peter Hillmen, Susan O'Brien, Jacqueline C. Barrientos, Nishitha M. Reddy, Steven Coutre, Constantine S. Tam, Stephen P. Mulligan, Ulrich Jaeger, Paul M. Barr, Richard R. Furman, Thomas J. Kipps, Patrick Thornton, Carol Moreno, Marco Montillo, John M. Pagel, Jan A. Burger, Jennifer A. Woyach, Sandra Dai, Remus Vezan, Danelle F. James and Jennifer R. Brown. Blood. 2019 Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE study in patients with previously treated CLL/SLL. J R Brown, P Hillmen, S O'Brien, J C Barrientos, N M Reddy, S E Coutre, C S Tam, S P Mulligan, U Jaeger, P M Barr, R R Furman, T J Kipps, F Cymbalista, P Thornton, F Caligaris-Cappio, J Delgado, M Montillo, S DeVos, C Moreno, J M Pagel, T Munir, J A Burger, D Chung, J Lin, L Gau, B Chang, G Cole, E Hsu, D F James & J C Byrd. Nature Leukemia. 2018 Improvement in Parameters of Hematologic and Immunologic Function and Patient Well-being in the Phase III RESONATE Study of Ibrutinib Versus Ofatumumab in Patients With Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Jacqueline C. Barrientos, Susan O'Brien, Jennifer R. Brown, Neil E. Kay, Nishitha M. Reddy, Steven Coutre, Constantine Tam, Stephen Mulligan, Ulrich Jaeger, Stephen Devereux, Christopher Pocock, Tadeusz Robak, Stephen J. Schuster, Anna Schuh, Devinder Gill, Adrian Bloor, Claire Dearden, Carol Moreno, Gavin Cull, Mike Hamblin, Jeffrey A. Jones, Karl Eckert, Isabelle G. Solman, Samuel Suzuki, Emily Hsu, Danelle F. James, John C. Byrd, and Peter Hillmen.: Clinical lymphoma myeloma and Leukemia, dec 2018. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, Devereux S, Barr PM, Furman RR, Kipps TJ, Cymbalista F, Pocock C, Thornton P, Caligaris-Cappio F, Robak T, Delgado J, Schuster SJ, Montillo M, Schuh A, de Vos S, Gill D, Bloor A, Dearden C, Moreno C, Jones JJ, Chu AD, Fardis M, McGreivy J, Clow F, James DF, Hillmen P; RESONATE Investigators. N Engl J Med. 2014
Study type and design	Multicenter, open-label, phase 3 study. Patients were randomly assigned to receive either ibrutinib or ofatumumab. Patients were stratified according to whether they rad resistance to purine analogue chemoimmunotherapy (defined as no response or relapse within 12 months after last dose of purine analogue) and whether they had a chromosome 17p13.1 deletion. Crossover was allowed for patients who received ofatumumab and progressed to receive ibrutinib.
Follow-up time	Median follow-up 9.4 months (range 0.1 – 16.6) Barrientos extension: Median follow-up 16.4 months Brown extension: Median follow-up 19 months Byrd extension: median follow-up for patients initially on Ibrutinib: 44 months (range: 0.2-50.1) Median follow-up time for patients initially assigned to ofatumumab who crossed over to ibrutinib at time of progression was 43.6 months (range, 7.2 to 50.0)
Population (inclusion and exclusion criteria)	Inclusion Criteria: •ECOG performance status of 0-1. •Diagnosis of CLL or SLL that meets IWCLL 2008 criteria. •Active disease meeting at least 1 of the IWCLL 2008 criteria for requiring treatment. •Must have received at least one prior therapy for CLL/SLL. •Considered not appropriate for treatment or retreatment with purine analog based therapy. •Measurable nodal disease by CT. •Patients must be able to receive outpatient treatment and laboratory monitoring at the institution that administers study drug for the entire study.

<table>
<tr><td>Trial name</td><td>RESONATE</td></tr>
<tr><td>NCT number</td><td>01578707</td></tr>
<tr><td></td><td>Exclusion Criteria:
•Known CNS lymphoma or leukaemia.
•No documentation of cytogenetic and/or FISH in patient records prior to first dose of study drug.
•Any history of Richter's transformation or prolymphocytic leukaemia.
•Uncontrolled Autoimmune Hemolytic Anemia (AIHA) or idiopathic thrombocytopenia purpura (ITP).
•Prior exposure to ofatumumab or to ibrutinib.
•Prior autologous transplant within 6 months prior to first dose of study drug.
•Prior allogeneic stem cell transplant within 6 months or with any evidence of active graft versus host disease or requirement for immunosuppressants within 28 days prior to first dose of study drug.
•History of prior malignancy, with the exception of certain skin cancers and malignancies treated with curative intent and with no evidence of active disease for more than 3 years.
•Serologic status reflecting active hepatitis B or C infection.
•Unable to swallow capsules or disease significantly affecting gastrointestinal function.
•Uncontrolled active systemic fungal, bacterial, viral, or other infection.
•History of stroke or intracranial hemorrhage within 6 months prior to the first dose of study drug.
•Requires anticoagulation with warfarin.</td></tr>
<tr><td>Intervention</td><td>Ibrutinib (oral tablet) dose 420 mg/daily - 195 patients received ibrutinib or
Ofatumumab i.v. for up to 24 weeks at an initial dose of 300 mg at week 1, followed by a dose of 2000 mg weekly for 7 weeks and then every 4 weeks for 16 weeks – 196 patients</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Characteristics</th><th>Ibrutinib
N=195</th><th>Ofatumumab
N=196</th></tr>
<tr><td>Patient with SLL – no. (%)</td><td>10 (5)</td><td>8 (4)</td></tr>
<tr><td>Median age (range) - yr</td><td>67 (30-86)</td><td>67 (37-88)</td></tr>
<tr><td>Male sex – no. (%)
Male</td><td>129 (66)</td><td>137 (70)</td></tr>
<tr><td>CIRS > 6 – no. (%)</td><td>38 (32)</td><td>39 (32)</td></tr>
<tr><td>Creatinine clearance < 60ml/min – no. (%)</td><td>62 (32)</td><td>61 (31)</td></tr>
<tr><td>Median haemoglobin (range) – g/dl</td><td>11 (7-16)</td><td>11 (6-16)</td></tr>
<tr><td>Median platelet count (range) – per mm³</td><td>116,500
(20,000-441,000)</td><td>122,000
(23,000-345,000)</td></tr>
<tr><td>Median lymphocyte count (range) – per mm³</td><td>29,470
(90-467,700)</td><td>29,930
(290-551,030)</td></tr>
<tr><td>ECOG score, no. (%)
0
1</td><td>
79 (41)
116 (59)</td><td>
80 (41)
116 (59)</td></tr>
<tr><td>Bulky disease ≥5 cm – no. (%)</td><td>124 (64)</td><td>101 (52)</td></tr>
<tr><td>Interphase cytogenetic abnormalities – no. (%)
Chromosome 11q22.3 deletion
Chromosome 17p13.1 deletion</td><td>
63 (32)
63 (32)</td><td>
59 (30)
64 (33)</td></tr>
<tr><td>B_2-microglobulin > 3.5 mg/liter – no. (%)</td><td>153 (78)</td><td>145 (74)</td></tr>
<tr><td>Previous therapies
Median no. (range)
≥3 – no. (%)</td><td>
3 (1-12)
103 (53)</td><td>
2 (1-13)
90 (46)</td></tr>
</table>
</td></tr>
</table>

Trial name	RESONATE		
NCT number	01578707		
	Type of therapy – no. (%)		
	Alkylator	181 (93)	173 (88)
	Bendamustine	84 (43)	73 (37)
	Purine analogue	166 (85)	151 (77)
	Anti-CD20	183 (94)	176 (90)
	Alemtuzumab	40 (21)	33 (17)
	Allogeneic transplantation	3 (2)	1 (1)
	Median time from last therapy (range) – no. - mo	8 (1-140)	12 (0-184)
	Resistance to purine analogue – no. (%)	87 (45)	88 (45)
Primary and secondary endpoints	**Primary endpoint:** IRC assessed PFS **Secondary endpoints:** Duration of OS Response rate FACIT-F Sustained hematologic response **Prespecified exploratory endpoints:** EORTC QLQ-C30 CTCAE AE		
Method of analysis	The primary end point, progression-free survival, was used in the calculation of the study sample size. The number of required events was based on a target hazard ratio for progression or death of 0.60, as calculated with the use of a two-sided log-rank test at an alpha level of 0.05, with a study power of at least 90% Primary analysis was a two-sided log-rank test stratified according to the presence or absence of chromosome 17p13.1 deletion and disease refractory status at randomisation.		

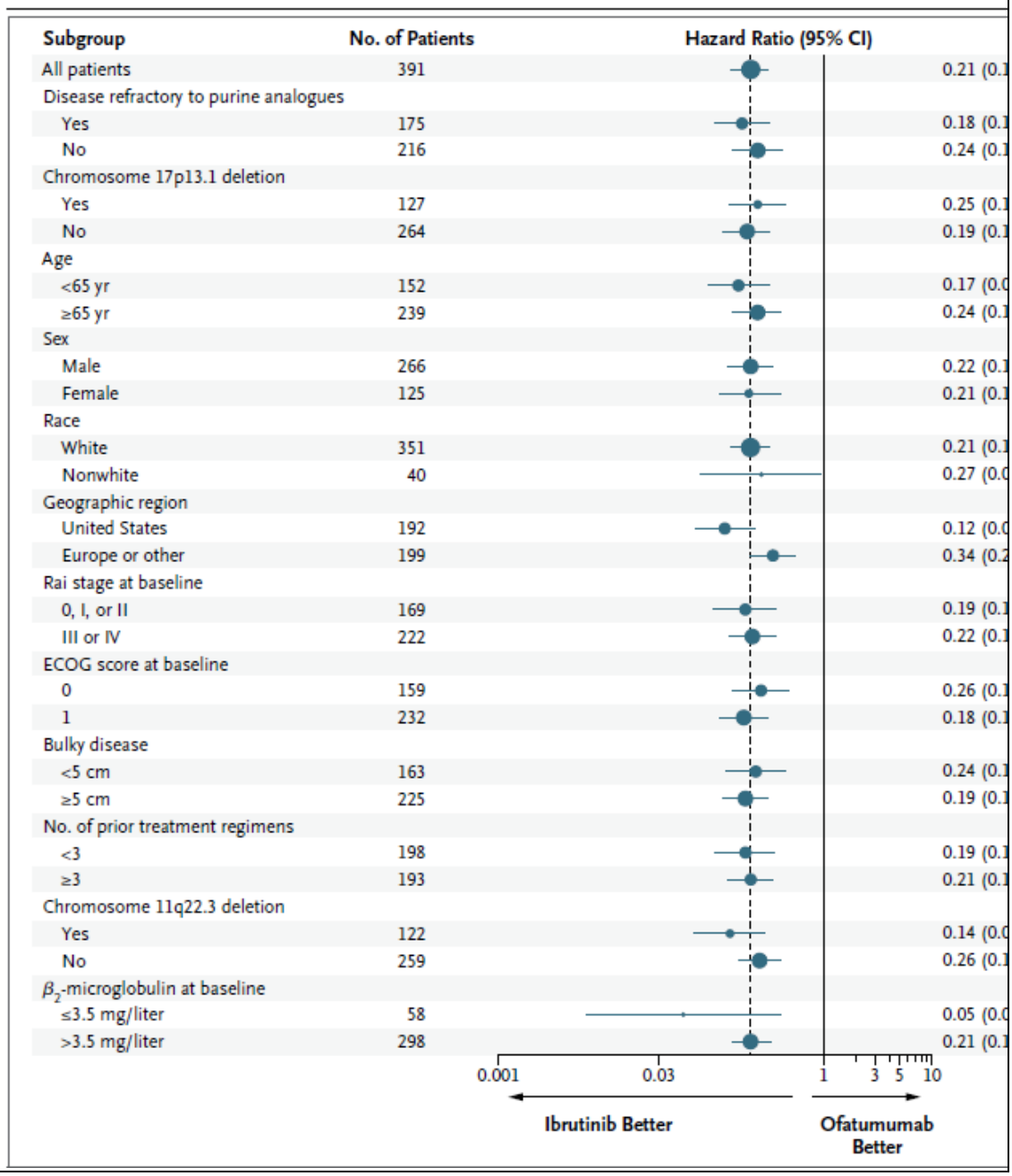
Trial name	RESONATE
NCT number	01578707
Subgroup analyses	

Table 2A: GREEN

Trial name	Green
NCT number	NCT01905943
Objective	Primary objective was to assess the overall safety and tolerability of obinutuzumabbased treatment. An exploratory objective was to investigate the effectiveness of different approaches to reduce infusion-related reactions (IRRs), which were observed during obinutuzumab infusion in the CLL11 trial, particularly during the first administration
Publications – title, author, journal, year	Véronique Leblond, Melih Aktan, Christelle M. Ferra Coll, Caroline Dartigeas, Jens Kisro, Marco Montillo, João Raposo, Jean-Louis Merot, Susan Robson, Ekaterina Gresko, Francesc Bosch, Stephan Stilgenbauer and Robin Foà Safety of obinutuzumab alone or combined with chemotherapy for previously untreated or relapsed/refractory chronic lymphocytic leukemia in the phase IIIb GREEN study. Hematologica. 2018.
Study type and design	Non-randomized, non-comparative, open-label study. Patients received intravenous obinutuzumab 1000 mg, alone or with chemotherapy [investigator's choice of fludarabinecyclophosphamide (FC), Clb or bendamustine (benda), based primarily on fitness. Adverse events (AEs) were graded by NCI Common Terminology Criteria for AEs version 4.0. Response was assessed by investigators according to NCI/iwCLL criteria at the final response assessment, scheduled 84 days after the last dose of study medication. RRs were defined as any AE occurring during/within 24 h of obinutuzumab infusion and considered related to obinutuzumab. IRR incidence in first-line patients was an exploratory end point. Safety was evaluated in patients treated with at least one dose of study medication. Response was assessed in the intent-to-treat (ITT) population comprising all enrolled patients. A sample size of 950 patients [630 first-line (approximately equal proportions of fit and unfit) and 320 R/R patients] was planned [based on adequate precision, by 95% Clopper-Pearson confidence intervals (CIs), to estimate incidence rate of grade ≥3 AEs if the observed rate was 1-25%], with no formal statistical hypothesis testing. As a non-randomized study, treatment comparability was not applicable.
Follow-up time	Time-to-event end points are not presented due to insufficient follow up (median, 20.8-28.8 months, depending on treatment); post-treatment follow up is still ongoing for patients who have not discontinued the study.
Population (inclusion and exclusion criteria)	Inclusion Criteria • Previously untreated patients with documented chronic lymphocytic leukemia (CLL) and requiring treatment according to National Cancer Institute (NCI)/International Workshop on CLL (iwCLL) criteria1 OR relapsed and/or refractory patients with documented CLL requiring treatment according to NCI/IWCLL criteria1 (patients with up to three relapses were eligible) • Refractory patients if their last treatment was with single-agent therapy, single-agent chemotherapy or single-agent antibody • Patients with 17p deletion and/or TP53 mutation could be included at the investigator's discretion. • Signed informed consent • Age ≥18 years • Eastern Cooperative Oncology Group performance status 0–2 • Life expectancy of >6 months according to the investigator's opinion • Adequate hematologic function, defined as follows (unless cytopenia is caused by the underlying disease, i.e. no evidence exists of additional bone marrow dysfunction such as myelodysplastic syndrome or hypoplastic bone marrow): o Hemoglobin ≥9.0 g/dL o Absolute neutrophil count ≥1.5×109/L o Platelets ≥75×109/L o For patients who will receive bendamustine: leukocyte count >3000/µL • Able to comply with study protocol procedures. Exclusion Criteria: • Patients who had received more than three previous CLL treatment lines • Documented transformation of CLL to aggressive lymphoma (Richter's transformation) • Patients who were refractory to immunochemotherapy

Trial name	Green
NCT number	NCT01905943

	• 4. Any of the following abnormal laboratory values (unless any of these abnormalities were due to underlying lymphoma):
	  ○ Calculated creatinine clearance (CrCl) <30 mL/min (using the Cockcroft–Gault formula)
	  ○ Aspartate transaminase or alanine transaminase >2.5×upper limit of normal (ULN)
	  ○ Total bilirubin ≥3×ULN
	• At least one individual organ or system with an impairment score of 4 as assessed by the Cumulative Illness Rating Scale (CIRS) definition, excluding the eyes, ears, nose, throat and larynx organ system.
	• Patients with a history of confirmed progressive multifocal leukoencephalopathy
	• History of severe allergic or anaphylactic reactions to monoclonal antibody therapy
	• Known hypersensitivity to the study drugs
	• History of prior malignancy, unless the malignancy had been treated with a curative intent and in remission without treatment for ≥5 years prior to enrollment, and with the exception of curatively treated basal cell carcinoma, squamous cell carcinoma of the skin, low-grade in situ carcinoma of the cervix and low-grade, early-stage localized prostate cancer treated surgically with curative intent
	• Regular treatment (i.e. >5 consecutive days) with corticosteroids during the 28 days prior to the start of cycle 1, day 1, unless administered for indications other than CLL at a dose of prednisone ≤30 mg/day or equivalent
	• Regular treatment with immunosuppressive medications following previous organ
	• transplantation
	• Evidence of significant, uncontrolled co-existing diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, severe arrhythmia, myocardial infarction within the previous 6 months, unstable arrhythmias and unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
	• Known active bacterial, viral, fungal, mycobacterial, parasitic or other infection (excluding fungal infections of nail beds), or any major episode of infection requiring treatment with intravenous antibiotics or hospitalization (relating to the completion of the course of antibiotics, except if for tumor fever) within 28 days prior to the start of cycle 1, day 1
	• Vaccination with live vaccines within 28 days prior to start of cycle 1, day 1
	• Major surgery (within 28 days prior to the start of cycle 1, day 1), other than for diagnosis
	• Positive test results for chronic hepatitis B infection (defined as positive hepatitis B virus surface antigen [HBsAg] serology) and/or hepatitis B core antibody (HBcAb); patients who had protective titers of hepatitis B surface antibody (HBsAb) after vaccination were eligible
	• Positive test results for hepatitis C (hepatitis C virus [HCV] antibody serology testing). Patients positive for HCV antibody were eligible only if polymerase chain reaction was negative for HCV ribonucleic acid (RNA)
	• Known history of human immunodeficiency virus (HIV) infection with seropositive status
	• Positive test results for human T-lymphotropic virus 1 (HTLV-1). HTLV testing was required in patients from disease-endemic countries (Japan, countries in the Caribbean basin, South America, Central America, sub-Saharan Africa and Melanesia)
	• Women who were pregnant or lactating
	• Fertile men or women of childbearing potential unless: (1) surgically sterile or ≥2 years after the onset of menopause; (2) willing to use a highly effective contraceptive method (Pearl Index <1) – such as oral contraceptives, an intrauterine device, sexual abstinence or a barrier method of contraception in conjunction with spermicidal jelly – during study treatment and in female patients for 12 months after the end of antibody treatment and in male patients for 6 months after the end of chemotherapy treatment
	• Participation in another clinical trial with drug intervention within 28 days prior to the start of cycle 1, day 1 and during the study.

Intervention	Patients received intravenous obinutuzumab 1000 mg, alone or with chemotherapy [investigator's choice of fludarabinecyclophosphamide (FC), Clb or bendamustine (benda), based primarily on fitness on days 1 (split over 2 consecutive days), 8 and 15 of cycle 1, and on day 1

Trial name	Green
NCT number	NCT01905943
	of cycles 2-6 (six 28-day cycles). Patients received intravenous prednisolone (or equivalent) 1 hour (h) pre-dose on day 1/day 2 of cycle 1.
Baseline characteristics	**Table 1. Demographics and baseline disease characteristics according to line of therapy and fitness of patients (intent-to-treat population).**

Characteristic	First-line fit (n=339)	First-line unfit (n=292)	First-line all (n=631)	R/R (n=341)	Total (n=972)
Median age, (range) years	59.0 (33-82)	72.0 (45-87)	65.0 (33-87)	68.0 (33-90)	66.0 (33-90)
Age ≥65 years, n (%)	102 (30.1)	223 (76.4)	325 (51.5)	213 (62.5)	538 (55.3)
Age ≥75 years, n (%)	15 (4.4)	114 (39.0)	129 (20.4)	98 (28.7)	277 (28.5)
Male, n (%)	233 (68.7)	166 (56.8)	399 (63.2)	218 (63.9)	617 (63.5)
ECOG performance status, n(%)					
0	237 (69.9)	154 (52.7)	391 (62.0)	188 (55.1)	579 (59.6)
1	98 (28.9)	127 (43.5)	225 (35.7)	134 (39.3)	359 (36.9)
2	4 (1.2)	11 (3.8)	15 (2.4)	19 (5.6)	34 (3.5)
Binet stage, n(%)					
A	97 (28.6)	72 (24.7)	169 (26.8)	77 (22.6)	246 (25.3)
B	161 (47.5)	112 (38.4)	273 (43.3)	127 (37.2)	400 (41.2)
C	81 (23.9)	108 (37.0)	189 (30.0)	131 (38.4)	320 (32.9)
Missing	0	0	0	6 (1.8)	6 (0.6)
B symptoms, n (%) *	120 (35.4)	87 (29.8)	207 (32.8)	114 (33.4)	321 (33.0)
Bulky disease (≥5 cm), n(%)	240 (70.8)	149 (51.0)	389 (61.6)	210 (61.6)	599 (61.6)
Lymphocytes ≥25x10⁹/L, n(%)	259 (76.4)	230 (78.8)	489 (77.5)	214 (62.8)	703 (72.3)
Total CIRS score, n(%)					
≤6	339 (100)	172 (58.9)	511 (81.0)	259 (76.0)	770 (79.2)
>6	0	120 (41.1)	120 (19.0)	82 (24.0)	202 (20.8)
CrCl at screening, n(%)					
<70 mL/min	0	230 (78.8)	230 (36.5)	149 (43.7)	379 (39.0)
≥70 mL/min	339 (100)	62 (21.2)	401 (63.5)	192 (56.3)	593 (61.0)
ZAP-70 expression, n(%)					
Negative	87 (25.7)	72 (24.7)	159 (25.2)	84 (24.6)	243 (25.0)
Positive	189 (55.8)	146 (50.0)	335 (53.1)	160 (46.9)	495 (50.9)
Missing	63 (18.6)	74 (25.3)	137 (21.7)	97 (28.4)	234 (24.1)
CD38 expression, n(%)					
Negative	140 (41.3)	104 (35.6)	244 (38.7)	93 (27.3)	337 (34.7)
Positive	134 (39.5)	115 (39.4)	249 (39.5)	153 (44.9)	402 (41.4)
Missing	65 (19.2)	73 (25.0)	138 (21.9)	95 (27.9)	233 (24.0)
Cytogenetics, n(%)					
17p deletion	14 (4.1)	20 (6.8)	34 (5.4)	46 (13.5)	80 (8.2)
11q deletion	55 (16.2)	33 (11.3)	88 (13.9)	67 (19.6)	155 (15.9)
12q trisomy	45 (13.3)	48 (16.4)	93 (14.7)	33 (9.7)	126 (13.0)
13q deletion	106 (31.3)	97 (33.2)	203 (32.2)	79 (23.2)	282 (29.0)
Other	18 (5.3)	7 (2.4)	25 (4.0)	16 (4.7)	41 (4.2)
No abnormality	58 (17.1)	43 (14.7)	101 (16.0)	33 (9.7)	134 (13.8)
Missing	43 (12.7)	44 (15.1)	87 (13.8)	67 (19.6)	154 (15.8)
IgVH mutation status, n (%)					
Mutated	101 (29.8)	90 (30.8)	191 (30.3)	64 (18.8)	255 (26.2)
Unmutated	181 (53.4)	146 (50.0)	327 (51.8)	188 (55.1)	515 (53.0)
Missing	57 (16.8)	56 (19.2)	113 (17.9)	89 (26.1)	202 (20.8)

R/R relapsed/refractory; ECOG Eastern Cooperative Oncology Group; CIRS Cumulative Illness Rating Scale; CrCl creatinine clearance; n: number; min: minute. *Patients with at least one B symptom (unexplained fever >38°C, drenching night sweats >1 month or weight loss >10% of body mass in preceding 6 months).

Primary and secondary endpoints	Primary endpoint: • AE • grade ≥3 AE • serious AE • AEs of special/particular interest Secondary endpoints: • Overall Response rate • Complete response • Infusion related reactions
Method of analysis	Data are presented using descriptive statistics. Incidence rates and two-sided 95% Clopper-Pearson CI were calculated for grade ≥3 AEs and ORR.

Trial name	Green
NCT number	NCT01905943
	Response was assessed in the intent-to-treat (ITT) population comprising all enrolled patients. A sample size of 950 patients [630 first-line (approximately equal proportions of fit and unfit) and 320 R/R patients] was planned [based on adequate precision, by 95% Clopper-Pearson confidence intervals (CIs), to estimate incidence rate of grade ≥3 AEs if the observed rate was 1-25%], with no formal statistical hypothesis testing. As a non-randomized study, treatment comparability was not applicable.
Subgroup analyses	Patients were stratified accord to following: Line of therapy and fitness: • First-line fit • First-line unfit • First-line all • R/R • Total Treatment: • G-Mono • G+FC • G+Clb • G+Benda

Table 2A: MABLE

Trial name	MABLE
NCT number	NCT01056510
Objective	This study aims to investigate the efficacy and safety of R-B and R-Clb in fludarabine-ineligible CLL patients.
Publications – title, author, journal, year	Anne-Sophie Michallet, Melih Aktan, Wolfgang Hiddemann, Osman Ilhan, Peter Johansson, Kamel Laribi, Balkis Meddeb, Carol Moreno, João Raposo, Anna Schuh, Ali Ünal, Tom Widenius, Alf Bernhardt, Kerstin Kellershohn, Dimitri Messeri, Stuart Osborne and Véronique Leblond Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study. Hematologica. 2018
Study type and design	Patients received Rituximab and either Bendamustine or Chlorambucil as written below. After treatment completion, patients were followed every three months for one year, then every six months until data cut-off. Treatment was discontinued if the patient had progressive disease.
Follow-up time	Median follow-up was 23.5 months (R-B) and 23.3 months (R-Clb).
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Signed and dated written informed consent • Aged 18 years or older • Tumor cell phenotype consistent with chronic lymphocytic leukemia (CLL) by cell surface marker analyses: CD5+, CD19+, and CD23+ (as per local confirmation of diagnosis) • Patients with active CLL (Binet B and C) who required therapy per criteria according to the National Cancer Institute criteria 2008. Symptomatic Binet A patients and/or patients with low/intermediate Rai stages could also be included • Eastern Cooperative Oncology Group performance status ≤2 • Ineligible for treatment with fludarabine • A negative serum pregnancy test within 1 week before the first cycle of treatment must have been available for women who were 2 years after the onset of menopause and not sterilized surgically Exclusion Criteria: • From amendment No. 2, patients treated second-line (2L) were not allowed to be entered in the study • 2. Any other concomitant anti-cancer therapy. Corticosteroids were allowed if they were given for reasons other than CLL and the dose was ≤20 mg of prednisolone equivalent per day • Patients with transformation to aggressive B-cell malignancy • Known or suspected central nervous system involvement of CLL • Any other malignancy within 5 years prior to enrollment except curatively treated carcinoma in situ of the cervix, squamous cell carcinoma of the skin, or basal cell skin cancer. Cervical carcinoma stage 1B or less, breast cancer in situ, or localized prostate cancer stage T1c or less was to be considered, provided that the patient was treated with curative intent and was relapse-free for at least 2 years prior to enrollment • Major surgery (excluding lymph node biopsy) within 28 days prior to first cycle of study treatment • Chronic or ongoing active infectious disease requiring systemic treatment • History of clinically significant cerebrovascular disease with residual sequelae • Patients who had known HIV, active hepatitis B virus, or hepatitis C virus infection • Serious underlying medical conditions that could have impaired the ability of the patient to participate in the study • Inadequate renal and hepatic function per the following laboratory values: creatinine clearance <30 mL/min, total bilirubin >1.5 × upper limit of normal (ULN), alanine aminotransferase and/or aspartate aminotransferase >2.5 × ULN, and alkaline phosphatase >2.5 × ULN • Inadequate hematologic function, defined as absolute neutrophil count <1.0 × 109/l (1000/µl), platelet count <50 × 109 /l (50,000/µl), or hemoglobin <9.0 g/dl, unless due to involvement of bone marrow (BM) by CLL • Known or suspected hypersensitivity to components of investigational product • Life expectancy less than 6 months • Patients known or suspected of not being able to comply with a study protocol

Trial name	MABLE
NCT number	NCT01056510
	• Pregnant or breast-feeding patients • Male and female patients with reproductive potential who were not willing to use an effective method of contraception during the study and 1 year after last dose of study medication • Patients unable to provide informed consent • Patients with severe autoimmune cytopenia as assessed by the physician (Coombs positive patients without clinical signs of autoimmune hemolytic anemia were eligible for study entry) • Patients who had received any investigational treatment within 30 days before screening • Medical condition requiring chronic use of oral corticosteroids in doses >20 mg of prednisolone equivalent/day. Inhaled or topical steroids were permitted
Intervention	Patients received rituximab (intravenous 375 mg/m2 Day [D] 1, Cycle [C] 1 and 500 mg/m2 D1, C2-C6) plus B (intravenous 90 mg/m2 [1L] or 70 mg/m2 [2L] D1 and D2, C1-C6) or Clb (oral 10 mg/m2 D1-D7, C1-C6) every four weeks for six cycles. R-Clb patients without CR after C6 received Clb monotherapy for ≤6 additional cycles or until CR

Trial name	MABLE
NCT number	NCT01056510
Baseline characteristics	Table 1. Demographic characteristics for patients receiving 1L therapy.

	1L therapy	
	R-B (N=121)	R-Clb (N=120)
Age (years)		
Median (min, max)	72 (41, 86)	72 (38, 91)
≥65 years, n (%)	86 (71)	90 (75)
≥75 years, n (%)	45 (37)	44 (37)
Sex		
Male, n (%)	70 (58)	80 (67)
Female, n (%)	51 (42)	40 (33)
Active medical conditions, n		
Median (min, max)	3 (0, 12)	3 (0, 18)
Binet stage, n (%)		
A	6 (5)	8 (7)
B	73 (60)	66 (55)
C	37 (31)	43 (36)
Missing	5 (4)	3 (3)
ECOG PS, n (%)		
0	62 (51)	59 (49)
1	50 (41)	51 (43)
2	9 (7)	8 (7)
Missing	0	2 (2)
Body surface area, m^2		
Mean (SD)	1.811 (0.2382)	1.807 (0.1706)
Min, max	1.30, 2.48	1.41, 2.29
IGVH mutational status, n (%)		
Mutated	41 (34)	46 (38)
Unmutated	73 (60)	59 (49)
Other[a]	3 (3)	8 (7)
Not tested	4 (3)	7 (6)
11q status, n (%)		
Heterozygous deletion	24 (20)	19 (16)
Normal	96 (79)	99 (83)
Not tested	1 (1)	2 (2)
17p status, n (%)		
Heterozygous deletion	10 (8)	3 (3)
Normal	110 (91)	114 (95)
Not tested	1 (1)	3 (3)
11q/17p deletion, n (%)		
Heterozygous deletion	32 (26)	22 (18)
Normal	88 (73)	96 (80)
Not tested	1 (1)	2 (2)
13q deletion (S25 or S319 probe)[b], n (%)		
Homozygous deletion	3 (3)	1 (1)
Two clones (one homozygote, one heterozygote)	15 (12)	6 (5)
Heterozygous deletion	42 (35)	5 (4)
Normal	61 (50)	60 (50)
Not tested	1 (1)	2 (2)
Trisomy 12, n (%)		
Trisomy	30 (25)	19 (16)
Normal	90 (74)	99 (83)
Not tested	1 (1)	2 (2)

[a]Other includes polyclonal and oligoclonal. [b]Deletion status according to at least one probe (NB, in the R-B group, one patient with two clones by S319 probe and heterozygous deletion by S25 probe is counted twice). 1L: first-line; ECOG PS: Eastern Cooperative Oncology Group performance status; R-B: rituximab plus bendamustine; R-Clb: rituximab plus chlorambucil; SD: standard deviation.

Primary and secondary endpoints	Primary endpoints: • Complete response rate in 1st line treated patients after cycle 6 Secondary endpoints: • Complete response rate in 2nd line treated patients after cycle 6 • Progression-free survival • Overall survival • Time to next leukemic treatment • Minimal residual disease • Safety Response was assessed after C3 and C6 as per iwCLL 2008 Guidelines. Response was also assessed in the R-Clb arm at C12, with treatment being discontinued for patients showing evidence of CR during C7-C12

Trial name	MABLE
NCT number	NCT01056510
Method of analysis	Efficacy analyses were conducted on the intent-to-treat (ITT) population. The safety population included all randomized patients who received treatment. For 1L patients, the between-arm difference in response rates was tested using a one-sided continuity-corrected $\chi 2$ test. A twosided continuity-corrected $\chi 2$ test assessed between-arm differences in overall response rates (ORRs) and molecular responses. PFS and OS were summarized by Kaplan–Meier estimates and compared via the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated based on the Cox proportional hazard model, with and without baseline Binet stage as a covariate
Subgroup analyses	Groups were divided according to treatment line, and endpoints were evaluated in 1st and 2nd line treatment.

7.1.5 Results per study

Table 3A: MURANO

					Estimated absolute difference in effect			Estimated relative difference in effect			Comments
Outcome	Arm	n	Result	CI	Difference	CI	p-value	HR/OR/RR	Ci	p-value	
Median PFS*	V+R	194	NR	NA	NA	NA	NA	HR: 0,17	0,12-0,26	<0,001	Assessed using Kaplan-Meier. ITT population. Stratified log-rank test
	B+R	195	17 months	NA							
Median PFS	V+R	194	NR	NA	NA	NA	NA	HR: 0.16	0.23-0.23	<0.001	Assessed using Kaplan-Meier. Log-rank Test.
	B+R	195	17 months	NA							
PFS 2 years *	V+R	194	85%	79,1-90,6	NA	NA	NA	HR: 0,17	0,11-0,25	<0,001	Investigator-assessed stratified log-rank test
	B+R	195	36%	28,5-44							
PFS 3 years	V+R	194	71%	64,8-78,1	NA	NA	NA	NA	NA	NA	
	B+R	195	15.2	9,1-21,4							
Overall survival 2 year estimate*	V+R	194	91.9%	NA	NA	NA	NA	HR: 0.48	0.25-0.90	NA	Assessed using Kaplan-Meier. ITT population. Stratified Log-rank test
	B+R	195	86.6%	NA							
Overall survival 3 year estimate	V+R	194	87.90%	NA	NA	NA	NA	HR: 0,50	0,30-0,85	0.0093	Assessed using Kaplan-Meier. Log-rank Test.
	B+R	195	79.50%	NA							
MRD at 9 monthsΔ	V+R	194	62.4%	NA	NA	NA	NA	NA	NA	NA	For further information regarding statistical analyses, see publications by Seymour et al and Kater et al listed in table text.
	B+R	195	13%	NA							
uMRD 24 months after EOT∞	V+R	130	64%	NA	NA	NA	NA	NA	NA	NA	
	B+R	NA	13%	NA							
uMRD 24 months after EOT, del17p∞	V+R	NA	56.9%	NA	NA	NA	NA	NA	NA	NA	
	B+R	NA	5.3%	NA							
AE grade 3-4*	V+R	194	159 (82%)	NA	NA	NA	NA	NA	NA	NA	
	B+R	188	132 (70.2%)	NA							
AE grade 3-4	V+R Combination Period	194	145 (74.7%)	NA	NA	NA	NA	NA	NA	NA	
	V Single agent peroid	171	59 (34.5%)	NA							
Median PFS* Del17p	V+R	46	NR	NA	NA	NA	NA	HR: 0.21	0.11-0.39	NA	
	B+R	46	15.4 months	NA							

PFS 2 year estimate* Del17p	V+R	46	81.5%	NA	NA	NA	NA	HR: 0.13	0.05-0.29	NA	Kaplan-Meier assessed using 7% Cutoff value. Investigator-assessed. Strafitied Log-rank test.
	B+R	46	27.8%	NA							
PFS* TP53 mutation	V+R	48	NR	NA	NA	NA	NA	HR: 0.19	0.10-0.36	NA	
	B+R	51	12.9	NA							
ORR*	V+R	194	93.3%	NA	25.6%	17.9-33.3	NA	NA	NA	NA	
	B+R	195	67.7%	NA							
CR/Cri*	V+R	194	26.8%	NA	18.6%	NA	NA	NA	NA	NA	
	B+R	195	8.2%	NA							

Source: Kater et al.(3), *Seymour et al.(4)

Note:

Δ I Peripheral blood at EOCTR-visit 8-12 weeks anfter Cycle 1 Day 1. MRD-negativity was defined as the presence of <1 malignant B-cell per 10000 normal B-cells in a sample of at least 200000 B-cells

∞ In peripheral blood 2 to 3 months after EOTC. Also assessed at C4 and every 3 to 6 months. considered undetectable (uMRD) if the result was less than one CLL cell in 10,000 leukocytes (MRD value less than 0.0001)

Table 3A: M13-982

					Estimated absolute difference in effect			Estimated relative difference in effect			Comments
Outcome	Arm	n	Result	CI	Difference	CI	p-value	HR/OR/RR	Ci	p-value	
Overall Response*	Ven mono	107	85 (79%)	NA	NA	NA	NA	NA	NA	NA	For further information regarding statistical method see Publications by Stilgenbauer et al. listed in table text.
PFS 12 months estimate*	Ven mono	107	72%	61.8–79.8	NA	NA	NA	NA	NA	NA	
OS 12 months estimate*	Ven mono	107	86.7%	78.6–91.9	NA	NA	NA	NA	NA	NA	
MRD i Peripheral blod*	Ven mono	45	18	NA	NA	NA	NA	NA	NA	NA	
MRD in BM*	Ven mono	45	10	NA	NA	NA	NA	NA	NA	NA	
AE Grade 3-4*	Ven mono	107	69 (65%)	NA	NA	NA	NA	NA	NA	NA	
PFS 12 months estimate*, TP53	Ven mono	60	69.3%	55.1-79.8	NA	NA	NA	NA	NA	NA	
PFS 24 months estimate, R/R	Ven mono	153	53%	44-61	NA	NA	NA	NA	NA	NA	

					Estimated absolute difference in effect			Estimated relative difference in effect			Comments
Outcome	Arm	n	Result	CI	Difference	CI	p-value	HR/OR/RR	Ci	p-value	
OS 24 months estimate, R/R	Ven mono	158	72%	65-79	NA	NA	NA	NA	NA	NA	
Median PFS, R/R	Ven mono	153	25.6 months	NA	NA	NA	NA	NA	NA	NA	
Median OS, R/R	Ven mono	153	38.8 months	NA	NA	NA	NA	NA	NA	NA	
MRD in Blood	Ven mono	158	48 (30%)	NA	NA	NA	NA	NA	NA	NA	
AE grade 3-4	Ven mono	158	119 (75%)	NA	NA	NA	NA	NA	NA	NA	

Source: Stilgenbauer et al 2016.(1) Stilgenbauer et al 2018(2)

Note: *MRD negativity is defined as fewer than one chronic lymphocytic leukaemia cell in 10 000 nucleated cells. See study method of analysis for full description

Tabel 3A: M14-032 study

					Estimated absolute difference in effect			Estimated relative difference in effect			Comments
Outcome	**Arm**	**n**	**Result**	**CI**	**Difference**	**CI**	**p-value**	**HR/OR/RR**	**Ci**	**p-value**	
Overall response	Main Cohort	43	70%	54-83	NA	NA	NA	NA	NA	NA	For further information regarding statistical method see Publication by Jones et al. listed in table text
	Expansion	48	60%	43-72							
CR/CRi	Main Cohort	43	9%	NA	NA	NA	NA	NA	NA	NA	
	Expansion	48	8%								
Median PFS	Ven Mono	127	25 months	19.6 NR	NA	NA	NA	NA	NA	NA	
PFS 12 and 24 months estimate	Ven Mono	127	77% 54%	68.1-83.4 41.8-64.6	NA	NA	NA	NA	NA	NA	
M14	Ven Mono	127	NR	27.8-NR	NA	NA	NA	NA	NA	NA	
OS 12 months estimate	Ven Mono	127	91.0%	85.6-95.6	NA	NA	NA	NA	NA	NA	
Overall response, Del17p or TP53 mutation	Ven Mono	46	61%	45-75	NA	NA	NA	NA	NA	NA	
Best MRD, In peripheral blood	Ven Mono	127	25%	NA	NA	NA	NA	NA	NA	NA	
SAE	Ven Mono	91	45 (50%)	NA	NA	NA	NA	NA	NA	NA	

Source: Jones et al.(5)

Tabel 3A: Venice II

NCT02980731					Estimated absolute difference in effect			Estimated relative difference in effect			Comment
Outcome	Arm	n	Result	CI	Difference	CI	p-value	HR/OR/RR	Ci	p-value	
AE grade 3+	V+R	169	82 (49%)		NA	NA	NA	NA	NA	NA	
Mean change EORTC QLQ-C30	V+R	22	+11.4	3.1-19.6	NA	NA	NA	NA	NA	NA	For further information regarding statistical method see Publication by Cochrane et al. listed in table text Mean change at week 48
Mean change Role functioning	V+R	22	+13.6	4.1-23.3	NA	NA	NA	NA	NA	NA	
Mean change emotional functioning	V+R	22	+4.5	-1.2-10.3	NA	NA	NA	NA	NA	NA	
Mean change Cognitive function	V+R	22	+5.3	-1.3-11.9	NA	NA	NA	NA	NA	NA	
Mean change Social function	V+R	22	+9.8	1.1-18.6	NA	NA	NA	NA	NA	NA	
Mean change Pain	V+R	22	-6.1	-14.1-2.0	NA	NA	NA	NA	NA	NA	
Mean change Fatique	V+R	22	-10.6	-20.2--1.1	NA	NA	NA	NA	NA	NA	
Mean change EORTC-QLQ-CLL16	V+R	22	-21.2	-41.9--0.5	NA	NA	NA	NA	NA	NA	

Source: Cochrane et al.(24)

Table 3A: HELIOS

					Estimated absolute difference in effect			Estimated relative difference in effect			Comments
Outcome	Arm	n	Result	CI	Difference	CI	p-value	HR/OR/RR	Ci	p-value	
PFS at 17 months follow-up*	Ibrutinib+BR	289	NR	NR	NA	NA	NA	HR: 0.203	0.150-0.276	<0.0001	Kaplan Meier assessed. Log Rank test. IRC-assessed
	BR	289	13.3 months	11.3-13.9							
PFS 18 months estimate*	Ibrutinib+BR	289	79%	73-83	NA	NA	NA	HR: 0.203	0.150-0.276	<0.0001	
	BR	289	24%	18-31							
PFS at 34,8 months follow-up	Ibrutinib+BR	289	NR	NR	NA	NA	NA	HR: 0.206	0.158-0.265	<0.0001	Kaplan Meier assessed. Log Rank test. Investigator-assessed
	BR	289	14.3 months	NA							
PFS 36 months estimate	Ibrutinib+BR	289	68%	NA	NA	NA	NA	NA	NA	NA	
	BR	289	13.9%	NA							
Overall survival*	Ibrutinib+BR	289	NR	NA	NA	NA	NA	HR: 0.62	0.39-1.02	0.0598	Kaplan Meier assessed. Log Rank test. Unadjusted for cross-over. IRC-assessed
	BR	289	NR	NA							
Overall survival at 34.8 months follow-up	Ibrutinib+BR	289	NR	NA	NA	NA	NA	0.652	0.454-0.935	0.019	Kaplan Meier assessed. Log Rank test. Unadjusted for cross-over. Investigator-assessed
	BR	289	NR	NA							
Overall survival 36 months rate	Ibrutinib+BR	289	81.6%	NA	NA	NA	NA	NA	NA	NA	For further information regarding statistical method see
	BR	289	72.9%	NA							
MRDΔ	Ibrutinib+BR	289	13%	NA	8%	NA	0.0011	NA	NA	NA	
	BR	289	5%	NA							
MRD	Ibrutinib+BR	289	26.3%	NA	NA	NA	NA	NA	NA	NA	
	BR	289	6.2%	NA							

AE Grade 3-4*	Ibrutinib+BR	287	222 (77%)	NA	NA	NA	NA	NA	NA	NA	Publication by Chanan-Khan et al. and Fraser et al. listed in table text
	BR	287	212 (74%)	NA							
TEAE grade 3 or above	Ibrutinib+BR	287	254 (88.5%)	NA	NA	NA	NA	NA	NA	NA	

Source: Fraser et al(11),* Chanan-Khan et al(10)

Note: ΔAssessed in patients with suspected clinical or radiographic complete response. Analyzed in ITT-population. (<1 chronic lymphocytic leukaemia cell per 10 000 leucocytes)

Table 3A: RESONATE

					Estimated absolute difference in effect			Estimated relative difference in effect			Comments
Outcome	Arm	n	Result	CI	Difference	CI	p-value	HR/OR/RR	Ci	p-value	
PFS at 9.4 months followup*	Ibrutinib	195	NR	NA	NA	NA	NA	HR: 0.22	0.15-0.32	<0.001	Log-rank test stratified according to presence or absence of chromosome 17p13.1 deletion and the disease refractory status at randomization. IRC-assessed
	Ofatumumab	196	8.1 Months	7.2-8.3							
PFS 12 months rate***	Ibrutinib	195	84%		NA	NA	NA	NA	NA	NA	Investigator-assessed. Otherwise equal to original article
	Ofatumumab	196	18%								
PFS at 19 months followup***	Ibrutinib	195	NR	NA	NA	NA	NA	HR: 0.106	0.075-0.151	<0.0001	
	Ofatumumab	196	8.1 Months	NA							
PFS at 44 months	Ibrutinib	195	NR	NA	NA	NA	NA	HR: 0,133	0,099-0,178	<0,0001	Investgator Assessed.
	Ofatumumab	196	8,11 Months	NA							
PFS 18 months rate***	Ibrutinib	195	76%	NA	NA	NA	NA	NA	NA	NA	Investigator-assessed. Otherwise equal to original article
	Ofatumumab	196	8%	NA							
PFS 24 months rate***	Ibrutinib	195	74%	NA	NA	NA	NA	NA	NA	NA	
	Ofatumumab	196	NA	NA							
PFS 3 years	Ibrutinib	195	59%	NA	NA	NA	NA	NA	NA	NA	Investigator-assessed.
	Ofatumumab	196	3%	NA							
Overall survival*	Ibrutinib	195	NR	NA	NA	NA	NA	Hr:0.43	0.24-0.79	0.005	Log-rank test stratified according to presence or absence of chromosome 17p13.1 deletion and the disease refractory status at randomization. IRC-assessed. Censored at the time of crossover.
	Ofatumumab	196	NR	NA							
12 months overall survival rate*	Ibrutinib	195	90%	NA	NA	NA	NA	NA	NA	NA	
	Ofatumumab	196	81.5%	NA							
Overall survival 18 months***	Ibrutinib	195	86%	NA	NA	NA	NA	HR: 0.36	0,208-0,628		Investigator-assessed. Otherwise equal to original article
	Ofatumumab	196	77%	NA							
OS at 3 years	Ibrutinib	195	NR	NA	NA	NA	NA	HR: 0,591	0,378-0,926	0.0208	Investigator-assessed. Censored for crossover.
	Ofatumumab	196	NR	NA							
AE grade 3-4 at 9.4 months*	Ibrutinib	195	99 (51%)	NA	NA	NA	NA	NA	NA	NA	

	Ofatumumab	191	74 (39%)	NA							
AE grade 3-4 at median 19 months***^	Ibrutinib	195	113 (58%)	NA	NA	NA	NA	NA	NA	NA	
	Ofatumumab	NA	NA	NA							
EORTC QLQ-C30 Baseline**	Ibrutinib	118	60	NA	NA	NA	NA	NA	NA	NA	
	Ofatumumab	89	58.3	NA							
Improvement in Global health status after 24 weeks**	Ibrutinib	132	9 ± 24.1	NA	NA	NA	NA	NA	NA	NA	
	Ofatumumab	107	5.8 ± 21.5	NA							
Overall survival*, Del17P	Ibrutinib	63	NA	NA	NA	NA	NA	HR: 0.46	0.20-1.07	NA	Log-rank Test. IRC-assessed
	Ofatumumab	64	NA	NA							
Median PFS*, Del17P	Ibrutinib	63	NR	NA	NA	NA	NA	HR: 0.25	0.14-0.45	NA	
	Ofatumumab	64	5.8 months	NA							
PFS 18 months rate***, Del17P	Ibrutinib	63	71%	NA	NA	NA	NA	NA	NA	NA	Log-Rank Test. Investigator assessed.
	Ofatumumab	64	7%	NA							
Median PFS***, Del17P	Ibrutinib	63	NA	NA	NA	NA	NA	HR: 0.129	0.073-0.227	<0.0001	
	Ofatumumab	64	NA	NA							
PFS at 44 months, Del17P	Ibrutinib	63	NA	NA	NA	NA	NA	HR: 0.125	0.074-0.21	NA	Investigator-assessed
	Ofatumumab	64	NA	NA							
OS at 44 months, TP53	Ibrutinib	79	NA	NA	NA	NA	NA	HR: 0.172	0.11-0.266	NA	
	Ofatumumab	68	NA	NA							

Source: *Byrd et al.(9), **Barrientos et al.(6), ***Brown et al(7), Byrd et al.(8)

Note: Δ All grade 3-4 summarized

Table 3A: MABLE

MABLE	NCT01056510				Estimated absolute difference in effect			Estimated relative difference in effect			Comments
Outcome	Arm	n	Result	CI	Difference	CI	p-value	HR/OR/RR	Ci	p-value	
Median PFS, 2L	B+R	57	26	NA	NA	NA	NA	0.701	0.431-1.138	0.151	Kaplan–Meier estimates and compared via the log-rank test. Investigator assessed. HR calculated based on the Cox proportional hazard model. Adjusted for Binet Stage.
	Clb+R	59	16.9	NA							
Median OS, 2L	B+R	57	NR	NA	NA	NA	NA	0.682	0.318-1.462	0.325	
	Clb+R	59	40.3	NA							
MRD, 2LΔ	B+R	57	5 (9%)	NA	NA	NA	NA	NA	NA	NA	For further information regarding statistical method see Publication by Michallet et al. listed in table text
	Clb+R	59	5 (9%)	NA							
AE grade 3-4∞	B+R	177	132 (75%)	NA	NA	NA	NA	NA	NA	NA	
	Clb+R	178	113 (64%)	NA							

Source: Michallet et al.(13)

Note:

ΔMRD was assessed in PB at baseline. For patients with CR/PR after C6, MRD was analyzed in BM aspirates (or PB when BM was unavailable) at the confirmation-of-response visit. MRD negativity was defined as a ratio of malignant B-cells to white blood cells of 0.0001

∞Pooled 1st and 2nd line patients

Table 3A: GREEN

					Estimated absolute difference in effect			Estimated relative difference in effect			Comments
Outcome	Arm	n	Result	CI	Difference	CI	p-value	HR/OR/RR	Ci	p-value	
AE above or equal to grade 3	First line Fit	339	266	NA	NA	NA	NA	NA	NA	NA	For further information regarding statistical method see Publication by LeBlond et al. listed in table text
	First line Unfit	291	233	NA							
	R/R	341	281	NA							
AE above or equal to grade 3	G-mono	126	95	NA	NA	NA	NA	NA	NA	NA	
	G+FC	193	169	NA							
	G+Clb	114	87	NA							
	G+Benda	538	429	NA							
ORR 1st line	G-mono	127	63.5%	50.4-75.3	NA	NA	NA	NA	NA	NA	
	G+FC	193	89.5%	83.6-93.9							
	G+Clb	114	82.4%	71.2-90.5							
	G+Benda	538	81.8%	77.4-85.8							
CR 1st line	G-mono	127	20.6%	NA	NA	NA	NA	NA	NA	NA	
	G+FC	193	82.5%	NA							
	G+Clb	114	54.3%	NA							
	G+Benda	538	72.8%	NA							
ORR, R/R	G-mono	127	42.2%	29.9-55.2	NA	NA	NA	NA	NA	NA	
	G+FC	193	82.5%	67.2-92.7							
	G+Clb	114	54.3%	39.0-69.1							
	G+Benda	538	72.8%	65.9-79.0							
CR, R/R	G-mono	127	4.7%	NA	NA	NA	NA	NA	NA	NA	
	G+FC	193	22.5%	NA							
	G+Clb	114	6.5%	NA							
	G+Benda	538	19.9%	NA							
ORR in del17p, n=80, R/R	G-mono	6	33.3%	NA	NA	NA	NA	NA	NA	NA	
	G+FC	6	83.3%	NA							
	G+Clb	7	71.4%	NA							
	G+Benda	27	44.4%	NA							

Source: Leblond et al.(12)

7.2 Statistical methodology

Computation of absolute difference in direct comparison for venetoclax+rituximab vs. bendamustine+rituximab has been based on estimated HRs on OS and PFS from the Murano study. These were used to estimate the absolute differences for these outcomes.

Risk Ratios (RRs) were estimated for MRD negativity and AE grade 3-4 using frequency data from the Seymour publication based on 24 md follow-up(4). The RRs were estimated using the Mantel-Haenszel risk ratio with 95% confidence intervals in fixed effects models in ReVman 5.3(23) (see Forest plots included in appendix 7.3).

Absolute effects, defined as risk-difference assuming comparator event rate were calculated using the estimated risk ratio in the following formula for OS and PFS:

- RD = EXP(ln(ACR) * HR)-ACR

  Where RD is risk difference, ACR is the event rate for the relevant outcome and HR is the hazard ratio

- RD = ACR * (RR-1)

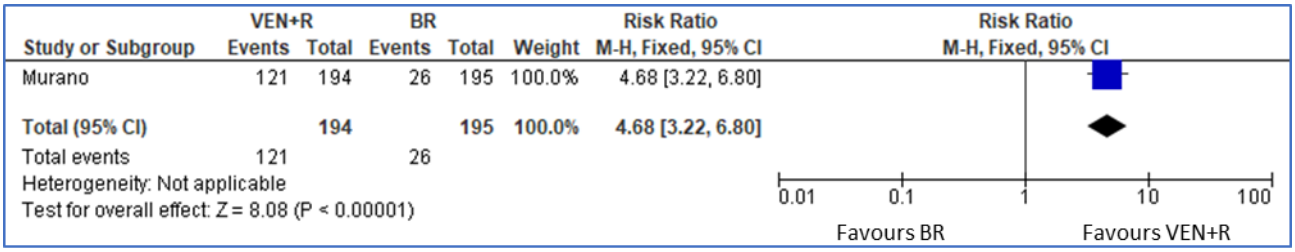
  Where RD is risk difference, ACR is the event rate for the relevant outcome

For both formulas, the ACR was the event rate in the BR arm of the Murano study.

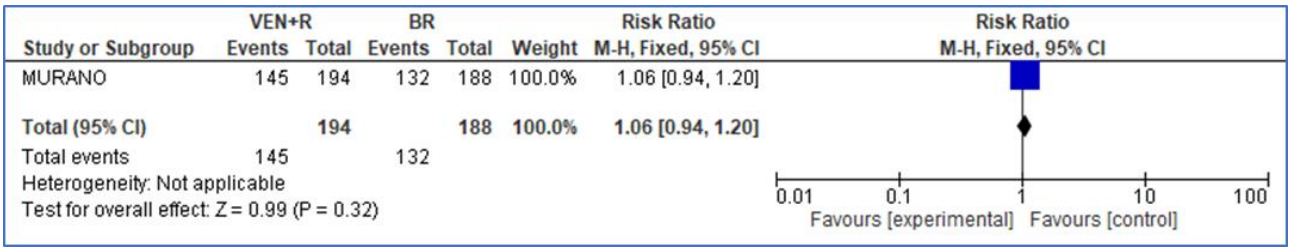
The estimated 95% confidence interval for RD was computed by inserting the low and high confidence limit estimated using the Mantel-Haenszel risk ratio 95% confidence intervals in the formula for RD.

7.3 Forest plots

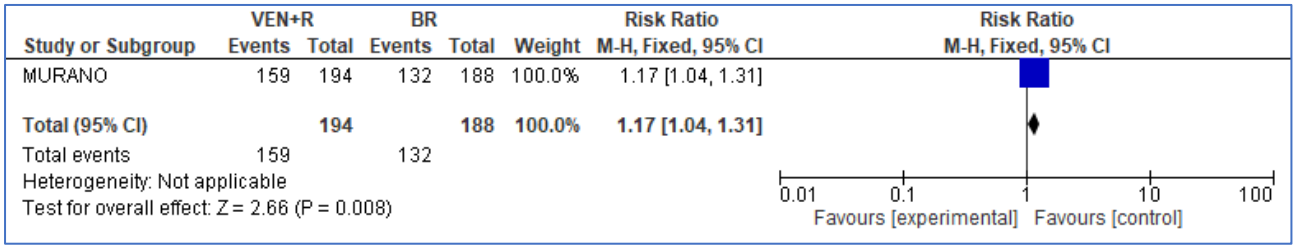
MRD



AE grade 3-4, EOCT



AE grade 3-4, EOT



7.4 Results per PICO

Table A4. PICO for VEN+R vs BR

Outcome	Studies included in the analysis	Absolute difference, Fixed Effects, ACR based on BR in MURANO		Relative difference in effect		Methods used
		Difference (%)	CI	HR/RR	CI	
OS	MURANO	9.7%	[13.8%;2.8%]	0.50	[0.3;0.85]	*
PFS	MURANO	58.8%	[64.6%;49.6%]	0.16	[0.12;0.23]	*
MRD	MURANO	48.9%	[29.5%;77.1%]	4.68	[3.22;6.8]	
EORTC-QLQ-C30						*See section 5.4*
AE grade 3-4, EOCT	MURANO	4.2%	[-4.2%;14%]	1.06	[0.94;1.2]	**
AE grade 3-4, EOT	MURANO	11.9%	[2.8%;21.8%]	1.17	[1.04;1.31]	**

Note: **Publis*

*hed HR used, **RR estimate using the fixed effects Mantel-Haenszel risk ratio with 95% confidence intervals in RevMan 5.3(23)*

Medicinrådet

Medicinrådets protokol for vurdering af venetoclax i kombination med rituximab til behandling af patienter med kronisk lymfatisk leukæmi der har modtaget mindst én tidligere behandling

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om protokollen

Protokollen er grundlaget for Medicinrådets vurdering af et nyt lægemiddel. Den indeholder et eller flere kliniske spørgsmål, som ansøger skal besvare i den endelige ansøgning, og som Medicinrådet skal basere sin vurdering på.

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	15. maj 2019
Ikrafttrædelsesdato	16. maj 2019
Dokumentnummer	49206
Versionsnummer	1.0

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil ansøgende virksomhed få besked.

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Udgivet af Medicinrådet, den 16. maj 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Venclyxto®
Generisk navn	Venetoclax
Firma	Abbvie
ATC-kode	L01XX52
Virkningsmekanisme	Venetoclax hæmmer det antiapoptotiske protein BCL-2, som er overekspresseret i B-cellerne hos patienter med kronisk lymfatisk leukæmi.
Administration/dosis	Venetoclax p.o. 20 mg dagligt i uge 1, 50 mg dagligt i uge 2, 100 mg dagligt i uge 3, 200 mg dagligt i uge 4, 400 mg dagligt i uge 5 og herefter 400 mg dagligt fra uge 6 og 24 måneder frem. Fra uge 6, i 6 serier a 28 dage rituximab 375 mg/m^2 i.v. på dag 1 i serie 1, 500 mg/m^2 på dag 1 i serie 2-6.
Forventet EMA-indikation	Venetoclax i kombination med rituximab til voksne patienter med kronisk lymfatisk leukæmi der har modtaget mindst en tidligere behandling.

2 Forkortelser

BCL-2:	B-celle-lymfom 2
CI:	Konfidensinterval
CIRS:	*Cummulative illness rating scale*
CLL:	Kronisk lymfatisk leukæmi
EMA:	*European Medicines Agency*
EORTC:	*European Organisation for Research and Treatment of Cancer*
FISH:	Flourescens in-situ hybridisering
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
IGHV:	*Immunoglobulin heavy chain variable region*
IWCLL:	*International workshop on Chronic Lymphatic Lymphoma*
OR:	*Odds ratio*
QLQ:	*Quality of life questionnaire*
RR:	Relativ risiko

3 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af venetoclax i kombination med rituximab som mulig standardbehandling af patienter med kronisk lymfatisk leukæmi, som har modtaget mindst én tidligere behandling. I protokollen angives en definition af population(er), komparator(er) og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende venetoclax i kombination med rituximab modtaget den 24. september 2018.

Protokollen danner grundlag for den endelige ansøgning for vurdering af venetoclax i kombination med rituximab sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem venetoclax i kombination med rituximab og komparator af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

4 Baggrund

Kronisk lymfatisk leukæmi er en hæmatologisk kræftsygdom, som opstår i kroppens B-lymfocytter og påvirker cellernes regulering af celledeling og celledød. Det fører til en ophobning af B-lymfocytter bl.a. i knoglemarv, lymfeknuder, milt og blod. B-cellernes normale funktioner svækkes, ligesom funktionen af knoglemarvens andre celler kan være påvirket. Symptomerne hos patienter med kronisk lymfatisk leukæmi er relaterede hertil og omfatter typisk hævede lymfeknuder, forstørret milt, blodmangel, træthed, uforklarlig feber, vægttab og øget infektionstendens.

Kronisk lymfatisk leukæmi er den almindeligste leukæmi i de vestlige lande, og diagnosen udgør her ca. 30 % af samtlige leukæmier [1]. Incidensen er i Danmark ca. 6-7 pr. 100.000 indbyggere pr. år, og der registreres ca. 450-500 nye tilfælde om året i Danmark. Det estimeres, at ca. 4.000 patienter lever med sygdommen i Danmark [2]. Medianalderen er ved diagnose 70 år, og dobbelt så mange mænd som kvinder får diagnosen [1,3].

Kronisk lymfatisk leukæmi er ofte asymptomatisk på diagnosetidspunktet og kan blive opdaget tilfældigt efter en blodprøve. Diagnosen stilles ved konstatering af persisterende lymfocytose, dvs. > 5 mia. monoklonale B-celler pr. liter blod i tre måneder eller derover. På diagnosetidspunktet foretages en vurdering af sygdomsstadie (baseret på sygdomsudbredelse, Binet-stadieinddeling) og sygdommens aggressivitet (risikoprofil på baggrund af cytogenetiske forandringer, *immunoglobulin heavy-chain variable region* (IGHV)-mutationsstatus). Både sygdomsstadie, patientens symptomer og risikoprofil har indflydelse på igangsættelse og valg af behandling, ligesom de har betydning for patienternes prognose. Kronisk lymfatisk leukæmi har ofte et indolent forløb, hvor patienterne med tidlige stadier og langsomt progredierende sygdom følges ved årlige kontroller eller afsluttes til egen læge. Median overlevelse fra diagnosetidspunktet varierer fra 4 til > 12 år afhængig af sygdomsstadie og risikoprofil.

4.1 Nuværende behandling

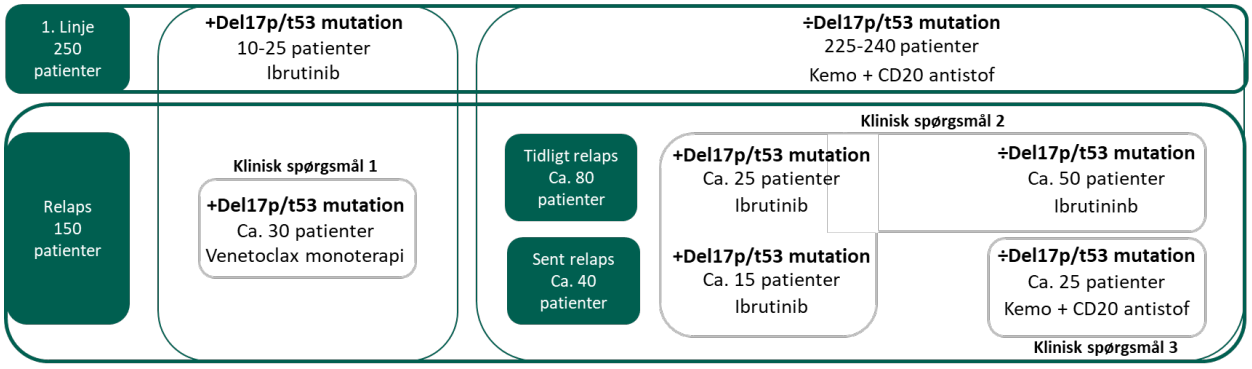
Behandlingen af kronisk lymfatisk leukæmi varetages af de hæmatologiske afdelinger. På diagnosetidspunktet skelnes mellem behandlingskrævende og ikkebehandlingskrævende sygdom. Ikkebehandlingskrævende sygdom følges med watch and wait, indtil sygdommen bliver behandlingskrævende ifølge kriterier defineret af IWCLL.

Behandlingsstrategien afhænger af patientspecifikke faktorer (performancestatus, komorbiditet (cumulative illnes rating scale (CIRS)), alder, præferencer), sygdomskarakteristika (tumorbyrde, stadie, risikoprofil (FISH), mutationsstatus) og behandlingsmuligheder.

I behandlingsøjemed opdeles patientpopulationen efter, hvorvidt de har deletion17p/p53-mutation eller ej og efter performancestatus, alder og komorbiditeter.

Hvorvidt patienterne har deletion17p/p53-mutation eller ej er afgørende for, om de i 1. linje er kandidater til cytostatika i form af enten chlorambucil, fluradabin og cyclofosfamid eller bendamustin i kombination med et CD20-antistof. Patienter med deletion17p/p53-mutation er ikke følsomme for behandling med cytostatika og behandles i stedet med proteinkinasehæmmeren ibrutinib. For patienter uden deletion17p/p53-mutation afgøres valget af cytostatika og CD20-antistof af patientens alder, performancestatus og mængden af komorbiditet [4]. Traditionelt har man anvendt cytostatika i første linje, når det var muligt, fordi de medicinske behandlingsmuligheder har været få, og fordi højere alder og deletion17p/p53-mutation senere i sygdomsforløbet kan udelukke behandling med cytostatika. Desuden har man god, langvarig dokumentation for effekt og bivirkninger ved de velkendte kemoterapier, mens viden om den langsigtede effekt af nyere behandlinger er sparsom. I takt med nye og mere målrettede behandlingsmuligheder er der dog påbegyndt en bevægelse væk fra anvendelse af cytostatika, blandt andet fordi cytostatika er forbundet med langvarig immundepletion.

Figur 1 viser nuværende behandlingsalgoritme. Der er ca. 150 patienter om året med behandlingsbehov i 2. linje [4]. Ved tidligt relaps behandles både patienter uden og patienter med nytilkommen deletion17p/p53-mutation med ibrutinib (ca. 90 patienter) [4]. Patienter, der i 1. linje blev behandlet med ibrutinib, behandles hovedsageligt med venetoclax monoterapi (ca. 30 patienter). Hos patienter uden deletion17p/p53-mutation med sent relaps (senere end 3 år efter sidste behandling) kan kemoterapi i kombination med et CD20-antistof gentages (ca. 25 patienter).



Figur 1: Behandlingsalgoritme med angivelse af fagudvalgets estimater af populationsstørrelser og mest anvendte behandling.

Fagudvalgets angivelse af antallet af patienter i de forskellige grupper er baseret på estimater fra tidligere RADS-behandlingsvejledning, viden om tid til første relaps og forekomsten af deletion17p/p53-mutation på forskellige tidspunkter i behandlingsforløbet [5–8].

I nuværende dansk klinisk praksis skelnes der i behandlingsøjemed ikke imellem, hvorvidt patienterne har IGHV-mutation eller ej, selvom det er af betydning for patienternes prognose. Patienter med non-muteret sygdom har en dårligere prognose end patienter med muteret sygdom. Studier viser, at en opdeling af patienterne i forhold til IGHV-mutation er relevant for effekten af nogle behandlinger, og fagudvalget forventer, at den praksis på sigt vil blive aktuel i dansk sammenhæng [9–11] .

4.2 Venetoclax i kombination med rituximab

Venetoclax hæmmer det antiapoptotiske protein BCL-2, som er overudtrykt i B-cellerne hos patienter med kronisk lymfatisk leukæmi. Forøget BCL-2 øger tumorcellernes overlevelse og er associeret med resistens mod kemoterapi.

Venetoclax er allerede godkendt som monoterapi til en del af den ansøgte indikation for venetoclax i kombination med rituximab.

Venetoclax i kombination med rituximab skal til den ansøgte indikation doseres som følger:

- Venetoclax p.o. 20 mg dagligt i uge 1, 50 mg dagligt i uge 2, 100 mg dagligt i uge 3, 200 mg dagligt i uge 4, 400 mg dagligt i uge 5 og herefter 400 mg dagligt fra uge 6 og 24 måneder frem.
- Fra uge 6, i 6 serier a 28 dage rituximab 375 mg/m^2 i.v. på dag 1 i serie 1, 500 mg/m^2 på dag 1 i serie 2-6.

5 Kliniske spørgsmål

De kliniske spørgsmål indeholder specifikation af patientgruppen, interventionen, alternativet/-erne til interventionen og effektmål.

5.1 Klinisk spørgsmål 1

Hvilken værdi har venetoclax i kombination med rituximab sammenlignet med venetoclax monoterapi til behandling af patienter med deletion17p/p53-mutation, som oplever relaps eller behandlingssvigt efter behandling med ibrutinib?

Population
Patienter med deletion17p/p53-mutation, som oplever behandlingssvigt under behandling med ibrutinib i 1. linje.

Intervention
Venetoclax i kombination med rituximab som angivet i afsnit 4.2.

Komparator
Venetoclax monoterapi, doseret som følger:

- Venetoclax p.o. 20 mg dagligt i uge 1, 50 mg dagligt i uge 2, 100 mg dagligt i uge 3, 200 mg dagligt i uge 4, 400 mg dagligt i uge 5 og herefter 400 mg dagligt fra uge 6 og frem til progression.

5.2 Klinisk spørgsmål 2

Hvilken værdi har venetoclax i kombination med rituximab sammenlignet med ibrutinib til 2.-linjebehandling af patienter, der er behandlet med kemoterapi i kombination med et CD20-antistof i 1. linje?

Population
Patienter med kronisk lymfatisk leukæmi, der oplever behandlingskrævende relaps eller behandlingssvigt mindre end 3 år efter behandling med kemoterapi i kombination med CD20-antistof og/eller patienter med sent relaps og nytilkommen deletion17p/p53-mutation.

Intervention
Venetoclax i kombination med rituximab som angivet i afsnit 4.2.

Komparator

- Ibrutinib p.o. 420 mg dagligt indtil progression.

Effektmål
Effektmålene fremgår af tabel 1 og er beskrevet i afsnit 5.4

5.3 Klinisk spørgsmål 3

Hvilken værdi har venetoclax i kombination med rituximab sammenlignet med kemoterapi i kombination med CD20-antistof til behandling af patienter uden deletion17p/p53-mutation, der har behandlingskrævende relaps mere end 3 år efter deres første behandling?

Population
Patienter med kronisk lymfatisk leukæmi uden deletion17p/p53-mutation, der oplever behandlingskrævende relaps mere end 3 år efter deres første behandling med kemoterapi i kombination med CD20-antistof.

Intervention
Venetoclax i kombination med rituximab som angivet i afsnit 4.2.

Komparatorer
Chlorambucil i kombination med obinutuzumab doseret som følger i 6 serier a 28 dage:

- Chlorambucil p.o. 0,5 mg/kg på dag 1 og 15
- Obinutuzumab s.c. 100 mg på dag 1, 900 mg på dag 2 og 1000 mg på dag 8 og 15 i 1. serie, herefter 1000 mg på dag 1 i serie 2-6.

Bendamustin i kombination med rituximab doseret som følger i op til 6 serier a 28 dage:

- Bendamustin i.v. 70-90 mg/m2 på dag 1 og 2
- Rituximab i.v. 375 mg/m^2 på dag 1 i første serie, herefter i.v. 500 mg/m^2 på dag 1 i efterfølgende serier.

5.4 Valg af effektmål

Tabel X summerer de valgte effektmål, deres vigtighed, den retningsgivende mindste klinisk relevante forskel, en evt. justeret mindste klinisk relevant forskel og effektmålskategori. I forbindelse med justeringen af Medicinrådets metodehåndbog, som trådte i kraft pr. 1. januar 2019, vil absolutte effektforskelle fremover blive kategoriseret ud fra konfidensintervaller (tabel 3, side 29 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2). Det er derfor nødvendigt at foretage en justering af den mindste klinisk relevante forskel. Den *retningsgivende* mindste klinisk relevante forskel er fremkommet på samme måde som under den tidligere metode og afspejler den mindste forskel, som, fagudvalget vurderer, er klinisk relevant. Når lægemidlets værdi for det enkelte effektmål skal kategoriseres, vil grænsen for konfidensintervallet blive sammenholdt med den *justerede* mindste klinisk relevante forskel. Den justerede værdi vil være det halve af den retningsgivende værdi i de tilfælde, hvor et konfidensinterval forventes at være tilgængeligt. Rationalet for denne tilgang er at sikre, at alle værdier i konfidensintervallet ligger tættere på den *retningsgivende mindste klinisk relevante forskel* end på 'ingen forskel' (absolut effektforskel på 0). Eller sagt på en anden måde: alle de sandsynlige værdier for effekten er tættere på en klinisk relevant effekt end på 'ingen effekt'.

Tabel X. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel (retningsgivende og evt. justeret) samt indplacering i de tre kategorier (”dødelighed” ”livskvalitet, alvorlige symptomer og bivirkninger” og ”ikkealvorlige symptomer og bivirkninger”).

Effektmål	Vigtighed	Kategori	Måleenhed	Retningsgivende mindste klinisk relevante forskel	Justeret mindste klinisk relevante forskel
Overlevelse	*Kritisk*	*Dødelighed*	Forskel i overlevelsesrate ved 3 år eller ved længst mulig opfølgningstid	5 %-point	2,5 %-point
	Vigtigt	*Livskvalitet, alvorlige symptomer og bivirkninger**	Forskel i andel der opnår PFS efter 3 år eller længst muligt opfølgningstid	10 %-point	5 %-point
	Vigtigt	*Livskvalitet, alvorlige symptomer og bivirkninger*	Andel af patienter der opnår MRD-negativitet indenfor 24 måneder	20 %-point	10 %-point
Bivirkninger	*Vigtigt*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Andel der oplever grad 3-4 uønskede hændelser (+ kvalitativ gennemgang)	10 %-point	5 %-point
Livskvalitet	*Vigtigt*	*Livskvalitet, alvorlige symptomer og bivirkninger*	EORTC QLQ-C30	10 point	5 point

* Eftersom PFS er et sammensat effektmål, der indeholder både progression og død, anvendes væsentlighedskriterierne for alvorlige symptomer og bivirkninger.

For alle effektmål ønskes både absolutte og relative værdier, jf. ansøgningsskemaet. Der ønskes både punktestimater og konfidensintervaller (for de absolutte værdier ønskes dog ikke konfidensintervaller, hvor metoderne til beregning af disse ikke er veldefinerede). For de absolutte værdier, hvor der kan beregnes konfidensintervaller efter veldefinerede metoder, vurderes den kliniske relevans (værdi), jf. tabel 3 i Medicinrådets håndbog for vurdering af nye lægemidler. For de relative værdier vurderes den kliniske relevans (værdi), jf. væsentlighedskriterierne beskrevet i Medicinrådets håndbog. De relative effektestimater skal angives i relativ risiko (RR) eller hazard ratio (HR). Hvis studierne resulterer i en odds ratio (OR), skal denne transformeres til relativ risiko, jf. appendiks 2 i Medicinrådets metodehåndbog. Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

5.5 Kritiske effektmål

5.5.1 Overlevelse

Overlevelsesrate

Det primære mål for behandling af CLL er at forbedre patientens overlevelse. Overlevelse defineres som tiden fra randomisering eller opstart af behandling til død, uanset årsag. Overlevelse opgøres typisk som en median overlevelse (overall survival, OS) eller som en andel af patienter, der er i live ved en given opfølgningstid. Den mediane overlevelse er oftest ikke tilgængelig ved godkendelsen af nye lægemidler til behandling af CLL, fordi overlevelsen med nuværende behandlingsmuligheder er mellem 4 og 12 år. Baseret på data fra en metaanalyse vurderer fagudvalget at overlevelsesraten ved 3 år er i omegnen af 90 % for

patienter, der behandles for relaps [12]. Overlevelsen ønskes derfor opgjort som andelen af patienter, der er i live efter 3 år eller efter længst mulig opfølgningstid. For 3-års overlevelsesrate vurderer fagudvalget, at 5 %-point er en klinisk relevant forskel mellem grupperne.

Da overlevelsesdata ofte er sparsomme for nye lægemidler ved godkendelsestidspunktet som følge af patienternes prognose, vurderer fagudvalget, at overlevelsesdata, i tilfælde hvor de ønskede overlevelsesdata ikke er tilgængelige, bør suppleres med information om surrogateffektmålene PFS-rate og *minimum residual disease* (MRD). Såfremt de ønskede overlevelsesdata er tilgængelige, vil data for PFS og MRD ikke anvendes i kategoriseringen. Såfremt den endelige ansøgning beror på PFS eller MRD-data (surrogateffektmål) bedes ansøger redegør for sammenhængen mellem surrogateffektmålene og det kliniske effektmål: overlevelse

PFS-rate
Progressionsfri overlevelse er defineret som tiden fra randomisering til sygdomsprogression, jf. iwCLL guidelines [13]. PFS anses desuden af EMA for at være et passende primært effektmål for vurdering af nye lægemidler til CLL, men den nødvendige opfølgningstid for modne PFS-data (median) er over fem år.

Fagudvalget ønsker derfor PFS opgjort som PFS rate ved 3 år eller med længst mulig opfølgningstid. PFS vurderes at være et vigtigt effektmål. Da hændelsesraterne for progression ved 3-års opfølgning vil være højere end hændelsesraterne for død, forventes der en større forskel i PFS-rate sammenlignet med OS-rate mellem grupperne ved 3-års opfølgning. Derfor vurderer fagudvalget, af den mindste klinisk relevante forskel for 3-års PFS-rate er 10 %-point.

Minimal residual disease (MRD)-negativitet
MRD er et objektivt mål for dybden af respons og defineres ud fra antallet af leukæmiceller, der er til stede i perifært blod eller knoglemarv. MRD-negativitet er betegnelsen for patienter, hvor antallet af leukæmiceller er under 1/10.000 leukocytter. MRD-negativitet er af EMA betragtet som et anvendeligt effektmål for godkendelse af nye lægemidler som følge af langvarige remissioner ved nye lægemidler til CLL [15]. MRD-negativitet ved afsluttet induktionsbehandling er desuden vist at være stærkt korreleret til OS og PFS uafhængigt af behandlingstype og -linje samt risikofaktorer (f.eks. deletion17p/p53, IGHW-status) [16]. MRD vurderes derfor at være et vigtigt effektmål til at supplere OS- og PFS-rater. Da der er tale om et surrogateffektmål, vurderer fagudvalget, at den mindste klinisk relevante forskel er 20 %-point.

5.6 Vigtige effektmål

5.6.1 Livskvalitet

EORTC-QLQ-C30 er et generisk spørgeskema, som anvendes til kræftpatienter. Redskabet måler livskvalitet, symptomer og overordnet helbredsstatus. Spørgeskemaet består af 30 spørgsmål og er udviklet til brug i klinisk forskning. Der anvendes en scoringsskala fra 0-100. En høj score på de fem funktionsskalaer repræsenterer et højt/positivt funktionsniveau. En høj score for global helbredsstatus repræsenterer høj livskvalitet, mens en høj score på de tre symptomskalaer repræsenterer høj forekomst af symptomer/problemer. Den mindste klinisk relevante forskel baserer sig på Osoba et al., hvor en lille ændring i livskvalitet er defineret som 10 point [17]. Fagudvalget vælger at anvende den mindste klinisk relevante forskel på 10 point mellem grupperne. Fagudvalget bemærker, at det kan være vanskeligt at foretage en meningsfuld sammenligning af patienternes livskvalitet på tværs af de forskellige behandlinger og studier, da behandlingsregimerne har forskellig varighed. Fagudvalget ønsker, at ansøger undersøger, hvorvidt der for intervention og komparator findes fælles opfølgningstider for ændringen i livskvalitet og opgøre disse i den endelige ansøgning.

5.6.2 Bivirkninger

Andel patienter med mindst én uønsket hændelse af grad 3-4
Fagudvalget ønsker alvorlige uønskede hændelser opgjort som andel af patienter, der oplever mindst en grad 3-4 bivirkning, og en forskel mellem grupperne på 10 procentpoint anses som klinisk relevant. Fagudvalget vurderer, at langt størstedelen af patienter (over 80 %) vil opleve en grad 3-4 uønskede hændelser i løbet af 3 år. Da fagudvalget ikke har kendskab til kliniske studier, der direkte sammenligner effekten af venetoclax i kombination med rituximab med alle komparatorer, bør ansøger lave en vurdering af, om sammenligning af hændelsesfrekvenser kan foretages på forsvarlig vis på baggrund af studiedesign, median opfølgningstid, dataindsamling og hvordan bivirkninger/hændelser er opgjort og rapporteret. Overvejelser omkring dette skal fremgå i den endelige ansøgning.

Kvalitativ gennemgang af uønskede hændelser og bivirkninger
Fagudvalget vil desuden foretage en kvalitativ gennemgang af bivirkningstyperne med udgangspunkt i SAE-lister fra studier med henblik på at vurdere, om der er forskel i bivirkningsprofilerne mht. alvorlighed, håndterbarhed og hyppighed af bivirkningerne. Den kvalitative gennemgang af bivirkningslisterne vil ligeledes belyse, hvorvidt en eventuel forskel mellem behandlingerne i andel af patienter, der oplever alvorlige bivirkninger, skyldes klinisk betydende bivirkninger. Fagudvalget vil inddrage produktresuméerne i det omfang, det er nødvendigt. Ansøger bedes derfor vedlægge disse.

6 Litteratursøgning

Vurderingen af klinisk merværdi baseres som udgangspunkt på data fra peer-reviewede publicerede fuldtekstartikler og data fra EMAs EPAR – public assessment report(s). Data skal derudover stemme overens med protokollens beskrivelser.

Sekretariatet har på baggrund af den foreløbige ansøgning undersøgt, om der findes en eller flere peer-reviewede publicerede fuldtekstartikler, hvor venetoclax i kombination med rituximab er sammenlignet direkte med bendamustin i kombination med rituximab.

Sekretariatet fandt følgende artikler [18,19], som er relevante, og som kan anvendes til direkte til besvarelse af dele af spørgsmål 3:

- Seymour JF, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Assouline S, et al. Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. N Engl J Med. 2018;378(12):1107–20.

- Kater AP, Seymour JF, Hillmen P, Eichhorst B, Langerak AW, Owen C, et al. Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III Study. J Clin Oncol. 2019;37(4):269–77.

Virksomheden skal derfor søge efter yderligere studier, der kan belyse klinisk spørgsmål 1 og 2 samt sammenligningen mellem interventionen og chlorambucil i kombination med obinutuzumab og effektmål i spørgsmål 3, der ikke er data for i de to angivne publikationer. Til det formål har sekretariatet udarbejdet søgestrenge, som skal anvendes i MEDLINE (via PubMed) og CENTRAL (via Cochrane Library). Søgestrengene kan findes i bilag 1. Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Kriterier for udvælgelse af litteratur
Virksomheden skal først ekskludere artikler på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en

eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Inklusions- og eksklusionskriterier

De inkluderede studier skal være randomiserede kontrollerede forsøg og skal stemme overens med de kliniske spørgsmål, hvad angår de beskrevne populationer, komparatorer og indeholde minimum et relevant effektmål. Studier, som er fase I- og IIa-studier, ekskluderes.

7 Databehandling og analyse

De inkluderede studier og baselinekarakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Fagudvalget ønsker en detaljeret opgørelse over, hvilke specifikke behandlinger patienterne har modtaget inden inklusion i de studier, der anvendes til besvarelse af de kliniske spørgsmål. Dette bør omfatte antal af tidligere behandlinger, behandlingernes indholdsstoffer, samt hvor mange patienter der har været behandlet med de tilgængelige behandlinger. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål.

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention to treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives, hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser, specielt i forhold til præspecificeret population og effektmål, begrundes dette.

Hvis data for et effektmål ikke er tilgængelig for alle deltagere i et studie, vil der ikke blive gjort forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (ORR, SAE, behandlingsstop pga. bivirkninger og ikkealvorlige bivirkninger), hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet, baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i Danmark ved behandling med komparator (hvis relativ risiko (RR) = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risikoreduktion (ARR) = 30 – 30 x 0,5 = 15 %-point).

Hvis der er mere end ét sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode [20]), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, vil eventuelle metaanalyser blive baseret på standardized mean difference (SMD). Den estimerede SMD vil blive omregnet

til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standardafvigelser i de inkluderede studier.

Hvis det ikke er en mulighed at udarbejde metaanalyser (herunder netværksmetaanalyser), syntetiseres data narrativt. Studie- og patientkarakteristika samt resultater fra de inkluderede studier beskrives narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er). Forskelle i patientkarakteristika og studiekontekst (f.eks. geografi og årstal) mellem studier skal beskrives og vurderes for at afgøre, hvorvidt resultaterne er sammenlignelige.

Valget af syntesemetode (metaanalyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

8 Andre overvejelser

Fagudvalget ønsker informationer, der kan belyse en vurdering af, hvorvidt og hvordan indførelsen af den ansøgte intervention i dansk klinisk praksis vil påvirke behandlinger i efterfølgende behandlingslinjer, hvad angår type, varighed og forventet effekt.

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kronisk lymfatisk leukæmi (CLL)

Formand	**Indstillet af**
Robert Schou Pedersen Overlæge	Lægevidenskabelige Selskaber og udpeget af Region Midtjylland
Medlemmer	**Udpeget af**
Thor Høyer Afdelingslæge	Region Nordjylland
Annika Rewes Afdelingslæge	Region Syddanmark
Nyudpegning i gang	Region Sjælland
Kan ikke udpege en kandidat, der opfylder Medicinrådets habilitetskrav	Region Hovedstaden
Stine Trolle Poulsen Farmaceut	Dansk Selskab for Sygehusapoteksledelse
Jakob Henriksen Læge	Dansk Selskab for Klinisk Farmakologi
To patienter/patientrepræsentanter	Danske Patienter

Medicinrådets sekretariat

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Sekretariatets arbejdsgruppe: Karen Kleberg Hansen (projekt- og metodeansvarlig) Heidi Møller Johnsen (projektdeltager) Thomas Linemann (projektdeltager) Anette Pultera Nielsen (fagudvalgskoordinator) Annemette Anker Nielsen (teamleder)

11 Bilag 1 – Søgeprotokol

MEDLINE via PubMed

#	Søgetermer	Kommentar
1	Leukemia, Lymphocytic, Chronic, B-Cell[mh]	Søgeord for indikation. De søges som MeSH termer, og som fritekst i titel og abstract
2	CLL[tiab] or chronic lymphocytic leukemia[tiab] or chronic lymphocytic leukaemia[tiab]	
3	chronic lymphatic leukemia[tiab] or chronic lymphatic leukaemia[tiab]	
4	chronic lymphoblastic leukemia[tiab] or chronic lymphoblastic leukaemia[tiab]	
5	chronic b-cell leukemia[tiab] or chronic b-cell leukaemia[tiab]	
6	#1 or #2 or #3 or #4 or #5	
7	venetoclax[nm]	Søgeord for ansøgers lægemiddel og komparator. De søges som MeSH-termer, Supplementary Concept/Substance og som fritekst i titel og abstract
8	venetoclax[tiab] or Venclyxto*[tiab] or Venclexta*[tiab] or ABT-199[tiab] or ABT199[tiab] or GDC-0199[tiab] or GDC0199[tiab] or RG-7601[tiab] or RG7601[tiab]	
9	PCI 32765[nm]	
10	ibrutinib[tiab] or Imbruvica*[tiab] or PCI-32765[tiab] or PCI32765[tiab]	
11	Chlorambucil[mh]	
12	chlorambucil[tiab] or Leukeran*[tiab] or NSC-3088[tiab] or NSC3088[tiab]	
13	obinutuzumab[nm]	
14	obinutuzumab[tiab] or Gazyva*[tiab] or afutuzumab[tiab] or GA-101[tiab] or GA101[tiab] or RO-5072759[tiab] or RO5072759[tiab]	
15	(#11 or #12) and (#13 or #14)	
16	Bendamustine Hydrochloride[mh]	
17	bendamustin*[tiab] or Levact*[tiab] or Treanda*[tiab]	
18	Rituximab[mh]	
19	rituximab[tiab] or Mabthera*[tiab] or Rituxan*[tiab] or GP-2013[tiab] or GP2013[tiab] or IDEC-C2B8[tiab] or IDECC2B8[tiab]	
20	(#16 or #17) and (#18 or #19)	
21	#7 or #8 or #9 or #10 or #15 or #20	
22	#6 and #21	**Indikation og lægemidler kombineres**
23	Animals[mh] not Humans[mh]	Eksklusion af (indekserede) dyreforsøg
24	#22 not #23	
25	Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]	Afgrænsning til randomiserede, kontrollerede forsøg.

26	#24 and #25	**Linje 26 = endeligt resultat, hvis I ikke ønsker afgrænsning på publikationstyper**
27	case report[ti] or Case Reports[pt] or Comment[pt] or Editorial[pt] OR Review[Publication Type] OR Systematic Review[pt]	Afgrænsning: eksklusion af (indekserede) bestemte publikationstyper (valgfrit)
28	**#26 not #27**	**Linje 28 = endeligt resultat**

Feltkoder

mh = MeSH Term, **nm** = Supplementary Concept/Substance, **tiab** = title/abstract, inkl. forfatterkeywords **og pt** = publication type

Central via Cochrane library

#	**Søgetermer**	
1	[mh "Leukemia, Lymphocytic, Chronic, B-Cell"]	Søgeord for indikationen. Der søges på fritekst i titel og abstract samt på indekserede termer fra både Medline og Embase.
2	(chronic next (lymphatic or lymphoblastic or lymphocytic or b-cell) next (leukemia or leukaemia)):ti,ab,kw or CLL:ti,ab	
3	#1 or #2	
4	(venetoclax or Venclyxto* or Venclexta or ABT-199 or ABT199 or GDC-0199 or GDC0199 or RG-7601 or RG7601):ti,ab,kw	Søgeord for ansøgers lægemiddel samt komparator. Der søges på fritekst i titel og abstract, MeSH-term, hvor muligt samt på indekseret term fra Embase (i kw-feltet)
5	(ibrutinib or Imbruvica* or PCI-32765 or PCI32765):ti,ab,kw	
6	(chlorambucil or Leukeran* or NSC-3088 or NSC3088):ti,ab,kw	
7	(obinutuzumab or Gazyva* or afutuzumab or GA-101 or GA101 or RO-5072759 or RO5072759):ti,ab,kw	
8	#6 and #7	
9	(bendamustin* or Levact* or Treanda*):ti,ab,kw	
10	(rituximab or Mabthera* or Rituxan* or GP-2013 or GP2013 or IDEC-C2B8 or IDECC2B8):ti,ab,kw	
11	#9 and #10	
12	#4 or #5 or #8 or #11	
13	**#3 and #12**	**Indikation og lægemidler kombineres**
14	("conference abstract" or review):pt	

15	NCT*:au	Afgrænsning (eksklusion) på publikationstype samt (en del) af de resultater, der kommer fra clinicaltrials.gov.
16	("clinicaltrials gov" or trialsearch):so	
17	#14 or #15 or #16	
18	**#13 NOT #17 in Trials**	**Linje 18 = endeligt resultat**

Feltkoder

ti: title, **ab:** abstract, **kw:** keywords, her kontrollerede/indekserede termer fra databaserne Medline og/eller Embase**, pt** = publication type

12 Versionslog

Version	Dato	Ændring
1.0	16. maj 2019	Godkendt af Medicinrådet.