abbvie

Sekretariatet for nye metoder
nyemetoder@helse-sorost.no

Fornebu, 3. desember 2019

Innspill til Nye metoder vedrørende venetoklaks (Venclyxto) - Indikasjon IV ID2019_096

ID2019_096 ble diskutert av Bestillerforum i møte 18.11.19. En eventuell åpning av saken betinger en beskrivelse av data som kan legges til grunn i en ny vurdering. Nedenfor vil vi redegjøre for dette.

Metodevurderingen ID2018_17 omhandler venetoklaks i behandling av blodkreft, kronisk lymfatisk leukemi. Den innsendte dokumentasjonen ble gjort i henhold til indikasjonen «*Venclyxto i kombinasjon med rituksimab er indisert til behandling av voksne pasienter med kronisk lymfatisk leukemi (KLL) som har fått minst én tidligere behandling.*». I tråd med retningslinjene for valg av komparator ble ibrutinib ansett som mest relevant. Det vil si at det var data vs. ibrutinib (komparator) som ble diskutert og vurdert. Den helseøkonomiske analysen baserte seg på denne sammenlikningen.

Data vs. idelalisib, eller i sekvens etter ibrutinib, ble ikke vurdert. Dette bekreftes i Legemiddelverkets kommentar: «*Basert på innsendt dokumentasjon i metodevurderingen kunne ikke Legemiddelverket vurdere kostnadseffektivitet for følgende populasjoner[.....]*». AbbVie sendte inn en dokumentasjonspakke til bestilling ID2016_073 som omhandlet monoterapi-indikasjonen i all hovedsak i sekvens etter signalveishemmerene ibrutinib eller idelalisib, men denne dokumentasjonen ble ikke vurdert i ID2018_017. Legemiddelverket etterspurte heller ikke supplerende informasjonen om dette i klokkestopp i løpet av utredningen.

Legemiddelverket har anført at det er et behov for data på relativ effekt sammenlignet med idelalisib, for effekt i sekvens etter ibrutinib.

Beslutningsforums vedtak er i henhold til dette, og det er behov for å undersøke venetoklaks i forhold til idelalisib. Det er to spesifikke forhold som bør undersøkes:

- **Bruk av venetoklaks vs. idelalisib i pasienter med del(17p) ved diagnosetidspunkt som er behandlet med ibrutinib i førstelinje**
- **Bruk av venetoklaks vs. idelalisib i pasienter uten del(17p) som er behandlet med ibrutinib i andrelinje**

I tabellen nederst presenteres en oppsummering av data (ikke uttømmende) som tidligere ikke er vurdert av Legemiddelverket. Ved å sammenstille relevante data for venetoklaks vs. idelalisib vil det være mulig å svare på behovet for dokumentasjon slik dette er kommentert av Legemiddelverket. På den måten vil man kunne vurdere "effekt i sekvens etter ibrutinib" og "relativ effekt vs. idelalisib", stratifisert på del(17p) ved diagnosetidspunkt. Dette vil muliggjøre en metodevurdering av venetoklaks i kombinasjon med rituksimab vs. idelalisib.

Det er to hovedutfordringer ved å ikke bestille en ny vurdering:

1. Å ikke bestille metoden innebærer i realiteten at man sier nei til metoden uten å i det hele tatt ha vurdert dataene, og man likestiller beslutningen med andre saker der man beslutter nei fordi man mener at metoden ikke skal innføres. Å bare si nei uten en reell vurdering er en mye mer usikker beslutning enn å basere en beslutning på de dataene som finnes.
2. Anbudet påvirkes uheldig av begrensningen, og dette får man ikke ryddet opp i uten en vurdering.

Vi håper dette er tilstrekkelig for å bestille saken på nytt, slik at en metodevurdering kan gjennomføres og danne grunnlag for en beslutning om hvorvidt man skal innføre venetoklaks i kombinasjon med rituksimab også til pasienter som har vært behandlet med ibrutinib.

Med vennlig hilsen
for AbbVie AS

Fredrik Holmboe
E-mail: fredrik.holmboe@abbvie.com
Tel.: +47 67 81 80 00
Mob.: +47 40 20 34 48

Forfatter	Tittel/innhold	Referanse link	Konklusjoner fra forfatter
Relativ effekt vs idelalisib			
Artiker/data med relevans for å vise relativ effekt vs idelalisib			
Seymour J, *et al*	*Four-Year Analysis of MURANO Study Confirms Sustained Benefit of Time-Limited Venetoclax-Rituximab (VenR) in R/R CLL*	https://ash.confex.com/ash/2019/webprogram/Paper123930.html 4 års oppdatering fra Murano studien: https://www.ncbi.nlm.nih.gov/pubmed/30523712	Four-year data from MURANO demonstrate sustained PFS and OS benefits with VenR versus BR. 24-month post-treatment cessation PFS was 68.0% in pts completing 2 years of Ven, and pts who attained PB uMRD showed particularly durable responses. These follow-up data provide further support for the application of time-limited VenR in R/R CLL.
Furman, *et al*	*Final Results of a Randomized, Phase III Study of Rituximab With or Without Idelalisib Followed by Open-Label Idelalisib in Patients With Relapsed Chronic Lymphocytic Leukemia*	https://www.ncbi.nlm.nih.gov/pubmed/30995176	The long-term efficacy and safety of treatment with IDELA was assessed in 110 patients who received at least one dose of IDELA in the primary study, 75 of whom enrolled in the extension study. The IDELA/R-to-IDELA group had a median PFS of 20.3 months (95% CI, 17.3 to 26.3 months) after a median follow-up time of 18 months (range, 0.3 to 67.6 months).
Nettetverksanalyser			
	MAIC analyse vs Furman et al	Data on file	Viser at VenR er bedre enn idelalisibR
Molica S, *et al*	*Comparison of venetoclax plus rituximab with B cell receptor inhibitors in patients with relapsed/ refractory chronic lymphocytic leukemia: a systematic review and network Meta-analysis*	https://www.ncbi.nlm.nih.gov/pubmed/31724894	Our findings suggest that both venetoclax-based and ibrutinibbased regimens appear to be superior to idelalisib-based regimens with respect to PFS. Since no differences in PFS were found between the Ibrutinib-based and venetoclax-based treatments, selection between these approaches in routine clinical practice may be based on side-effect profile, cost, availability and patient choice.
Chen, *et al*	*Treatment Outcomes of Novel Targeted Agents in Relapse/Refractory Chronic Lymphocytic Leukemia: A Systematic Review*	https://www.ncbi.nlm.nih.gov/pubmed/?term=Treatment+outcomes+of+novel+targeted+agents+in+relapse%2Frefractory	All novel targeted therapies were significantly more effective than ofatumumab and demonstrated promising prolongation of progression free survival (PFS), with a hazard ratio (HR) ranging from 0.10 to 0.52. Two novel targeted agent regimens, venetoclax plus rituximab and ibrutinib monotherapy, resulted in greater

AbbVie AS
Martin Linges vei 25
Postboks 1
N-1330 Fornebu, Norway

Tel.: +47 67 81 80 00
Bank acct. 8397.10.85846
Org. no.: NO 998 085 497 MVA
kontakt@abbvie.com

	and Network Meta-Analysis	+chronic+lymphocytic	overall survival (HR, 0.335 and 0.361, respectively).
Effekt etter ibrutinib med og uten del(17p) og ulike linjer			
Effekt av venetoklaks etter signalveishemmer (ibrutinib og idelalisib)-tidligere sendt inn for medodevurdering ID2016_073 men ikke vurdert			
Jones JA, *et al*	*Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial*	https://www.ncbi.nlm.nih.gov/pubmed/29246803	The results of this interim analysis show that venetoclax has durable clinical activity and favourable tolerability in patients with relapsed or refractory chronic lymphocytic leukaemia whose disease progressed during or after discontinutation of ibrutinib therapy.
Coutre S, *et al*	*Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy*	https://www.ncbi.nlm.nih.gov/pubmed/29305552	Venetoclax demonstrated promising clinical activity and favorable tolerability in patients with CLL whose disease progressed during or after idelalisib therapy.
Stilgenbauer, *et al*	*Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial.*	https://www.ncbi.nlm.nih.gov/pubmed/29715056 and data on file	Including subgroup analysis of R/R CLL patients with del(17p) that received ibrutinib prior to venetoclax For all patients, investigator-assessed objective response rate was 77% (122 of 158 patients; 20% complete remission) and estimated progression-free survival at 24 months was 54% (95% CI, 45% to 62%). **For 16 patients who received prior kinase inhibitors, objective response rate was 63% (10 of 16 patients) and 24-month progression-free survival estimate was 50% (95% CI, 25% to 71%).**
Artiker/data med relevans for å beskrive en hensiktsmessig sekvensiering av venetoklaks og signalveishemmere			
Mato A, *et al*	*Efficacy of Therapies Following Venetoclax Discontinuation in CLL: Focus on B-Cell Receptor Signal Transduction Inhibitors and Cellular Therapies*	https://ash.confex.com/ash/2019/webprogram/Paper123747.html	An international study to identify a large cohort of pts who discontinued VEN and have been subsequently treated
Mato A, *et al*	*Treatment Sequences and*	https://ash.confex.com/ash/2019/	We conclude that BTKi in naïve or previously responsive pts and alloHSCT

AbbVie AS
Martin Linges vei 25
Postboks 1
N-1330 Fornebu, Norway

Tel.: +47 67 81 80 00
Bank acct. 8397.10.85846
Org. no.: NO 998 085 497 MVA
kontakt@abbvie.com

	Outcomes of Patients with CLL Treated with Venetoclax and Other Novel Agents Post Introduction of Novel Therapies	webprogram/Paper123747.html Follow-up from https://www.ncbi.nlm.nih.gov/pubmed/28453705	following VEN appear to be the most effective strategies with durable responses. **These data suggest that a number of effective regimens exist for post VEN pts, providing support for VEN use earlier in the course of CLL**.
Brander DM, *et al*	*Durability of Responses on Continuous Therapy and Following Drug Cessation with Venetoclax and Rituximab: Long-Term Follow-up Analysis of a Phase1b Study in Patients with Relapsed CLL*	https://ash.confex.com/ash/2019/webprogram/Paper126508.html follow-up from: https://www.ncbi.nlm.nih.gov/pubmed/28089635	In relapsed CLL, VenR induces deep responses within 12 mo in 67% of pts. These responses are highly durable whether on continuous or limited duration therapy, with treatment-free remissions of >4 yr now being observed. **Re-treatment of pts with Ven or VenR re-exposure has resulted in response in some pts.** In addition to long PFS, which represents time to first PD or death, pts who cease Ven in deep response have the opportunity for further disease control through reintroduction of Ven.
Artikler/data som viser effekt av ibrutinib etter venetoklaks			
Kater AP, *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*	https://www.ncbi.nlm.nih.gov/pubmed/30523712 data on file	In the VenR arm, 27 of the 194 total patients received subsequent therapy, 8 of which received ibrutinib as their next therapy.
Anderson MA, *et al*	*Clinicopathological features and outcomes of progression of CLL on the BCL2 inhibitor venetoclax*	https://www.ncbi.nlm.nih.gov/pubmed/28473407	A retrospective study evaluated 67 BTKi-naïve R/R CLL/SLL patients treated with Ven monotherapy or in combination with rituximab in 1 of 3 early phase trials (M12-175, M13-365, M13-982) at 2 Australian institutions between June 2011 and March 2016
Brown J, *et al*	*Outcomes of Ibrutinib Therapy*	https://ashpublications.org/blood/	A retrospective chart review data analysis from 4 centers was conducted on 11

	Given after Prior Venetoclax Therapy in Ibrutinib-Naïve Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)	article/132/Supplement%201/5556/263295/Outcomes-of-Ibrutinib-Therapy-Given-after-Prior	ibrutinib-naïve, R/R CLL patients previously treated with Ven
Mato R, *et al*	*Efficacy of Therapies Following Venetoclax Discontinuation in CLL: Focus on B-Cell Receptor Signal Transduction Inhibitors and Cellular Therapies*	https://ash.confex.com/ash/2019/webprogram/Paper123747.html	We demonstrated that therapy selection following VEN requires consideration of prior novel agent exposure and reasons for discontinuation. We conclude that BTKi in naïve or previously responsive pts and alloHSCT following VEN appear to be the most effective strategies with durable responses. These data suggest that a number of effective regimens exist for post VEN pts, providing support for VEN use earlier in the course of CLL.
Mato A, *et al*	*Clinicopathological features and outcomes of progression of CLL on the BCL2 inhibitor venetoclax*	https://www.ncbi.nlm.nih.gov/pubmed/28473407	A multicenter, retrospective cohort study of 141 CLL patients (98% had R/R CLL) treated with Ven across 19 United States academic and community cancer centers, evaluated outcomes, toxicities, and treatment selection following Ven discontinuation
Tilleggslitteratur for respons i ulike subgrupper og verdi av å legge rituksimab til venetoklaks			
Roberts AW, *et al*.	*Duration of response: Efficacy of venetoclax in relapsed chronic lymphocytic leukemia is influenced by disease and response variables*	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6624969/figure/absf1/	In multiple regression analyses, bulky lymphadenopathy (≥5 cm) and refractoriness to B-cell receptor inhibitor (BCRi) therapy were significantly associated with lower CR rate and shorter DoR. Fewer prior therapies were associated with higher CR rate, but not DoR. Chromosome 17p deletion and/or *TP53* mutation and *NOTCH1* mutation were consistently associated with shorter DoR, but not probability of response. Thus, both pretreatment factors and depth of response correlated with DoR with venetoclax. Patients without bulky lymphadenopathy, BCRi-refractory CLL, or an adverse mutation profile had the most durable benefit.
O' Brien S, *et al*	*Outcomes with ibrutinib by line of therapy and post-ibrutinib*	https://www.ncbi.nlm.nih.gov/pubmed/30767298	This integrated analysis included 271 ibrutinib-treated non-del(17p) patients with CLL (136 TN and 135 R/R). Median progression-free survival (PFS) was not reached for subgroups with 0 and 1/2 prior

	discontinuation in patients with chronic lymphocytic leukemia: Phase 3 analysis		therapies but was 40.6 months for patients with ≥3 therapies (median follow-up: TN, 36 months; R/R, 44 months).
Roberts AW, *et al*	*Impact of Adding Rituximab to Venetoclax on the Rate, Quality, and Duration of Response in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia: A Cross-study Multivariable Analysis*	Roberts AW, et al. Poster #P209. 21st EHA Annual Meeting; June 9 – 12, 2016	Combination with rituximab, bulkiness of adenopathy, del(17p), del(11q) and dose of venetoclax were identified as response-modifiers for CR and/or risk of relapse in the multivariable analysis across two trials **Combination with rituximab significantly increases CR rates (51% versus 20% with monotherapy)** and the durability of remissions over venetoclax monotherapy, after adjustment for other response-modifiers
Freise KJ, *et al*	Relationship between venetoclax exposure, rituximabcoadministration, and progression-free survival in patients withrelapsed or refractory chronic lymphocytic leukemia:demonstration of synergy	https://onlinelibrary.wiley.com/doi/epdf/10.1002/hon.2373	**The analysis demonstrates a concentration-dependent effect of venetoclax on PFS and also a synergistic effect with rituximab.** Com-bining venetoclax with the CD20 targeting monoclonal antibody rituximab in R/R CLL/SLLpatients provides substantial synergistic benefit compared with increasing the venetoclax monotherapy dose

AbbVie AS
Martin Linges vei 25
Postboks 1
N-1330 Fornebu, Norway

Tel.: +47 67 81 80 00
Bank acct. 8397.10.85846
Org. no.: NO 998 085 497 MVA
kontakt@abbvie.com