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NCCN Guidelines® Panel: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

On behalf of AbbVie and Genentech, I respectfully request the NCCN Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) Guideline Panel to consider the enclosed data on cost-effectiveness and total cost of care (TCC) for Venclexta® (venetoclax) plus Gazyva® (obinutuzumab) in first-line (1L) CLL and data on cost-effectiveness for venetoclax plus Rituxan® (rituximab) in relapsed-refractory (R/R) CLL.

Specific Changes:

Request an update of the CLL/SLL NCCN Affordability Evidence Blocks for venetoclax in combination with obinutuzumab and venetoclax in combination with rituximab from 2 blocks (expensive) to 3 blocks (moderately expensive) (CSLL-D EB-1, CSLL-D EB-2, CSLL-D EB-3, CSLL-D EB-4).

FDA Clearance:

- **Venclexta® (venetoclax)** is approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with CLL/SLL.
    - Please refer to Venclexta® (venetoclax) prescribing information for full FDA-approved indications and safety information, available at: https://www.rxabbvie.com/pdf/venclexta.pdf.

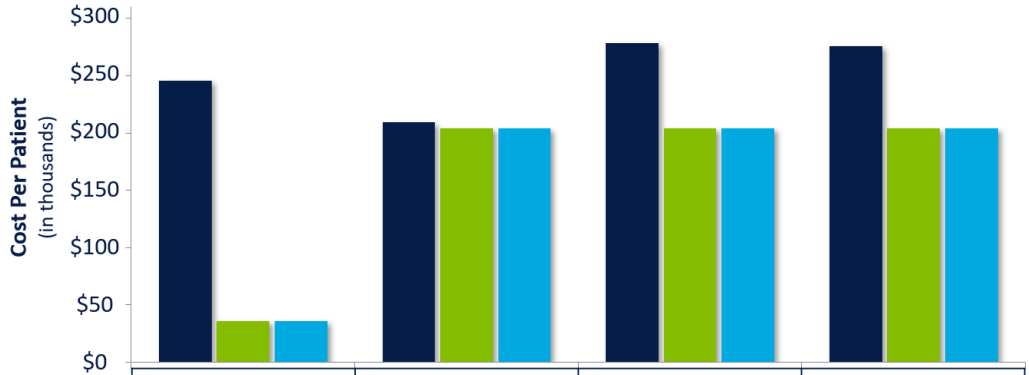
- **Gazyva® (obinutuzumab) in combination with Leukeran® (chlorambucil)** is approved by the US FDA for the treatment of patients with previously untreated CLL.[2]
    - Please refer to Gazyva® (obinutuzumab) prescribing information for full FDA-approved indications and safety information, available at: https://www.gene.com/download/pdf/gazyva_prescribing.pdf.

- **Rituxan® (rituximab)** is approved for the treatment of patients with CLL.[2]
    - Please refer to Rituxan® (rituximab) prescribing information for full FDA-approved indications and safety information available at: https://www.gene.com/download/pdf/rituxan_prescribing.pdf

Rationale: Health economic studies in 1L and R/R CLL demonstrated that venetoclax-based fixed-treatment duration regimens result in cost-savings to the US payer system and are cost-effective options vs ibrutinib-based regimens, obinutuzumab + chlorambucil (GClb), idelalisib + rituximab and bendamustine + rituximab (BR).[1-3]

In a recently published study, Cho and colleagues assessed the TCC and US payer system budget impact for patients with CLL who received commonly used 1L regimens.[1] Select treatment regimens included in the analysis were venetoclax + obinutuzumab (VenG), ibrutinib, ibrutinib + rituximab, and ibrutinib + obinutuzumab. The budget impact and TCC per patient were compared for each treatment regimen and included drug costs, wastage, drug administration, adverse events (AEs), monitoring, and routine costs of care in CLL. The costs of AEs were estimated based on the AEs of Grade ≥3 severity occurring in at least 5% of patients treated with any regimen.

Results showed the TCC per patient in Year 1 was lower for VenG compared with ibrutinib-based combination regimens (Figure 1). By Year 2, the TCC was significantly reduced with VenG compared with all other therapies shown due to VenG's 12-month fixed-treatment duration. The TCC with VenG in Year 2 and 3 was $35,570, reflecting the routine cost of care in CLL, while the TCC with ibrutinib and ibrutinib-based regimens was $204,130 due to the need for continuous therapy. More specifically, treatment costs (inclusive of drug, administration and wastage costs) with VenG were $180,521 in Year 1 and $0 in Years 2 and 3. In contrast, the treatment costs over 3 years for ibrutinib-based regimens ranged between $505,674 to $570,940 (Table 1)



	VenG	Ibrutinib	Ibrutinib + R	Ibrutinib + G
Year 1	$245,736	$209,560	$278,401	$275,619
Year 2	$35,570	$204,130	$204,130	$204,130
Year 3	$35,570	$204,130	$204,130	$204,130

Figure 1. Comparison of Annual TCC Per Patient by Choice of Therapy
G, obinutuzumab; R, rituximab; Ven, venetoclax

	Year 1	Year 2	Year 3	Total
VenG	$180,521	$0	$0	$180,521
Ibrutinib	$168,558	$168,558	$168,558	$505,674
Ibrutinib+R	$233,824	$168,558	$168,558	$570,940
Ibrutinib+G	$228,817	$168,558	$168,558	$565,933

Table 1. Total Treatment Costs* Per Regimen Per Patient

*Total treatment costs include cost of the drug, wastage and administration

Over the 3-year time horizon, the assessment showed a 49-54% reduction in cumulative TCC per patient with VenG compared to ibrutinib-based regimens, largely attributed to lower treatment costs with VenG (Figure 2). Monitoring costs due to TLS did not have a large impact on the TCC cost of care with VenG.

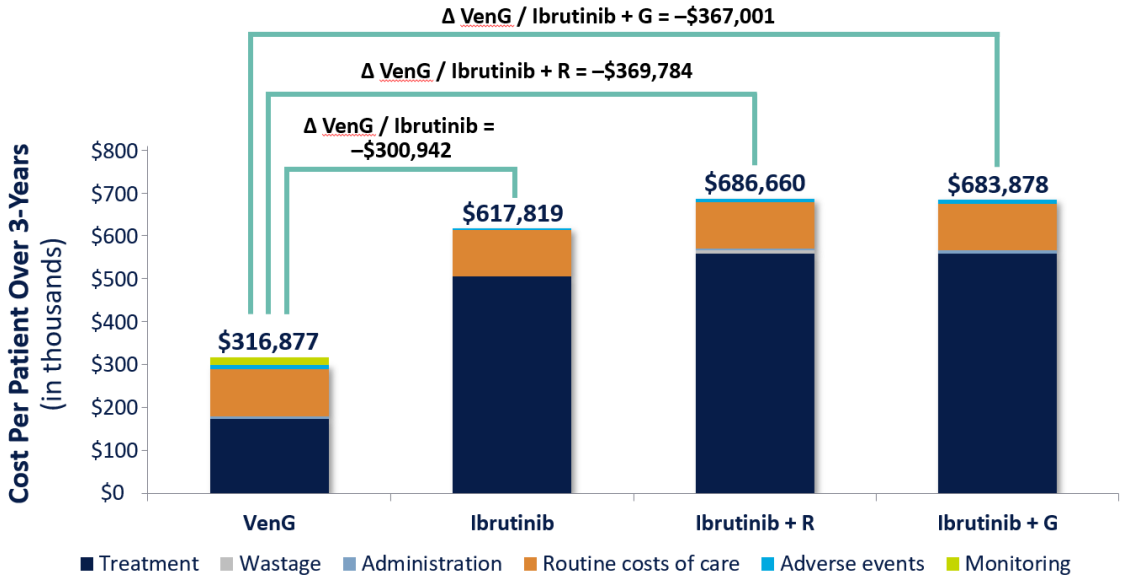


Figure 2. Comparison of Cumulative Total Cost of Care Per Patient per Regimen (3 year)
G, obinutuzumab; R, rituximab; Ven, venetoclax

By Year 3, when compared to VenG, the cumulative differences in per patient TCC amounted to a cost savings of $300,942 vs. ibrutinib; $369,784 vs. ibrutinib + rituximab; and $367,001 vs. ibrutinib + obinutuzumab (Figure 2).

The adoption of VenG as a 1L therapy for CLL/SLL patients is predicted to lead to reduction in cumulative and per patient TCC (after Year 1) when compared with ibrutinib and ibrutinib combinations, from a US payer perspective. Budget impact analysis demonstrates that the addition of VenG to the formulary may result in economic savings for the US healthcare payer that amount to $1,550,663 for a 1-million-member health plan over 3 years.

In addition, two health economic studies evaluated cost-effectiveness of VenG and VenR regimens in 1L CLL and R/R CLL, respectively, from a US payer perspective.[2,3] In the 1L CLL analysis, the cost-effectiveness of VenG was estimated by comparing long-term survival for a 12-month fixed duration of VenG versus GClb, ibrutinib, ibrutinib + rituximab, ibrutinib + obinutuzumab, and BR.[2] VenG is estimated to accrue higher quality adjusted life years (QALYs) than GClb, BR, ibrutinib, and ibrutinib + rituximab with incremental benefits of 0.344 vs GClb; 0.395 vs BR; 0.195 vs ibrutinib; and, 0.228 vs ibrutinib + rituximab. In contrast, ibrutinib + obinutuzumab is estimated to accrue higher QALYs than VenG, with an incremental difference of 0.097. Regarding cost, VenG is projected to be less costly when compared with all other regimens (incremental costs between: -$1,319,019 to -$545,083). In this analysis, VenG was estimated to be dominant (more efficacious and cost saving) compared with ibrutinib-based treat-to-progression regimens (ibrutinib, ibrutinib + rituximab), GClb, and BR. In summary, 12-month fixed-

duration treatment with VenG is projected to be cost-effective versus GClb, BR, and ibrutinib-based treat-to-progression regimens (ibrutinib, ibrutinib + rituximab) within accepted US cost-effectiveness thresholds.

In the R/R CLL analysis the cost-effectiveness of VenR vs BR, ibrutinib, ibrutinib + BR, and idelalisib + rituximab was evaluated. Results showed VenR increased QALYs compared with other evaluated regimens with incremental benefits for VenR of 2.83 versus BR; 2.31 versus ibrutinib; 1.43 versus ibrutinib + BR; and, 4.43 versus idelalisib + rituximab. The fixed-duration of VenR also resulted in lower incremental costs vs treat-to-progression oral regimens. VenR was more costly than BR (incremental cost: $175,591), which translated into an incremental cost-effectiveness ratio (ICER) of approximately $62,000/ QALY, falling within the US accepted cost-effectiveness threshold of $150,000 per QALY gained. In this study, the 24-month fixed-duration treatment with VenR was more efficacious and cost saving compared with the treat-to-progression oral agents ibrutinib, ibrutinib + BR, and idelalisib + rituximab; and, more cost-effective vs BR within the US accepted cost-effectiveness thresholds.

Economic benefits regarding cost savings and effectiveness were seen with venetoclax-based fixed-treatment duration regimens in both the 1L and R/R CLL setting compared with other available treatment options.

References:

1. Cho SK, Manzoor BS, Sail KR, et al. Budget impact of 12-month fixed treatment duration venetoclax in combination with obinutuzumab in previously untreated chronic lymphocytic leukemia patients in the United States [published online ahead of print, 2020 May 8]. *Pharmacoeconomics*. 2020; 10.1007/s40273-020-00919-1. doi:10.1007/s40273-020-00919-1.
2. Davids MS, Chatterjee A, Ravelo A, et al. Cost-effectiveness of a 12-month fixed duration of venetoclax in combination with obinutuzumab in first-line chronic lymphocytic leukemia in the United States. Poster presented at the American Society of Hematology Annual Meeting; December 7-10, 2019. Orlando, Florida. Poster Presentation 4741.
3. Huntington SF, Strunz-McKendry T, Masaquel AS, et al. Cost-effectiveness of a 24-month fixed duration of venetoclax in combination with rituximab in relapsed or refractory chronic lymphocytic leukemia in the United States. Poster presented at the International Society for Pharmacoeconomics and Outcomes Research; May 18-22, 2019. New Orleans, LA. Poster Presentation PCN122.

Respectfully submitted,

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