UMBRALISIB IMPROVES TOLERABILITY AND ASSOCIATED COST BURDEN OF ADVERSE EVENTS OVER PI3K INHIBITORS IN RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA PATIENTS; RESULTS FROM MATCHING-ADJUSTED INDIRECT COMPARISON

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BACKGROUND

- Targeted therapies, such as phosphoinositide 3-kinase inhibitors (PI3Kis), provide chemotherapy-free options for relapsed / refractory (R/R) follicular lymphoma (FL) patients.
- PI3Kis provide viable treatment options for R/R FL patients, but are associated with some significant toxicities [1-3], creating an unmet need for improved tolerability. In addition to the burden on patients, payers are known to be concerned about the high cost of management associated with adverse events (AEs) for their R/R FL patients.
- Umbralisib (UKONIQ®) is an oral, once-daily, first and only multikinase inhibitor of PI3K-delta (δ) and casein kinase 1 (CK1)-epsilon (ε) that is pharmacologically distinct from currently approved PI3Kis with high selectivity for the delta isoform of PI3K.
- Given the single-arm nature of umbralisib's clinical trial (UNITY-NHL), the comparative effectiveness and safety of umbralisib vs. PI3Kis is not yet established.

OBJECTIVE

- To compare the efficacy and safety of umbralisib with PI3Kis in R/R FL through a matching-adjusted indirect comparison (MAIC) and quantify the cost burden associated with AEs leading to discontinuation of treatment.

METHODS

OVERVIEW

- MAIC is a validated indirect comparison technique that uses individual patient data (IPD) from one trial and aggregate data from another to enable comparison of treatment outcomes after matching baseline characteristics. [4]
- An MAIC was conducted using IPD from the UNITY-NHL trial (NCT02793583)[5] vs. published comparator data identified via a systematic literature review. [3, 6-7]
- After matching, differences in discontinuation rate due to AEs and median duration of response (DoR) were compared using statistical tests.
- AE discontinuation cost burden was calculated using trial AE rates [1-3] and cost of AE treatment from public databases. [8]

MATCHING CHARACTERISTICS

- Patients in UNITY-NHL were matched and reweighted based on ≥1 of the following characteristics: age, sex, prior lines of therapy, ECOG status, cancer stage, FL grade, LDH and B-symptoms.
- Selection of factors included in matching for each comparison was determined by a combination of data availability and impact on estimated sample size (ESS) for umbralisib.
- Patient characteristics for each comparison before and after matching are shown in **Tables 1-3.**

METHODS CONT'D

Table 1. Baseline Matching Characteristics vs. Copanlisib

CHARACTERISTIC	BEFORE MATCHING	AFTER MATCHING	LEPPA 2019[6]
	UMBRALISIB (N=117)	UMBRALISIB (ESS = 87.87)	COPANLISIB (N=104)
Median Age (years)	65.0	61.5	62.0
Sex – Male (%)	61.5%	51.9%	51.9%
Median Prior Lines of Therapy	3.0	2.8	3.0
Proportion of Patients with ECOG Status 0/1 (%)	96.6%	96.1%	96.1%
Proportion of Patients with FL Grade 1/2 (%)	70.9%	71.2%	71.2%
Proportion of Patients with B Symptoms (%)	25.6%	13.0%	13.0%

Table 2. Baseline Matching Characteristics vs. Duvelisib

CHARACTERISTIC	BEFORE MATCHING	AFTER MATCHING	FLINN 2019[3]
	UMBRALISIB (N=117)	UMBRALISIB (ESS = 81.45)	DUVELISIB (N=83)
Median Age (years)	65.0	63.5	64.0
Sex – Male (%)	61.5%	68.0%	68.0%
Median Prior Lines of Therapy	3.0	2.25	3.0
Proportion of Patients with ECOG Status 0/1 (%)	96.6%	93.0%	93.0%
Median Time since Diagnosis (months)	68.6	47.9	48.0

Table 3. Baseline Matching Characteristics vs. Idelalisib

CHARACTERISTIC	BEFORE MATCHING	AFTER MATCHING	SALLES G 2017[7]
	UMBRALISIB (N=117)	UMBRALISIB (ESS=70.24)	IDELALISIB (N=72)
Median Prior Lines of Therapy	3.0	3.34	4.0
Proportion of Patients with prior CD-20 (%)	100%	100%	100%
Proportion of Patients with ECOG Status 0/1 (%)	96.6%	91.7%	91.7%
Proportion of Patients with Cancer Stage ≥ 3 (%)	72.6%	83.3%	83.3%
Proportion of Patients with FL Grade 1/2 (%)	70.9%	83.4%	83.4%
Proportion of Patients with LDH (%)	13.7%	29.0%	29.0%

ECONOMIC INPUTS

- AE rates were sourced directly from products' clinical trials considered as part of the MAIC.
- To determine the economic impact of AEs, the incidence of AEs in Table 4 was multiplied by the unit cost per AE.

Table 4. Adverse Event (grade ≥3) Rates and Management Cost

ADVERSE EVENT	Umbralisib[5]	Copanlisib[1]	Idelalisib[2]	Duvelisib[3]	Cost Per Episode[8]
Neutropenia	14.00%	24.00%	27.00%	24.80%	$8,994
Pneumonia	0.00%	0.00%	7.00%	5.40%	$13,037
Tumor Lysis Syndrome	0.00%	0.00%	0.00%	0.00%	$15,853
Anemia	6.00%	4.00%	2.00%	14.70%	$6,043
Thrombo-cytopenia	0.00%	7.00%	6.00%	11.60%	$8,114
Diarrhea/Colitis	7.00%	6.00%	13.00%	20.16%	$7,168
Hypertension	0.00%	24.00%	0.00%	0.00%	$7,022
Lymphopenia	0.00%	0.00%	0.00%	0.00%	$8,994
Pneumonitis	0.00%	1.00%	0.00%	0.00%	$12,713

RESULTS

RESULTS VS. COPANLISIB

- After matching, umbralisib significantly reduced discontinuations due to AE compared to copanlisib [10.4% vs. 27.9%], p<0.001.
- The median DoR (months) for umbralisib showed a positive trend in comparison to copanlisib [12.2, 95% CI 7.6-22.3 months vs. 11.1, 95% CI 7.2-NE months].

Figure 1. Discontinuation rate due to adverse events post-matching, umbralisib vs. copanlisib

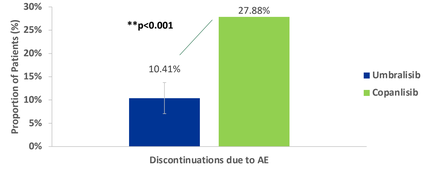
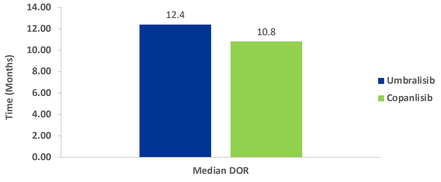


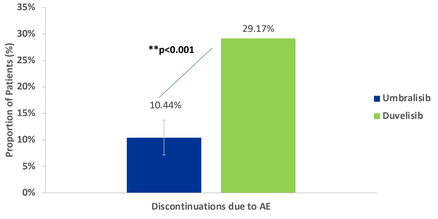
Figure 2. Duration of response post-matching, umbralisib vs. copanlisib



RESULTS VS. DUVELISIB

- After matching, umbralisib significantly reduced discontinuations due to AE compared to duvelisib [10.4% vs. 29.2%], p<0.001.
- No DoR data were available for duvelisib.

Figure 3. Discontinuation rate due to adverse events post-matching, umbralisib vs. duvelisib



RESULTS CONT'D

RESULTS VS. IDELALISIB

- After matching, umbralisib significantly reduced discontinuations due to AE compared to idelalisib [7.8% vs. 25.0%] , p<0.001.
- The median DoR (months) for umbralisib showed a positive trend in comparison to idelalisib [12.4, 95% CI 8.54-NE vs. 10.8, range 0-26.9 months].

Figure 4. Discontinuation rate due to adverse events post-matching, umbralisib vs. idelalisib

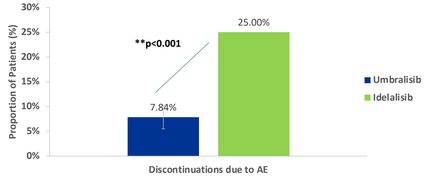
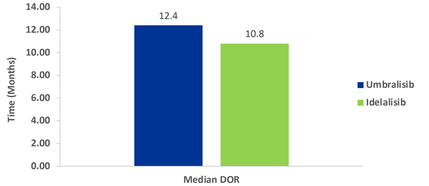


Figure 5. Duration of response post-matching, umbralisib vs. idelalisib



ECONOMIC IMPACT OF AE MANAGEMENT

- The annual per patient cost of managing AEs was determined to be lowest for umbralisib ($2,123) compared to copanlisib ($5,211), duvelisib ($6,209), and idelalisib ($4,880).

Figure 6. Total cost of adverse event management, umbralisib vs. PI3Kis

DISCUSSION

- In the absence of head-to-head trials, MAIC can be a useful tool to assess comparative effectiveness of therapies.
- Patient populations across trials for umbralisib vs. PI3Kis were successfully matched based on key clinical characteristics available across trials.
- Across comparisons against all PI3Kis, umbralisib resulted in the lowest rates of discontinuations due to AEs after adjusting for baseline patient characteristics.

CONCLUSIONS

- In an indirect treatment comparison accounting for differences in cross-trial characteristics, umbralisib demonstrated significantly lower AE discontinuations (~3 times lower), favorable DoR, and a lower AE management cost burden (>2 times lower) than currently approved PI3Kis for R/R FL patients.

LIMITATIONS

- Not all patient characteristics are reported across trials, and thus matching on the same characteristics was not possible across all products.
- Not all prognostic factors could be adjusted for within these analyses due to data availability and impact on ESS; notably, characteristic selection was guided by clinician recommendation.
- Not all AEs were included as part of the economic management analysis; however, all AEs consistently reported were included.

REFERENCES

1. Dreyling M et al., J Clin Oncol. 2017.
2. Gopal AK et al., N Engl J Med. 2014.
3. Flinn IW et al., J Clin Oncol. 2019.
4. Signorovitch JE et al., Value in Health 2012.
5. Zinzani PLS et al., ASH 2020.
6. Leppa S et al., J Clin Oncol 2019.
7. Salles G et al., Haematologica 2017.
8. AHRQ HCUPnet. https://hcupnet.ahrq.gov/

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