To PALKO/COHERE

Helsinki, 1 August 2025

Astellas comment to PALKO/COHERE draft recommendation “tsolbetuksimabi mahalaukun ja ruokatorvi-mahalaukkurajan adenokarsinooman ensilinjan hoidossa

Astellas appreciates the opportunity to comment on the draft recommendation from COHERE regarding “*tsolbetuksimabi mahalaukun ja ruokatorvi-mahalaukkurajan adenokarsinooman ensilinjan hoidossa”.* Astellas is concerned regarding COHERE’s assessment and would like to provide additional insights on the following three topics:

1. The comparative efficacy of zolbetuximab versus standard chemotherapy.
2. The transferability of the study results to a Finnish population.
3. The safety profile and adverse events associated with zolbetuximab.

The comparative efficacy of zolbetuximab versus standard chemotherapy

Efficacy outcomes from SPOTLIGHT and GLOW demonstrated that the addition of zolbetuximab to first-line chemotherapy significantly reduces risk of disease progression by 29% (PFS HR: 0.71; 95%: 0.61, 0.83) and death by 23% (OS HR: 0.77; 95% CI: 0.67, 0.89) compared with chemotherapy alone in patients with HER2-negative, CLDN18.2-positive, locally advanced or metastatic G/GEJC. [1, 2].

The EMA concluded that the efficacy analysis of SPOTLIGHT and GLOW demonstrated statistically significant improvements in PFS and OS that can be considered clinically meaningful to support a benefit for the addition of zolbetuximab to standard 1L chemotherapy in advanced GEJ/gastric cancer in the overall study population [1]. The efficacy of zolbetuximab has also been considered meaningful and recommended for patients who are CLDN18.2 positive in international gastric cancer guidelines, e.g. ESMO Clinical Practice Guidelines for Gastric Cancer and NCCN Clinical Practice Guidelines in Oncology for Gastric Cancer [3,4].

Comparatively, PD-(L)-1 inhibitors recommended in Finland and considered to have shown clinically meaningful improvement by EMA in patients with locally advanced or metastatic G/GEJC, have reported a similar but smaller reduction in the hazard of progression or death. FIMEA agreed that the indirect treatment comparison submitted by Astellas, supports the conclusion that zolbetuximab in combination with chemotherapy is as effective as PD-(L)-1 inhibitors in combination with chemotherapy in prolonging the overall survival and progression-free survival in advanced gastric cancer patients [5].

The transferability of the study results to a Finnish population

As noted by COHERE, subgroup analyses indicate a trend that Caucasian patients may experience a lower relative treatment effect (measured by hazard ratio) compared to Asian patients. This concern was also raised during the EMA approval process. In response, additional analyses were conducted, leading to the following conclusions:

- There were no differences in the baseline characteristics between Asian/Caucasian patients that would explain the observed differences in HRs for PFS and OS. [1 (p 152)]
- There were no differences in CLDN18.2 expression that would explain the observed differences in HRs for PFS and OS. [1 (p 151)]

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- Population pharmacokinetic modelling showed that race/ethnicity was not identified as a statistically significant covariate and hence cannot explain the observed differences in HRs for PFS and OS. [1 (p 50)]
- The overall exposure (i.e. duration of exposure in days, median cumulative actual dose) to zolbetuximab and partly also to oxaliplatin, however, was lower in Caucasians compared to Asians. [1 (p 153)]
- Zolbetuximab discontinuations/interruptions were observed more in Caucasians as compared to Asians, which would be a plausible reason for the different exposure values. [1 (p 157-159)]
- To further study the potential impact of zolbetuximab early discontinuation/ interruptions, post-hoc analysis of PFS and OS were conducted. [1 (p 162-163)]
    - For these sensitivity analyses TEAEs leading to dose interruptions with a relative exposure intensity (REI) of <75% and/or TEAEs leading to discontinuation of zolbetuximab/placebo within 180 days were considered.
    - The analyses confirmed the higher rate of dose interruptions and discontinuations in Caucasian vs Asian participants.
    - Exploratory efficacy analyses suggest that PFS and OS were both affected and were lower regardless of race in participants who experienced TEAE leading to dose interruptions/discontinuations compared to those who did not experience such interruption or withdrawal of study drug.

In summary, the explorative analyses *concluded* that the main factor that impacted efficacy was a difference in exposure to zolbetuximab (i.e. duration of exposure in days, median cumulative actual dose). A consistent correlation of drug exposure with efficacy outcomes was observed that could explain the difference in benefit by subgroups. It can be also concluded that higher rates of zolbetuximab discontinuations/interruptions were observed in Caucasian as compared to Asian and this was a plausible reason for the different exposure values. When comparing Asian and Caucasian patients with and without TEAE leading to dose interruption/ discontinuation of study drug it was observed that same effects were observed across race, i.e. Caucasians without dose interruption/ discontinuation had similar PFS/OS effect as Asians without dose interruption/discontinuation.

Based on the discussion of the subgroup analysis and possible explanations for the observed pattern, EMA concluded:

> *"the results of these additional analyses overall support the hypothesis that the lower exposure due to discontinuations/dose interruptions could be the main factor for the observed lower treatment effect in the Caucasian subgroup."* [1 (p173)]

Astellas agree with COHERE that it is well-known that the incidence of gastric cancer is higher in Asian than in Western countries. It is also well established that national screening programs in Korea and Japan contribute to earlier detection and improved prognosis in these populations [6,7]. However, Astellas has not identified any scientific rationale suggesting that the Finnish population would differ significantly from the following statement made by EMA [1]:

> *"Analyses of baseline/disease characteristics, biomarker (CLDN18.2) status, exposure-response models by race and a review of literature data could not sufficiently explain the differences. Data did not reveal a biological rationale for a different treatment effect in the Caucasian vs Asian."* [1 (p. 172)]

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The safety profile and adverse events associated with zolbetuximab

Chemotherapy-induced nausea and vomiting are frequent symptoms in cancer patients. In SPOTLIGHT and GLOW, the rate of these symptoms was higher in patients receiving zolbetuximab in combination with chemotherapy compared to chemotherapy alone [2]. However, these events were non-serious and manageable, leading to a small number of zolbetuximab-treated patients discontinuing treatment due to nausea- or vomiting-related TEAE (treatment-emergent adverse events). A higher proportion of dose interruptions and dose rate reductions was observed in the zolbetuximab arms due to nausea and vomiting compared to the placebo arms. Notably, these elevated rates were predominantly reported during the first infusion of zolbetuximab, likely due to initial exposure to monoclonal antibody therapy and the administration of a higher loading dose during the first infusion.

Due to the above, the following amendments have been made to the SmPC [8]:

- Removal of restrictions on steroids use. Whereas the protocol for the phase 3 trials stated: “Antiemetics" (e.g., corticosteroids) and “Cautionary Concomitant Treatment” were to be avoided or minimized while participants were on study treatment unless required for management of an emergent medical condition.
- Inclusion of recommendation for earlier intervention for the management of nausea and vomiting in the SmPC in the “Dose Modification” guidance compared to dose modification guidance in the study protocols.

The SmPC modifications will allow clinicians to properly manage these events and consequently reduce the frequency of discontinuation from therapy [1]. Clinical experts with experience from the clinical studies have also contributed to the development of a guideline for the prevention and management of nausea and vomiting associated with treatment with zolbetuximab [9].

The use of antiemetics and infusion rate reduction, especially during the first loading dose, is expected to mitigate the risk and improve the management of nausea and vomiting. The effect of the use of antiemetics are illustrated in the not yet published analysis presented in Figure 1 and Figure 2. The analysis shows that patients who received zolbetuximab and steroids in SPOTLIGHT and GLOW at any time during the study period, had a statistically significant HR of [redacted] with an OS benefit of [redacted] months compared to the placebo arm with steroids (Figure 1). Patients who received zolbetuximab and steroids also showed a statistically significant HR of [redacted] with an OS benefit of [redacted] months compared to patients who received zolbetuximab and no steroids at any time during the study period (Figure 2). Early experiences from Japan (RWE) have also shown that nausea and vomiting are reduced in clinical practice when the recommendations for prevention and management of these side effects are followed [10,11].

In conclusion, Astellas hopes that COHERE will align with the EMA’s assessment and recognize that enhanced prevention and management of nausea and vomiting associated with zolbetuximab treatment can contribute to delayed disease progression and improved overall survival outcomes for Finnish patients.

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Figure 1. Kaplan-Meier Plot on Overall Survival in patients who receive zolbetuximab and corticosteroids vs placebo and corticosteroid (SPOTLIGHT and GLOW full analysis set)

Source: Data on file, Astellas

Figure 2. Kaplan-Meier Plot on Overall Survival in patients who receive zolbetuximab and corticosteroids vs zolbetuximab and no corticosteroid (SPOTLIGHT and GLOW full analysis set)

Source: Data on file, Astellas

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