On-Treatment Cancer Safety Events with Daprodustat versus Erythropoiesis-Stimulating Agents – Post Hoc Analyses of ASCEND-ND and ASCEND-D

Aims

These post hoc time-to-event analyses were performed to assess the impact of different dosing intervals on cancer-related adverse events (AEs) for daprodustat versus erythropoiesis-stimulating agents (ESAs) in the ASCEND-ND and ASCEND-D trials.

Background

Previous analyses have reported concerns for cancer-related AEs with use of ESAs among patients with chronic kidney disease (CKD) and ESKD. In ASCEND-ND, patients with anemia of CKD not receiving dialysis (ASCEND-ND; vs. darbepoetin alfa) and receiving dialysis (ASCEND-D; vs. epoetin alfa) had cancer-related AEs. In ASCEND-D, a pre-specified on-treatment analysis of ACSF-N was raised concerns about a higher absolute risk of cancer-related AEs with daprodustat versus darbepoetin alfa, which was not raised in dialysis patients enrolled in ASCEND-D.

Methods

Pre-specified on-treatment analyses of ASCEND-ND and -D examined relative risks for cancer-related AEs up to 1 year after the last dose (LDD) of randomized therapy. ESMs compared using different dosing intervals in the trials: 3 times per week (TIW), once per week, every 2 weeks, or every 4 weeks. Daprodustat was dosed daily at various follow-up periods, darbepoetin alfa was dosed daily, weekly, twice per week, 3 times per week, or 1–24 mg daily. Analyses that account for longer darbepoetin alfa dosing intervals, plus association with longer LDD follow-up duration (considering the relative latency of cancer-related diagnoses), likely provide a more valid estimate of risk.

On-treatment cancer-related AEs and follow-up duration

In ASCEND-ND, the effect estimates of daprodustat versus darbepoetin alfa in terms of cancer-related AEs depended on the definition of on-treatment and duration of follow-up (Figure 3).

The HR (95% CI) censoring at:

- LDD + 1 day was 1.50 (1.04–2.15)
- LDD + dosing interval was 1.12 (0.81–1.56)
- End of study was 1.04 (0.77–1.44)

In ASCEND-D, no excess risk was observed with daprodustat for cancer-related AEs during any the follow-up periods examined.

The HR (95% CI) censoring at:

- LDD + 1 day was 0.92 (0.61–1.37)
- LDD + dosing interval was 0.80 (0.50–1.33)
- End of study was 0.83 (0.60–1.16)

Cancer-related AEs in relation to LDD

- In ASCEND-ND, 24/87 patients (29%) in the daprodustat arm, and 37/84 patients (44%) in the darbepoetin alfa arm developed a first cancer-related AE that occurred on or after the LDD.
- In ASCEND-D, the rate of cancer-related AEs was similar between treatment arms in the first 90 days preceding the LDD. Cancer-related AEs were more frequent in the daprodustat arm on and within 10 days after the LDD, compared to darbepoetin alfa, but this difference attenuated with further follow-up (Figure 4A).

In ASCEND-D, 26/55 patients (34%) in the daprodustat arm, and 27/33 patients (82%) in the darbepoetin alfa arm, developed a first cancer-related AE that occurred on or after the LDD.

In ASCEND-D, landmark analyses show similar AE rates in both treatment arms extending beyond the LDD.

Conclusions

- Time-to-event analyses of ASCEND ND and D support the findings of the ASCEND trial and provide additional evidence for the use of daprodustat in patients with CKD, ESKD, and malignancy.
- These findings are consistent with the ASCEND trial in terms of safety profile and cancer-related AEs and provide additional evidence for the use of daprodustat in patients with CKD, ESKD, and malignancy.

References


Figure 1: ASCEND-ND on-treatment cancer AE study analysis design (safety pop’nby LDD in (A) ASCEND-ND and (B) ASCEND-D)

Figure 2: Dosing frequency of ESA and daprodustat median (IQR) Hb (g/dL) over time in ASCEND-ND and ASCEND-D

Figure 3: Kaplan-Meier curves (panels A–C) for ASCEND-ND on-treatment analyses (cancer-related AEs in the safety pop’nby LDD in (A) ASCEND-ND and (B) ASCEND-D).

Figure 4: Kaplan-Meier curves (endpoint CTE) for cancer-related AEs in the safety pop’n by LDD in (A) ASCEND-ND and (B) ASCEND-D.