7-1-2021

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Recommended Citation

Ajani J, El Hajbi F, Cunningham D, Alsina M, Thuss-Patience P, Scagliotti G, Van den Eynde M, Rybkin I, Shen L, Kato K, Kim S, D'Alonzo S, Yu W, Tao A, and Van Cutsem E. O-15 Randomized, phase 3 study of second-line tislelizumab vs chemotherapy in advanced or metastatic esophageal squamous cell carcinoma (RATIONALE 302) in the overall population and Europe/North America subgroup. Ann Oncol 2021; 32:S225.

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O-15 Randomized, phase 3 study of second-line tislelizumab vs chemotherapy in advanced or metastatic esophageal squamous cell carcinoma (RATIONALE 302) in the overall population and Europe/North America subgroup

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Background: The global Phase 3 study RATIONALE 302 (NCT03430843) evaluated the efficacy and safety of second-line tislelizumab, an anti-PD-1 antibody, in patients with advanced or metastatic esophageal squamous cell carcinoma (ESCC). Here, we report data from the overall and Europe/North America (EU/NA) populations.

Methods: Eligible adult patients had disease progression during or after first-line systemic therapy, $\geq$1 evaluable lesion per RECIST v1.1 and an Eastern Cooperative Oncology Group performance score (ECOG PS) of $\leq$1. Patients were randomized (1:1) to receive tislelizumab 200 mg intravenously Q3W or investigator-chosen chemotherapy (paclitaxel, docetaxel, or irinotecan) and treated until disease progression, intolerable toxicity, or withdrawal. Stratification factors included chemotherapy option, region, and ECOG PS. The primary endpoint was overall survival (OS) in all patients (ITT population). The key secondary endpoint was OS in PD-L1 positive (vCPS $\geq$10%) patients; other secondary endpoints included progression-free survival (PFS), overall response rate (ORR), duration of response (DoR), health-related quality of life and safety.

Results: 512 patients (overall population) were randomized to tislelizumab (n=256) or chemotherapy (n=256), of which 108 (21%) patients were enrolled into EU/NA subgroup (n=55 tislelizumab, n=53 chemotherapy). On 1 December 2020 (data cut-off), median follow-up was 6.9 and 6.8 months in the overall population and EU/NA subgroup, respectively. Tislelizumab improved OS vs chemotherapy in the overall population (median OS 8.6 vs 6.3 months; HR 0.70, 95% CI 0.57–0.85; p=0.0001); survival benefit was consistently observed in the EU/NA subgroup (median OS 11.2 vs 6.3 months; HR 0.55; 95% CI 0.35–0.87). Treatment with tislelizumab was associated with improved ORR (20.3% [95% CI 15.6%–25.8%] vs 9.8% [95% CI 6.4%–14.1%]) and median DoR (7.1 vs 4.0 months; HR 0.42, 95% CI 0.23–0.75) vs chemotherapy in the overall population. Improvement in ORR (20.0% [95% CI 10.4%–33.0%] vs 11.3% [95% CI 4.3%–23.0%]) and median DOR (5.1 vs 2.1 months; HR 0.42, 95% CI 0.13–1.39) was also observed in the EU/NA subgroup. Fewer patients had Grade $\geq$3 treatment-emergent adverse events (TEAE) with tislelizumab vs chemotherapy in both the overall and EU/NA populations (46% vs 68% and 56% vs 71%, respectively). Of these, fewer Grade $\geq$3 AEs were treatment-related with tislelizumab vs chemotherapy (overall: 19% vs 56%; EU/NA: 13% vs 51%). AEs leading to death were similar with tislelizumab vs chemotherapy (overall: 14% vs 12%; EU/NA: 6% vs 5%).

Conclusions: Second-line tislelizumab demonstrated statistically significant and clinically meaningful improvement in OS versus chemotherapy in patients with advanced or metastatic ESCC. Tislelizumab demonstrated a tolerable safety profile. Efficacy and safety results from the EU/NA subgroup were consistent with the overall population.

Clinical trial identification: NCT03430843.

Editorial acknowledgement: Medical writing support for the development of this abstract, under direction of the authors, was provided by Kirsty Millar, MSc, of Ashfield MedComms, an Ashfield Health company, and was funded by BeiGene Ltd.

Legal Entity Responsible for this Study: BeiGene, Ltd.

Funding: This study is sponsored by BeiGene, Ltd.

Disclosures: J. Ajani: Honoraria (self): BeiGene; D. Cunningham: Advisory / Consultancy: OVIBIO on Scientific Advisory Board. Research grant / Funding (institution): AstraZeneca / MedImmune, Celgene, Bayer, 4SC, Eli Lilly, Clovis, Natera, Roche, Leap. K. Kato: Advisory / Consultancy: BMS, Beigene, MSD. Research grant / Funding (institution): ONO, BMS, MSD. S. D'Alonzo: Full / Part-time employment: BeiGene. W. Yu: Full / Part-time employment: Beigene. E. Van Cutsem: Advisory / Consultancy: Bayer, Lilly, Roche, Servier, Bristol-Myers Squibb, Celgene, Merck Sharp & Dohme, Merck KGaA, Novartis, AstraZeneca, Halozyme, Array BioPharma, Biocartis, GlaxoSmithKline, Daiichi Sankyo, Pierre Fabre, Sirtex Medical, Taiho Pharmaceutical, Incyte. Research grant / Funding (institution): Amgen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2021.05.807