Modeling analysis of RATIONALE-305: impact of peritoneal metastasis (PM) representation on clinical outcomes in patients (pts) treated with tislelizumab plus chemotherapy (TIS+CT) with gastric cancer/gastroesophageal junction cancer (GC/GEJC)

Authors: Mohamad Bassam Sonbol, MD,[1]* Sun Young Rha, MD, PhD,[2] Rui-Hua Xu, MD,[3] Filippo Pietrantonio, MD,[4] Markus Moehler, MD,[5] Ken Kato, MD, PhD,[6] Maria Alsina Maqueda, MD, PhD,[7] Hyung-Don Kim, MD, PhD,[8] Yaling Xu, MD,[9] Xuan Kong, MD, PhD,[9] Na Zhao, PhD,[10] Sylvie Lorenzen, MD, PhD[11]

Affiliations: [1]Division of Hematology/Oncology, Mayo Clinic Comprehensive Cancer Center, Phoenix, AZ, USA [2]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea [3]Medical Oncology, Sun Yat-sen University Cancer Center State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China [4]Department of Medical Oncology, National Cancer Institute Fondazione IRCCS, Milan, Italy [5]Johannes Gutenberg-University Clinic, Department of Internal Medicine I, Mainz, Germany [6]Department of Head and Neck, Esophageal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan [7]Department of Medical Oncology, Hospital Universitario de Navarra, Pamplona, Spain [8]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea [9]Clinical Development, BeOne Medicines Ltd., Shanghai, China [10]Global Statistics and Data Science, BeOne Medicines Ltd., Shanghai, China [11]TUM University Hospital, Rechts der Isar, Department of Medicine III, Munich, Germany

ABSTRACT

Background: RATIONALE-305 (NCT03777657) enrolled the highest number of pts with PM among similar trials and stratified pts with advanced GC/GEJC by presence of PM. We used statistical modeling to evaluate the impact of varying PM levels on outcomes with TIS+CT.

Methods: We randomized adults with GC/GEJC (1:1) to TIS or placebo (PBO) + CT. Primary endpoints: OS in intent-to-treat (ITT) population and pts with programmed death-ligand 1 (PD-L1) Tumor Area Positivity (TAP) score ≥5%. We weighted pts using the method of moments to match a hypothetical population to ITT, with the same distribution of sex, primary tumor location, PD-L1 (TAP score <5% vs ≥5%), number of metastatic sites (0-2 vs 3+), and liver metastasis. PM representation was set from 20% to 45%. Weighted OS, PFS, and objective response rate (ORR) were estimated.

Results: Of 997 pts enrolled, 434 (43.5%) had PM. Among pts with PD-L1 TAP scores ≥5% (54.8%), 39.7% had PM, and among pts with scores ≥1% (88.9%), 43.6% had PM (data cutoff Feb 28, 2024). Fewer pts with (+) PM had PD-L1 high tumors (TAP score ≥5%: 50.0%) and more had primary stomach tumors (86.6%) compared to those without (-) PM (58.4% and 75.5%). TIS+CT improved OS, PFS, and ORR in ITT and in pts +/- PM vs PBO+CT (Table). Across 20%–45% PM, TIS+CT showed consistent benefit, with stable HRs for OS and PFS (20% and 45% shown). TIS+CT showed survival benefits in pts with PM and PD-L1 TAP score ≥5% (OS: HR=0.71; PFS: HR=0.65) and ≥1% (OS: HR=0.79; PFS: HR=0.79) vs PBO+CT. ORR was higher with TIS+CT vs PBO+CT in pts + PM and PD-L1 TAP scores ≥5% (47.3% vs 30.8%) and ≥1% (44.2% vs 33.2%).

Conclusions: Our analysis showed that lowering PM representation marginally improved OS and ORR, underscoring the poor prognosis of peritoneal disease. In RATIONALE-305, TIS+CT provides clinically meaningful response and survival benefits irrespective of PM, with higher responses in PD-L1+ GC/GEJC.

Table:

	Arm (95% CI)	ITT	+ PM	- PM	20% + PM	45% + PM
OS, months	TIS+CT	15.0 (13.6, 16.5)	12.3 (10.6, 14.3)	17.3 (15.0, 20.3)	15.4 (13.9, 18.0)	15.0 (13.5, 16.5)
	PBO+CT	12.9 (12.1, 14.1)	11.8 (10.5, 13.0)	14.0 (12.6, 16.0)	13.1 (12.3, 14.5)	12.8 (12.1, 14.1)
	HR	0.79 (0.69, 0.91)	0.78 (0.64, 0.96)	0.79 (0.65, 0.95)	0.81 (0.69, 0.95)	0.79 (0.69, 0.90)
PFS, months	TIS+CT	6.9 (5.7, 7.2)	5.8 (5.6, 7.3)	7.0 (5.7, 8.4)	6.9 (5.7, 7.3)	6.9 (5.7, 7.2)
	PBO+CT	6.2 (5.6, 6.9)	5.7 (5.3, 6.9)	6.9 (5.7, 7.1)	6.5 (5.6, 7.0)	6.2 (5.6, 6.9)
	HR	0.79 (0.68, 0.91)	0.80 (0.64, 0.98)	0.77 (0.64, 0.94)	0.79 (0.67, 0.94)	0.79 (0.69, 0.91)
ORR, %	TIS+CT	47.3 (42.9, 51.8)	43.6 (37.0, 50.5)	50.2 (44.2, 56.2)	48.0 (42.9, 53.1)	47.3 (42.8, 51.8)
	PBO+CT	40.5 (36.2, 45.0)	32.2 (26.0, 39.0)	46.8 (40.9, 52.8)	43.1 (38.1, 48.3)	40.3 (36.0, 44.8)
ORR difference, %		6.8 (0.6, 12.9)	11.4 (2.3, 20.3)	3.4 (-4.9, 11.6)	4.9 (-2.2, 11.9)	6.9 (0.8, 13.0)