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Tislelizumab Plus Chemotherapy vs Placebo Plus Chemotherapy as First-line Treatment for Recurrent or Metastatic Nasopharyngeal Cancer: 3-year Follow-up from the RATIONALE-309 Study

Wenfeng Fang,[1] Jianji Pan,[2] Hui Wang,[3] Shenhong Qu,[4] Nianyong Chen,[5] Xiaozhong Chen,[6] Yan Sun,[7] Xiaohui He,[8] Chaosu Hu,[9] Lizhu Lin,[10] Chia-Jui Yen,[11] Yanjie Wu,[12] Shuai Yuan,[12] Chenqi Chen,[12] Yunpeng Yang,[1] Shiangjiin Leaw,[12] Li Zhang[1]

[1]Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China; [2]Fujian Cancer Hospital, Fuzhou, Fujian, China; [3]Hunan Cancer Hospital, Changsha, Hunan, China; [4]The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, Guangxi, China; [5]West China Hospital of Sichuan University, Chengdu, China; [6]Zhejiang Cancer Hospital, Hangzhou, Zhejiang, China; [7]Beijing Cancer Hospital, Beijing, China; [8]Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China; [9]Fudan University Shanghai Cancer Centre, Shanghai, China; [10]The First Affiliated Hospital of Guangzhou Traditional Chinese Medicine University, Guangzhou, Guangdong, China; [11]National Cheng Kung University Hospital, Tainan, Taiwan; [12]BeiGene (Shanghai) Co., Ltd., Shanghai, China

Declaration of Interests

Wenfeng Fang

Wenfeng Fang has no conflicts of interest to disclose

Background

- Recurrent/metastatic (R/M) NPC has suboptimal survival outcomes with 1L CT (gemcitabine plus cisplatin)[1,2]
- The RATIONALE-309 study met its primary endpoint at the interim analysis, with 1L TIS plus CT demonstrating statistically and clinically superior progression-free survival (PFS) compared with PBO plus CT for patients with R/M NPC[3]
- In recent years, data from this and other studies[4,5] have informed updates to international treatment guidelines, which now recommend an anti–programmed cell death protein-1 monoclonal antibody plus CT as the preferred 1L treatment for patients with R/M NPC[6,7]

Here we report 3-year follow-up results of the RATIONALE-309 study

Abbreviations: 1L, first line; CT, chemotherapy; NPC, nasopharyngeal cancer; PBO, placebo; TIS, tislelizumab.

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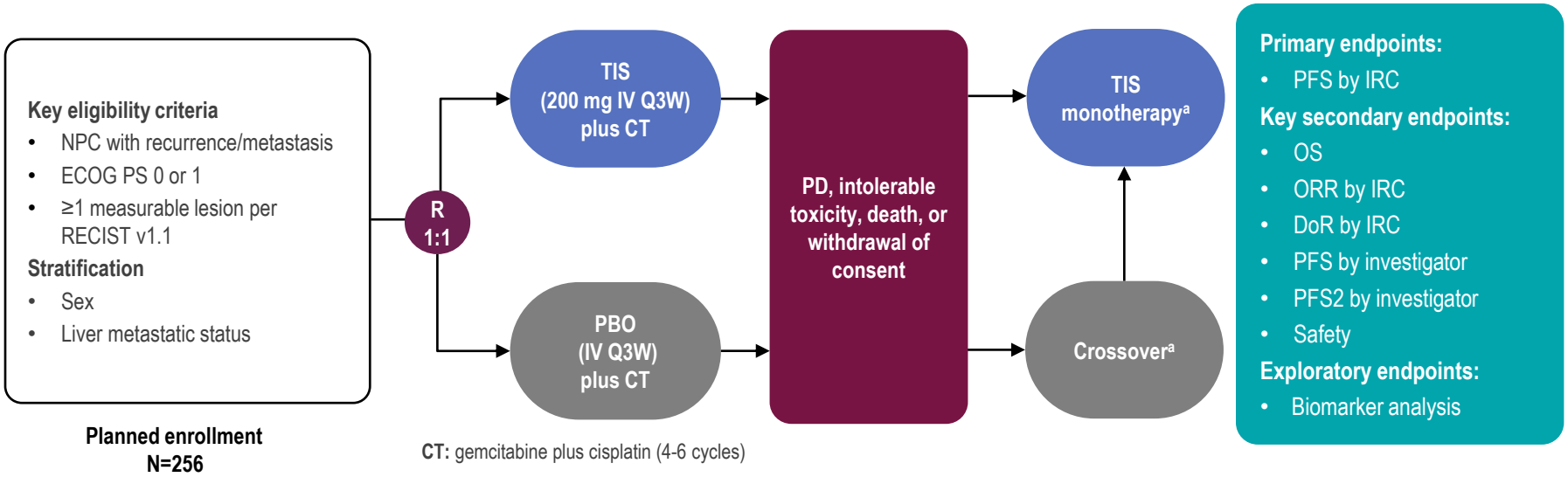
RATIONALE-309 Study Design



Planned enrollment
N=256

CT: gemcitabine plus cisplatin (4-6 cycles)

Data cutoff: December 8, 2023

Median survival follow-up time was 41.4 months (95% CI: 40.1 to 42.2 months) for TIS plus CT and 40.8 months (95% CI: 39.8 to 41.7 months) for PBO plus CT[b]

ClinicalTrials.gov Identifier: NCT03924986.

[a] If considered beneficial by investigator. [b] Median survival follow-up time was calculated using reverse Kaplan-Meier method.

Abbreviations: CT, chemotherapy; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; IV, intravenously; NPC, nasopharyngeal cancer; ORR, overall response rate; OS, overall survival; PBO, placebo; PD, progressive disease; PFS, progression-free survival; PFS2, progression-free survival after next line of treatment; Q3W, once every 3 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; TIS, tislelizumab.

Demographics and Baseline Characteristics

ITT Analysis Set

Baseline Demographics and Characteristics, n (%)	TIS + CT (n=131)	PBO + CT (n=132)
Median age (range), years	50 (26-74)	50 (23-73)
Patients aged <65 years	121 (92.4)	120 (90.9)
Male sex	103 (78.6)	103 (78.0)
ECOG PS		
0	51 (38.9)	46 (34.8)
1	80 (61.1)	86 (65.2)
Histology		
Undifferentiated non-keratinized	98 (74.8)	96 (72.7)
Differentiated non-keratinized	18 (13.7)	21 (15.9)
Keratinized squamous cancer	8 (6.1)	10 (7.6)
Unclassified	7 (5.3)	5 (3.8)
Location of metastases[a]		
Bone	58 (44.3)	63 (47.7)
Liver	56 (42.7)	56 (42.4)
Lung	61 (46.6)	63 (47.7)
Brain	3 (2.3)	2 (1.5)
Lymph nodes	88 (67.2)	73 (55.3)
Other	18 (13.7)	18 (13.6)

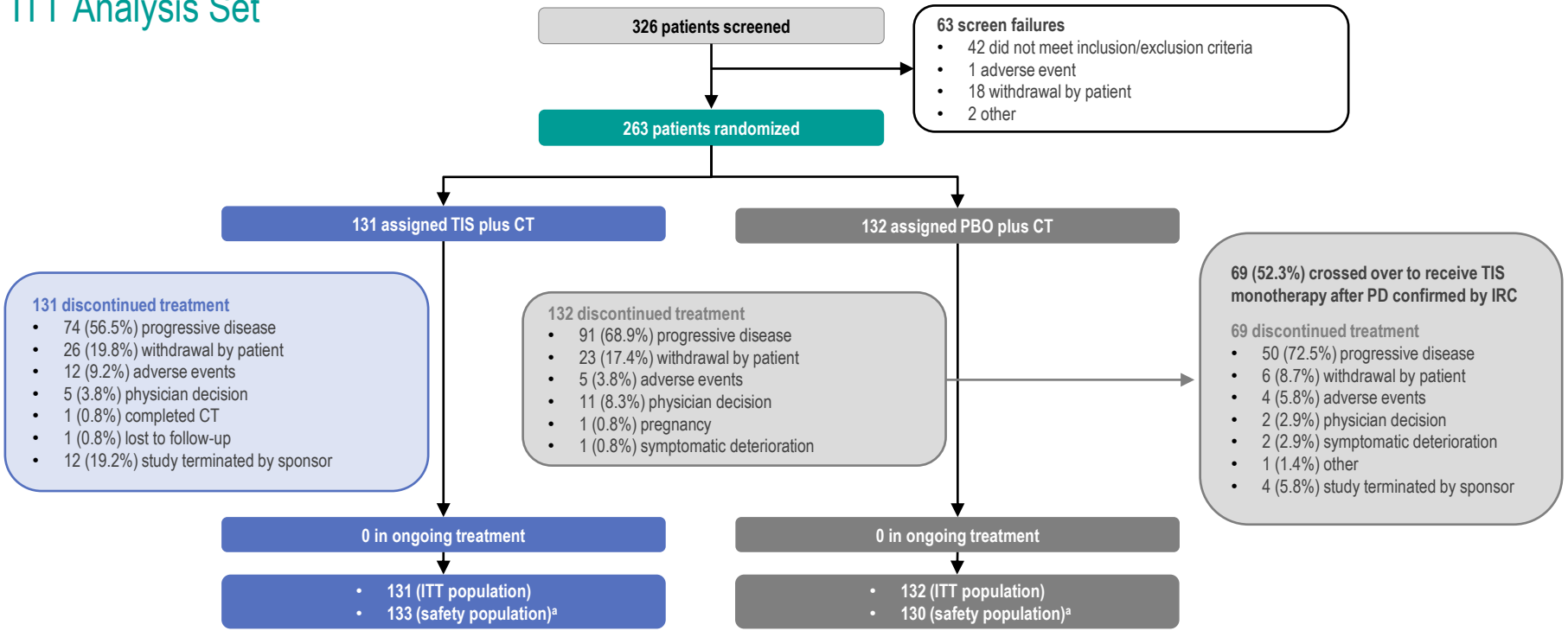
Baseline Demographics and Characteristics, n (%)	TIS + CT (n=131)	PBO + CT (n=132)
Smoking status		
Never	74 (56.5)	66 (50.0)
Current or former	57 (43.5)	66 (50.0)
Current disease stage		
Local recurrent	5 (3.8)	7 (5.3)
Metastatic	126 (96.2)	125 (94.7)
Primary	46 (35.1)	40 (30.3)
Recurrent	80 (61.1)	85 (64.4)
Baseline plasma EBV DNA level		
<500 IU/mL	26 (19.8)	37 (28.0)
≥500 IU/mL	105 (80.2)	95 (72.0)
Patients with any prior anticancer drug therapy[a,b]	83 (63.4)	88 (66.7)
Adjuvant	36 (43.4)	32 (36.4)
Neoadjuvant	55 (66.3)	59 (67.0)
Concurrent with radiotherapy	61 (73.5)	67 (76.1)
Other	6 (7.2)	4 (4.5)
Patients with any prior anticancer surgeries	6 (4.6)	4 (3.0)
Patients with any prior anticancer radiotherapy	84 (64.1)	91 (68.9)

[a] Patients were counted only once within each category but may be counted in multiple categories. [b] Percentages were based on the number of patients with any prior anticancer drug therapy.

Abbreviations: CT, chemotherapy; EBV, Epstein-Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent to treat; IU, international unit; PBO, placebo; TIS, tislelizumab.

Patient Disposition

ITT Analysis Set



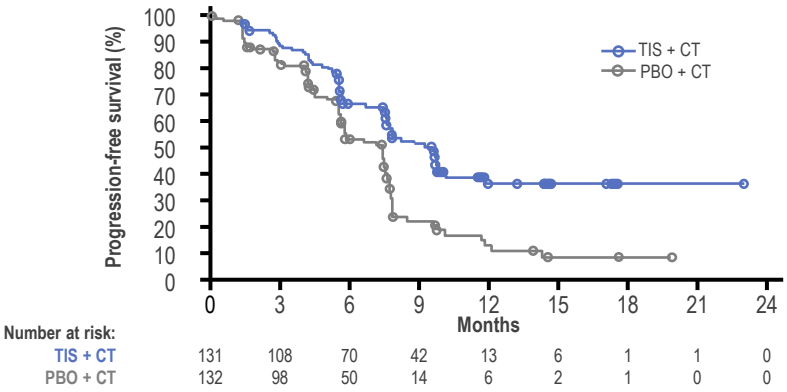
Data cutoff: December 8, 2023. The ITT analysis set included all randomized patients. The safety population included all randomized patients who received ≥1 dose of the study drug, with analysis based on the actual treatment regimen received. All percentages are calculated based on n=131 for TIS plus CT and n=132 for PBO plus CT arms. [a] For the safety population analysis, 2 patients initially randomized to the PBO plus CT arm but who erroneously received 100 mg TIS were included in the TIS plus CT arm.

Abbreviations: CT, chemotherapy; IRC, independent review committee; ITT, intent to treat; PBO, placebo; PD, progressive disease; TIS, tislelizumab.

Progression-free Survival

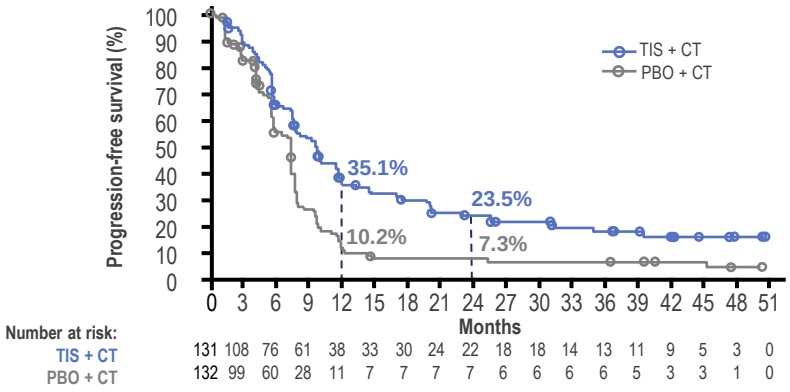
Per IRC (ITT Analysis Set)

Interim analysis (DCO March 26, 2021)



	Events (%)	Median (95% CI), months	HR (95% CI)	*P*-value
TIS + CT	65 (49.6)	9.2 (7.6, 10.1)	**0.52 (0.38, 0.73)**	**<0.0001**
PBO + CT	87 (65.9)	7.4 (5.6, 7.5)		

Updated analysis (DCO December 8, 2023)



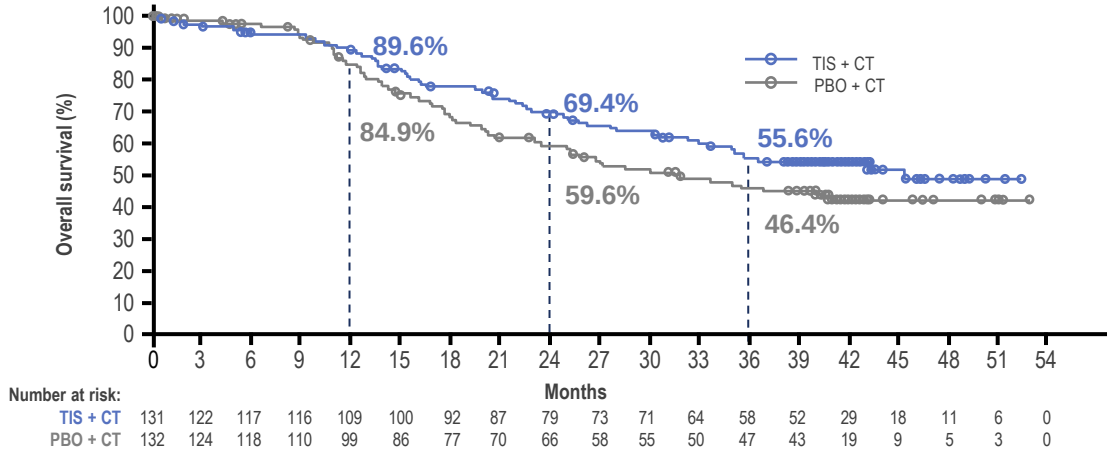
	Events (%)	Median (95% CI), months	HR (95% CI)
TIS + CT	95 (72.5)	9.6 (7.6, 11.6)	**0.53 (0.39, 0.71)**
PBO + CT	106 (80.3)	7.4 (5.6, 7.6)	

Sustained PFS per IRC improvement was observed for TIS plus CT vs PBO plus CT

At DCO of September 30, 2021, median (95% CI) PFS was 9.6 months (7.6, 11.7) for TIS + CT and 7.4 months (5.7, 7.6) for PBO + CT; HR, 0.50 (95% CI: 0.37, 0.68). HR was estimated from stratified Cox model with the PBO plus CT arm as a reference group.
Abbreviations: CI, confidence interval; CT, chemotherapy; DCO, data cutoff; HR, hazard ratio; IRC, independent review committee; ITT, intent to treat; PBO, placebo; PFS, progression-free survival; TIS, tislelizumab.

Overall Survival

ITT Analysis Set



	Events (%)	Median (95% CI), months	Stratified HR (95% CI)
TIS + CT	55 (42.0)	45.3 (33.4, NE)	**0.73 (0.51, 1.05)**
PBO + CT	64 (48.5)	31.8 (25.0, NE)	

TIS plus CT demonstrated clinically meaningful and sustained OS improvement vs PBO plus CT, despite the high crossover rate (52.3%) in the control arm

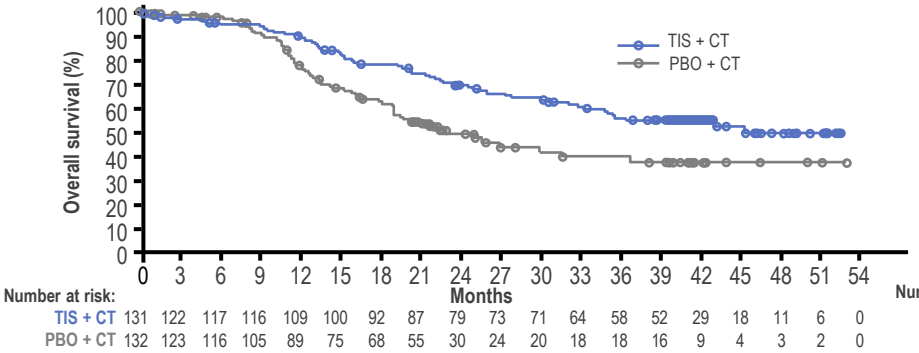
Data cutoff: December 8, 2023. OS was not mature by the time of interim analysis; thus an updated analysis was performed in the longer follow-up updates. HR was estimated from stratified Cox model with the PBO plus CT arm as a reference group.

Abbreviations: CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ITT, intent to treat; NE, not estimable; OS, overall survival; PBO, placebo; TIS, tislelizumab.

Overall Survival Analysis Adjusted for Crossover Patients Only

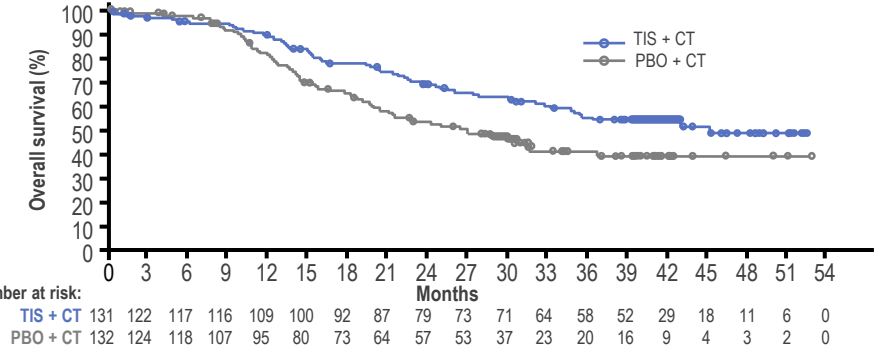
ITT Analysis Set

RPSFTM Without Multivariate Adjustments



	Events (%)	Median (95% CI), months	HR (95% CI)
TIS + CT	55 (42.0)	45.3 (33.4, NE)	**0.56 (0.27, 1.19)**
PBO + CT	62 (47.0)	23.0 (19.1, 31.6)	

Two-stage Method



	Events (%)	Median (95% CI), months	HR (95% CI)
TIS + CT	55 (42.0)	45.3 (33.4, NE)	**0.62 (0.40, 0.97)**
PBO + CT	64 (48.5)	27.0 (20.0, 36.8)	

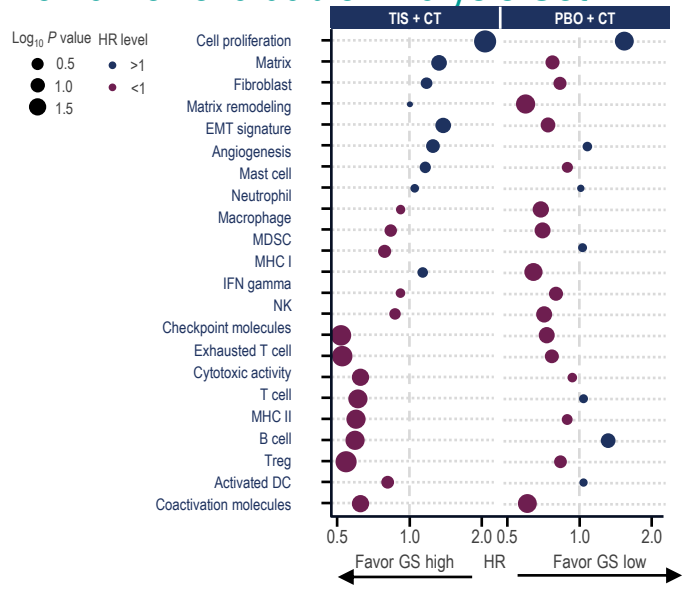
OS analyses using 2 different statistical models, adjusting for crossover effect, demonstrated consistent OS improvement in favor of TIS plus CT

Data cutoff: December 8, 2023. HR was estimated from Cox model with the PBO plus CT arm as a reference group without multivariate adjustments.

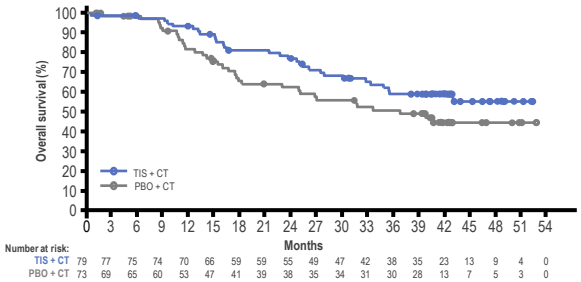
Abbreviations: CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ITT, intent to treat; NE, not estimable; OS, overall survival; PBO, placebo; RPSFTM, rank-preserving structural failure time model; TIS, tislelizumab.

Exploratory Biomarker Analysis

Biomarker-evaluable Analysis Set

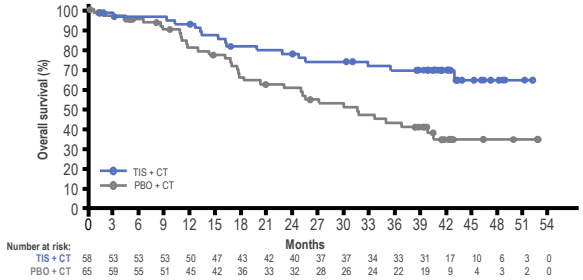


TME hot



	TIS + CT vs PBO + CT	
TME	Cold	Hot
Median OS (months)	35.1 vs 26.7	NR vs 36.8
HR (95% CI)	0.9 (0.51, 1.60)	0.66 (0.40, 1.08)

B-cell signature high



	TIS + CT vs PBO + CT	
B-cell signature	Low	High
Median OS (months)	33.4 vs NR	NR vs 31.6
HR (95% CI)	1.14 (0.69, 1.90)	0.41 (0.23, 0.74)

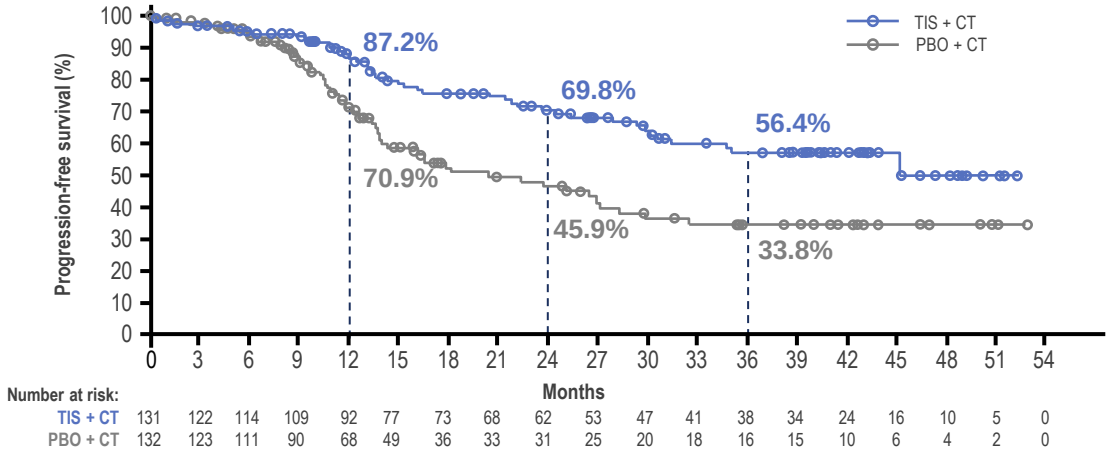
OS benefits were observed in patients with activated immune signatures. A greater OS improvement trend with TIS plus CT vs PBO plus CT was observed in the TME hot and B-cell signature high clusters

Data cutoff: April 7, 2024. HR was estimated from Cox model with the PBO plus CT arm as a reference group without multivariate adjustments.

Abbreviations: CI, confidence interval; CT, chemotherapy; DC, dendritic cell; EMT, epithelial-to-mesenchymal transition; GS, gene signature; HR, hazard ratio; IFN, interferon; NK, natural killer; OS, overall survival; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; NA, not available; NR, not reached; OS, overall survival; PBO, placebo; TIS, tislelizumab, TME, tumor microenvironment; Treg, regulatory T cell.

Progression-free Survival After Next Line of Treatment

Per Investigator (ITT Analysis Set)



	Events (%)	Median (95% CI), months	HR (95% CI)
TIS + CT	44 (33.6)	45.3 (31.5, NE)	**0.51 (0.34, 0.75)**
PBO + CT	58 (43.9)	20.5 (13.9, 27.2)	

PFS2 results were supportive of the observed OS benefit for TIS plus CT vs PBO plus CT

Data cutoff: December 8, 2023. HR was estimated from unstratified Cox model with the PBO plus CT arm as reference group.
Abbreviations: CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ITT, intent to treat; NE, not estimable; PBO, placebo; PFS2, progression-free survival after next line of treatment; TIS, tislelizumab.

Summary of Treatment-emergent Adverse Events

Safety Analysis Set

Events, n (%)	TIS + CT (n=133)	PBO + CT (n=130)
Patients with ≥1 TEAE	133 (100)	129 (99.2)
Grade ≥3	113 (85.0)	111 (85.4)
Serious	47 (35.3)	46 (35.4)
Serious grade ≥3	40 (30.1)	37 (28.5)
TEAEs leading to death	6 (4.5)	2 (1.5)
TEAEs leading to permanent discontinuation of any component of study treatment	22 (16.5)	14 (10.8)
Leading to permanent discontinuation of TIS/PBO	12 (9.0)	6 (4.6)
TEAEs leading to treatment modification[a,b] of any component of study treatment	97 (72.9)	93 (71.5)
Leading to treatment modification[a] of TIS/PBO	66 (49.6)	53 (40.8)
TEAE not related to disease progression	133 (100)	129 (99.2)
Grade ≥3	111 (83.5)	111 (85.4)
Serious	42 (31.6)	43 (33.1)
Infusion-related reaction	5 (3.8)	6 (4.6)
Immune-mediated TEAE[c]	71 (53.4)	49 (37.7)
Grade ≥3	6 (4.5)[d]	1 (0.8)[e]

TIS plus CT maintained a manageable safety profile without new safety signals throughout the extended follow-up period

Data cutoff: December 8, 2023. TEAEs related to disease progression were identified per investigator ticked box on AE eCRF. AE grades were evaluated based on NCI CTCAE (version 5.0). [a] Treatment modification of TIS/PBO included dose delay, infusion interruption, and infusion rate decrease. [b] Treatment modification of CT included dose reduction, infusion interruption, dose delay, and infusion rate decrease. [c] Immune-mediated TEAEs were immune-mediated AEs determined using a predefined programmatic algorithmic approach and were based on a list of preferred terms, without manual medical adjudication. [d] Five patients had grade ≥3 skin toxicity; one patient had grade ≥3 endocrinopathy. [e] One patient had grade ≥3 hepatitis.

Abbreviations: AE, adverse event; CT, chemotherapy; eCRF, electronic case report form; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PBO, placebo; TEAE, treatment-emergent adverse event; TIS, tislelizumab.

Conclusions

- At 3-year follow-up, RATIONALE-309 demonstrated sustained benefits of TIS plus CT treatment over PBO plus CT:
  - TIS plus CT showed continued PFS per IRC advantage over PBO plus CT (HR=0.53)
  - Clinically meaningful improvements in both OS (13.5 months mOS improvement and HR=0.73) and PFS2 (HR=0.51) were observed with TIS plus CT over PBO plus CT, despite a high rate (>50%) of crossover from the PBO arm
  - TIS plus CT demonstrated greater OS benefits in patients with activated immune signatures
  - The TIS plus CT combination maintained a manageable safety profile throughout extended follow-up
- Taken together, the 3-year follow-up results support TIS plus CT as an effective 1L treatment option for patients with R/M NPC

Abbreviations: 1L, first line; CT, chemotherapy; HR, hazard ratio; IRC, independent review committee; mOS, median overall survival; NPC, nasopharyngeal cancer; OS, overall survival; PBO, placebo; PFS, progression-free survival; PFS2, progression-free survival after next line of treatment; R/M, recurrent/metastatic; TIS, tislelizumab.

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SINGAPORE 2024 ESMO ASIA

THANK YOU

European Society for Medical Oncology (ESMO)
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org