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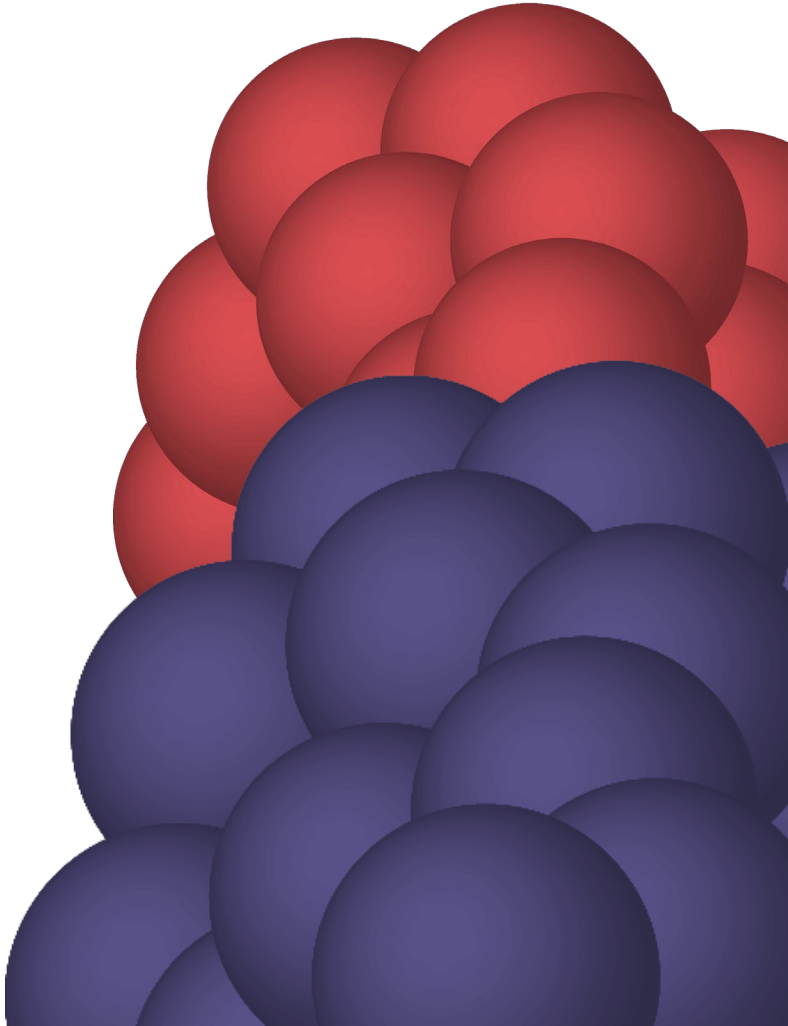

RATIONALE 309

A randomized, double-blind, Phase 3 trial of tislelizumab + gemcitabine + cisplatin vs placebo + gemcitabine + cisplatin, as first-line treatment for recurrent or metastatic nasopharyngeal cancer

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DECLARATION OF INTERESTS

Yunpeng Yang

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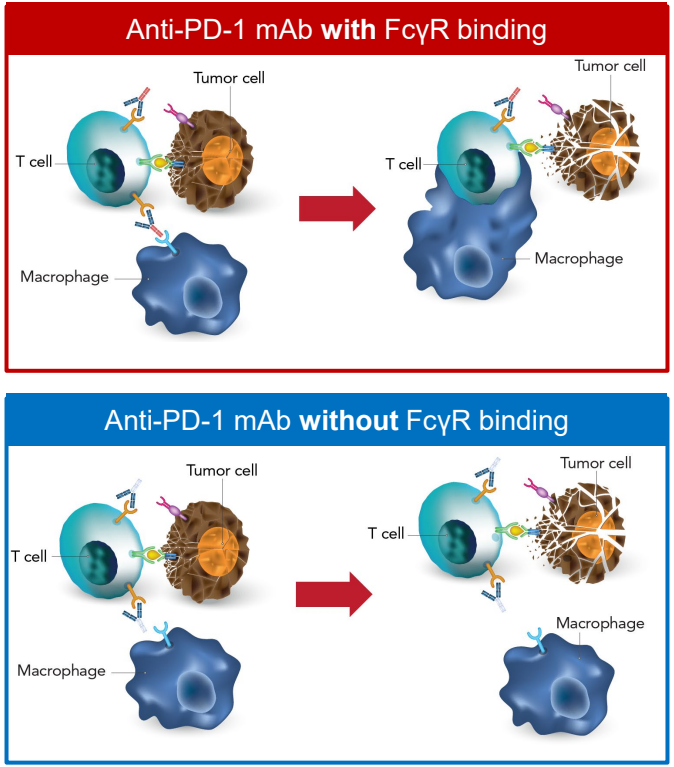
RATIONALE 309

Background

- NPC accounts for ≈133,000 new cancer cases and 80,000 deaths per year worldwide, and is particularly frequent among Asian and African populations[1]
- The prognosis for patients with recurrent or metastatic (RM) NPC treated with the first-line SOC gemcitabine + cisplatin is poor, with a mPFS of 7 months and mOS of 22.1 months[2,3]
- Tislelizumab, a humanized anti-PD-1 IgG4 monoclonal antibody, was engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent cellular phagocytosis, a mechanism of T-cell clearance and potential anti-PD-1 resistance[4,5]
- The antitumor efficacy of tislelizumab has been demonstrated in clinical trials across multiple tumor types, including NPC, NSCLC, GC, EC, HCC, UC and MSI-high-dMMR solid tumors[6–13]
- RATIONALE 309 (NCT03924986) is a Phase 3 randomized, double-blind, controlled trial investigating the efficacy and safety of tislelizumab plus chemotherapy compared with placebo plus chemotherapy, as a first-line treatment for RM NPC.[14] Here, we report results of the interim analysis



Ab, antibody; dMMR, deficient mismatch repair; FcγR, Fcγ receptors; mAb, monoclonal antibody; EC, esophageal carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; MHC, major histocompatibility complex; mOS, median overall survival; mPFS, median progression-free survival; MSI, microsatellite instability; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PD-1, programmed death-protein 1; PD-L1, programmed death-ligand 1; RM NPC, recurrent or metastatic nasopharyngeal carcinoma; SOC, standard of care; TCR, T cell receptor; UC, urothelial carcinoma.

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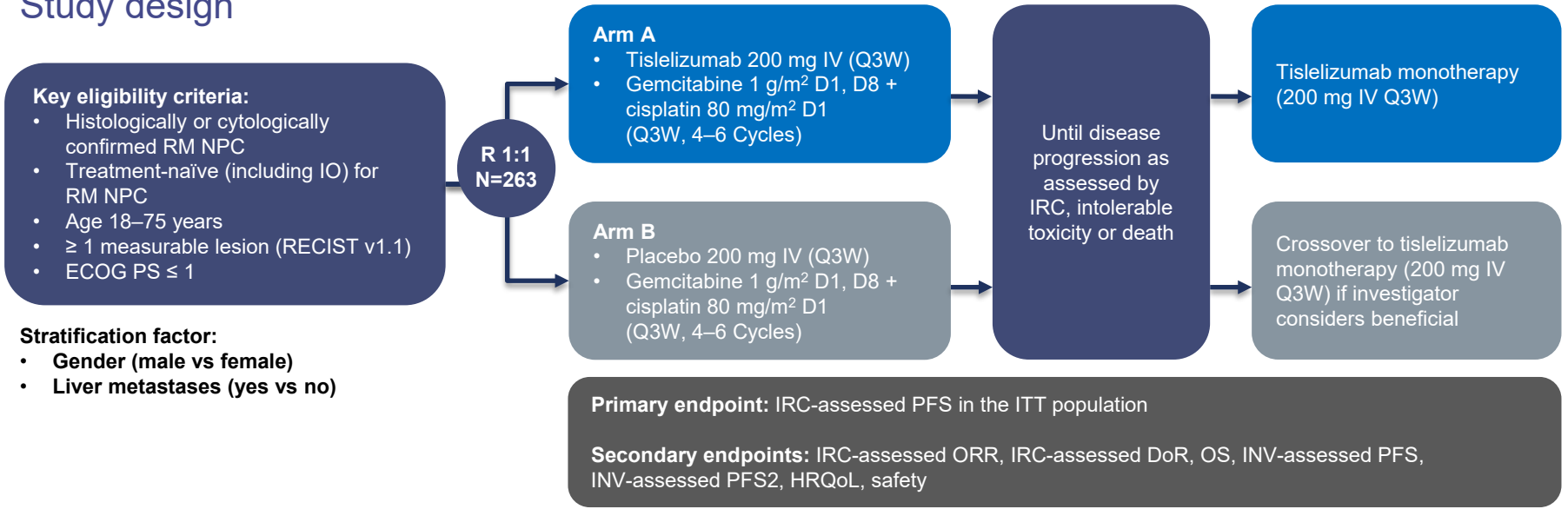
Randomized double-blind Phase 3 trial: Study design



Safety monitoring and interim efficacy data review will be performed by an Independent Data Monitoring Committee (iDMC)

D, Day; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IO, immunotherapy; IRC, independent review committee; ITT, intention-to-treat; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PFS2, progression-free survival after next line of treatment; Q3W, every 3 weeks; RECIST, response evaluation criteria in solid tumors; RM NPC, recurrent or metastatic nasopharyngeal carcinoma

RATIONALE 309

Statistical considerations

Primary endpoint: PFS in the ITT population as assessed by an IRC per RECIST v1.1

Sample size consideration: 181 PFS events were required to provide 82% power to detect a difference under target HR of 0.65 for PFS

Overall type I error: Strictly controlled at one-sided 0.025

- One planned interim analysis with approximately 127 (70% information rate) events in ITT population
- The α spending was through O'Brien-Fleming method

Analysis methods:

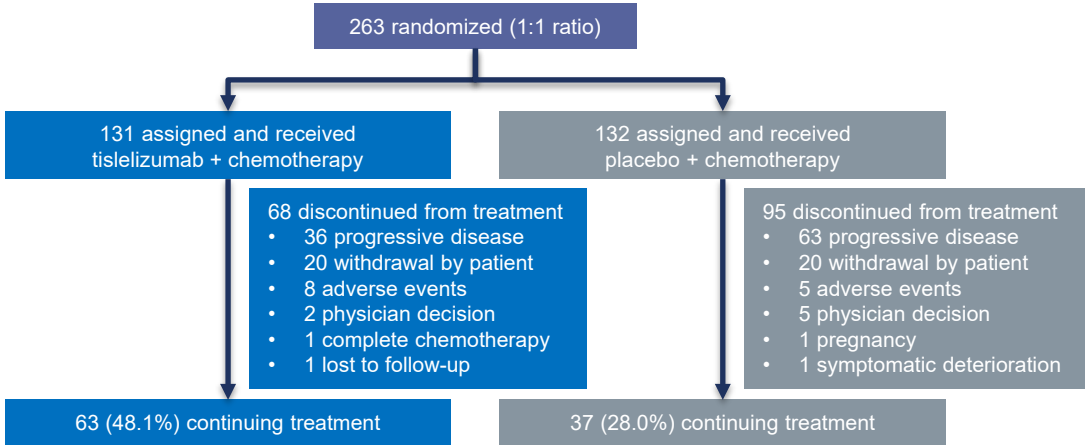
- P-value comparing PFS in treatment arms was calculated from stratified log-rank test
- PFS was estimated using Kaplan-Meier method and HR was through stratified cox regression model

HR, hazard ratio; IRC, independent review committee; ITT, intention-to-treat; PFS, professional-free survival; RECIST, response evaluation criteria in solid tumors

RATIONALE 309

Patient disposition and treatment exposure

First patient in: April 17, 2019
IA data cutoff date: March 26, 2021
Median follow-up: 10.0 months*



	Tisle + chemo	Placebo + chemo
Patients randomized, n (%)	**131 (100.0)**	**132 (100.0)**
Patients remaining on study, n (%)	104 (79.4)	103 (78.0)
Patients receiving tislelizumab monotherapy after disease progression†, n (%)	5 (3.8)	51 (38.6)

*Study follow-up time was defined as the time from the randomization date to date of death or end of study date (whichever occurs first) for patient discontinued from the study or the database cut-off date for ongoing patients; †As assessed by IRC
Chemo, chemotherapy; IA, interim analysis; IRC, independent review committee; tisle, tislelizumab

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Baseline demographics and disease characteristics (ITT population)

	Tisle + chemo (n=131)	Placebo + chemo (n=132)
Median age, years (range)	50.0 (26–74)	50.0 (23–73)
Male, n (%)	103 (78.6)	103 (78.0)
Asian, n (%)	131 (100.0)	132 (100.0)
ECOG PS, n (%)		
0	51 (38.9)	46 (34.8)
1	80 (61.1)	86 (65.2)
Smoking status, n (%)		
Never	74 (56.5)	66 (50.0)
Current	7 (5.3)	6 (4.5)
Former	50 (38.2)	60 (45.5)
Histology, n (%)		
Undifferentiated non-keratinized	97 (74.0)	95 (72.0)
Differentiated non-keratinized	17 (13.0)	18 (13.6)
Keratinized squamous carcinoma	9 (6.9)	8 (6.1)
Unclassified	8 (6.1)	11 (8.3)

	Tisle + chemo (n=131)	Placebo + chemo (n=132)
Disease status, n (%)		
Primary metastatic	126 (96.2)	124 (93.9)
Recurrent	5 (3.8)	8 (6.1)
Liver metastases at baseline, n (%)	56 (42.7)	57 (43.2)
Prior anticancer therapy, n (%)*	83 (63.4)	88 (66.7)
Prior surgeries, n (%)	6 (4.6)	4 (3.0)
Prior radiotherapy, n (%)	84 (64.1)	91 (68.9)
EBV DNA level, n (%)		
< 500 IU/mL	26 (19.8)	37 (28.0)
≥ 500 IU/mL	105 (80.2)	95 (72.0)
PD-L1 expression, n (%)		
≥ 10%	80 (61.1)	84 (63.6)
< 10%	42 (32.1)	33 (25.0)
Not evaluable	9 (6.9)	15 (11.4)

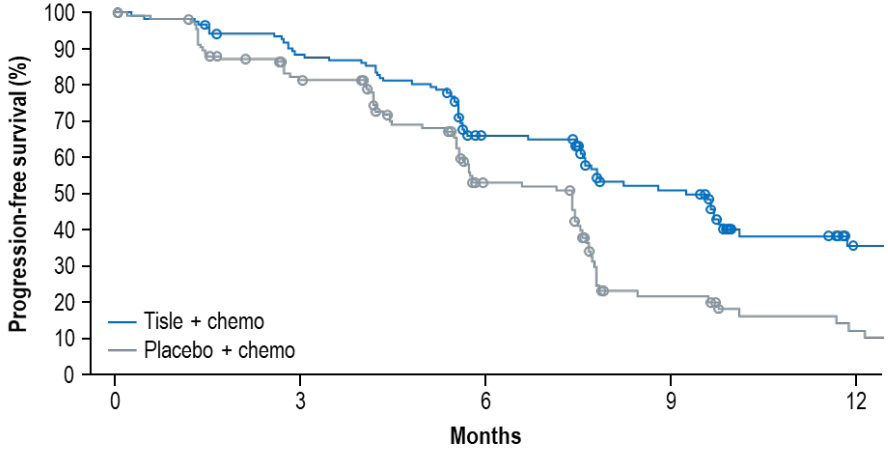
Baseline characteristics were generally balanced between treatment arms

*A patient was counted only once within each category but may be counted in multiple categories. Percentages were based on the number of patients with any prior anticancer drug therapy

Chemo, chemotherapy; EBV, Epstein-Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status; IO, immunotherapy; ITT, intent-to-treat; PD-L1, programmed cell death protein ligand-1; tisle, tislelizumab

RATIONALE 309: PRIMARY ENDPOINT

IRC-assessed PFS (ITT population)



Number at risk:

Tisle + chemo	131	108	70	42	13
Placebo + chemo	132	98	50	14	6

	Tisle + chemo (n=131)	Placebo + chemo (n=132)
PFS events, n (%)	65 (49.6)	87 (65.9)
Median PFS (95% CI), months	9.2 (7.6, 10.1)	7.4 (5.6, 7.5)
Stratified HR (95% CI)	0.52 (0.38, 0.73)	
P value*	< 0.0001	
PFS rate, % (95% CI)		
6 months	66.1 (56.9, 73.8)	53.0 (43.4, 61.8)
9 months	51.0 (41.1, 60.1)	21.6 (13.5, 30.9)
12 months	35.7 (25.2, 46.4)	12.2 (5.6, 21.4)

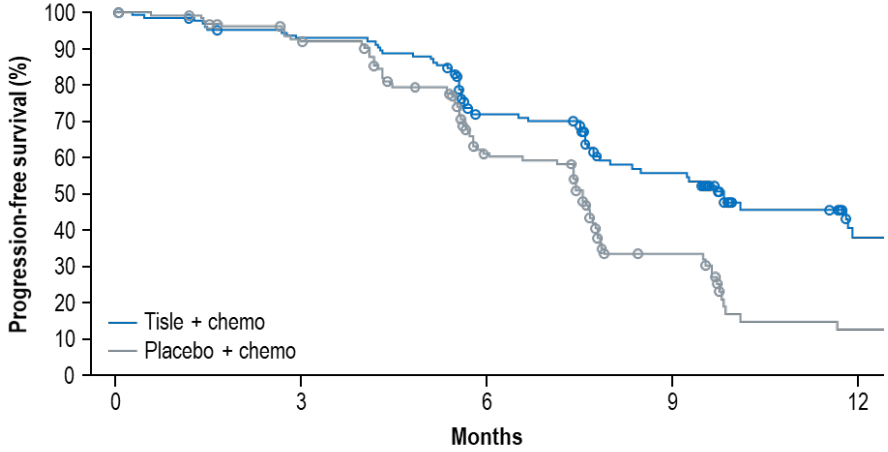
IRC-assessed PFS was significantly longer with tisle + chemo compared with placebo + chemo (HR: 0.52)

*One-sided stratified log-rank test P-value

Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; PFS, progression-free survival; tisle, tislelizumab

RATIONALE 309

INV-assessed PFS (ITT population)



Number at risk:

Tisle + chemo	131	114	78	47	15
Placebo + chemo	132	113	62	21	6

	Tisle + chemo (n=131)	Placebo + chemo (n=132)
PFS events, n (%)	61 (46.6)	81 (61.4)
Median PFS (95% CI), months	9.8 (7.8, 11.9)	7.6 (6.6, 7.8)
Stratified HR (95% CI)	0.54 (0.38, 0.76)	

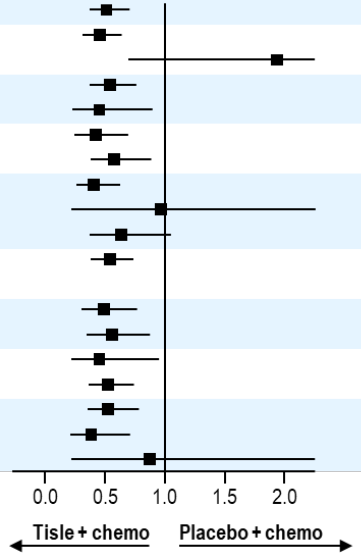
INV-assessed PFS was consistent with IRC-assessed PFS (HR: 0.54)

Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; INV, investigator; ITT, intent-to-treat; PFS, progression-free survival; tisle, tislelizumab

RATIONALE 309

Subgroup analysis of IRC-assessed PFS (ITT population)

Subgroup		Events/patients Tisle + chemo	Events/patients Placebo + chemo	HR for PD or death (95% CI)
Overall		65/131	87/132	0.51 (0.37, 0.71)
Age group	< 65 years	57/121	80/120	0.46 (0.32, 0.64)
	≥ 65 years	8/10	7/12	1.93 (0.69, 5.38)*
Sex	Male	50/103	68/103	0.53 (0.37, 0.77)
	Female	15/28	19/29	0.44 (0.22, 0.89)
ECOG PS	0	27/51	35/46	0.42 (0.25, 0.70)
	1	38/80	52/86	0.58 (0.38, 0.88)
Smoking status	Never	38/74	45/66	0.40 (0.26, 0.63)
	Current	4/7	4/6	0.97 (0.22, 4.35)*
	Former	23/50	38/60	0.63 (0.37, 1.05)
Disease status	Primary Metastatic	64/126	83/124	0.53 (0.38, 0.74)
	Recurrent	1/5	4/8	NE (NE, NE)
Liver metastases at baseline	Yes	33/56	46/57	0.48 (0.31, 0.77)
	No	32/75	41/75	0.55 (0.34, 0.87)
EBV DNA level	< 500 IU/mL	11/26	20/37	0.45 (0.21, 0.94)
	≥ 500 IU/mL	54/105	67/95	0.52 (0.36, 0.75)
PD-L1 expression on tumor cell	PD-L1 ≥ 10%	42/80	57/84	0.53 (0.35, 0.79)
	PD-L1 < 10%	20/42	23/33	0.38 (0.20, 0.72)
	NE	3/9	7/15	0.87 (0.22, 3.49)*



A consistent PFS benefit was observed for tisle + chemo versus placebo + chemo in almost all subgroups

*The CI of this subgroup is not shown completely due to space limit. Chemo, chemotherapy; CI, confidence interval; EBV, Epstein-Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; NE, not estimable; PD, progressive disease; PD-L1, programmed cell death protein ligand-1; PFS, progression-free survival' tisle, tislelizumab

RATIONALE 309

Tumor response by IRC per RECIST v1.1 (ITT population)

	Tisle + chemo (n=131)	Placebo + chemo (n=132)
Best overall response, n (%)		
Complete response	**21 (16.0)**	**9 (6.8)**
Partial response	70 (53.4)	64 (48.5)
Stable disease	19 (14.5)	34 (25.8)
Non-CR/Non-PD*	7 (5.3)	5 (3.8)
Progressive disease	4 (3.1)	14 (10.6)
Could not be determined†	10 (7.6)	6 (4.5)
Objective response rate, n (%)	91 (69.5)	73 (55.3)
Odds ratio (95% CI)	1.85 (1.11, 3.07)	
Disease control rate, n (%)	117 (89.3)	112 (84.8)
Median duration of response, months (95% CI)	8.5 (6.5, NE)	6.1 (4.7, 6.2)

IRC-assessed ORR was greater with tisle + chemo (69.5%) vs placebo + chemo (55.3%)

*Non-CR/non-PD was due to no measurable target lesion per IR; †Best overall response of could not be determined included patients who had post-baseline tumor assessment, none of which were evaluable; or patients who had no post-baseline tumor assessments due to death, withdrawal of consent, lost to follow up or any other reasons. Chemo, chemotherapy, CI, confidence interval; CR, complete response; IRC, independent review committee; ITT, intent-to-treat; NE, not evaluable; PD, progressive disease; RECIST, response evaluation criteria in solid tumors; tisle, tislelizumab

RATIONALE 309

Exposure, safety and tolerability (safety population)

	Tisle + chemo (n=131)	Placebo + chemo (n=132)
Median duration of tislelizumab and placebo exposure, weeks (range)	35.9 (1.1–101.3)	32.1 (2.4–90.6)
Median relative dose intensity of tislelizumab and placebo, % per patient (range)	96.3 (45.9–102.8)	95.5 (67.5–100.9)

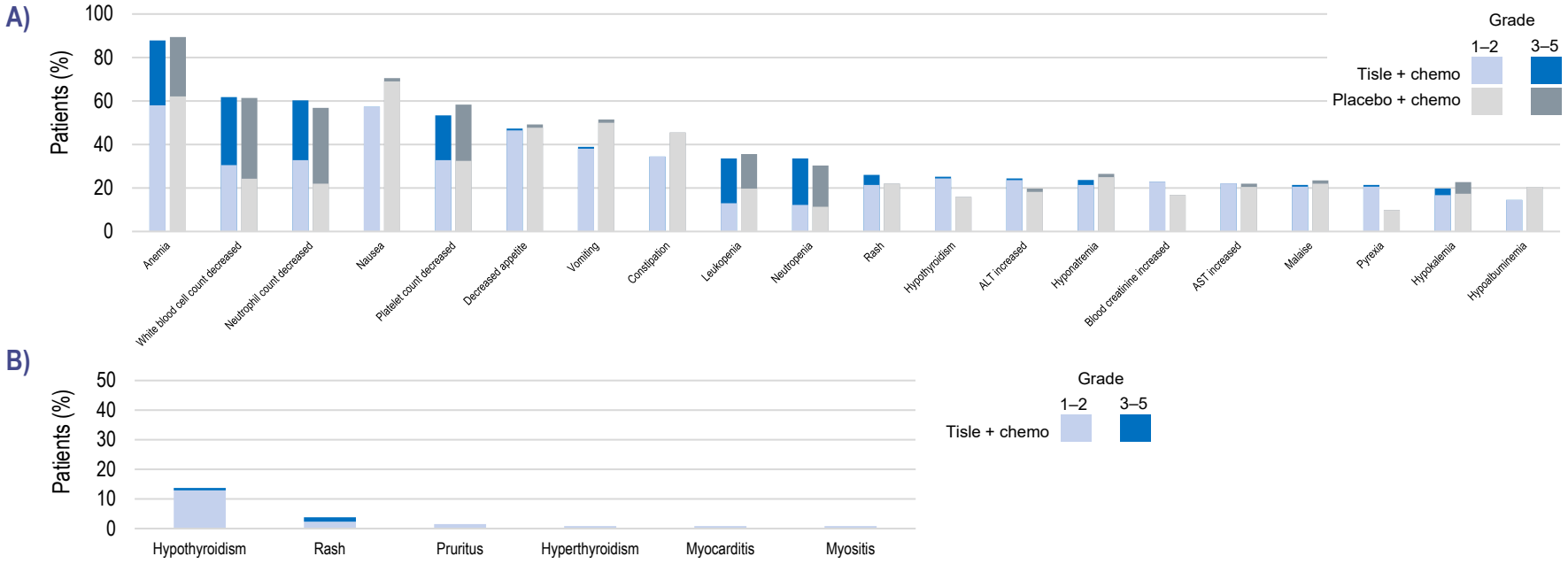
n (%)	Tisle + chemo (n=131)	Placebo + chemo (n=132)
TEAE	131 (100.0)	131 (99.2)
≥ Grade 3	106 (80.9)	108 (81.8)
Serious TEAE	36 (27.5)	44 (33.3)
≥ Grade 3	30 (22.9)	35 (26.5)
TEAE leading to death	5 (3.8)	2 (1.5)
TEAE leading to permanent discontinuation of all treatments*	2 (1.5)	3 (2.3)
Immune-mediated TEAE	24 (18.3)	NA
≥ Grade 3	3 (2.3)	NA
Total number of deaths	18 (13.7)	16 (12.1)

The safety profile of tisle + chemo was manageable and consistent with previous reports, with no new safety signals

*This category included patients who discontinued tislelizumab or placebo, cisplatin, and gemcitabine because of an adverse event
Chemo, chemotherapy; TRAE, treatment-related adverse event; TEAE, treatment-emergent adverse events; tisle, tislelizumab

RATIONALE 309

A) TEAEs (≥ 20% patients for all grades) and B) immune-mediated TEAEs (safety population)



ALT, alanine aminotransferase increased; AST, aspartate aminotransferase increased; TEAE, treatment-emergent adverse event; tisle, tislelizumab; chemo, chemotherapy

RATIONALE 309

Summary and conclusion

- The primary endpoint of PFS was met at the interim analysis of RATIONALE 309, as the addition of tislelizumab to chemotherapy significantly prolonged PFS compared with chemotherapy alone as first-line treatment of RM NPC
  - HR 0.52 (95% CI: 0.38, 0.73); $p < 0.0001$; mPFS: 9.2 vs 7.4 months
- The PFS benefit with tislelizumab vs placebo was consistent across the majority of patient subgroups, including PD-L1 expression subgroups
- OS and PFS2 data were not mature at data cut-off and are not reported
- The safety profile of tislelizumab combined with gemcitabine plus cisplatin was consistent with the known risks of each treatment agent. The addition of tislelizumab to gemcitabine plus cisplatin did not impact the known safety profile of each chemotherapy agent
  - The frequency and severity of TEAEs were similar between arms and the incidence of immune-mediated TEAEs were consistent with prior tislelizumab studies without new safety signals

Tislelizumab in combination with chemotherapy represents a stand of care as first-line therapy for patients with RM NPC

CI, confidence interval; HR, hazard ratio; mPFS, median progression-free survival; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PFS2, progression-free survival after next line of treatment; RM NPC, recurrent or metastatic nasopharyngeal carcinoma; TEAE, treatment-emergent adverse event

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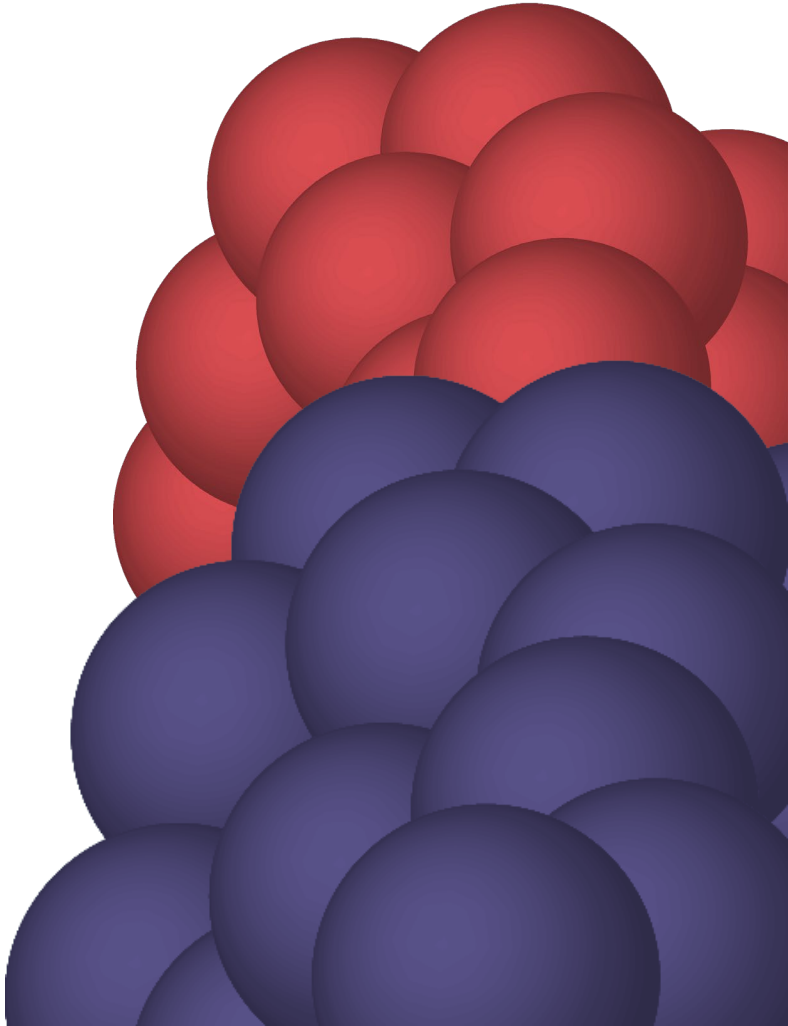

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