17P

Safety and tolerability of sintilimab (sint) combination therapy in patients with advanced or recurrent non-small cell lung cancer (NSCLC): pooled safety analysis of ORIENT 11 and ORIENT 12 studies

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OBJECTIVE

- The current analysis was to support the pooled safety assessments by summarizing treatment-related adverse events (TRAE) and immune-related TRAE (ir-TRAE).
- Furthermore, the association of ir-TRAE with efficacy in the pooled ORIENT-11 and ORIENT-12 studies was also evaluated.

KEY RESULT

- The TRAE rates were comparable between the two arms.
- Although sintilimab arm had higher ir-TRAE occurrence than placebo arm, ≥ grade 3 ir-TRAEs were comparable in both arms.
- TRAE leading to drug discontinuation and death were comparable between the two arms.

Table 2. Overall Safety

	Sintilimab arm (N = 445)		Placebo arm (N = 309)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
TRAE	382 (85.8)	141 (31.7)	252 (81.6)	94 (30.4)
ir-TRAE	189 (42.5)	27 (6.1)	95 (30.7)	15 (4.9)
TRAE leading to drug discontinuation	29 (6.5)	20 (4.5)	13 (4.2)	13 (4.2)
TRAE leading to death	4 (0.9)	4 (0.9)	7 (2.3)	7 (2.3)

Data are presented as n (%). TRAEs (overall, leading to discontinuation/death) and ir-TEAEs ≥1 are presented; TRAEs presented are sintilimab/placebo related TRAEs.
N = number of patients in each treatment arm; n = number of patients in specified category; TRAE = treatment-related adverse events; ir-TRAE = immune-related TRAE.

KEY RESULT

- Higher ir-TRAEs were reported in sintilimab arm for rash, hypothyroidism, and immune-mediated pneumonitis.

Table 3. ir-TRAE by preferred term (≥3%)

	Sintilimab arm N = 445		Placebo arm N = 309	
Preferred term	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
ir-TRAE	189 (42.5)	27 (6.1)	95 (30.7)	15 (4.9)
Rash	38 (8.5)	4 (0.9)	11 (3.6)	3 (1.0)
Hypothyroidism	37 (8.3)	0	11 (3.6)	0
Aspartate aminotransferase increased	19 (4.3)	0	10 (3.2)	0
Alanine aminotransferase increased	18 (4.0)	0	10 (3.2)	0
Hyperthyroidism	17 (3.8)	0	5 (1.6)	0
Immune-mediated pneumonitis	16 (3.6)	2 (0.4)	2 (0.6)	1 (0.3)
Blood thyroid stimulating hormone increased	16 (3.6)	0	7 (2.3)	0
Diarrhea	16 (3.6)	0	7 (2.3)	0
Pyrexia	14 (3.1)	0	7 (2.3)	0

Data are presented as n (%).
N = number of patients in each treatment arm; n = number of patients in specified category; TRAE = treatment-related adverse events; ir-TRAE = immune-related TRAE.

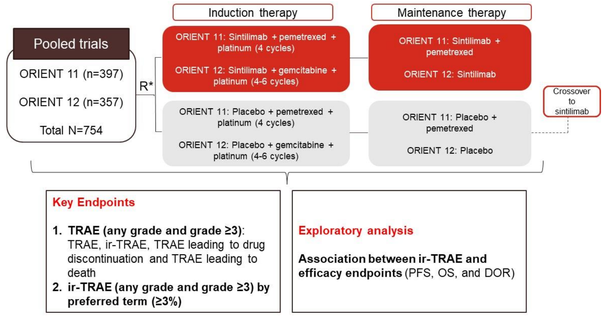
CONCLUSIONS

- The baseline characteristics were similar between patients in sintilimab and Placebo arm, and in patients with and without ir-TRAE in sintilimab arm.
- The occurrence of TRAE (any grade and grade ≥3), ir-TRAE (grade ≥3), TRAE leading to discontinuation and leading to death were similar between both the arms except ir-TRAE for any grade which showed higher occurrence in sintilimab arm.
- The exploratory analysis indicated that, the patients in sintilimab arm with ir-TRAE showed trend for longer PFS and OS than those without ir-TRAE.
- Overall, in this pooled analysis sintilimab in combination with chemotherapy demonstrated a tolerable and manageable safety profile in Chinese patients consistent with the individual ORIENT-11 and ORIENT-12 trials, with no new safety concerns.

Background

- Sintilimab is a selective anti-programmed cell death protein 1 (anti–PD-1) antibody that inhibits interactions between PD-1 and its ligand, programmed death-ligand 1 (PD-L1).[1]
- Sintilimab has shown efficacy in randomized, double-blind, phase 3 studies in Chinese patients with non-small cell lung cancer (NSCLC) in the ORIENT-11 and ORIENT-12 trials.[2,3]
- The results from ORIENT-11 showed that in Chinese patients with previously untreated, locally advanced or metastatic nonsquamous NSCLC, the addition of sintilimab to chemotherapy with pemetrexed and platinum resulted in considerably longer progression-free survival (PFS) than with chemotherapy alone with manageable safety profiles, with no new safety signals observed.[2]
- ORIENT-12 demonstrated clinical benefit with sintilimab plus gemcitabine and platinum (GP) over GP alone with acceptable toxicity and no new safety signals as first-line therapy in patients with locally advanced or metastatic sqNSCLC.[3]
- To further ascertain the safety profile of sintilimab, we conducted this pooled analysis of safety and tolerability data from ORIENT-11 and ORIENT-12 studies.

Study Design



*Randomization was: ORIENT 11 - 2:1 and ORIENT 12 – 1:1
DOR = duration of response; N = total number of patients (pooled); n = number of patients each trial; OS = overall survival; PFS = progression free survival; R = randomization; TRAE = treatment-related adverse events; ir-TRAE = immune-related TRAE.

Results

- Of 754 patients pooled from two studies (ORIENT-11, n=397; ORIENT-12, n=357), 445 were included in the sintilimab arm and 309 in the placebo arm.
- The demographics and baseline characteristics were well balanced between the treatment arms and were similar between patients with and without ir-TRAE in the sintilimab arm.

Table 1: Demographic and baseline characteristics

	Sintilimab arm (N = 445)	Placebo arm (N = 309)	Sintilimab arm	
			With ir-TRAE (N = 189)	**Without ir-TRAE (N = 256)**
Age (years), median (range)	62 (30; 75)	61 (33; 75)	63.0 (30;75)	61.5 (39;75)
Male, n (%)	367 (82.5)	263 (85.1)	157 (83.1)	210 (82.0)
ECOG PS, n (%)				
0	106 (23.8)	56 (18.1)	42 (22.2)	64 (25.0)
1	339 (76.2)	253 (81.9)	147 (77.8)	192 (75.0)
Smoking status, n (%)				
Current/Former	326 (73.3)	234 (75.7)	142 (75.1)	184 (71.9)
Never	119 (26.7)	75 (24.3)	47 (24.9)	72 (28.1)
Disease stage, n (%)				
IIIB/IIIC	60 (13.5)	59 (19.1)	22 (11.6)	38 (14.8)
IV	385 (86.5)	250 (80.9)	167 (88.4)	218 (85.2)
PD-L1 TPS, n (%)				
<1%[a]	144 (32.4)	107 (34.6)	59 (31.2)	85 (33.2)
1% to 49%	136 (30.6)	78 (25.2)	54 (28.6)	82 (32.0)
≥50%	165 (37.1)	124 (40.1)	76 (40.2)	89 (34.8)
Platinum choice, n (%)				
Cisplatin	140 (31.5)	99 (32.0)	52 (27.5)	88 (34.4)
Carboplatin	305 (68.5)	210 (68.0)	137 (72.5)	168 (65.6)

[a]Patients with missing PDL1 were included in the <1% group.
ECOG PS = Eastern Cooperative Oncology Group performance status; N = number of patients in each treatment arm; n = number of patients in specified category; PD-L1 = programmed death ligand 1; TRAE = treatment-related adverse events; ir-TRAE = immune-related TRAE; TPS = tumor proportion score.

- In the sintilimab arm, patients with ir-TRAE showed the trend of longer PFS and OS than those without ir-TRAE.

Table 4. Association between ir-TRAE and efficacy endpoints

Endpoints	Sintilimab arm	N/n (%)	Median[a] (95% CI), months	Hazard ratio[a] (95% CI)	P value[a]
PFS	With ir-TRAE	189/91(48.1%)	9.0 (6.8, 10.9)	0.646 (0.510, 0.820)	0.00033
	Without ir-TRAE	256/148(57.8%)	6.9 (6.0, 7.2)		
OS	With ir-TRAE	189/40(21.2%)	NR	0.641 (0.458, 0.898)	0.00983
	Without ir-TRAE	256/76(29.7%)	14.9 (13.8, NR)		
DOR[b]	With ir-TRAE	98/32(32.7%)	12.3 (8.0, NR)	1.102 (0.706, 1.719)	0.66873
	Without ir-TRAE	120/53(44.2%)	7.6 (5.8, 9.6)		

P values presented are between-group and two-sided. [a]Median and 95% CI are estimated based on unstratified Kaplan-Meier method. P-value and Hazard Ratio are estimated using a stratified time-dependent Cox proportional hazard regression model with ir-TRAE onset flag as factor and CRF stratification factors at randomization as stratification variables. [b]N based on number of patients that achieved CR or PR.
CR = complete response; DOR = duration of response; N = number of patients in each specified group; n = number of patients with events; NR=not reached; OS = overall survival; PFS = progression free survival; PR = partial response; TRAE = treatment-related adverse events; ir-TRAE = immune-related TRAE

References:
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3. Zhou C, et al. J Thorac Oncol. 2021;16:1501-1511.

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