

P1.258: Biomarker-guided precision sintilimab monotherapy/combo in untreated advanced NSCLC: a phase II umbrella trial (CTONG1702)

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INTRODUCTION

- For patients with non-small-cell lung cancer (NSCLC) without driver alterations, standard-of-care treatment is PD-1 inhibitor alone or with chemotherapy.
- However, the impact of tumor mutation burden (TMB), KRAS/TP53 co-mutations and PDL1 expression on immunotherapy are still unclear.
- Additionally, the differences in the efficacy of the combination of immunotherapy and anti-angiogenic target tyrosine kinase inhibitors (TKIs) at different expression levels of PD-L1 are yet to be elucidated.

METHODS

Design:

- We designed an open-label, multicenter, phase II umbrella trial CTONG1702 employing a Simon two-stage design, to evaluate the efficacy and safety of sintilimab-based regimens in driver alterations negative advanced NSCLC (Figure 1).
- The primary endpoint was objective response rate (ORR) per RECIST v1.1.
- Secondary endpoints were progression free survival (PFS), overall survival (OS), disease control rate (DCR) and safety.

Figure 1. Trial Design

Advanced NSCLC without driver alterations							
	Arm14	Arm15	Arm16	Arm17	Arm18	Arm22	Arm23
PD-L1	≥50%	<50%	<50%	0%	0%	1%-49%	≥50%
TMB		≥10					
KRAS&TP53			KP+				
Pathology				Adeno	Squam		
IO arms	PD-1 inhibitor	PD-1 inhibitor	PD-1 inhibitor	PD-1+ chemo	PD-1+ chemo	PD-1+ VEGFR	PD-1+ VEGFR

This report presents data from seven IO Arms:

- Sintilimab monotherapy: Arm 14 (PD-L1 TPS ≥ 50%), Arm 15 (PD-L1 TPS < 50%&TMB-High), Arm 16 (PD-L1 TPS < 50% KRAS/TP53 co-mutations) ;
- Sintilimab plus platinum-based chemotherapy* : Arm 17&18 (PD-L1 TPS < 1%: non-squamous cell carcinoma, pemetrexed + cisplatin/carboplatin; squamous, gemcitabine + carboplatin);
- Sintilimab + fruquintinib: Arm 22 (1%≤ PD-L1 TPS < 50%) and Arm 23 (PD-L1 TPS ≥ 50%).

*Arm17&18 were merged into one treatment arm after statistical adjustment.

RESULTS

Patient Characteristics

- From June 2019 to March 2026, a total of 208 patients with advanced NSCLC were enrolled in the IO-guided seven arm group.
- As of April 27, 2026, the median follow-up time for PD1 monotherapy in arms 14-16 was 24.0, 24.8, and 16.6 months, respectively; The median follow-up time for PD1+chemotherapy in arms 17-18 was 12.0 and 18.9 months, respectively; The median follow-up time for PD1+anti vascular 22-23 arms was 19.6 and 24.8 months, respectively.

Table1. Baseline characteristics of patients in seven arms

	Total (N=208)	Arm 14 (N=34)	Arm 15 (N=29)	Arm 16 (N=28)	Arm 17-18 (N=41)	Arm 22 (N=37)	Arm 23 (N=39)
Age, n (%)							
>65	101(48.6%)	16 (47.1%)	14 (48.3%)	14 (50.0%)	17 (41.5%)	20 (54.1%)	20 (51.3%)
≤65	107 (51.4%)	18 (52.9%)	15 (51.7%)	14 (50.0%)	24 (58.5%)	17 (45.9%)	19 (48.7%)
Sex, n (%)							
Female	21 (10.1%)	2 (5.9%)	0 (0.0%)	2 (7.1%)	6 (14.6%)	7 (18.9%)	4 (10.3%)
Male	187(89.9%)	32 (94.1%)	29 (100.0%)	26 (92.9%)	35 (85.4%)	30 (81.1%)	35 (89.7%)
ECOG Status, n (%)							
0	3 (1.4%)	1 (3.0%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
1	199 (95.7%)	32 (97.0%)	28 (100.0%)	27 (96.4%)	40 (100.0%)	36 (100.0%)	36 (97.3%)
Missing		1	1	0	1	1	2
Smoking Status, n (%)							
Current Smoker	28 (13.5%)	11 (32.4%)	7 (24.1%)	2 (7.1%)	3 (7.3%)	2 (5.4%)	3 (7.7%)
Former Smoker	134 (64.4%)	15 (44.1%)	20 (69.0%)	21 (75.0%)	26 (63.4%)	25 (67.6%)	27 (69.2%)
Never Smoker	46 (22.1%)	8 (23.5%)	2 (6.9%)	5 (17.9%)	12 (29.3%)	10 (27.0%)	9 (23.1%)
Histology, n (%)							
Adenocarcinoma	139 (66.8%)	22 (64.7%)	20 (69.0%)	25 (89.3%)	28 (68.3%)	24 (64.9%)	20 (52.6%)
Squamous Cell Carcinoma	45 (21.6%)	8 (23.5%)	8 (27.6%)	1 (3.6%)	9 (22.0%)	8 (21.6%)	11 (28.9%)
Other	23 (11.1%)	4 (11.8%)	1 (3.4%)	2 (7.1%)	4 (9.8%)	5 (13.5%)	7 (18.4%)
Clinical Stage, n (%)							
IIlb	3 (1.4%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	1 (2.7%)	0 (0.0%)
IIlc	5 (2.4%)	2 (5.9%)	1 (3.4%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (2.6%)
IVa	86 (41.3%)	18 (52.9%)	14 (48.3%)	12 (42.9%)	13 (31.7%)	14 (37.8%)	15 (39.5%)
IVb	113 (54.3%)	13 (38.2%)	14 (48.3%)	16 (57.1%)	26 (63.4%)	22 (59.5%)	22 (57.9%)
Brain metastases, n (%)							
No	166 (79.8%)	29 (85.3%)	17 (58.6%)	22 (78.6%)	37 (90.2%)	31 (83.8%)	30 (76.9%)
Yes	42 (20.2%)	5 (14.7%)	12 (41.4%)	6 (21.4%)	4 (9.8%)	6 (16.2%)	9 (23.1%)
PD-L1 status, n (%)							
≥50%	73 (35.1%)	34 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	39 (100.0%)
1-49%	75 (36.1%)	0 (0.0%)	18 (62.1%)	20 (71.4%)	0 (0.0%)	37 (100.0%)	0 (0.0%)
< 1%	60 (28.81%)	0 (0.0%)	11 (37.9%)	8 (28.6%)	41 (100.0%)	0 (0.0%)	0 (0.0%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

Efficacy

- Overall ORR was 51.4%, median PFS (mPFS) was 9.9 months, and median OS (mOS) was 26.4 months, which is superiority over prior published studies (Pembrolizumab+chemo of Keynote 189¹:mOS:22.0 months, Keynote 407²:mOS:17.2 months).
- Across Arm 14,15 and 16, sintilimab yielded an ORR of 41.8%, mPFS of 9.5 months and mOS of 20.5 months.
- Across Arm 17and 18, sintilimab plus chemo yielded an ORR of 31.7%, mPFS of 4.3 months and mOS of 12.0 months.
- Across Arm 22 and 23, sintilimab plus fruquintinib yielded an ORR of 73.7%, mPFS of 14.5 months and mOS of 35.0 months. Owing to the outstanding efficacy data from these two arms, the mOS of all seven study arms was significantly improved.
- Furthermore, the patients with PD-L1 expression ≥50% in Arm 23 exhibited even greater potential for superior clinical outcomes. (mPFS: 19.7 months, mOS: not reached)

Table 2. Efficacy outcomes by in seven arms

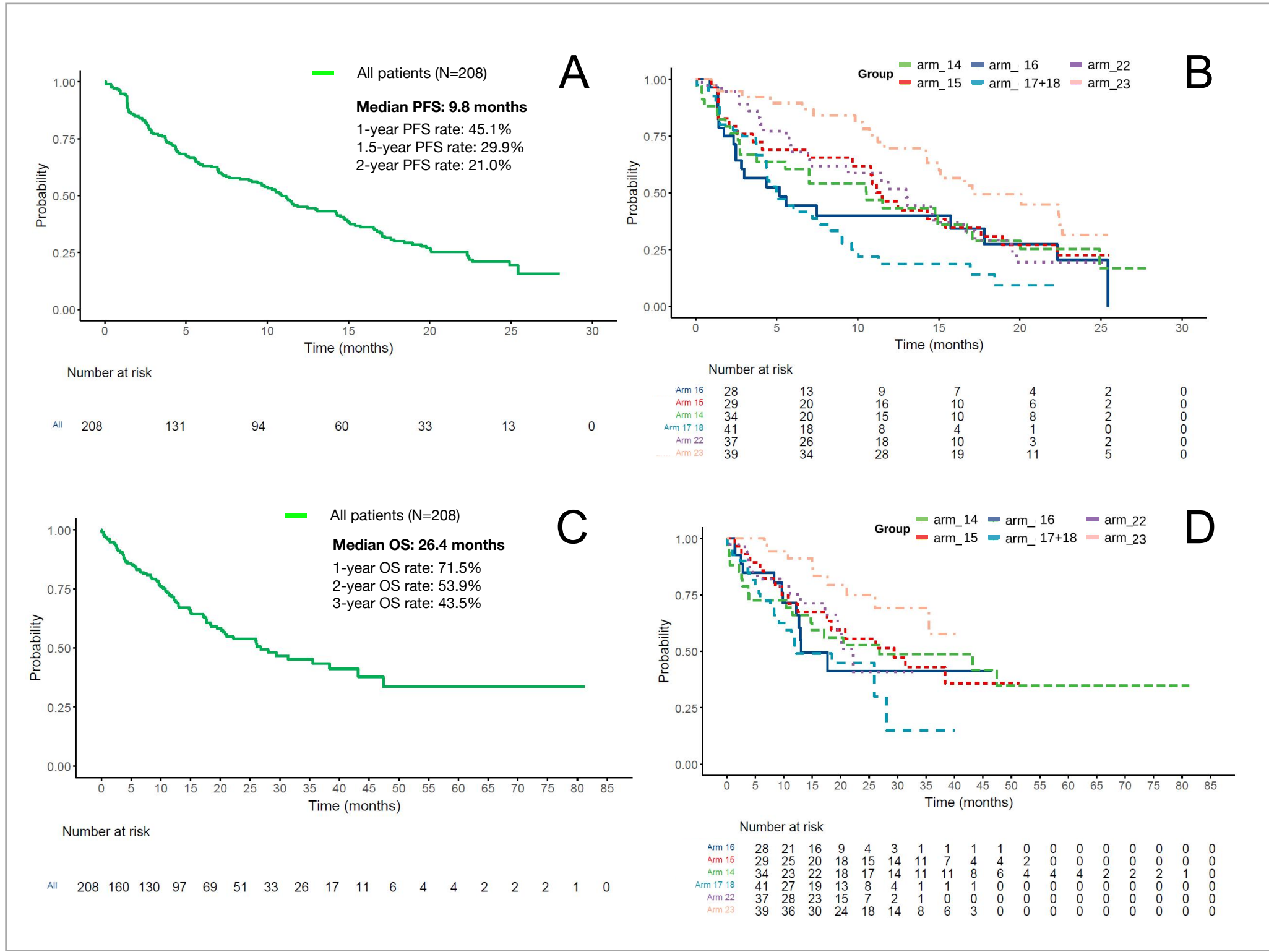
		Arm 14 (N=34)	Arm 15 (N=29)	Arm 16 (N=28)	Arm 17-18 (N=41)	Arm 22 (N=37)	Arm 23 (N=39)
Patients	Total (N=208)	PDL1 ≥ 50%	PDL1 < 50% & TMB-High	PDL1 < 50% & KRAS/TP53mut	PDL1 < 1%	49%>PD- L1≥1%	PDL1 ≥ 50%
Treatment		Sintilimab			Sintilimab +chemo	Sintilimab + fruquintinib	
Best overall response, n (%)							
PR	107 (51.4)	38 (41.8)			13 (31.7)	56 (73.7)	
SD	67 (32.2)	31 (34.1)			20 (48.8)	16 (21.1)	
PD	18 (8.7)	12 (13.2)			3 (7.3)	3 (3.9)	
NA	16 (7.7)	10 (11.0)			5 (12.2)	1 (1.3)	
ORR, %	51.4	41.8			31.7	73.7	
(95% CI)	(44.4, 58.4)	(31.5, 52.6)			(18.1, 48.1)	(62.3, 83.1)	
DCR, %	83.7	75.8			80.5	94.7	
(95% CI)	(77.9, 88.4)	(65.7, 84.2)			(65.1, 91.1)	(87.1, 98.6)	
mDOR, months	17.9	22.4			7.2	20.7	
(95% CI)	(11.4-NE)	(11.1-NE)			(2.9-9.7)	(11.5-NE)	
mPFS, months	9.8	9.5			4.3	14.5	
(95% CI)	(6.9-11.5)	(4.3-14.1)			(2.8-5.9)	(11.2-19.8)	
mOS, months	26.4	20.5			12.0	35.0	
(95% CI)	(19.2-42.5)	(14.6-42.5)			(9.0-27.6)	(20.8-NE)	

Two-sided 95% CIs for ORR and DCR were calculated using the Clopper-Pearson exact method. Time-to-event endpoints were analyzed using the Kaplan–Meier method.

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; CI, confidence interval; NA, not available; NE, not estimable.

Two-sided 95% CIs for ORR and DCR were calculated using the Clopper-Pearson exact method. Time-to-event endpoints were analyzed using the Kaplan-Meier method. Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; CI, confidence interval; NA, not available; NE, not estimable.

Figure 2. Kaplan-Meier estimates of PFS (A: seven arms, B: by arms) and OS (C: seven arms, D: by arms)



Safety

- Overall safety data across seven arms showed that the incidence of grade ≥3 treatment-related adverse events (TRAEs) was only 13.5%, and the rate of TRAE leading to treatment discontinuation was merely 1.4%.
- Stratified by treatment modality, no new unexpected adverse events were observed across all three groups: sintilimab monotherapy (Arms 14, 15, 16), sintilimab plus chemotherapy (Arms 17, 18), and sintilimab plus fruquintinib (Arms 22, 23).
- In the sintilimab + fruquintinib, the most frequent TRAE was proteinuria, all of which were grade 1-2. Consistent with the known VEGF-related toxicity profile of fruquintinib, only 2 cases of grade 3 hypertension and 2 cases of grade 3 hand-foot syndrome were observed, all clinically manageable.

Table 3. Summary of Safety by treatment modality

	Total (N=208)	Arm 14&15&16 (N=91)	Arm 17&18 (N=41)	Arm 22&23 (N=76)
Treatment		Sintilimab	Sintilimab + chemo	Sintilimab + fruquintinib
Any TRAE, n (%)	112 (53.8%)	60 (65.9%)	19 (46.3%)	33 (43.4%)
Grade ≥3 TRAE, n (%)	28 (13.5%)	15 (16.5%)	5 (12.2%)	8 (10.5%)
TRAE leading to SAE, n (%)	14 (6.7%)	8 (8.8%)	2 (4.9%)	4 (5.3%)
Any IRAE, n (%)	112 (53.8%)	60 (65.9%)	19 (46.3%)	33 (43.4%)
TRAE leading to treatment interruption, n (%)	29 (13.9%)	19 (20.9%)	3 (7.3%)	7 (9.2%)
TRAE leading to treatment discontinuation, n (%)	3 (1.4%)	2 (2.2%)	1 (2.4%)	0 (0.0%)
TRAE leading to death, n (%)	1 (0.5%)	1 (1.1%)	0 (0.0%)	0 (0.0%)

Table 4. Most Common(≥5% in arm 22&23) TRAE

	Arm 22-23 (N=76)			
	All Grades	Grade ≥3		
Proteinuria	11 (14.5%)	0	(0.0%)	
Hyponatremia	6 (7.9%)	0	(0.0%)	
Rash	6 (7.9%)	0	(0.0%)	
Increased blood thyroid stimulating hormone	6 (7.9%)	0	(0.0%)	
Hyperglycemia	6 (7.9%)	0	(0.0%)	
Hypertension	5 (6.6%)	2	(2.6%)	
Increased aspartate aminotransferase (AST)	5 (6.6%)	0	(0.0%)	
Thyroid disease	5 (6.6%)	0	(0.0%)	
Increased conjugated bilirubin	5 (6.6%)	0	(0.0%)	
Hand-foot syndrome	4 (5.3%)	2	(2.6%)	
Increased amylase	4 (5.3%)	1	(1.3%)	
Increased alanine aminotransferase (ALT)	4 (5.3%)	0	(0.0%)	
Joint pain	4 (5.3%)	0	(0.0%)	
Decreased lymphocyte count	4 (5.3%)	0	(0.0%)	
Increased blood pressure	4 (5.3%)	0	(0.0%)	
Anemia	4 (5.3%)	0	(0.0%)	
Hyperuricemia	4 (5.3%)	0	(0.0%)	

CONCLUSION

- Biomarker-guided precision immunotherapy can provide patients with promising long-term survival outcomes, accompanied by a more favorable safety profile.
- Sintilimab + Fruquintinib has prolonged PFS and manageable safety in PD-L1 ≥ 1% patients, especially in PD-L1 ≥ 50%, adding key prospective evidence for chemo-free immunotherapy-antiangiogenesis regimens.
- Limitations** : Non-randomized design with limited cohort sample size; cross-arms comparisons are exploratory. Further large-scale randomized trials with long-term follow-up are warranted for confirmatory validation.

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