Sacituzumab tirumotecan (sac-TMT) plus pembrolizumab versus chemotherapy plus pembrolizumab as first-line treatment for PD-L1-negative advanced nonsquamous NSCLC: randomized phase 3 OptiTROP-Lung06 study

Background

- Pembrolizumab plus platinum-based chemotherapy is a widely used standard 1L treatment option for patients with PD-L1-negative advanced nsq- NSCLC without targetable genomic alterations, but outcomes remain suboptimal, with median PFS ~6 months and median OS ~17 months[1-3].
- TROP2 is broadly expressed in NSCLC, and its high TROP2 expression is associated with a less inflamed, more immunosuppressive tumor microenvironment.
- Sac-TMT is a TROP2-directed ADC with a unique bifunctional linker that maximizes delivery of a novel belotecan-derived topoisomerase I inhibitor payload to tumor cells.
- Sac-TMT plus pembrolizumab improved PFS versus pembrolizumab alone in PD-L1-positive advanced NSCLC in OptiTROP-Lung05[4].
- In a previous phase 2 study, sac-TMT combination with PD-L1 blockade showed encouraging antitumor activity in PD-L1-negative advanced nsq-NSCLC[5].

OptiTROP-Lung06 Study Design

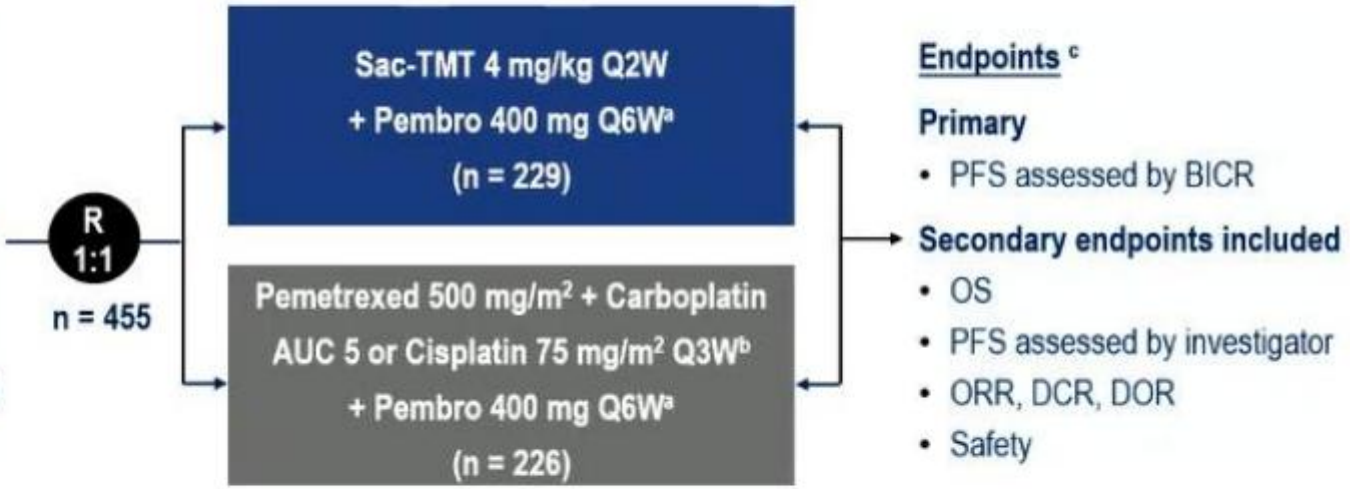
Randomized, multicenter, open-label, phase 3 trial (NCT06711900)

Key eligibility criteria

- Locally advanced (stage IIIB/IIIC) or metastatic (stage IV) nsq-NSCLC
- No prior systemic therapy for advanced disease
- No sensitizing *EGFR* or *ALK* alteration
- PD-L1 TPS< 1% (IHC 22C3, central lab)
- ECOG PS score 0 or 1

Stratification factors

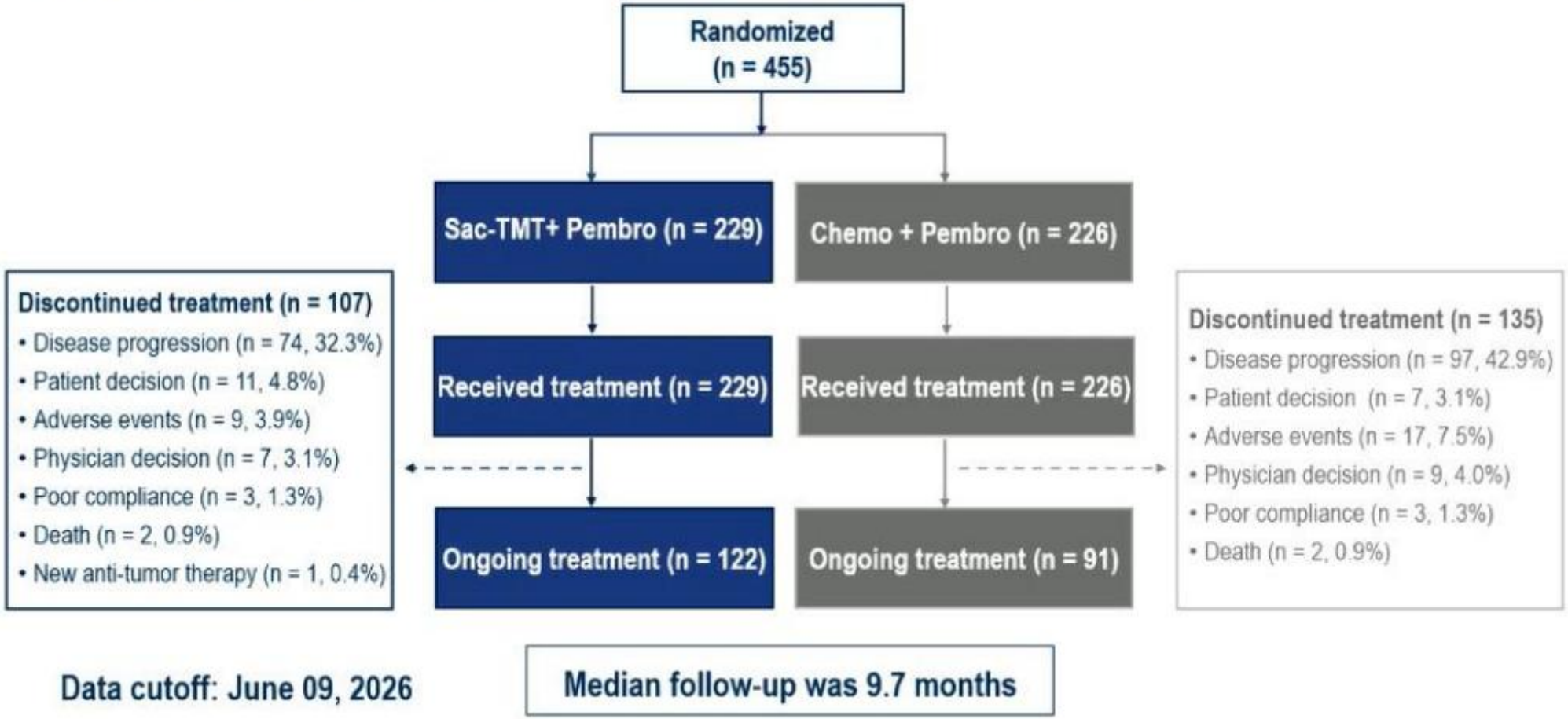
- Sex (male vs. female)
- ECOG PS score (0 vs. 1)
- Disease stage (IIIB/IIIC vs. IV)



Statistical Analysis

- Estimated sample size
  - A sample size of 432 patients was planned to provide 90% power for PFS (assuming PFS HR=0.68) and 81% power for OS (assuming OS HR=0.72).
- A hierarchical testing strategy was applied for PFS followed by OS, each at a two-sided α level of 0.05.
  - One interim PFS analysis was planned.
  - A Lan-DeMets alpha-spending function with O'Brien-Fleming boundaries was used to control the overall type I error rate.
- This presentation is based on the prespecified PFS interim analysis:
  - Planned at 201 PFS events.
  - Actually observed 205 PFS events.
  - Corresponding statistically significant efficacy boundary: two-sided $P \leq 0.0160$.
- OS was summarized descriptively at this analysis; no formal hypothesis testing was planned.

Patient Disposition



Data cutoff: June 09, 2026

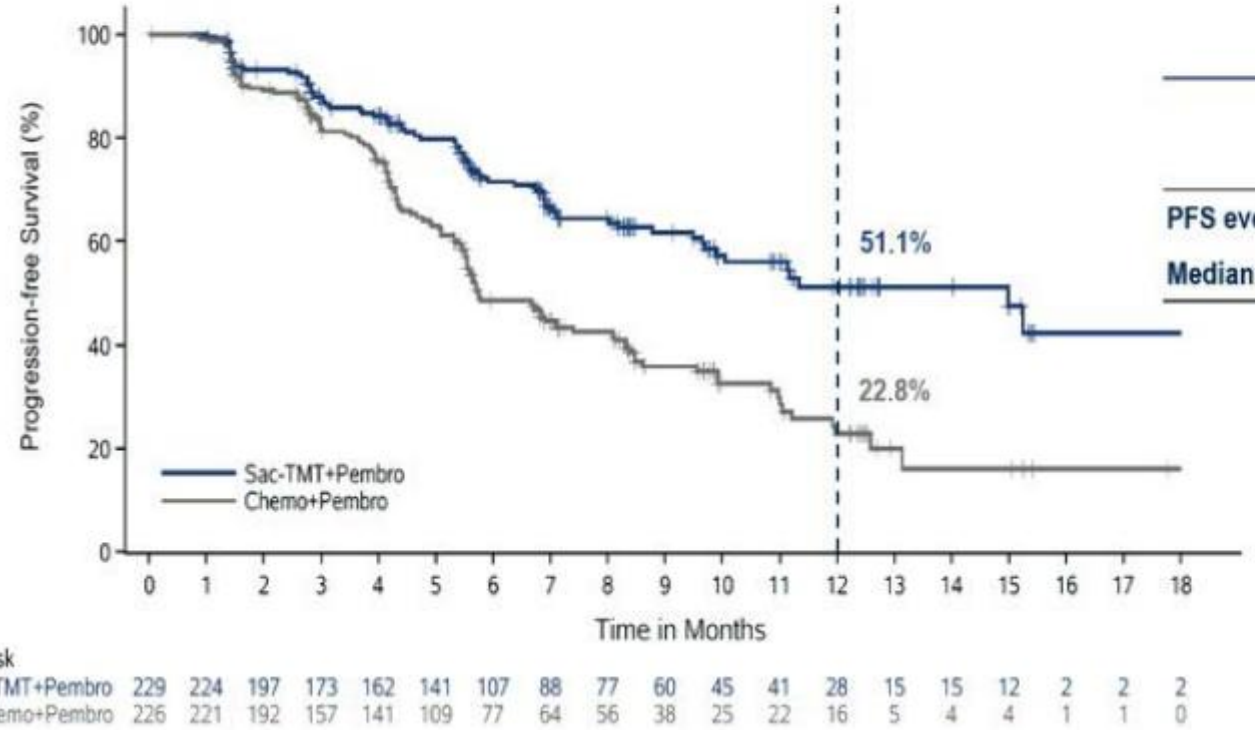
Median follow-up was 9.7 months

Baseline Characteristics

Characteristic		Sac-TMT + Pembro (n = 229)	Chemo + Pembro (n = 226)
Age	Median (range), years	63 (29, 75)	63 (37, 75)
	≥ 65	103 (45.0)	104 (46.0)
Sex	Male	165 (72.1)	163 (72.1)
ECOG PS score	1	189 (82.5)	186 (82.3)
Smoking history	Current or former smoker	150 (65.5)	142 (62.8)
	Never smoker	79 (34.5)	84 (37.2)
Histology	Adenocarcinoma	228 (99.6)	226 (100)
	Large-cell carcinoma	1 (0.4)	0
Disease stage	IIIB/IIIC	19 (8.3)	19 (8.4)
	IV	210 (91.7)	207 (91.6)
Metastases	≥ 3 Distant metastatic sites	52 (22.7)	58 (25.7)
	Brain	5(2.2)	6 (2.7)
	Liver	17(7.4)	26 (11.5)
	Bone	75 (32.8)	89 (39.4)

PFS by BICR

Sac-TMT + pembro significantly improved PFS vs. Chemo + pembro, with a 51% reduction in risk of disease progression or death.



	Sac-TMT + Pembro (n = 229)	Chemo + Pembro (n = 226)
PFS events, n (%)	79 (34.5)	126 (55.8)
Median, mo (95% CI)	15.0 (9.9–NE)	5.7 (5.5–7.4)

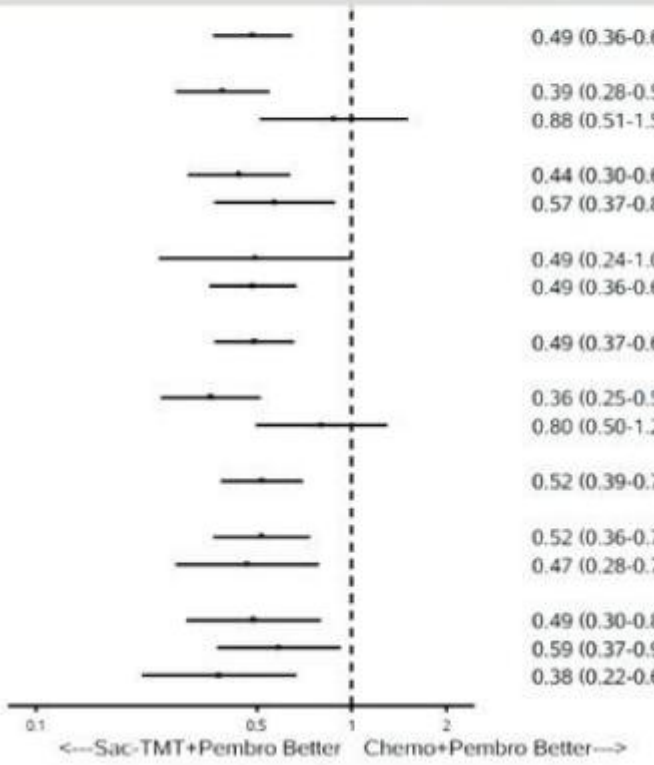
HR 0.49 (95% CI: 0.36–0.65)

P < 0.0001[a]

PFS (BICR) in Subgroups

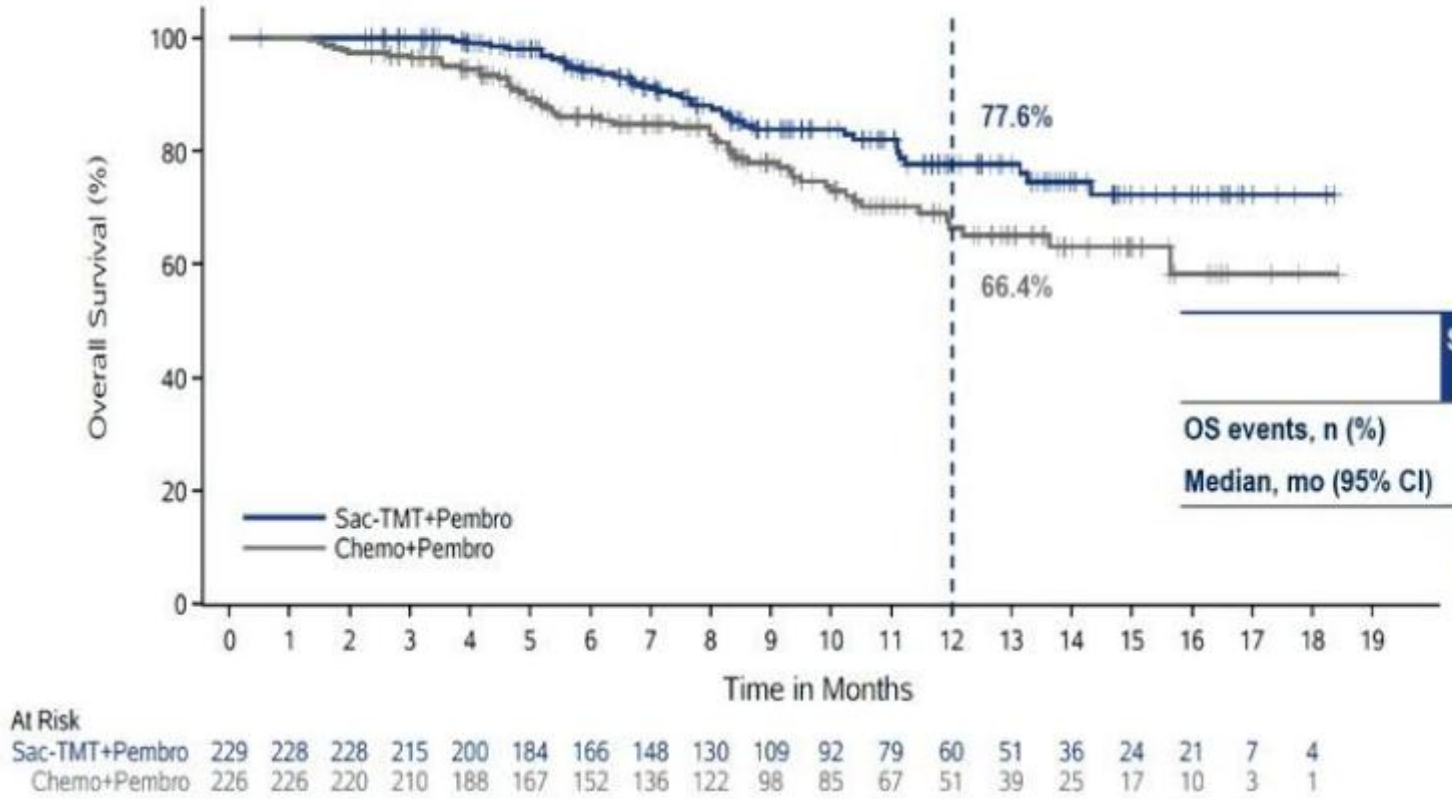
A generally consistent PFS benefit of sac-TMT + pembro over chemo + pembro was observed across subgroups.

Subgroup	Number of Events/Patients		Hazard Ratio (95% CI)
	Sac-TMT+Pembro	Chemo+Pembro	
All subjects	79/229	126/226	0.49 (0.36-0.65)
Sex			
Male	53/165	99/163	0.39 (0.28-0.55)
Female	26/64	27/63	0.88 (0.51-1.51)
Age			
<65 years	46/126	75/122	0.44 (0.30-0.64)
≥ 65 years	33/103	51/104	0.57 (0.37-0.88)
ECOG Performance Status			
0	13/40	22/40	0.49 (0.24-1.00)
1	66/189	104/186	0.49 (0.36-0.66)
Clinical stage at enrollment			
Stage IV	75/210	120/207	0.49 (0.37-0.66)
Smoking history			
Current or former smoker	47/150	88/142	0.36 (0.25-0.51)
Never smoker	32/79	38/84	0.80 (0.50-1.29)
Liver metastasis			
No	73/212	108/200	0.52 (0.39-0.70)
Number of distant metastatic sites			
<3	52/158	78/149	0.52 (0.36-0.74)
≥ 3	23/52	42/58	0.47 (0.28-0.78)
TROP2 expression			
Low (H-score ≤ 200)	26/77	47/87	0.49 (0.30-0.80)
High (H-score >200)	32/89	47/83	0.59 (0.37-0.92)
Unknown	21/63	32/56	0.38 (0.22-0.67)



Descriptive Overall Survival at PFS IA

A favorable trend in overall survival was observed with sac-TMT + pembro over chemo + pembro.



	Sac-TMT + Pembro (n = 229)	Chemo + Pembro (n = 226)
OS events, n (%)	36 (15.7)	55 (24.3)
Median, mo (95% CI)	NR (NE–NE)	NR (15.6–NE)

HR 0.58 (95% CI: 0.38–0.88)

Subsequent Anticancer Therapy

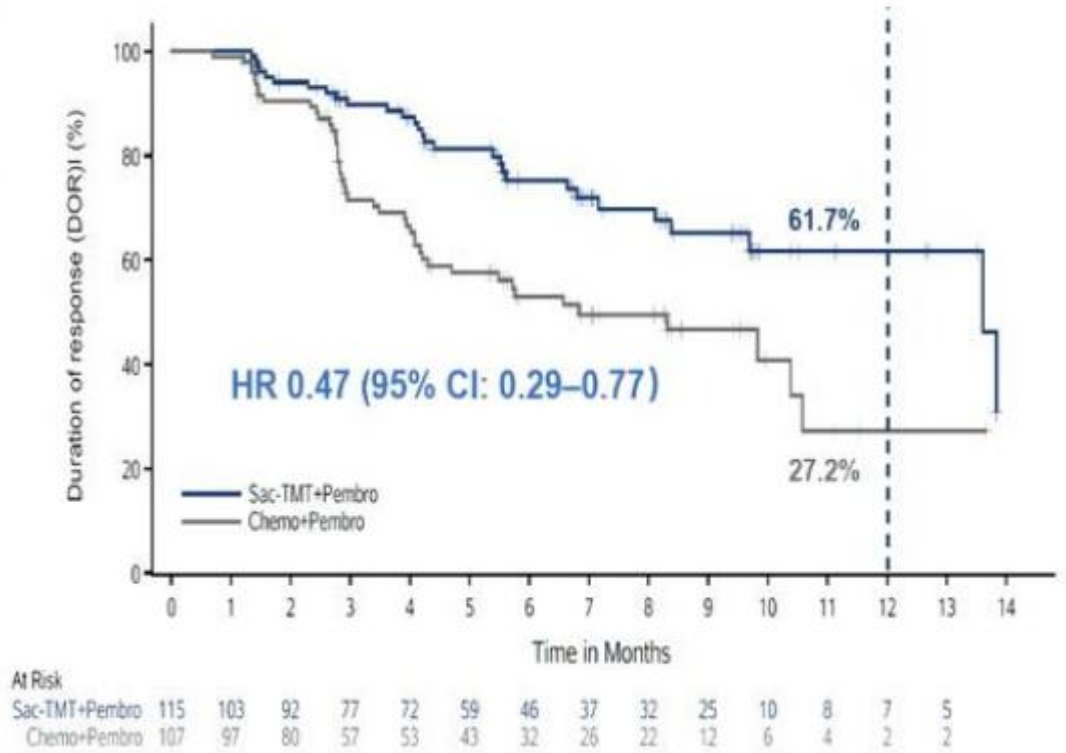
Among patients who discontinued study treatment, 57.0% vs. 54.1% received subsequent systemic therapy, mainly chemotherapy (platinum-based: 40.2% vs. 14.8%).

	Sac-TMT + Pembro (n = 229)	Chemo + Pembro (n = 226)
Study treatment discontinuation — no.	107	135
At least one subsequent systemic therapy — n (%)	61 (57.0)	73 (54.1)
Types of systemic therapy — n (%)		
Chemotherapy	54 (50.5)	45 (33.3)
Platinum-based therapy	43 (40.2)	20 (14.8)
Targeted therapy	30 (28.0)	26 (19.3)
Antiangiogenic therapy[a]	27 (25.2)	20 (14.8)
Immunotherapy	24 (22.4)	25 (18.5)
Antibody-drug conjugate	2 (1.9)	23 (17.0)
Other	0	3 (2.2)

ORR, Deep Response, and DOR (BICR)

ORR was similar between groups, with deeper and more durable responses observed with sac-TMT + pembro.

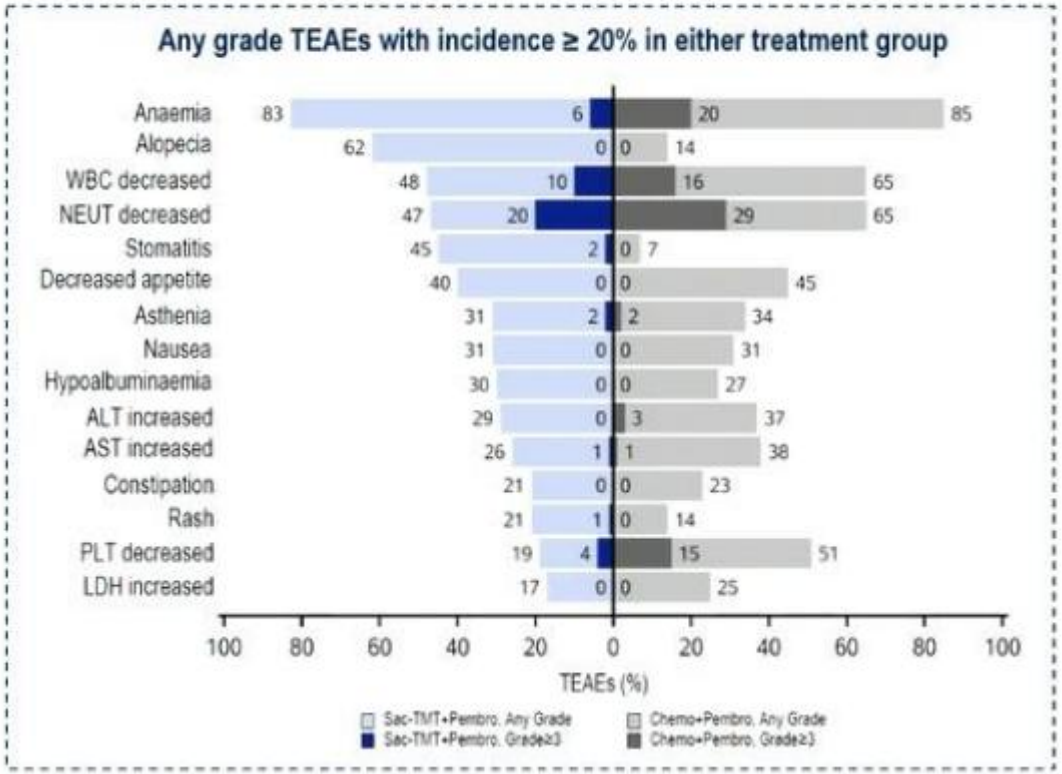
	Sac-TMT + Pembro (n = 229)	Chemo + Pembro (n = 226)
ORR, % (95% CI)	50.2 (43.6–56.9)	47.3 (40.7–54.1)
Deep response, %	28.8	17.3
DCR, % (95% CI)	90.4 (85.8–93.9)	88.5 (83.6–92.3)
Median DOR, mo (95% CI)	13.6 (9.7–NE)	6.8 (4.2–10.6)
HR (95% CI)	0.47 (0.29–0.77)	
12-mo DOR rate, % (95% CI)	61.7 (47.5–73.1)	27.2 (11.2–46.0)



Summary of Safety

Grade ≥3 TEAEs were less frequent with sac-TMT + pembro (47.6% vs. 60.6%), particularly hematologic events.

Event, n (%)	Sac-TMT + Pembro (n = 229)	Chemo + Pembro (n = 226)
TEAEs	228 (99.6)	225 (99.6)
Grade ≥3 TEAEs	**109 (47.6)**	**137 (60.6)**
Serious TEAEs	82 (35.8)	82 (36.3)
TEAEs Leading to dose reduction[a]	**11 (4.8)**	**45 (19.9)**
TEAEs Leading to discontinuation of any study drug	**13 (5.7)**	**32 (14.2)**
TEAEs Leading to death	**5 (2.2)**	**14 (6.2)**
TRAEs Leading to death	**1 (0.4)**	**3 (1.3)**



Adverse Events of Special Interest

		Sac-TMT + Pembro (n = 229)		Chemo + Pembro (n = 226)	
		Any grade	Grade ≥3	Any grade	Grade ≥3
Sac-TMT AEOSI	Anaemia	189 (82.5)	14 (6.1)	191 (84.5)	46 (20.4)
	Stomatitis[b]	117 (51.1)	5 (2.2)	19 (8.4)	0
	Neutrophil count decreased[c]	108 (47.2)	46 (20.1)	149 (65.9)	67 (29.6)
	Ocular surface toxicity[d]	31 (13.5)	0	6 (2.7)	0
	Infusion-related reaction	10 (4.4)[e]	0	3 (1.3)	0
Pembro AEOSI[a]	Pneumonitis[f]	24 (10.5)	4 (1.7)	31 (13.7)	7 (3.1)
	Hypothyroidism	23 (10.0)	0	20 (8.8)	0
	Hyperthyroidism	18 (7.9)	0	10 (4.4)	0
	Infusion reaction	10 (4.4)[e]	0	3 (1.3)	0
	Adrenal insufficiency	6 (2.6)	1 (0.4)	3 (1.3)	0
	Severe skin reactions	5 (2.2)	4 (1.7)	0	0

- Stomatitis occurred in 51.1% of patients receiving sac-TMT + pembro: grade 1 in 21.8%, grade 2 in 27.1%, and grade 3 in 2.2%.
- All ocular surface toxicities were grade 1–2; the most common were dry eye (8.3%), conjunctivitis (5.7%), and increased tearing (5.2%).
- No apparent excess of pneumonitis, including ILD, was observed with sac-TMT + pembro (10.5% vs. 13.7%).

Conclusions

- Sac-TMT + pembro demonstrated a statistically significant and clinically meaningful improvement in PFS compared with chemo + pembro.
- Sac-TMT + pembro showed a higher deep response rate and longer DOR, reflecting deeper and more durable responses.
- OS data were immature, but a favorable trend was observed (HR 0.58; 95% CI, 0.38–0.88).
- The safety profile was manageable and consistent with the known profiles of the individual agents, with no new safety signals identified.



Results from OptiTROP-Lung06 study support sac-TMT + pembro as a potential new first-line treatment option for PD-L1-negative advanced nonsquamous NSCLC without EGFR or ALK alterations