elcc European Lung Cancer Congress

Final OS results and subgroup analysis of savolitinib in patients with *MET* exon 14 skipping mutations (*MET*ex14+) NSCLC

SHUN LU, JIAN FANG, XINGYA LI, LEJIE CAO, JIANYING ZHOU, QISEN GUO, ZONGAN LIANG, YING CHENG, LIYAN JIANG, NONG YANG, ZHIGANG HAN, JIANHUA SHI, YUAN CHEN, HUA XU, HELONG ZHANG, GONGYAN CHEN, RUI MA, SANYUAN SUN, YUN FAN, WEIGUO SU

MET proto-oncogene

- Mesenchymal epithelial transition factor (*MET)* proto-oncogene maps to the 7q31 locus of chromosome 7
- It encodes for a receptor tyrosine kinase (RTK) for *HGF*, also known as scatter factor
- *MET* dysregulation were initially recognized as one of the secondary mechanisms of resistance to EGFR tyrosine kinase inhibitors (TKIs)
- Subsequently, MET exon 14 skipping mutation has been reported in 3–4% of NSCLC cases
- Prevalence : sarcomatoid carcinoma (4.9–31%) > adenosquamous (4–8%) > adenocarcinoma (3–4%) > squamous histology (2%)

Savolitinib

- Savolitinib (HMPL-504, AZD6094, volitinib) is a highly selective oral MET tyrosine kinase inhibitor
- Has been used in various malignancies including gastric and papillary renal cell carcinoma and NSCLC
- **TATTON study** : Phase Ib study, advanced *EGFR*-mutant NSCLC with *MET* amplification → ORR of 44% (95% CI, 22–69) in the 18 patients who received the combination of savolitinib and osimertinib
- **SAVANNAH** (NCT03778229)[64] and **ORCHARD** (NCT03944772) are ongoing trials evaluating this combination

Meeting Abstract | 2020 ASCO Annual Meeting I

LUNG CANCER—NON-SMALL CELL METASTATIC

Phase II study of savolitinib in patients (pts) with pulmonary sarcomatoid carcinoma (PSC) and other types of non-small cell lung cancer (NSCLC) harboring MET exon 14 skipping mutations (METex14+).

- As of October 31, 2019, 593 pts were pre-screened/screened, 87 identified with METex14+ and 70 treated
- ORR was 47.5% (95% CI: 34.6%, 60.7%), disease control rate 93.4% (95% CI: 84.1%, 98.2%) and median duration of response not reached
- The median progression-free survival was 6.8 months (95% CI 4.2, 13.8) among all treated pts
- The most common (≥20%) treatment-related adverse events (TRAEs) were peripheral edema, nausea, increased AST/ALT, vomiting and hypoalbuminemia
- The incidence of ≥ grade 3 TRAEs was 41.4%
- TRAEs leading to treatment discontinuation occurred in 14.3% pts, among which liver injury and hypersensitivity were most common (each 2.9%)

Background of the study

- Previous data showed a clinically meaningful overall response rate (ORR) and manageable toxicity profile in patients with *MET*ex14–mutated (*MET*ex14+) pulmonary sarcomatoidcarcinoma (PSC) and other non-small cell lung cancer (NSCLC).
- Savolitinib had been approved in China for the treatment of patients with *MET*ex14+ NSCLC based on the phase II study (NCT02897479).
- Here, authors reported the final OS results and subgroup analysis of the phase II study.

Phase II study of savolitinib in *MET*ex14+ PSC/other NSCLC (NCT02897479)

Study population:

- Unresectable/metastatic PSC or other NSCLC
- *MET*ex14+ & EGFR/ALK/ROS1-
- Failed/or medically unfit for chemotherapy
- Naïve to *MET* inhibitor

Savolitinib treatment:

- 600mg (BW≥50kg), or
- 400mg (BW<50kg)

Orally, once daily, 21 days/cycle

Tumor evaluation by investigators

- 1st year: every 6 weeks
- After 1 year: every 12 weeks

(Independent review retrospectively)

Treatment until disease progression or unacceptable toxicity

Primary Endpoint:

- ORR (RECIST v1.1)

Secondary Endpoints:

- DCR, DoR, TTR, PFS, 6-month PFS rate, OS
- Safety and tolerability

Baseline Characteristics: 70 pts enrolled & assigned to treatment (FAS)

- 25 diagnosed as PSC, 45 as other NSCLCs.
- 28 were treatment-naïve, 42 were pretreated.
- 15 pts had CNS lesions.

Data cutoff for final analysis: Jun 28, 2021

- 14 (20%) pts with >18 months treatment.
- Median follow up 28.4 months (IQR 26.2–36.3).

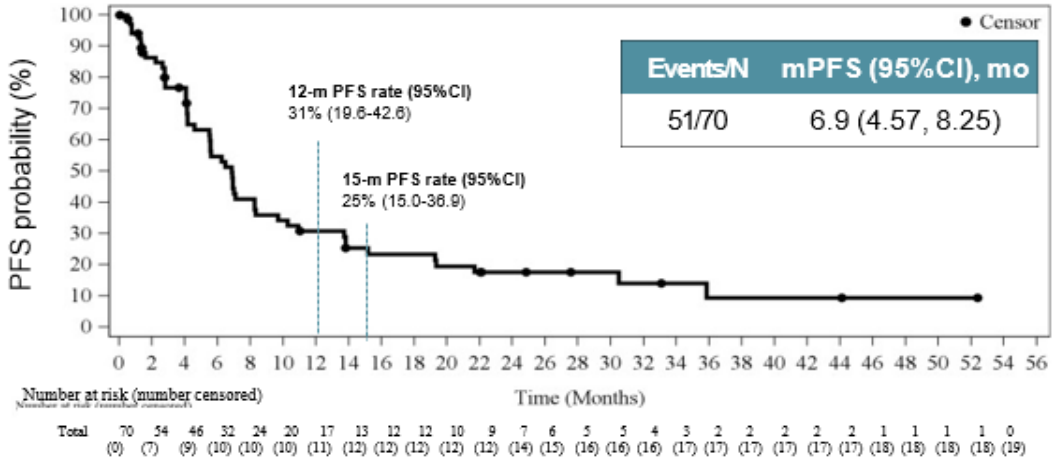
ORR: Objective response rate; DCR: disease control rate; DoR: duration of response; TTR: time to response; PFS: progression free survival; OS: overall survival; PSC: pulmonary sarcomatoid carcinoma; NSCLC: non-small cell lung cancer; RECIST, Response Evaluation Criteria In Solid Tumors.

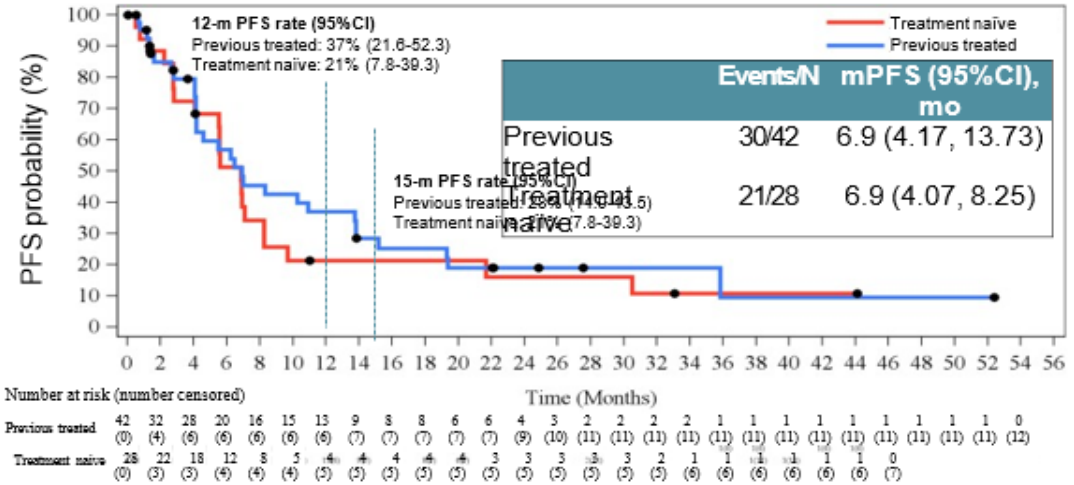
Demographics and Baseline Characteristics

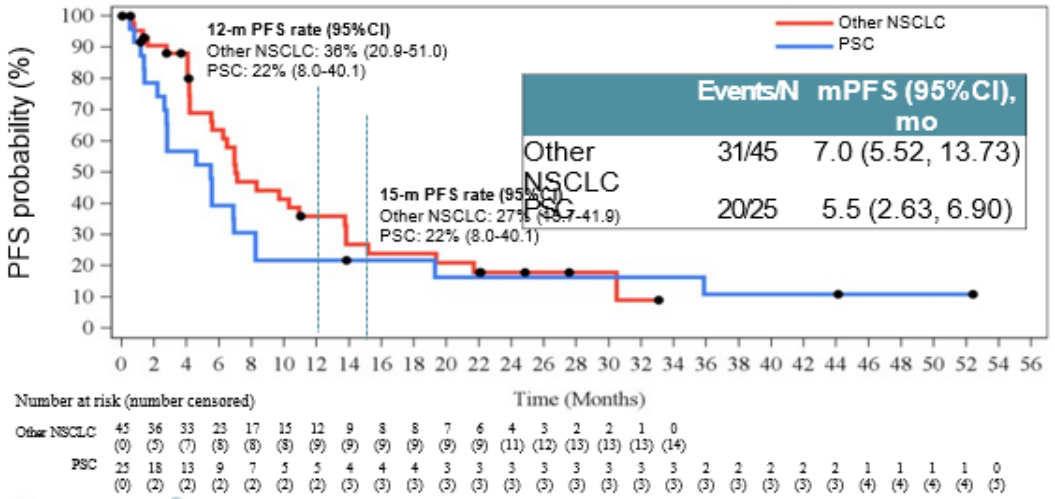
	Full analysis set (n=70)	Type of primary tumor		Prior antitumor treatment		Brain metastases status	
		PSC (n=25)	Other NSCLC (n=45)	Pre-treated (n=42)	Treatment-naive (n=28)	Brain metastases (n=15)	Non-brain metastases (n=55)
Demographics							
Age							
Median age, years	68.7 (51.7–85.0)	69.3 (54.1–84.8)	68.1 (51.7–85.0)	67.7 (51.7–84.8)	74.5 (56.0–85.0)	68.6 (51.7–84.8)	68.7 (51.9–85.0)
<75 years	54 (77%)	19 (76%)	35 (78%)	38 (90%)	16 (57%)	11 (73%)	43 (78%)
≥75 years	16 (23%)	6 (24%)	10 (22%)	4 (10%)	12 (43%)	4 (27%)	12 (22%)
Sex							
Female	29 (41%)	8 (32%)	21 (47%)	17 (40%)	12 (43%)	7 (47%)	22 (40%)
Male	41 (59%)	17 (68%)	24 (53%)	25 (60%)	16 (57%)	8 (53%)	33 (60%)
Smoking history							
Non-smokers	42 (60%)	13 (52%)	29 (64%)	28 (67%)	14 (50%)	11 (73%)	31 (56%)
Smokers	28 (40%)	12 (48%)	16 (36%)	14 (33%)	14 (50%)	4 (27%)	24 (44%)
Disease characteristics							
ECOG performance status*							
0	12 (17%)	3 (12%)	9 (20%)	8 (19%)	4 (14%)	3 (20%)	9 (16%)
1	57 (81%)	22 (88%)	35 (78%)	34 (81%)	23 (82%)	12 (80%)	45 (82%)
3	1 (1%)	0	1 (2%)	0	1 (4%)	0	1 (2%)
Histology							
Pulmonary sarcomatoid carcinoma	25 (36%)	25 (100)	0	12 (29%)	13 (46%)	2 (13%)	23 (42%)
Other NSCLC subtypes	45 (64%)		45 (100%)	30 (71%)	15 (54%)	13 (87%)	32 (58%)
Adenocarcinoma	40 (57%)		40 (89%)	27 (64%)	13 (46%)	13 (87%)	27 (49%)
Squamous cell carcinoma	3 (4%)	0	3 (7%)	2 (5%)	1 (4%)	0	3 (5%)
Adenosquamous carcinoma	1 (1%)		1 (2%)	1 (2%)	0	0	1 (2%)
NSCLC, not otherwise specified	1 (1%)		1 (2%)	0	1 (4%)	0	1 (2%)
Brain involvement at baseline	15 (21%)	2 (8%)	13 (29%)	11 (26%)	4 (14%)	15 (100%)	0
Previous treatments							
Prior antitumor treatment							
Yes	42 (60%)	12 (48%)	30 (67%)	NA	NA	11 (73%)	31 (56%)
No	28 (40%)	13 (52%)	15 (33%)			4 (27%)	24 (44%)

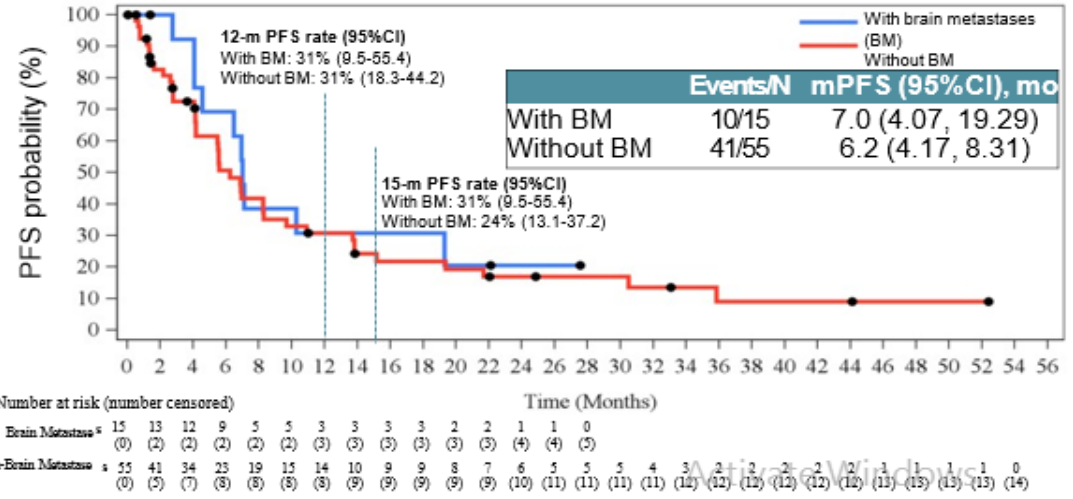
Data are median (min-max), or n (%). ECOG=Eastern Cooperative Oncology Group. NA=not applicable. *One patient with ECOG 3 was included in the study.

PFS results in FAS & subgroups (assessed by investigators)

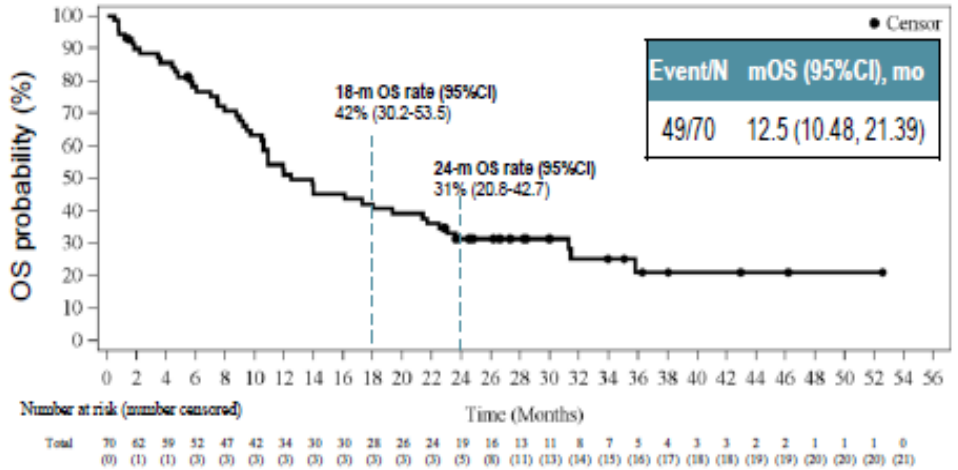


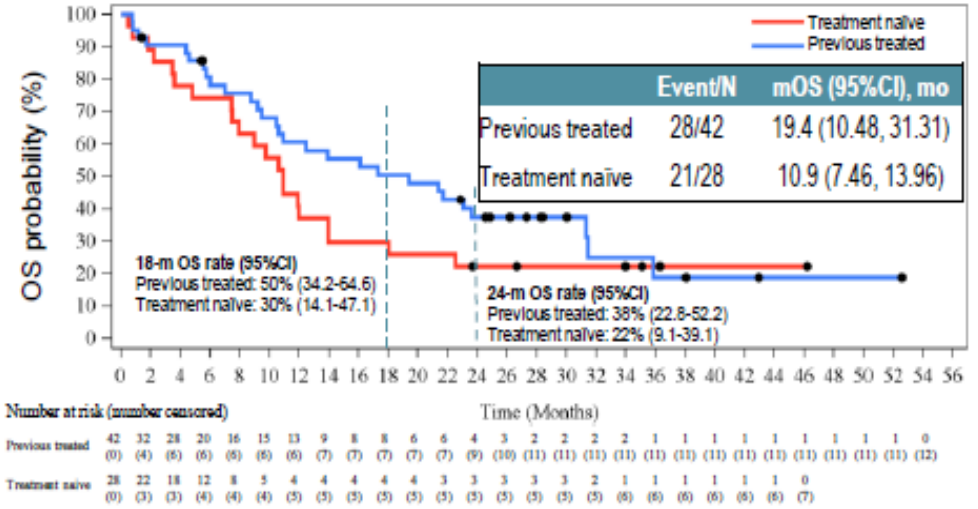


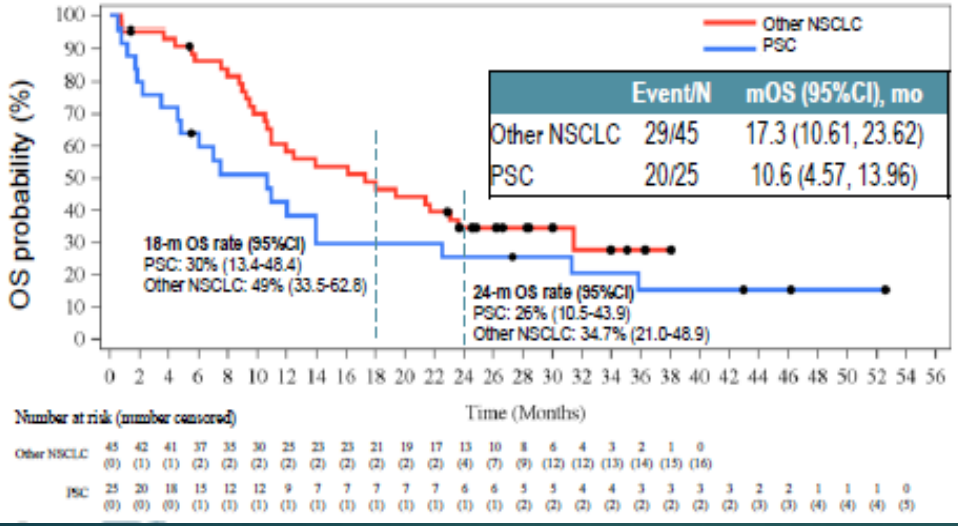


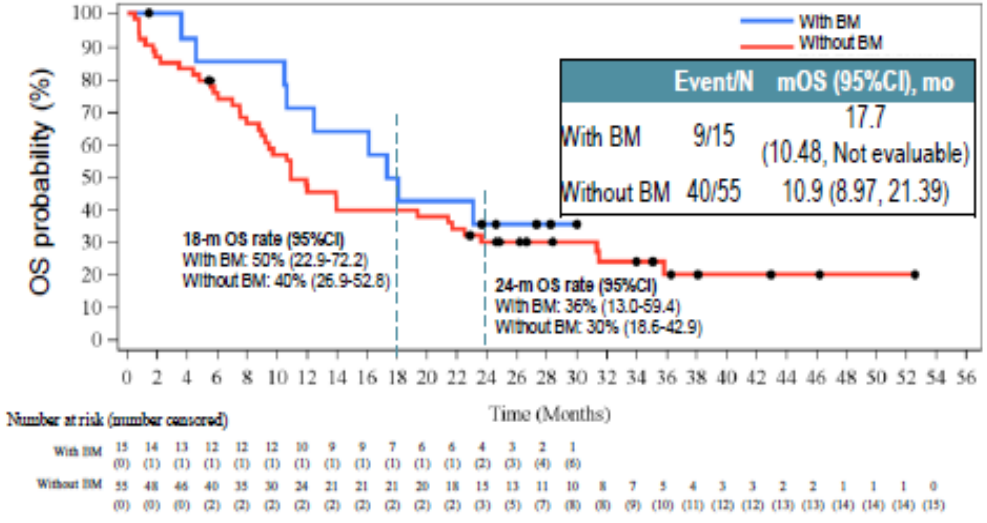


OS results in FAS & subgroups









Safety summary and Conclusion

The most common (≥30%) TEAEs:

TEAEs	N=70, n (%)	
	Any grade	≥ grade 3
Oedema peripheral	40 (57.1)	6 (8.6)
Nausea	37 (52.9)	0
Hypoalbuminaemia	29 (41.4)	1 (1.4)
Alanine aminotransferase increased	27 (38.6)	7 (10.0)
Aspartate aminotransferase increased	27 (38.6)	9 (12.9)
Decreased appetite	24 (34.3)	0
Vomiting	23 (32.9)	0
Pyrexia	21 (30.0)	1 (1.4)

With prolonged follow-up and exposure, the incidences of AE were similar to previously reported data

CONCLUSION

The updated results further confirm the favorable benefit of savolitinib in patients with *METex14*+ NSCLC and in each subgroup, and the acceptable safety profile.

Is Messi The New Maradona???

Thank You