# ctDNA Analysis in the Savolitinib Phase II Study in Non-Small Cell Lung Cancer (NSCLC) Patients Harboring *MET* Exon 14 Skipping Alterations (*MET*ex14)

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AACR# CT158

## BACKGROUND

- *MET* exon14 skipping (*MET*ex14) alterations in NSCLC ranges between 1% to 3% and appears to be most prevalent in pulmonary sarcomatoid carcinoma (PSC) (13% to 22%)[1,2].
- Savolitinib is a potent and highly selective MET tyrosine kinase inhibitor. It demonstrated clinical efficacy and a manageable safety profile in Chinese patients with PSC and other NSCLC harboring *MET*ex14 alterations in a phase 2 study (NCT02897479). In this study, 70 patients received savolitinib with objective response rate (ORR) at 42.9% and median progression-free survival (PFS) 6.8 months (data cutoff: Aug 3, 2020)[3].
- A post-hoc ctDNA analysis of *MET*ex14 at baseline and clearance upon treatment and the association of these findings with clinical outcome was performed. In addition, concurrent gene alterations in ctDNA samples from the patients treated with savolitinib and impact on clinical efficacy is explored.

## METHODS

- **Blood samples collection:** Plasma samples were prospectively collected at pre-dose and each visit of tumor evaluation until disease progression or end of treatment. Total 66 out of 70 pts provided baseline plasma specimens for baseline ctDNA detection, 37 provided paired baseline and post- baseline plasma samples and 21 had samples at the end of treatment due to disease progression (PD).
- **ctDNA extraction & sequencing:** Circulating tumor DNA (ctDNA) was isolated from the plasma using QIAamp Circulating Nucleic Acid Kit (QIAGEN) quantified by Qubit 2.0, sequenced with next generation sequencing (425-gene panel, Geneseeq).
- **Somatic mutation and copy number calling:** VarScan2 and ADTEx was used for detection of candidate somatic mutations and copy number variations, respectively.
- ***MET*ex14 alteration analysis:** A minimum variant supporting reads of 3 was set as the cut-off values for *MET*ex14 skipping detectable presented as SNV or deletion. *MET*ex14 ctDNA clearance was defined as undetectable levels in ctDNA on savolitinib treatment while it was detectable at baseline.

## RESULTS

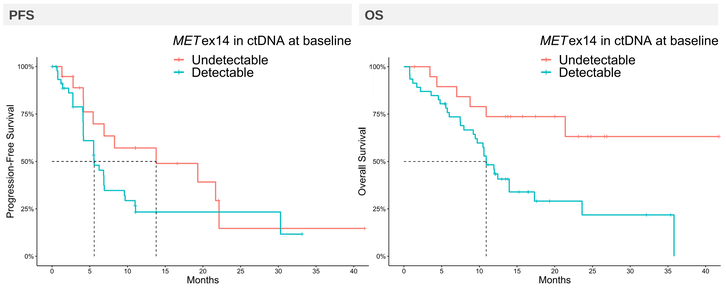
### A. Patient characteristics and clinical outcome by METex14 in ctDNA at baseline

- *MET*ex14 alteration was detected in ctDNA at baseline in 46 out of 66 (70%). Among of the 46 ctDNA detectable pts, 19 were PSC (19/22, 86%) and 27 were other NSCLC (27/44, 61%), respectively (Table 1).
- *MET*ex14 ctDNA detectable at baseline occurred more frequently in pts with larger tumor size or poor physical status (ECOG≥ 1) (Table 1).
- *MET*ex14 baseline undetectable pts tended to have longer mPFS and mOS (Fig 1, Table 2).

**Table 1. Baseline demographics, disease characteristics, prior treatment and *MET*ex14 status in ctDNA**

| Parameter | Total (N=66) | *MET*ex14 status at baseline | |
|---|---|---|---|
| | | Detectable (N=46) | Undetectable (N=20) |
| **Age : median (Min, Max)** | 68.7 (51.7-85.0) | 69.3 (51.9-85.0) | 67.1 (51.7-79.5) |
| **Gender** | | | |
| Female | 26 (39.4%) | 15 (32.6%) | 11 (55.0%) |
| Male | 40 (60.6%) | 31 (67.4%) | 9 (45.0%) |
| **Smoking History** | | | |
| Never | 39 (59.1%) | 24 (52.2%) | 15 (75.0%) |
| Current or former | 27 (40.9%) | 22 (47.8%) | 5 (25.0%) |
| **ECOG performance status** | | | |
| 0 | 12 (18.2%) | 4 (8.7%) | 8 (40.0%) |
| 1 | 53 (80.3%) | 41 (89.1%) | 12 (60.0%) |
| 3 | 1 (1.5%) | 1 (2.2%) | 0 (0%) |
| **Disease stage** | | | |
| III | 5 (7.6%) | 3 (6.5%) | 2 (10.0%) |
| IV | 61 (92.4%) | 43 (93.5%) | 18 (90.0%) |
| **Histology** | | | |
| PSC | 22 (33.3%) | 19 (41.3%) | 3 (15.0%) |
| Other NSCLC | 44 (66.7%) | 27 (58.7%) | 17 (85.0%) |
| **Organs involved with tumors (≥20%)** | | | |
| Lung | 62 (93.9%) | 44 (95.7%) | 18 (90%) |
| Lymph node | 61 (92.4%) | 43 (93.5%) | 18 (90%) |
| Pleura | 36 (54.5%) | 27 (58.7%) | 9 (45%) |
| Bone | 39 (59.1%) | 31 (67.4%) | 8 (40%) |
| Pleural effusion | 40 (60.6%) | 33 (71.7%) | 7 (35%) |
| Brain | 15 (22.7%) | 11 (23.9%) | 4 (20%) |
| Adrenal gland | 17 (25.8%) | 15 (32.6%) | 2 (10%) |
| **Sum of target lesion (cm): median (range)** | 86 (17.0, 327) | 95.6 (18, 327) | 51.8 (17.0,149) |
| **Prior systemic treatment for advanced disease** | | | |
| 0 | 25 (37.9%) | 18 (39.1%) | 7 (35.0%) |
| 1 | 31 (47.0%) | 19 (41.3%) | 12 (60.0%) |
| ≥2 | 10 (15.1%) | 9 (19.5%) | 1 (5.0%) |
| **Type of prior systemic treatment for advanced disease** | | | |
| Chemotherapy | 39 (59.1%) | 27 (58.7%) | 12 (60%) |
| Immunotherapy | 3 (4.5%) | 2 (4.3%) | 1 (5%) |
| Targeted therapy | 5 (7.6%) | 4 (8.7%) | 1 (5%) |
| Other (antiangiogenic drugs) | 15 (22.7%) | 11 (23.9%) | 4 (20%) |

**Fig 1. Clinical outcome by *MET*ex14 status in ctDNA at baseline**




### B. Associations of METex14 ctDNA clearance and clinical outcome

- Of the 46 baseline-detectable pts, 24 were clearance evaluable upon savolitinib treatment and 22 had no post baseline samples for clearance evaluation. (Table 2)
- Of the 24 clearance evaluable pts, 14 achieved ctDNA clearance and the median time to first clearance is 1.4 months (min 1.2 m, 4.2 m) (Fig 2).
- *MET*ex14 clearance upon savolitinib treatment was correlated with significantly longer PFS and OS compared with those who had detectable *MET*ex14 (Fig 3, Table 2).

**Fig 2. Time to *MET*ex14 ctDNA clearance**

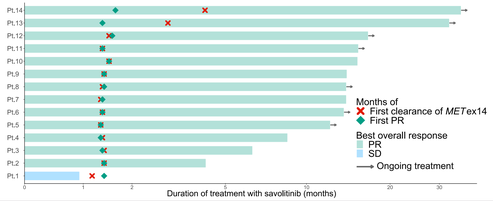



**Fig 3. *MET*ex14 ctDNA clearance and clinical benefit**

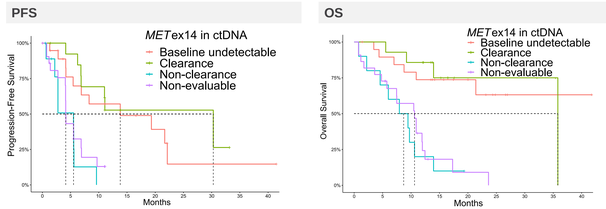



**Table 2. Clinical outcome by *MET*ex14 status**

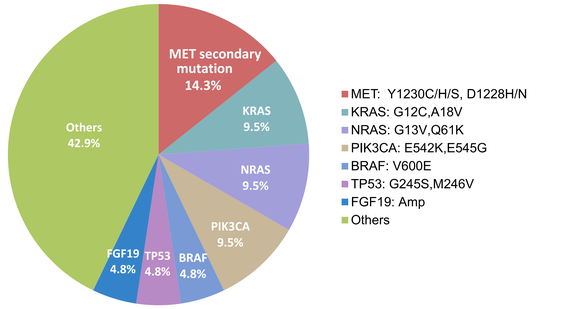
| *MET*ex14 ctDNA | mPFS (mo, 95% CI) | HR (95% CI) | *P value* | mOS (mo, 95% CI) | HR (95% CI) | *P value* |
|---|---|---|---|---|---|---|
| **Baseline undetectable (n=20)** | 13.8 (4.2, 22.1) | - | - | NC (10.9, NC) | - | - |
| **Baseline detectable (n=46)** | 5.6 (4.1, 6.9) | 1.77 (0.88, 3.57) | *0.108* | 10.9 (9.2, 14.0) | 3.26 (1.35, 7.89) | *0.006* |
| - Clearance (n=14) | 30.3 (6.8, NC) | 0.72 (0.28, 1.87) | *0.501* | 35.8 (14, NC) | 0.89 (0.25, 3.18) | *0.835* |
| - Non-clearance (n=10) | 5.5 (0.66, 5.6) | 4.94 (1.83, 13.36) | *0.002* | 8.7 (0.8, 10.6) | 7.06 (2.39, 20.89) | *<0.001* |
| - Non-evaluable (n=22) | 4.1 (4.1, 6.9) | 3.45 (1.48, 8.03) | *0.006* | 10.6 (4.8, 12.0) | 5.88 (2.24, 15.47) | *<0.001* |

CI, confidence interval; HR, hazard ratio; NC, non-calculable

### C. Concurrent gene alterations with METex14 in ctDNA

- Landscape of genomic alterations were analyzed in 21 pts who had ctDNA samples at baseline and progressed disease on savolitinib treatment.
- Known secondary MET resistance mutations such as D1228H/N or Y1230C/H/S were observed in 3 (14.3%) patients at PD.
- Assumptive bypass mechanisms of resistance to savolitinib involved driver gene alterations such as *KRAS, NRAS, BRAF, PIK3CA, FGF19, TP53* which accounted for 42.9%.

**Fig 4. Genomic alterations likely associated with resistance to savolitinib**




## CONCLUSION

ctDNA *MET*ex14 undetectable at baseline or clearance upon savolitinib treatment may define favorable treatment outcome. Confirmation of this finding and the predictive value of the ctDNA with larger sample size is desirable.

## REFERENCES

1. Liu X, et al. J Clin Oncol 2016;34:794-802
2. Vuong HG. et al. Lung Cancer 2018:123:76-82
3. Lu S. et al. J Clin Oncol 2020:38, no. 15_suppl 9519.