Tepotinib + gefitinib in patients with *EGFR*-mutant NSCLC with *MET* amplification: Final analysis of INSIGHT

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CONCLUSIONS

- **INSIGHT is the only randomized trial of a targeted therapy vs chemotherapy in patients with *EGFR*-mt NSCLC and MET-driven resistance to EGFR TKIs**
- **In this final analysis, tepotinib + gefitinib greatly improved PFS and OS vs chemotherapy and was well tolerated in the prespecified subgroup of patients with *MET*amp, confirming earlier findings from the trial[1]**
- **The median OS of 37.3 months with tepotinib + gefitinib in patients with *MET*amp is in the same range as that reported for first-line osimertinib in *EGFR*-mt NSCLC,[2] and should be considered in the context of the median duration of prior EGFR TKI therapy which was 10.6 months in our cohort**
- **Several patients with *MET*amp had a long duration of tepotinib + gefitinib treatment of more than 1 year, which appeared unrelated to the duration of prior EGFR TKI therapy**
- **A marked benefit of tepotinib + gefitinib vs chemotherapy was also seen in patients with MET IHC 3+**
- **Gefitinib remains an option for patients with *EGFR*-mt NSCLC; however, the third-generation EGFR TKI osimertinib is now preferred in many countries[3,4]**
- **INSIGHT 2 (NCT03940703) is evaluating tepotinib + osimertinib in patients with first-line osimertinib resistance due to *MET*amp[3]**

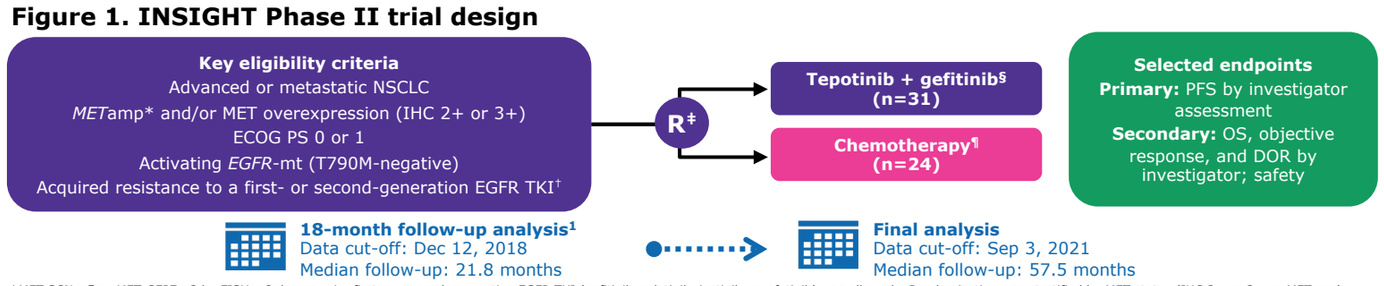
INTRODUCTION

- *MET*amp commonly mediates resistance to EGFR TKIs in patients with *EGFR*-mt NSCLC[5,6]
- This mechanism of resistance may be overcome by combining a MET TKI with an EGFR TKI[7,8]
- Tepotinib is a potent, highly selective, once-daily, oral MET TKI[9] approved for the treatment of advanced/metastatic NSCLC with *MET* exon 14 skipping[10]
- The Phase Ib/II INSIGHT trial evaluated tepotinib + gefitinib in patients with *EGFR*-mt NSCLC with *MET*amp and/or MET overexpression who are resistant to EGFR TKIs[1]
- In the 18-month follow-up analysis, tepotinib + gefitinib showed improved efficacy vs chemotherapy in preplanned subgroup analyses of patients with *MET*amp (and patients with MET IHC 3+)[1]
- We report final analyses from INSIGHT, with a focus on patients with *MET*amp

METHODS

- INSIGHT (NCT01982955) was an open-label, Phase Ib/II, randomized, multicenter trial (**Figure 1**)[1]
- Preplanned subgroup analyses evaluated patients with *MET*amp or MET IHC 3+

Figure 1. INSIGHT Phase II trial design



*MET GCN ≥5 or *MET*:*CEP7* ≥2 by FISH; †Only one prior first- or second-generation EGFR TKI (gefitinib, erlotinib, icotinib, or afatinib) was allowed; ‡Randomization was stratified by MET status (IHC 2+ vs 3+ vs *MET*amp) and type of prior EGFR TKI (gefitinib, erlotinib, icotinib, or afatinib); §500 mg (450 mg active moiety) tepotinib and 250 mg gefitinib, each given orally, once daily, until progression, intolerable toxicity, or consent withdrawal; ¶Pemetrexed 500 mg/m², plus cisplatin 75 mg/m² or carboplatin (area under the curve 5–6) by intravenous infusion on Day 1 of each 21-day cycle for up to six cycles or four cycles plus pemetrexed maintenance.

RESULTS

Patients and treatment

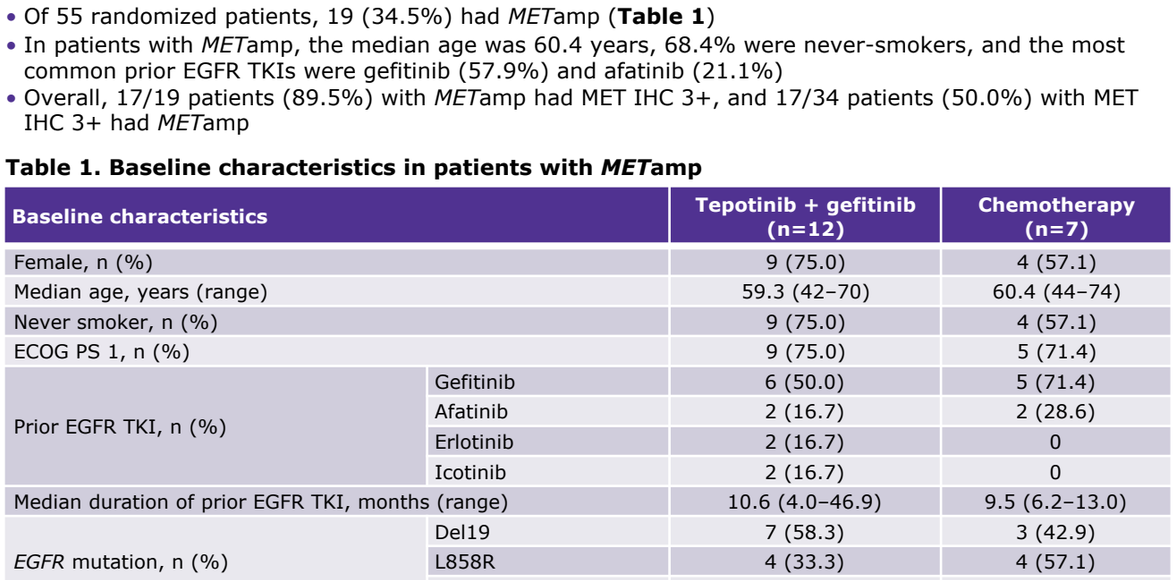
- Of 55 randomized patients, 19 (34.5%) had *MET*amp (**Table 1**)
- In patients with *MET*amp, the median age was 60.4 years, 68.4% were never-smokers, and the most common prior EGFR TKIs were gefitinib (57.9%) and afatinib (21.1%)
- Overall, 17/19 patients (89.5%) with *MET*amp had MET IHC 3+, and 17/34 patients (50.0%) with MET IHC 3+ had *MET*amp

Table 1. Baseline characteristics in patients with *MET*amp

Baseline characteristics		Tepotinib + gefitinib (n=12)	Chemotherapy (n=7)
Female, n (%)		9 (75.0)	4 (57.1)
Median age, years (range)		59.3 (42–70)	60.4 (44–74)
Never smoker, n (%)		9 (75.0)	4 (57.1)
ECOG PS 1, n (%)		9 (75.0)	5 (71.4)
Prior EGFR TKI, n (%)	Gefitinib	6 (50.0)	5 (71.4)
	Afatinib	2 (16.7)	2 (28.6)
	Erlotinib	2 (16.7)	0
	Icotinib	2 (16.7)	0
Median duration of prior EGFR TKI, months (range)		10.6 (4.0–46.9)	9.5 (6.2–13.0)
EGFR mutation, n (%)	Del19	7 (58.3)	3 (42.9)
	L858R	4 (33.3)	4 (57.1)
	G719X	1 (8.3)	0
*MET*amp, n (%)	Overall	12 (100)	7 (100)
	MET GCN ≥5	11 (91.7)	7 (100)
	MET:*CEP7* ≥2	7 (58.3)	6 (85.7)
MET IHC 3+, n (%)		11 (91.7)	6 (85.7)

- Tepotinib + gefitinib duration was >1 year in six (50.0%) and >4 years in three patients (25.0%) (**Figure 2**); scan the supplementary materials QR code in the bottom right of the poster to view **case studies of the three patients with treatment duration >4 years** (**Figure S1**)
- At the end of the study, two patients had treatment ongoing and transitioned to receive tepotinib + gefitinib via an Expanded Access Program; both were still on treatment as of March 2022 with a total treatment duration of >5 years
- The duration of tepotinib + gefitinib appeared unrelated to the duration of prior EGFR TKI therapy
- Six patients (31.6%) received post-study therapies, which included kinase inhibitors in two patients (16.7%) in the tepotinib + gefitinib arm and three patients (42.9%) in the chemotherapy arm

Figure 2. Treatment duration in patients with *MET*amp



Efficacy (patients with *MET*amp)

- In patients with *MET*amp, tepotinib + gefitinib greatly improved both PFS (unstratified HR 0.13; 90% CI: 0.04, 0.43) and OS (unstratified HR 0.10; 90% CI: 0.02, 0.36) compared with chemotherapy (**Figures 3** and **4**)

Figure 3. PFS (patients with *MET*amp)

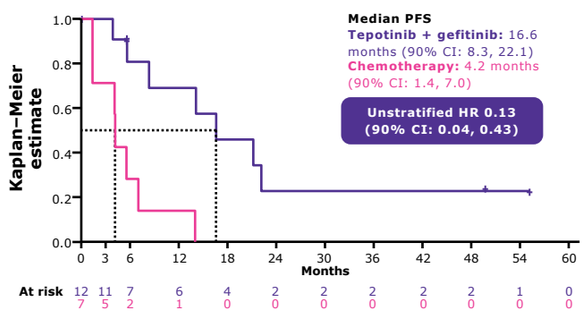
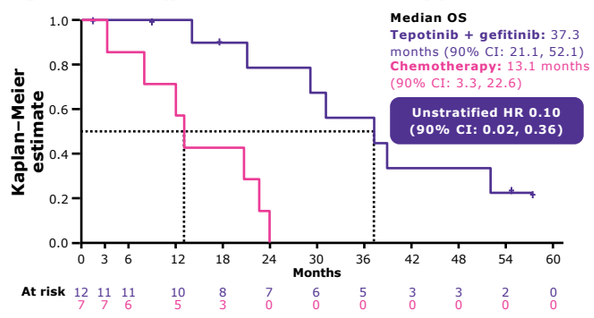


Figure 4. OS (patients with *MET*amp)

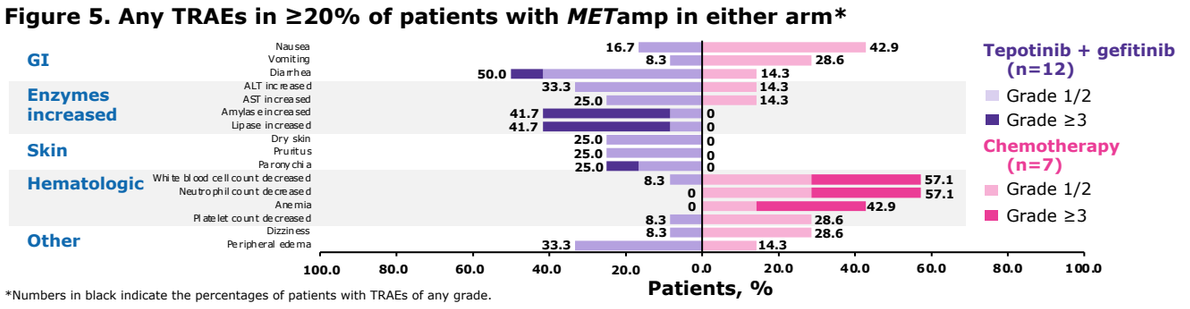


- ORR was higher in the tepotinib + gefitinib arm (66.7%; 90% CI: 39.1, 87.7) than in the chemotherapy arm (42.9%; 90% CI: 12.9, 77.5), with an odds ratio of 2.67 (90% CI: 0.37, 19.6)
- Median DOR was substantially longer with tepotinib + gefitinib (19.9 months; 90% CI: 7.0, NE) than with chemotherapy (2.8 months; 90% CI: 2.8, NE)

Safety (patients with *MET*amp)

- Median duration of tepotinib + gefitinib was 11.3 months (range: 1.1–56.5; mean: 20.7; std. dev.: 20.7)
- In the chemotherapy arm, median (range) treatment duration was 4.1 months (1.4–13.9) for pemetrexed, 2.8 months (1.5–5.8) for cisplatin, and 2.9 months (1.4–4.5) for carboplatin
- All patients had ≥1 TRAE; Grade ≥3 TRAEs were reported in seven patients (58.3%) in the tepotinib + gefitinib arm and five (71.4%) in the chemotherapy arm (**Figure 5**); scan the supplementary materials QR code in the bottom right of the poster to view **TRAEs in the overall population** (**Figure S2**)

Figure 5. Any TRAEs in ≥20% of patients with *MET*amp in either arm*



*Numbers in black indicate the percentages of patients with TRAEs of any grade.

Efficacy (patients with MET IHC 3+)

- In patients with MET IHC 3+, tepotinib + gefitinib also markedly improved PFS (unstratified HR 0.35; 90% CI: 0.17, 0.74) and OS (unstratified HR 0.44; 90% CI: 0.23, 0.84) vs chemotherapy (**Figures 6** and **7**)

Figure 6. PFS (patients with MET IHC 3+)

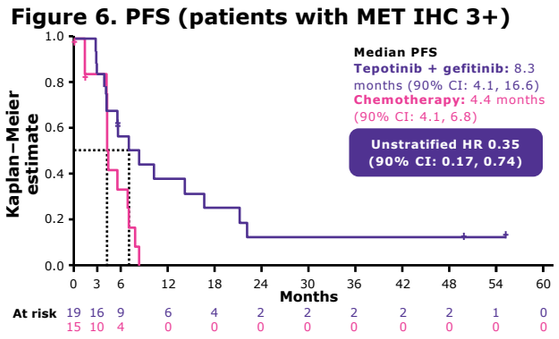
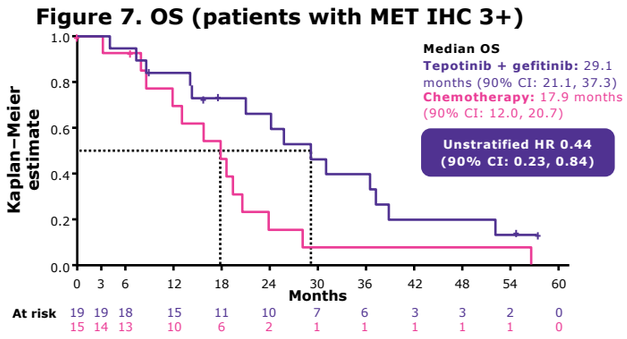


Figure 7. OS (patients with MET IHC 3+)



Efficacy (overall population)

- In the overall population (i.e. *MET*amp and/or MET IHC 2+/3+, including 19 patients with MET IHC 2+ without *MET*amp), outcomes were similar between tepotinib + gefitinib and chemotherapy:
  - Median PFS: 4.9 vs 4.4 months, respectively (stratified HR 0.67; 90% CI: 0.35, 1.28)
  - Median OS: 17.3 vs 19.5 months, respectively (stratified HR 0.67; 90% CI: 0.34, 1.32)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FISH, fluorescence *in situ* hybridization; GCN, gene copy number; GI, gastrointestinal; HR, hazard ratio; IHC, immunohistochemistry; MET, mesenchymal–epithelial transition factor; *MET*amp, *MET* amplification; mt, mutant; NE, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event.

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