Tepotinib plus an EGFR TKI in patients with EGFR-mutant NSCLC and resistance to EGFR TKIs due to MET amplification

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## Disclosure

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<td>Honoraria and fees for lectures and advisory board meetings</td>
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• **METamp** is a common mechanism of acquired resistance to EGFR TKIs in patients with *EGFR*-mutant NSCLC\(^1,2\)
• These patients have a high unmet need for effective treatments\(^1\)
• Combination therapy with a MET TKI plus an EGFR TKI may overcome *MET*-driven EGFR TKI resistance\(^3,4\)
• Tepotinib, an oral, potent and highly selective MET TKI,\(^5\) induced tumor regression in preclinical models of NSCLC with *MET*-driven EGFR TKI resistance\(^6\)
• In the Phase Ib/II INSIGHT study (NCT01982955), tepotinib + gefitinib demonstrated antitumor activity in patients with *EGFR*-mutant NSCLC, with METamp or MET overexpression and acquired resistance to an EGFR TKI\(^7\)

**Mechanisms of resistance to 1L osimertinib\(^1\)**

**Transformations**

- **Acquired EGFR mutations**
  - 6–10%
  - 7–15%
  - 1–2%
  - 1–5%
- **HER2 amplification**
- **Acquired oncogenic fusions**
- **Acquired MAPK-P13K mutations**
- **Acquired cell-cycle gene alterations**
- **Unknown**

*1L, first-line; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; MAPK, mitogen-activated protein kinase; MET, mesenchymal-epithelial transition factor; METamp, MET amplification; NSCLC, non-small cell lung cancer; PI3K, phosphoinositide 3-kinase; TKI, tyrosine kinase inhibitor.*


**We report further data on the clinical activity of tepotinib plus an EGFR TKI in patients with *EGFR*-mutant NSCLC with METamp from both clinical trials and clinical practice**
Open-label, Phase Ib/II, randomized, multicenter trial (NCT01982955)\(^1\)

**Key eligibility criteria**

**Both phases:**
- Advanced or metastatic NSCLC
- MET overexpression (IHC 2+ or 3+ and/or METamp)
- ECOG PS 0 or 1

**Phase Ib only:**
- Failed on prior gefitinib for reasons other than toxicity or compliance*  \(‡\)
- Activating EGFR mutation (other than T790M\(^†\))
- Acquired resistance to a first- or second-generation EGFR TKI*

**Phase II only:**
- MET overexpression (IHC 2+ or 3+ and/or METamp)
- ECOG PS 0 or 1

**Both phases:**
- Advanced or metastatic NSCLC
- MET overexpression (IHC 2+ or 3+)
- ECOG PS 0 or 1

**Phase Ib:**
- Primary: DLTs in Cycle 1, other AEs
- Secondary: ORR by investigator, PK

**Phase II:**
- Primary: PFS by investigator
- Secondary: ORR and DOR by investigator, OS, and safety

**Selected endpoints**

**Phase Ib:**
- Primary: DLTs in Cycle 1, other AEs
- Secondary: ORR by investigator, PK

**Phase II:**
- Primary: PFS by investigator
- Secondary: ORR and DOR by investigator, OS, and safety

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\(*\) In the Phase Ib part of the study, patients could receive other EGFR TKIs before/after gefitinib; in the Phase II part, only one prior first- or second-generation EGFR TKI (gefitinib, erlotinib, icotinib, or afatinib) was allowed; \(‡\) In the Phase II part of the study, an exploratory single-arm cohort enrolled a fixed number of patients (n=15) with T790M, all of whom received tepotinib plus gefitinib; \(†\) T3 = 3 dose-escalation design, followed by dose confirmation; \(\dagger\) 500 mg tepotinib contains 270 mg active moiety and 500 mg tepotinib contains 450 mg active moiety; *Administered orally, once daily, until disease progression, intolerable toxicity, or withdrawal of consent; **Consisting of pemetrexed 500 mg/m\(^2\), plus cisplatin 75 mg/m\(^2\) or carboplatin (area under the curve 5–6) by intravenous infusion on Day 1 of each 21-day cycle for up to six 21-day cycles or four cycles plus pemetrexed maintenance.

**AE, adverse event; DLT, dose-limiting toxicity; 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; IHC, immunohistochemistry; MET, mesenchymal–epithelial transition factor; ME7amp, ME7 amplification; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; TKI, tyrosine kinase inhibitor.**

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Of 49 patients treated with tepotinib + gefitinib, 18 (36.7%) had METamp

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Phase Ib</th>
<th>Phase II</th>
<th>Chemotherapy (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>4 (66.7)</td>
<td>3 (25.0)</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>67.5 (45–77)</td>
<td>59.3 (42–70)</td>
<td>60.4 (44–74)</td>
</tr>
<tr>
<td><strong>Smoker, n (%)</strong></td>
<td>3 (50.0)</td>
<td>3 (25.0)</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td><strong>ECOG PS 1, n (%)</strong></td>
<td>5 (83.3)</td>
<td>9 (75.0)</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td><strong>Prior EGFR TKI, n (%)</strong></td>
<td>Gefitinib</td>
<td>6 (100.0)</td>
<td>6 (50.0)</td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
<td>1 (16.7)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td></td>
<td>Icotinib</td>
<td>0</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td></td>
<td>Afatinib</td>
<td>1 (16.7)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td></td>
<td>Osimertinib</td>
<td>2 (33.3)</td>
<td>0</td>
</tr>
<tr>
<td><strong>EGFR mutation, n (%)</strong></td>
<td>Del19</td>
<td>3 (50.0)</td>
<td>7 (58.3)</td>
</tr>
<tr>
<td></td>
<td>L858R</td>
<td>3 (50.0)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td></td>
<td>G719X</td>
<td>0</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td><strong>MET GCN ≥5, n (%)</strong></td>
<td>6 (100.0)</td>
<td>11 (91.7)</td>
<td>7 (100.0)</td>
</tr>
<tr>
<td><strong>MET:CEP7≥2, n (%)</strong></td>
<td>2 (33.3)</td>
<td>7 (58.3)</td>
<td>6 (85.7)</td>
</tr>
<tr>
<td><strong>MET IHC 3+, n (%)</strong></td>
<td>4 (66.7)</td>
<td>11 (91.7)</td>
<td>6 (85.7)</td>
</tr>
</tbody>
</table>

Data cut-off: Dec 12, 2018. *Among patients with METamp in Phase Ib, two received tepotinib 300 mg and four received tepotinib 500 mg. ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; GCN, gene copy number; MET, mesenchymal–epithelial transition factor; METamp, MET amplification; TKI, tyrosine kinase inhibitor.

In Phase Ib and II combined, 12/18 patients (66.7%) with MET amp had a response.

**Phase Ib and II: Response (patients with METamp)**

- In Phase Ib and II combined, 12/18 patients (66.7%) with METamp had a response.

  **Tepotinib + gefitinib**

<table>
<thead>
<tr>
<th></th>
<th>Phase Ib (n=6*)</th>
<th>Phase II (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>4 (66.7)</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td>DOR, months</td>
<td>5.5, 5.6, 11.7, 12.5</td>
<td>Median: 19.9 [90% CI: 7.0, NE]</td>
</tr>
</tbody>
</table>

- In Phase II, PFS and OS were greatly improved with tepotinib + gefitinib versus chemotherapy.

- Efficacy of tepotinib + gefitinib also compared favorably with previous data for chemotherapy after progression on gefitinib in the IMPRESS trial (median PFS, 5.4 months [95% CI: 4.6, 5.5]; median OS, 19.5 months).

  **Phase Ib (n=6*)**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Tepotinib + gefitinib</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

HR = 0.13; 90% CI: 0.04, 0.43

**Phase II: OS (patients with METamp)**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Tepotinib + gefitinib</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

HR = 0.08; 90% CI: 0.01, 0.51

**INSIGHT: Tepotinib + gefitinib was generally well tolerated in patients with METamp** (data cut-off: Dec 12, 2018; Wu Y-L, et al. *Lancet Respir Med.* 2020¹)

<table>
<thead>
<tr>
<th>Phase II: TRAEs reported at any grade in ≥20%, n (%)</th>
<th>Tepotinib + gefitinib (n=12)</th>
<th>Chemotherapy (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Any TRAE</td>
<td>12 (100)</td>
<td>7 (58.3)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>1 (8.3)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (50.0)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (16.7)</td>
<td>0</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>5 (41.7)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>5 (41.7)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>4 (33.3)</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>3 (25.0)</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>3 (25.0)</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>3 (25.0)</td>
<td>0</td>
</tr>
<tr>
<td>Paronychia</td>
<td>3 (25.0)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3 (25.0)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (8.3)</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>1 (8.3)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (8.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data cut-off: Dec 12, 2018.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; MET, mesenchymal–epithelial transition factor; METamp, MET amplification; TRAE, treatment-related adverse event.

Of 18 patients with MET amp, treatment duration was >1 year in eight patients (44.4%), and >4 years in three patients (16.7%).

At the end of the study, two patients transitioned to continue tepotinib + gefitinib outside the study via an Expanded Access Program.

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**Table:**

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Sex</th>
<th>EGFR mutation</th>
<th>MET GCN</th>
<th>MET: CEP7 ratio</th>
<th>MET IHC score</th>
<th>Best response</th>
<th>Prior EGFR inhibitor</th>
<th>Tepotinib + gefitinib</th>
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</thead>
<tbody>
<tr>
<td>42</td>
<td>F</td>
<td>Del19</td>
<td>13.9</td>
<td>4.8</td>
<td>3+</td>
<td>PR</td>
<td></td>
<td>5.8</td>
</tr>
<tr>
<td>66</td>
<td>M</td>
<td>L858R</td>
<td>13.3</td>
<td>3.2</td>
<td>3+</td>
<td>PR</td>
<td></td>
<td>10.0</td>
</tr>
<tr>
<td>68</td>
<td>F</td>
<td>Del19</td>
<td>6.7</td>
<td>1.8</td>
<td>3+</td>
<td>PR</td>
<td></td>
<td>16.1</td>
</tr>
<tr>
<td>52</td>
<td>F</td>
<td>Del19</td>
<td>12.4</td>
<td>5.7</td>
<td>3+</td>
<td>PR</td>
<td></td>
<td>27.2</td>
</tr>
<tr>
<td>53</td>
<td>F</td>
<td>Del19</td>
<td>7.7</td>
<td>2.8</td>
<td>3+</td>
<td>PR</td>
<td></td>
<td>46.9</td>
</tr>
<tr>
<td>67</td>
<td>M</td>
<td>G719X</td>
<td>5.2</td>
<td>1.5</td>
<td>3+</td>
<td>SD</td>
<td></td>
<td>6.7</td>
</tr>
<tr>
<td>60</td>
<td>M</td>
<td>Del19</td>
<td>5.4</td>
<td>2.1</td>
<td>3+</td>
<td>PR</td>
<td></td>
<td>11.7</td>
</tr>
<tr>
<td>63</td>
<td>M</td>
<td>L858R</td>
<td>7.3</td>
<td>1.3</td>
<td>3+</td>
<td>PR</td>
<td></td>
<td>13.1</td>
</tr>
</tbody>
</table>

Data cut-off: 12 Dec 2018. *At start of treatment with tepotinib + gefitinib; †Prior to the data cut-off; ‡Both patients with METamp in Phase Ib with treatment duration >12 months received tepotinib at the 500 mg dose; §Most recent EGFR inhibitor; ¶Prior treatment also included gefitinib and chemotherapy.

EGFR, epidermal growth factor receptor; GCN, gene copy number; IHC, immunohistochemistry; MET, mesenchymal–epithelial transition factor; METamp, MET amplification; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
**INSIGHT case study 1: Prolonged PR with tepotinib + gefitinib after progression on afatinib in a patient with METamp**

- **Diagnosis**: Adenocarcinoma, Stage IV (T4/N3/M1), EGFR del19
- **1L therapy**: Best response: PR; Duration of treatment: 5.8 months
- **Enrolled in INSIGHT Phase II**
- **MET GCN**: 13.9; **MET CEP7**: 4.8; **MET IHC 3+**; **EGFR T790M-negative**
- **Afatinib 30 mg**
- **Gefitinib 250 mg**
- **Primary analysis data cut-off**
- **Gefitinib regularly interrupted to manage paronychia**

**Timeline**

- **Baseline (24-Oct-16)**
- **08-Dec-16**: PR at first post-baseline assessment (48% decrease in SOLD)
- **03-Sep-18**: Response maintained over >4.5 years of treatment
- **31-Jul-19**: Total duration of tepotinib + gefitinib within the study: 56.5 months
- **21-Sep-20**: After the end of the study, the patient continued treatment via an Expanded Access Program

**Courtesy of Azura Rozila Ahmad (Malaysia).** *Age at enrollment into INSIGHT.

1L, first-line; EGFR, epidermal growth factor receptor; GCN, gene copy number; IHC, immunohistochemistry; MET, mesenchymal–epithelial transition factor; METamp, MET amplification; PR, partial response; SOLD, sum of longest diameter.

**Abstract number:** 47

**Presented by Chong Kin Liam**
INSIGHT case study 2: Prolonged duration of tepotinib + gefitinib after progression on erlotinib in a patient with METamp

66-year-old Asian male,* former smoker (Taiwan)

Diagnosis: Adenocarcinoma, Stage IV (T4/N2/M1b), EGFR L858R

Enrolled in INSIGHT Phase II

1L therapy
Best response: PR
Duration of treatment: 10.0 months

MET GCN: 13.3
MET:CEP7: 3.2
MET IHC 3+
EGFR T790M-negative

Enrolled in INSIGHT Phase II

Primary analysis data cut-off

Tepotinib interruption to manage elevations in lipase and amylase

No PD observed as of May 2021

Erlotinib 150 mg

Gefitinib 250 mg

Tepotinib 500 mg

GRADE

Change in SOLD from baseline, %

PR per IRC attained at first post-baseline assessment

PR maintained during follow-up

Total duration of tepotinib + gefitinib within the study: 52.0 months

After the end of the study, the patient continued treatment via an Expanded Access Program

Disease progression

Abstract number: 47
Presented by Chong Kin Liam
INSIGHT case study 3: Prolonged duration of tepotinib + gefitinib after progression on erlotinib in a patient with METamp

Diagnosis: Adenocarcinoma, Stage IIIA (T2a/N2/M0), EGFR del19

Primary treatment: Left lower lobectomy (R0 resection)

Adjuvant therapy

1L therapy: Best response: PR
DOR: 11.1 months
Duration of treatment: 16.1 months

Enrolled in INSIGHT Phase II

MET GCN: 6.7
MET:CEP7: 1.8
MET IHC 3+
EGFR T790M-negative EGFR del19

Primary analysis data cut-off

SBRT 24 Gy to C2 vertebra

Progression due to increase in a single axillary node (target lesion). Treatment continued beyond progression based on stability of other target and non-target lesions and symptom control

Increase in liver lesions. Treatment continued as patient declined chemotherapy or biopsy to evaluate for additional targetable alterations

Tepotinib dose reduction due to Grade 3 peripheral edema

Baseline CT (21-Mar-17)

CT (05-May-17)

PR at first post-baseline assessment (Week 6)

Disease recurrence

Disease progression

Death

68-year-old Asian female,* never smoker (Malaysia)

Erlotinib 150 mg

Tepotinib 500 mg + gefitinib 250 mg

Tepotinib 300 mg

SBRT 24 Gy to C2 vertebra

Duration of treatment: 16.1 months

Total duration of tepotinib + gefitinib: 51.8 months

Increase in liver lesions. Treatment continued as patient declined chemotherapy or biopsy to evaluate for additional targetable alterations

Tepotinib dose reduction due to Grade 3 peripheral edema

Baseline CT (21-Mar-17)

CT (05-May-17)

PR at first post-baseline assessment (Week 6)

Disease recurrence

Disease progression

Death

Presented by Chong Kin Liam

Abstract number: 47

*Age at enrollment into INSIGHT; †Carboplatin + gemcitabine.

1L, first-line; CT, computed tomography; DOR, duration of response; EGFR, epidermal growth factor receptor; GCN, gene copy number; IHC, immunohistochemistry; MET, mesenchymal–epithelial transition factor; METamp, MET amplification; PR, partial response; SBRT, stereotactic body radiotherapy.

Disease recurrence

Disease progression

Death

Erlotinib 150 mg

Tepotinib 500 mg + gefitinib 250 mg

Tepotinib 300 mg

SBRT 24 Gy to C2 vertebra

Duration of treatment: 16.1 months

Total duration of tepotinib + gefitinib: 51.8 months

Increase in liver lesions. Treatment continued as patient declined chemotherapy or biopsy to evaluate for additional targetable alterations

Tepotinib dose reduction due to Grade 3 peripheral edema

Baseline CT (21-Mar-17)

CT (05-May-17)

PR at first post-baseline assessment (Week 6)

Disease recurrence

Disease progression

Death

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Disease recurrence

Disease progression

Death

Erlotinib 150 mg

Tepotinib 500 mg + gefitinib 250 mg

Tepotinib 300 mg

SBRT 24 Gy to C2 vertebra

Duration of treatment: 16.1 months

Total duration of tepotinib + gefitinib: 51.8 months

Increase in liver lesions. Treatment continued as patient declined chemotherapy or biopsy to evaluate for additional targetable alterations

Tepotinib dose reduction due to Grade 3 peripheral edema

Baseline CT (21-Mar-17)

CT (05-May-17)

PR at first post-baseline assessment (Week 6)

Disease recurrence

Disease progression

Death

Erlotinib 150 mg

Tepotinib 500 mg + gefitinib 250 mg

Tepotinib 300 mg

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Baseline CT (21-Mar-17)

CT (05-May-17)

PR at first post-baseline assessment (Week 6)
Further data on tepotinib plus an EGFR inhibitor in patients with EGFR-mutant NSCLC and METamp: INSIGHT 2

- INSIGHT 2 (NCT03940703) is an ongoing Phase II trial evaluating tepotinib + osimertinib in patients with EGFR-mutant NSCLC with acquired resistance to 1L osimertinib due to METamp, which opened in September 2019 and had key protocol amendments implemented in April 2020¹

Original protocol
- Eligible patients must have advanced/metastatic NSCLC harboring activating EGFR mutations with acquired resistance to prior first- to third-generation EGFR TKIs, with METamp
- METamp determined by LBx

Protocol following key amendments
- Eligible patients must have advanced/metastatic NSCLC harboring activating EGFR mutations that have relapsed on first-line osimertinib due to METamp
- METamp determined by FISH testing with TBx (central or local), or by central LBx, with the primary efficacy analysis set consisting of patients with METamp centrally confirmed by FISH testing with TBx

- A case report of a patient enrolled through the original protocol is shown on the next slide; this patient will not be included in the primary efficacy analysis set of INSIGHT 2²

INSIGHT 2 case study: Response to tepotinib + osimertinib in a patient with METamp and acquired osimertinib resistance

78-year-old Asian male, never smoker (Malaysia)

Diagnosis: Adenocarcinoma, Stage IVB (cT3/N2/M1c), EGFR del19

1L therapy: Best response: PR
Duration of treatment: 15.1 months

Osimertinib 80 mg

Tepotinib 500 mg
Osimertinib 80 mg

CT (20-May-20): Resistance to 1L osimertinib

CT (18-Aug-20): PR to 2L tepotinib + osimertinib

Duration of tepotinib + osimertinib: 6.4 months

Enrolled in INSIGHT 2
METHAMP by ArcherDX-NGS liquid biopsy assay
Treatment discontinued due to disease progression

Disease progression

Courtesy of Chong Kin Liam (Malaysia).

1L, first-line; 2L, second-line; CT, computed tomography; EGFR, epidermal growth factor receptor; MET, mesenchymal–epithelial transition factor; METamp, MET amplification; NGS, next-generation sequencing; PR, partial response.

Further data on tepotinib plus an EGFR inhibitor in patients with **EGFR-mutant NSCLC** and **METamp**: Clinical practice

- Outside clinical trials, several patients have received tepotinib plus an EGFR TKI in clinical practice (including compassionate use)

- A case report based on a patient in the US receiving this combination for >7 months is shown on the next slide

<table>
<thead>
<tr>
<th>Country</th>
<th>Age</th>
<th>Sex</th>
<th>Prior treatment</th>
<th>Time on most recent prior EGFR TKI, months</th>
<th><strong>METamp, GCN</strong></th>
<th>EGFR TKI*</th>
<th>Time on treatment, ‡ months</th>
<th>Treatment ongoing‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>62</td>
<td>Female</td>
<td>Chemo, afatinib, osimertinib, immunotherapy</td>
<td>12.0</td>
<td>N/A (NGS, Archer)</td>
<td>Osimertinib 80 mg</td>
<td>7.8</td>
<td>Yes</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>79</td>
<td>Male</td>
<td>Gefitinib, osimertinib</td>
<td>11.5</td>
<td>10 (NGS; Foundation Medicine)</td>
<td>Osimertinib 80 mg</td>
<td>10.4</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*At the beginning of combination treatment; †EGFR TKI given in combination tepotinib 500 mg (450 mg active moiety) treatment; ‡As of August 2021.*

EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; GCN, gene copy number; MET, mesenchymal–epithelial transition factor; METamp, MET amplification; N/A, not available; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.
Clinical practice case study: Ongoing benefit from tepotinib + osimertinib after progression on afatinib and osimertinib in a patient with METamp

Diagnosis
Adenocarcinoma, Stage IV
(T1/N2/M1a), EGFR L858R

62-year-old Caucasian female, never smoker (US)

01-Jan-18
Afatinib 20–30 mg

01-Jan-19
2L therapy
Best response: PR
Duration of treatment: 20.5 months

EGFR T790M

3L therapy
Best response: PR
Duration of treatment: 4.6 months

01-Jan-20
T-cell therapy (clinical trial)

01-Jan-21
Osimertinib 80 mg

Osimertinib 80 mg†

Treatment ongoing as of August 2021
(total duration: 7.8 months)

Disease progression
Before tepotinib + osimertinib
SD with shrinkage of lung tumor and metastatic lymph node

PET (Dec 2020)
CT (Dec 2020)
PET (Jan 2021)
CT (Feb 2021)

Courtesy of Xiuning Le and John Heymach (US). *Carboplatin + pemetrexed; †Osimertinib was restarted as monotherapy while awaiting approval for compassionate use of tepotinib.

1L, first-line; 2L, second-line; 3L, third-line; CT, computed tomography; EGFR, epidermal growth factor receptor; MET, mesenchymal–epithelial transition factor; METamp, MET amplification; NGS, next-generation sequencing; PET, positron emission tomography; PR, partial response; RT, radiotherapy; SD, stable disease.

Abstract number: 47
Presented by Chong Kin Liam
Clinical practice case study: Ongoing benefit from tepotinib + osimertinib after progression on gefitinib and osimertinib in a patient with METamp

79-year-old male (Hong Kong)

1L therapy
Best response: SD
Duration of treatment: 6 months

2L therapy
Best response: PR
Duration of treatment: 11.5 months

Treatment ongoing as of August 2021
(best response: PR; total duration: 10.4 months)

Tepotinib 500 mg
Osimertinib 80 mg

Gefitinib
Osimertinib

August 2020

August 2020 – February 2021
LUL lung metastasis improved
Left SCF LN resolved

Presented by Chong Kin Liam

Abstract number: 47

Courtesy of Jacky Yu-Chung Li (Hong Kong).
1L, first-line; 2L, second-line; GCN, gene copy number; LN, lymph nodes; LUL, left upper lobe; MET, mesenchymal–epithelial transition factor; METamp, MET amplification; NGS, next generation sequencing; PR, partial response; RT, radiotherapy; SCF, supraclavicular fossa; SD, stable disease.

Clinical practice case study: Ongoing benefit from tepotinib + osimertinib after progression on gefitinib and osimertinib in a patient with METamp

1L therapy
Best response: SD
Duration of treatment: 6 months

2L therapy
Best response: PR
Duration of treatment: 11.5 months

LUL lung metastasis improved
Left SCF LN resolved

Presented by Chong Kin Liam

Abstract number: 47

Courtesy of Jacky Yu-Chung Li (Hong Kong).
1L, first-line; 2L, second-line; GCN, gene copy number; LN, lymph nodes; LUL, left upper lobe; MET, mesenchymal–epithelial transition factor; METamp, MET amplification; NGS, next generation sequencing; PR, partial response; RT, radiotherapy; SCF, supraclavicular fossa; SD, stable disease.
Conclusions

• The combination of tepotinib with an EGFR TKI, including osimertinib, shows clinical activity in the treatment of patients with EGFR TKI-resistant NSCLC due to METamp; the relevance of MET IHC 3+ in this setting warrants further investigation.

• In INSIGHT, three patients with METamp received tepotinib + gefitinib for >4 years, of whom two continued treatment after study end via an Expanded Access Program.

• Tepotinib + osimertinib is currently being investigated in patients with METamp EGFR-mutant NSCLC with acquired resistance to 1L osimertinib in the INSIGHT 2 study (see Abstract 167).

• Currently, 108 sites are active in 17 countries; encouraging preliminary activity has been observed.

Key eligibility criteria (N≈120)
- Locally advanced/metastatic NSCLC with activating EGFR mutation
- METamp on tissue biopsy (FISH) or liquid biopsy
- Acquired resistance to 1L osimertinib

Global, open-label, two-arm, Phase II INSIGHT 2 trial (NCT03940703)

Key eligibility criteria (N≈120)
- Locally advanced/metastatic NSCLC with activating EGFR mutation
- METamp on tissue biopsy (FISH) or liquid biopsy
- Acquired resistance to 1L osimertinib

INSIGHT 2
POSTER

- Locally advanced/metastatic NSCLC with activating EGFR mutation
- METamp on tissue biopsy (FISH) or liquid biopsy
- Acquired resistance to 1L osimertinib

*Initially, eligible patients who are positive for METamp will be randomly assigned in a ratio of 2:1 to either the combination of tepotinib + osimertinib or tepotinib alone, until 12 are enrolled in the monotherapy arm. After this, all patients will be assigned to the combination. Patients who are randomized to tepotinib monotherapy will have the opportunity to switch over to the combination at the time of disease progression; †Treatment continues until disease progression, death, an adverse event leading to discontinuation, study withdrawal, or consent withdrawal.


Abstract number: 47
Presented by Chong Kin Liam
INSIGHT 2 resources

- VIEW INSIGHT 2 POSTER
- GET INSIGHT 2 TRIAL CARD
- GET INSIGHT 2 TRIAL ANIMATION
- GET INSIGHT 2 PATIENT BROCHURE
- GET INSIGHT 2 PHYSICIAN BROCHURE

Abstract number: 47
Presented by Chong Kin Liam
Acknowledgements

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