Erlotinib versus Gemcitabine plus Cisplatin as Neoadjuvant Treatment for Stage IIIA-N2 EGFR-mutation Positive Non-small-cell Lung Cancer (EMERGING-CTONG 1103): multicentre phase 2 randomized study

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EMERGING-CTONG 1103 Study Design

- Treatment naïve IIIA-N2 NSCLC
- N2 confirmed by mediastinoscopy / EBUS / PET-CT
- EGFR activating mutation
- ECOG 0-1
- Age ≥18y

Randomization 1:1
N=72

Erlotinib 150mg/d for 42 days

Primary endpoint
- ORR

Secondary endpoint
- Downstaging rates of pathological lymph node
- pCR
- PFS
- 3y and 5y OS rate
- Safety & Tolerability

Surgery (Non-PD)

Erlotinib 150mg/d for 12 months

G 1250mg/m² d1 8 + C 75mg/m² d1, q3w for 2 cycles

GC q3w for 2 cycles

Stratification by lymph node status, histology, smoking status and sex.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; G, gemcitabine; C, cisplatin; ORR, objective response rate; pCR, pathological complete response; PFS, progression free survival; OS, overall survival.

Data cut-off: April 2018; NCT01407822; PI: Yi-long Wu

Presented on: ESMO, October 19-23, 2018, Munich, Germany
Primary Endpoint: ORR (ITT Population)

**Erlotinib**

ORR, objective response rate; PR, partial response; SD, stable disease; PD, progressive disease

**GC**
Conclusions

- CTONG 1103 is the first phase II, randomized controlled trial comparing EGFR-TKI versus doublet chemo in neoadjuvant setting;
- Neoadjuvant Erlotinib improved ORR (although not significantly), MPR, operation rate, R0 resection and LN down staging in stage IIIA-N2 EGFRm;
  - ORR: 54.1% vs 34.3%(P=0.092); Operation rate: 83.8% vs 68.6%; R0 resection: 73.0% vs 62.9%;
  - LN Down staging: 10.8% vs 2.9%; MPR: 10.7% vs 0% ;
- Erlotinib has longer PFS compared with GC chemo in the neoadjuvant/adjuvant setting of stage IIIA-N2 EGFRm NSCLC. OS data is immature.
  - mPFS: 21.5 vs 11.9 months (HR 0.42, P=0.003) NSCLC
- The AEs profile were in line with that reported previously;
- The promising biomarker-guided treatment regimens for stage IIIA-N2 NSCLC warrants further exploration in neoadjuvant setting.
Phase 2 study of tepotinib + gefitinib in met-positive/epidermal growth factor receptor-mutant NSCLC

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Presented by Yi-Long Wu
Phase IB results: RP2D identified for tepotinib in combination with gefitinib

- Open-label, single-arm, Phase Ib dose escalation study in Asian patients with MET-positive NSCLC that failed prior gefitinib therapy (N=18)
  - MET2+ or 3+ by IHC (DIC1 antibody) and/or MET amplification by ISH (GCN ≥5 and/or MET/CEP-7 ratio ≥2)
- Classical 3 + 3 design with expansion group at the proposed RP2D
- Recommended Phase II dose: tepotinib established as 500 mg once daily in combination with gefitinib 250 mg/day
- Antitumor activity greatest in tumors with MET IHC3+ and/or MET amplification

MET amplification, defined as mean GCN ≥5 and/or MET/CEP-7 copy number ratio ≥2.
EGFR, epidermal growth factor receptor; GCN, gene copy number; ISH, in situ hybridization; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; QD, once daily; RP2D, recommended Phase II dose; TKI, tyrosine kinase inhibitor.

Presented on: ESMO, October 19-23, 2018, Munich, Germany
Phase II study design

**Asian patients with:**
- Locally advanced/metastatic stage IV NSCLC, EGFR+, T790M-, MET+
  - MET2+ or 3+ by IHC (D1C1 antibody) and/or
  - MET amplification by ISH (CCN ≥2 and/or MET/CEP-7 ratio ≥2)
- Resistance to prior EGFR TKI (Jackman criteria)*
- No prior HGF/MET pathway-directed therapy

**Stratification factors:**
- Type of MET+ (IHC2+ vs IHC3+ vs MET amplification)‡
- Prior EGFR-TKI treatment

*Endpoints:*
- **Primary:** investigator-assessed PFS
- **Secondary:** ORR, safety

**Pre-planned analyses:**
- MET IHC3+ subgroup
- MET amplification subgroup

**Initial plan to enrol 156 patients**
- Enrolment halted after 55 patients randomized due to difficulties in identifying patients who met the eligibility criteria

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†Initially 1:1 and changed to 2:1 on implementation of protocol amendment (30-Sep-2016).‡Patients with coexistence of MET amplification and MET IHC overexpression were included in the MET amplification group. AUC, area under the curve; EGFR, epidermal growth factor receptor; GCN, gene copy number; IHC, immunohistochemistry; ISH, in situ hybridization; i.v., intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, disease progression; PFS, progression-free survival; QD, once daily; TKI, tyrosine kinase inhibitor."
Increased PFS with tepotinib/gefitinib in high MET-expressing tumors

Presented on: ESMO, October 19-23, 2018, Munich, Germany

Chemotherapy, pemetrexed + cisplatin or carboplatin.
CI, confidence interval; HR, hazard ratio; IHC, Immunohistochemistry; KM, Kaplan-Meier; PFS, progression-free survival.
Increased PFS with tepotinib/gefitinib in tumors with MET amplification

PFS in MET amplification subgroup (n=19)

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At risk

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Median PFS, months [90% CI]:
- Tepotinib + gefitinib: 21.2 [8.3, 21.2]
- Chemotherapy: 4.2 [1.4, 7.0]

(Unstratified) HR [90% CI]:
- 0.17 [0.05, 0.57]

MET-amplified, defined as mean gene copy number ≥5 and/or MET/CEP-7 copy number ratio ≥2.
Chemotherapy, pemetrexed + cisplatin or carboplatin.
CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival.

Presented on: ESMO, October 19-23, 2018, Munich, Germany
Conclusions

- This is the first randomized study to compare tepotinib plus gefitinib with chemotherapy in relapsed EGFR-mutant NSCLC with MET overexpression (IHC3+) and/or MET amplification
  - Enrolment was halted early due to low recruitment

- Patients whose tumors harbor MET amplifications experienced improved PFS with the tepotinib/gefitinib combination compared with chemotherapy (HR 0.17 [90% CI 0.05, 0.57])
  - MET can be considered a suitable biomarker for treatment with tepotinib

- Higher ORR with the tepotinib/gefitinib combination (45.2%) than chemotherapy (33.3%)
  - ORR was highest in patients with MET IHC3+ and MET-amplified tumors in the tepotinib/gefitinib combination arm (68.4% and 66.7%, respectively)

- Treatment with tepotinib and gefitinib was generally well-tolerated and most AEs were mild to moderate in severity

MET – amplified, defined as mean gene copy number ≥5 and/or MET/CEP-7 copy number ratio ≥2
AE, adverse event; CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival.