ESTADIOS TEMPRANOS Y LOCALMENTE AVANZADOS

Dra. Virginia Calvo
• Is EGFR TKI effective as pre-operative therapy for IIIA (N2) NSCLC?
  • CTONG 1103: Erlotinib versus Gemcitabine plus Cisplatin as Neo-adjuvant Treatment for stage IIIA-N2 EGFR mutation non-small-cell lung cancer (EMERGING): a randomised study (Zhong et al, LBA48)

• What is the biological role of immune checkpoint inhibition in early stage NSCLC?
  • Neoadjuvant Nivolumab or Nivolumab plus Ipilimumab for resectable non-small cell lung cancer (Cascone et al, LBA49)

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

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
- Surgery (Non-PD)
- Erlotinib 150mg/d for 12 months
- GC q3w for 2 cycles

Primary endpoint
- ORR

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

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
LBA48. EMERGING-CTONG 1103: Erlotinib versus Gemcitabine plus Cisplatin as Neoadjuvant Treatment for Stage IIIA-N2 EGFR-mutation Positive Non-small-cell Lung Cancer: multicentre phase 2 randomized study

Primary Endpoint: ORR (ITT Population)

- ORR 54% vs 34%, p=0.092

Secondary Endpoint: Complete Resection and Lymph Node Downstage

- Operation rate 83.8% vs 68.6%
- R0 resection 73.0% vs 62.9%
- LN Down staging: 10.8 vs 2.9%

Secondary Endpoint: Pathological Complete Response (pCR) Rate

- No pathological CR was observed
  - MPR: 10.7% vs 0%

Secondary Endpoint: PFS (ITT population)

- mPFS: 21.5 VS 11.9 MONTHS (HR 0.42, p=0.003)
LBA48. EMERGING-CTONG 1103: Erlotinib versus Gemcitabine plus Cisplatin as Neoadjuvant Treatment for Stage IIIA-N2 EGFR-mutation Positive Non-small-cell Lung Cancer: multicentre phase 2 randomized study

Safety results consistent with prior studies
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.
LBA49. NEOSTAR: Neoadjuvant Nivolumab (N) or Nivolumab plus Ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC)

- N=36 patients
- 26 evaluable for efficacy analysis
- 5 patients out of 31 could not have surgery (16%)
LBA49. NEOSTAR: Neoadjuvant Nivolumab (N) or Nivolumab plus Ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC)

Study design, hypothesis and endpoints

Design and Statistical plan:
- Single center, open label, phase 2, multi-arm, randomized study
- Primary hypothesis: Induction N and/or NI will produce a MPR rate of at least 40%, which is greater than the MPR rate to induction platinum-based chemotherapy (as compared to historical controls, 15%). The trial has 90% power when the MPR rate is 40%.

Primary endpoint
MPR rate in patients treated with induction N and NI

Secondary endpoints
- Toxicity, peri-operative morbidity and mortality
- ORR, RFS, OS
- To correlate MPR and RECIST responses with RFS and OS
- Complete resection rate; pathologic complete response (pCR)
- CD8+ TILs in resected tumors; to correlate tissue, blood, and stool biomarkers with efficacy and toxicity

Exploratory endpoints
Blood, tissue and stool biomarkers and their modulation by treatment
LBA49. NEOSTAR: Neoadjuvant Nivolumab (N) or Nivolumab plus Ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC)

### Major pathologic response (≤10% viable tumor cells)

<table>
<thead>
<tr>
<th>Evaluable (Resected)</th>
<th>N (n=14)</th>
<th>NI (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPR + pCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0% viable tumor cells (pCR)</td>
<td>4 (28%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>1-10% viable tumor cells</td>
<td>2 (14%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Overall** Resected + unresectable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPR + pCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0% viable tumor cells (pCR)</td>
<td>2 (13%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>1-10% viable tumor cells</td>
<td>2 (13%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Path response pending</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

pCR is 16%

MPR is 10%
LBA49. NEOSTAR: Neoadjuvant Nivolumab (N) or Nivolumab plus Ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC)

Radiographic responses

<table>
<thead>
<tr>
<th>Evaluable*</th>
<th>N Arm (n=16)</th>
<th>NI Arm (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response (RECIST)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PR</td>
<td>6 (19)</td>
<td>5 (31)</td>
</tr>
<tr>
<td>SD</td>
<td>19 (59)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>PD</td>
<td>6 (19)</td>
<td>3 (19)</td>
</tr>
</tbody>
</table>

Not yet evaluable
| *1 pending, 1 on therapy; **2 on therapy

ORR (CR+PR): 22% (7/32)

ORR by Arm:
N: 31% (5/16)
NI: 12% (2/16)

*Considered SD in target lesion but overall PD due to new radiographic lesions
LBA49. NEOSTAR: Neoadjuvant Nivolumab (N) or Nivolumab plus Ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC)

Neo-adjuvant Chemo-immunotherapy

- Neoadjuvant treatment:
  - Nivolumab 360 mg + Paclitaxel 200mg/m² + Carboplatin AUC 6 IV, Q3W
  - 3 Cycles

- Surgery (in the 3rd or 4th week from day 21 of cycle 3 of neoadjuvant treatment)

- Adjuvant treatment:
  - Nivolumab 240mg Q2W for 4 months and Nivolumab 480 mg Q4W for 8 months
  - IV (1 year)

- Follow up

Abstract 8521
Provencia-Pulla et al. - 9/13 pts had pathologic complete response

Abstract 8532 Shu et al.
- 4 cycles carbo/ nab-pac & atezo – 7/14 (50%) pts had MPR
- 3/14 (21%) had pCR
PACIFIC: study design
Phase 3, randomised, double-blind, placebo-controlled, multicentre, international study

- Patients with stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks
- Archived tissue was collected

All-comers population

Durvalumab 10 mg/kg q2w for up to 12 months N=476
2:1 randomization, stratified by age, sex, and smoking history N=713

Placebo 10 mg/kg q2w for up to 12 months N=237

Co-primary endpoints
- PFS by BICR using RECIST v1.1*
- OS

Key secondary endpoints
- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs
13630. Exploratory analyses of overall survival in PACIFIC

**PACIFIC: PFS and OS in the ITT population**

**mPFS 16.8 vs 5.6 months**

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (95% CI) months</th>
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<tbody>
<tr>
<td>Durvalumab</td>
<td>16.8 (13.0–18.1)</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.6 (4.6–7.8)</td>
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**mOS NR vs 28.7 months**

<table>
<thead>
<tr>
<th></th>
<th>Median OS (95% CI) months</th>
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<tbody>
<tr>
<td>Durvalumab</td>
<td>NR (34.7–NR)</td>
</tr>
<tr>
<td>Placebo</td>
<td>28.7 (22.9–NR)</td>
</tr>
</tbody>
</table>

- PFS HR = 0.52
- 95% CI, 0.42–0.65
- P<0.001

- OS HR = 0.68
- 99.73% CI, 0.47–0.997
- P=0.0025

*Median duration of follow-up was 25.2 months (range 0.2–43.1); †adjusted for interim analysis*
Exploratory analyses of overall survival in PACIFIC

**Improvement in PFS by PD-L1 TC ≥1% and <1%**

- **mPFS ≥ 1%**: 17.8 vs 5.6 months
  - HR 0.46 (95% CI, 0.33-0.64)
- **mPFS < 1%**: 10.7 vs 5.6 months
  - HR 0.73 (95% CI, 0.48-1.11)
13630. Exploratory analyses of overall survival in PACIFIC

**OS by PD-L1 TC ≥1% and <1%**

- **mOS ≥ 1%**: NR vs 29.1 months
  - HR 0.53 (95% CI, 0.36-0.77)

- **mOS < 1%**: NR vs NR months
  - HR 1.36 (95% CI, 0.79-2.34)
13630. Exploratory analyses of overall survival in PACIFIC

**Improved outcomes irrespective of time from radiation**

<table>
<thead>
<tr>
<th>PFS (BICR)</th>
<th>OS</th>
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<tbody>
<tr>
<td>ITT (^2)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>Durvalumab</td>
</tr>
<tr>
<td></td>
<td>214/476 (46.0)</td>
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<tr>
<td></td>
<td>183/476 (38.4)</td>
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<table>
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<tr>
<th>Time from last radiotherapy to randomisation</th>
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<tbody>
<tr>
<td>&lt;14 days</td>
</tr>
<tr>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>ITT (^1)</td>
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<tr>
<td></td>
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<tr>
<td>Any-gra ade all-causality AEs, n (%)</td>
</tr>
<tr>
<td>Durvalumab (N=120)</td>
</tr>
<tr>
<td>Placebo (N=60)</td>
</tr>
<tr>
<td>Durvalumab (N=355)</td>
</tr>
<tr>
<td>Placebo (N=174)</td>
</tr>
<tr>
<td>Any-gra ade all-causality AEs, n (%)</td>
</tr>
<tr>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Outcome of death</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
</tr>
<tr>
<td>Serious AEs, n (%)</td>
</tr>
<tr>
<td>Any-gra ade pneumonitis/radiation pneumonitis, n (%)</td>
</tr>
<tr>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Outcome of death</td>
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</tbody>
</table>

**Similar toxicity profiles regardless of time from radiation**

Patients with multiple AEs are counted once at the maximum reported CTCAE grade.
Conclusions

- PACIFIC study was designed to evaluate the benefit of durvalumab in an all-comers population.
- Post-hoc exploratory subgroup analyses have shown:
  - For PD-L1 by TC 1% subgroups:
    - ≥1% subgroup – PFS and OS improvement
    - <1% subgroup – PFS benefit, OS confounded by performance of placebo arm
  - Similar safety across all PD-L1 subgroups:
  - Improved PFS and OS with durvalumab regardless of type of chemotherapy, radiation dose used or time from radiation to randomisation
  - These analyses have known limitations that preclude definitive conclusions
- These data support the PACIFIC regimen of durvalumab following CRT as the new standard of care in the treatment of patients with unresectable, Stage III NSCLC.

- PACIFIC was designed to evaluate Durvalumab in the ITT (all-comers)
- PD-L1 testing was not mandatory and status was unknown for 37% of patients