PRACTICE CHANGING STUDIES IN THORACIC MALIGNANCIES IN 2019

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Switzerland
Disclosure information – Solange Peters

I have received education grants, provided consultation, attended advisory boards and/or provided lectures for the following organizations, from whom I have received honoraria (all fees to institution):

- **Consultation / Advisory role:** Abbvie, Amgen, AstraZeneca, Bayer, Biocartis, Bioinvent, Blueprint Medicines, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, Eli Lilly, F. Hoffmann-La Roche, Foundation Medicine, Illumina, Janssen, Merck Sharp and Dohme, Merck Serono, Merrimack, Novartis, Pharma Mar, Pfizer, Regeneron, Sanofi, Seattle Genetics and Takeda

- **Talk in a company’s organized public event:** AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, F. Hoffmann-La Roche, Illumina, Merck Sharp and Dohme, Novartis, Pfizer, Sanofi, Takeda

- **Receipt of grants/research supports:** (Sub)investigator in trials (institutional financial support for clinical trials) sponsored by Amgen, AstraZeneca, Biodesix, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, F. Hoffmann-La Roche, Illumina, Merck Sharp and Dohme, Merck Serono, Novartis, and Pfizer
Cancer incidence rates increase with increasing levels of socioeconomic development, not mortality.

Age-standardized (world population) incidence and mortality rates of all cancer types, by average level of socioeconomic development in 2012. Socioeconomic development is measured by the education and income index (EDI), which is similar to the Human Development Index (HDI) but excludes life expectancy.
Lung cancer continues to be the leading cause of cancer death worldwide (18% of deaths)

- Incidence rates in men have declined during the past 4 decades in most countries, whereas incidence rates in women continue to rise, with a few exceptions
African lung cancer incidence is lower than the worldwide picture
Practice changing chapters in 2019

- **SCLC-ED**
  - Chemotherapy +/- Atezolizumab or Durvalumab?

- **NSCLC stage I-II**
  - Surgery -> Chemotherapy
  - Vs Neoadjuvant Chemo+IO?

- **NSCLC stage III**
  - Radiochemotherapy -> Durvalumab
  - Vs Neoadjuvant Chemo+IO?

- **NSCLC stage IV**
  - Actionable mutation: Targeted therapy
    - Osimertinib
    - AMG510
  - PDL1 ≥ 50%: Pembrolizumab or Atezolizumab?
  - Others: Chemotherapy + Pembrolizumab or Nivo+Ipi?
Small Cell Lung Cancer

The role of immunotherapy in extensive disease
ES SCLC: Where we are

Platinum-etoposide: #4-6

±PCI / ±CHEST-RT

On PD:
Chemo
Re-challenge, CAV, topo
FDA: Nivolumab ad Pembrolizumab post 2 lines

CheckMate 032 >2lines

KN158-G / KNo28-C1 >2lines

Hellmann et al. ASCO (2017); Ott et al. JCO (2017)
2\textsuperscript{nd} line randomized data CM 331

Reck et al. ESMO IO (2018)
Maintenance IO randomized data CM 451

Owonikoko et al. ELCC (2019)
First-line chemo-IO
IMP133 and CASPIAN, the second wave

**IMP133**

**CASPIAN**
OS and PFS: IMP133 & CASPIAN

Liu al. WCLC (2018); Paz-Ares ESMO (2019)
Immunotherapy for SCLC-ED

- Two positive phase III trials frontline with chemotherapy
- Patient selection unclear - no biomarker defined
- Moderate but significant OS benefit
- No evidences available in later line – despite signal of activity
- Cost-efficacy to be demonstrated
Non Small Cell Lung Cancer

Without identified actionnable driver
NSCLC Outcome: 8th TNM as a basis

<table>
<thead>
<tr>
<th>Proposed</th>
<th>Events / N</th>
<th>MST</th>
<th>24 Month</th>
<th>60 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1</td>
<td>68 / 781</td>
<td>NR</td>
<td>97%</td>
<td>92%</td>
</tr>
<tr>
<td>IA2</td>
<td>505 / 3105</td>
<td>NR</td>
<td>94%</td>
<td>83%</td>
</tr>
<tr>
<td>IA3</td>
<td>546 / 2417</td>
<td>NR</td>
<td>90%</td>
<td>77%</td>
</tr>
<tr>
<td>IB</td>
<td>560 / 1928</td>
<td>NR</td>
<td>87%</td>
<td>68%</td>
</tr>
<tr>
<td>IIA</td>
<td>215 / 585</td>
<td>NR</td>
<td>79%</td>
<td>60%</td>
</tr>
<tr>
<td>IIB</td>
<td>605 / 1453</td>
<td>66.0</td>
<td>72%</td>
<td>53%</td>
</tr>
<tr>
<td>IIIA</td>
<td>2052 / 3200</td>
<td>29.3</td>
<td>55%</td>
<td>36%</td>
</tr>
<tr>
<td>IIIB</td>
<td>1551 / 2140</td>
<td>19.0</td>
<td>44%</td>
<td>26%</td>
</tr>
<tr>
<td>IIIC</td>
<td>831 / 986</td>
<td>12.6</td>
<td>24%</td>
<td>13%</td>
</tr>
<tr>
<td>IVA</td>
<td>336 / 484</td>
<td>11.5</td>
<td>23%</td>
<td>10%</td>
</tr>
<tr>
<td>IVB</td>
<td>328 / 398</td>
<td>6.0</td>
<td>10%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Non Small Cell Lung Cancer

Without identified actionnable driver

*Surgical stages I-III*
Adujvant vs neoadjuvant systemic therapy? The concern is micro-metastatic disease
Many ongoing adjuvant trials

**Primary endpoints**
- DFS
- DFS in PDL1+
- DFS overall
- DFS & OS
- DFS in II-IIIA
- DFS in PDL1+ in II-IIIA
- DFS in ITT

**PEARLS**
- NCT02504372
  - N=1080
  - Pembrolizumab: 200 mg Q3W 1 y.
  - Placebo
- BR31
  - NCT02273375
  - N=1360
  - Durvalumab: 10 mg/Kg Q2W 1 y.
  - Placebo
- ANVIL
  - NCT02595944
  - N=903
  - Nivolumab: 240 mg Q2W 1 y.
  - Observation
- IMpower 010
  - NCT02486718
  - N=1280
  - Atezolizumab 1200 mg Q3W 1 y.
  - Observation

Post Surgery R0 IB (≥ 4 cm)-IIIA (7th classification) ACT as indicated PS 0-1
Neoadjuvant Immunotherapy and proof of concept
Influx of CD8+ T-cells after 2 doses of nivolumab

Few intratumoral macrophages are seen expressing PD-L1
CD8+ and PD-1+ immune cells
Why do we use MPR in all new neo-adjuvant trials?

The association between <10% residual tumor tissue and survival is strong.

Hellmann M et al. Lancet Oncol 2014
Modified from Diehn, ASCO 2019

## Neoadjuvant IO: what we know today

<table>
<thead>
<tr>
<th>Study (phase)</th>
<th>No patients</th>
<th>IO agents</th>
<th>No cycles</th>
<th>MPR rate</th>
<th>MPR correlated with RECIST</th>
<th>MPR associated with PD-L1</th>
<th>MPR correlation with TMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSKCC/JHH (Ib/II)</td>
<td>22</td>
<td>Nivolumab</td>
<td>2</td>
<td>45%</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>NEOSTAR (II)</td>
<td>44</td>
<td>Nivo &amp; Nivo/Ipi</td>
<td>3</td>
<td>19%</td>
<td>YES</td>
<td>YES</td>
<td>?</td>
</tr>
<tr>
<td>LCMC3 (II)</td>
<td>101</td>
<td>Atezolizumab</td>
<td>2</td>
<td>19%</td>
<td>YES</td>
<td>?</td>
<td>NO</td>
</tr>
<tr>
<td>Sintilimab Ib/II</td>
<td>40</td>
<td>Sintilimab</td>
<td>2</td>
<td>40%</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
NADIM: neoadjuvant chemotherapy and IO in stage III

<table>
<thead>
<tr>
<th>Response</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>2</td>
<td>4.3</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>32</td>
<td>69.6</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>12</td>
<td>26.1</td>
</tr>
</tbody>
</table>

NSCLC IIIA resectable patients.

Provenciano, ASCO and WCLC 2019
Lee, ASCO 2019
Surgery

<table>
<thead>
<tr>
<th>Procedure</th>
<th>N=41 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobectomy</td>
<td>38 (92.7)</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>3 (7.3)</td>
</tr>
<tr>
<td>Ro Resection</td>
<td>41 (100)</td>
</tr>
</tbody>
</table>

No intraoperative complications were documented

Pathologic response

<table>
<thead>
<tr>
<th>Pathologic Response (MPR)</th>
<th>N=41</th>
<th>% (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Pathological Response (MPR)</td>
<td>34/41</td>
<td>83 (68-93)</td>
</tr>
<tr>
<td>Complete Response (CR)</td>
<td>24/41</td>
<td>59 (42-74)</td>
</tr>
<tr>
<td>&gt; 10% residual viable tumor</td>
<td>7/41</td>
<td>17 (7-32)</td>
</tr>
</tbody>
</table>

Overall Survival at 12 months: 98% (95% CI: 85; 100)
Overall Survival at 18 months: 91% (95% CI: 73; 97)
Neo-adjuvant immuno(chemo)therapy studies

KEYNOTE 617
NCT03425643
N=786
IB -IIIA
PS 0-1
CT + Pembro.: 200 mg
CT + Placebo Q3W x 4
Pembro 1y.
Placebo 1y.
EFS/OS

CHECKMATE 816
NCT02998528
N=350
IB -IIIA
PS 0-1
CT + Nivo.: 360 mg
CT Q3W x 3
EFS/pCR

IMPOWER 030
NCT03456063
N=374
II–IIIB
(T3N2)
PS 0-1
CT + Atezo.: 1200 mg
CT + Placebo Q3W x 4
Atezo 1y.
Placebo 1y.
EFS/MPR

AEGEAN
NCT03800134
N=300
IIA -IIIB
PS 0-1
CT + Durva.: 1500 mg
CT + Placebo Q3W x 4
Durva 1y.
Placebo 1y.
MPR

Primary Endpoints
Adapted from J. Remon
Defining the role of IO for early NSCLC

• Surgery for locally advanced disease has regained interest thanks to neo-adjuvant immunotherapy
• The strategy might impose amazingly demanding pathological assessments
• MPR rates of single agent IO alone are consistent with chemotherapy alone, combinations are very promising
• MPR is not a valid surrogate endpoint for OS yet
• Randomized trials are needed and results are strongly awaited
Non Small Cell Lung Cancer

Without identified actionable driver

*Stage IV*
A low bar: platinum-based chemotherapy

- Efficacy of platinum-based CT
- Same Efficacy across different schedules
- No selection factor
- Limitation by toxicity

1 year OS: 33%

Med OS: 7.9 months
PD-L1 expression on tumor cells & predictive ability

- Virtually every PD(L)-1 inhibitors-based NSCLC trial has shown a positive relationship between clinical benefit and PD-L1 expression
- IHC systematic assessment, price, and quality are limitations in many countries
- PD-L1 expression is a biological continuum
- FNA, biopsy, large block can be used
- Heterogeneity is the background
## PD-L1 expression is differently measured across cancers

<table>
<thead>
<tr>
<th>Disease type</th>
<th>PD-L1 assessment</th>
<th>Threshold used</th>
<th>Clinical context</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSCLC</strong></td>
<td>TC</td>
<td>≥50% ≥1%</td>
<td>Stage IV frontline mono</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stage III consolidation/ IV late lines mono</td>
</tr>
<tr>
<td><strong>SCLC</strong></td>
<td>CPS</td>
<td>≥1%</td>
<td>Stage IV pretreated mono</td>
</tr>
<tr>
<td><strong>Breast Cancer (Triple Negative)</strong></td>
<td>IC</td>
<td>≥1%</td>
<td>Frontline neoadjuvant, stage IV</td>
</tr>
<tr>
<td><strong>Cervical Cancer</strong></td>
<td>CPS</td>
<td>≥1%</td>
<td>Stage IV pretreated mono</td>
</tr>
<tr>
<td><strong>Gastric Cancer</strong></td>
<td>CPS</td>
<td>≥1% ≥10%</td>
<td>Stage IV frontline with chemo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IV frontline mono</td>
</tr>
<tr>
<td><strong>Oesophageal Cancer</strong></td>
<td>CPS</td>
<td>≥10%</td>
<td>Stage IV pretreated mono</td>
</tr>
<tr>
<td><strong>HNSCC carcinoma</strong></td>
<td>TC, CPS</td>
<td>≥50% ≥1%</td>
<td>Stage IV pretreated mono</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IV frontline mono or with chemo</td>
</tr>
<tr>
<td><strong>UC</strong></td>
<td>IC</td>
<td>≥5%</td>
<td>Stage IV frontline mono (?)</td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
<td>TC</td>
<td>≥1%</td>
<td>Stage IV ipi/nivo frontline</td>
</tr>
</tbody>
</table>
Chemotherapy-free expectations:
Pembrolizumab is better than chemo in PD-L1 ≥50%

- Primary endpoint PFS
- OS & RR improved

PD-L1 ≥50%
EGFR/ALK WT
Thresholds < 50% do not favor anti-PD(L)-1 above chemo

CheckMate 026: 5% PD-L1

MYSTIC: 25% PD-L1

KEYNOTE-042: PD-L1 1-49%
**IMpower110 study design: hierarchy defining threshold**

Chemotherapy-naive, PD-L1-selected (≥ 1% TC or IC; SP142) patients with stage IV nsq or sq NSCLC

Stratification factors
- Sex
- ECOG PS
- PD-L1 IHC expression\(^a\)
- Histology

\[ \text{N} = 572\] \(^b\)

### Arm A
Atezolizumab 1200 mg q3w

### Arm B
- nsq: cisplatin/carboplatin + pemetrexed\(^c\)
- sq: cisplatin/carboplatin + gemcitabine\(^d\)

4 or 6 cycles

Maintenance therapy (no crossover permitted)

- PD or loss of clinical benefit
- PD

**Survival follow-up**

**Chemotherapy-naive, PD-L1-selected (≥ 1% TC or IC; SP142) patients with stage IV nsq or sq NSCLC**

**Stratification factors**
- Sex
- ECOG PS
- PD-L1 IHC expression\(^a\)
- Histology

\[ \text{N} = 572\] \(^b\)

- Primary endpoint: OS in WT population\(^e\): hierarchy
- Key secondary endpoints: investigator-assessed PFS, ORR and DOR (per RECIST version 1.1)

---

\(^a\) TC1/2/3 and any IC vs TC0 and IC1/2/3. \(^b\) 554 patients in the WT population. \(^c\) Cisplatin 75 mg/m\(^2\) or carboplatin area under the curve (AUC) 6 + pemetrexed 500 mg/m\(^2\) IV q3w. \(^d\) Cisplatin 75 mg/m\(^2\) + gemcitabine 1250 mg/m\(^2\) or carboplatin AUC 5 + gemcitabine 1000 mg/m\(^2\) IV q3w. \(^e\) WT population excludes patients with EGFR+ and/or ALK+ NSCLC.
SP142 (TC3 or IC3-WT)\textsuperscript{a}  

![Graph showing OS for SP142 (TC3 or IC3-WT)]

<table>
<thead>
<tr>
<th></th>
<th>Atezo (n = 107)</th>
<th>Chemo (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, mo</td>
<td>20.2</td>
<td>13.1</td>
</tr>
<tr>
<td>HR\textsuperscript{b} (95% CI)</td>
<td>0.59</td>
<td>(0.40, 0.89)</td>
</tr>
</tbody>
</table>

22C3 BEP-WT (TPS ≥ 50%)\textsuperscript{a}  

![Graph showing OS for 22C3 BEP-WT (TPS ≥ 50%)]

<table>
<thead>
<tr>
<th></th>
<th>Atezo (n = 134)</th>
<th>Chemo (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, mo</td>
<td>20.2</td>
<td>11.0</td>
</tr>
<tr>
<td>HR\textsuperscript{b} (95% CI)</td>
<td>0.60</td>
<td>(0.41, 0.86)</td>
</tr>
</tbody>
</table>

SP263 BEP-WT (TC ≥ 50%)\textsuperscript{a}  

![Graph showing OS for SP263 BEP-WT (TC ≥ 50%)]

<table>
<thead>
<tr>
<th></th>
<th>Atezo (n = 150)</th>
<th>Chemo (n = 143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, mo</td>
<td>19.5</td>
<td>16.1</td>
</tr>
<tr>
<td>HR\textsuperscript{c} (95% CI)</td>
<td>0.71</td>
<td>(0.50, 1.00)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} SP142 TC1/2/3 or IC1/2/3-WT (n = 554); 22C3 BEP-WT (n = 534); SP263 BEP-WT (n = 546). \textsuperscript{b} Stratified. \textsuperscript{c} Unstratified.
OS in PD-L1–Positive Subgroups in IMpower110

SP142 (TC1/2/3 or IC1/2/3-WT)$^a$

<table>
<thead>
<tr>
<th></th>
<th>Atezo (n = 277)</th>
<th>Chemo (n = 277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, mo</td>
<td>17.5</td>
<td>14.1</td>
</tr>
<tr>
<td>HR$^b$</td>
<td>0.83</td>
<td>(95% CI)</td>
</tr>
<tr>
<td></td>
<td>(0.65, 1.07)</td>
<td></td>
</tr>
</tbody>
</table>

22C3 BEP-WT (TPS ≥ 1%)$^a$

<table>
<thead>
<tr>
<th></th>
<th>Atezo (n = 213)</th>
<th>Chemo (n = 201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, mo</td>
<td>17.8</td>
<td>14.0</td>
</tr>
<tr>
<td>HR$^c$</td>
<td></td>
<td>(95% CI)</td>
</tr>
<tr>
<td></td>
<td>0.73</td>
<td>(0.55, 0.97)</td>
</tr>
</tbody>
</table>

SP263 BEP-WT (TC ≥ 1%)$^a$

<table>
<thead>
<tr>
<th></th>
<th>Atezo (n = 212)</th>
<th>Chemo (n = 210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, mo</td>
<td>17.8</td>
<td>14.0</td>
</tr>
<tr>
<td>HR$^c$</td>
<td></td>
<td>(95% CI)</td>
</tr>
<tr>
<td></td>
<td>0.77</td>
<td>(0.58, 1.02)</td>
</tr>
</tbody>
</table>

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$^a$ SP142 TC1/2/3 or IC1/2/3-WT (n = 554); 22C3 BEP-WT (n = 534); SP263 BEP-WT (n = 546). $^b$ Stratified. $^c$ Unstratified.
A cut-off of 50% can be used

<table>
<thead>
<tr>
<th>Exp Arm Numbers</th>
<th>KN-024 Pembro vs CT (N = 305, PD-L1 TC ≥50%, 1:1)</th>
<th>KN-042 Pembro vs CT (N = 1274, PD-L1 TC ≥1%, 1:1)</th>
<th>MYSTIC Durva vs CT (N = 568, PD-L1 TC ≥1%, 1:1)</th>
<th>IMpower 110 Atezo vs CT (N = 568, PD-L1 TC ≥1%, 1:1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC ≥50%</td>
<td>TC ≥50%</td>
<td>TC ≥50%</td>
<td>TC ≥50%*</td>
<td>TC3 or IC3</td>
</tr>
<tr>
<td>n = 305</td>
<td>n = 299</td>
<td>n = 118</td>
<td></td>
<td>N = 206</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>30 vs 14.2</td>
<td>20.0 vs 12.2</td>
<td>18.3 vs 12.7</td>
<td>20.2 vs 13.1</td>
</tr>
<tr>
<td>HR</td>
<td><strong>0.63</strong></td>
<td><strong>0.69</strong></td>
<td><strong>0.76</strong></td>
<td><strong>0.59</strong></td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>10.3 vs 6.0</td>
<td>7.1 vs 6.4</td>
<td>-</td>
<td>8.1 vs 5.0</td>
</tr>
<tr>
<td>HR</td>
<td><strong>0.50</strong></td>
<td><strong>0.81</strong></td>
<td>-</td>
<td><strong>0.63</strong></td>
</tr>
<tr>
<td>12-mo PFS, %</td>
<td>-</td>
<td>37.4 vs 27.3</td>
<td>-</td>
<td>36.9 vs 21.6</td>
</tr>
<tr>
<td>ORR, %</td>
<td>45.5 vs 29.8</td>
<td>39.5 vs 32.0</td>
<td>-</td>
<td>38.3 vs 28.6</td>
</tr>
</tbody>
</table>

Combining IO and chemotherapy: a progress for all?

**Immunotherapy can sensitize to chemotherapy**
- Reduce support to cancer cells (effect on MDSC / macrophages)
- Reprogram tumor vessels

**Chemotherapy can boost the immune response**
- Immunogenic cell death
- Deplete myeloid cells & Tregs
- Influx of TILs, inflammation

---

KEYNOTE-189 ad CheckMate 227
## Phase 3 randomized triplet platinum-based/PD-(L)1 trials
### Non-squamous NSCLC

<table>
<thead>
<tr>
<th>Trials incl. non-squamous NSCLC</th>
<th>Patients</th>
<th>PFS</th>
<th>OS</th>
<th>1yr OS IO</th>
</tr>
</thead>
</table>
| KN 189  
(Pembro/Cis or Carb/Pem vs Cis or Carb/Pem) | 616      | 5.6 vs 4.9 m  
HR 0.52  
p<0.00001 | Nr vs 11.3 m  
HR 0.49  
p<0.00001 | 69%       |
| Impower 150  
(Atezo/Bev/Carb/Pac vs Bev/Carb/Pac) | 800      | 8.3 vs 6.8 m  
HR 0.59  
p<0.00001 | 19.2 vs 14.7 m  
HR 0.78  
p=0.016  | 67%       |
| Impower 130  
(Atezo/Carbo/Nab-Pac vs Carbo/Nab-Pac) | 679      | 7.0 vs 5.5 m  
HR 0.64  
p<0.0001 | 18.6 vs 13.9 m  
HR 0.79  
P= 0.033 | 63%       |
| Impower 132  
(Atezo/Plat/Pem vs Plat/Pem) | 578      | 7.6 vs 5.2 m  
HR 0.6  
p<0.0001 | 18.1 vs 13.6 m  
HR 0.81  
P= 0.797 | 60%       |
| CheckMate 227 part 2  
(Nivo/Plat/Pem vs Plat/Pem) | 543      | 8.7 vs 5.8 m  
HR 0.67  
- | 18.8 vs 15.6 m  
HR 0.86  
P = 0.1859 | 67%       |
# Phase 3 randomized triplet platinum-based/PD-(L)1 trials

## Squamous NSCLC

<table>
<thead>
<tr>
<th>Trials incl. squamous NSCLC</th>
<th>Patients</th>
<th>PFS</th>
<th>OS</th>
<th>1yr OS IO</th>
</tr>
</thead>
<tbody>
<tr>
<td>KN 407</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Pembro/Carb/Pac or nab-Pac vs Carb/Pac or nab-Pac)</td>
<td>559</td>
<td>6.4 vs 4.8 m</td>
<td>15.9 vs 11.3</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR 0.56</td>
<td>HR 0.64</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P&lt;0.001</td>
<td>p=0.0008</td>
<td></td>
</tr>
<tr>
<td>Impower 131</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Atezo/Carb/nab-Pac vs Carb/nab-Pac)</td>
<td>684</td>
<td>6.3 vs 5.6 m</td>
<td>14.0 vs 13.9</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR 0.71</td>
<td>HR 0.96</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>p=0.001</td>
<td>p=0.69</td>
<td></td>
</tr>
<tr>
<td>CheckMate 227 part 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Nivo/carbo/Pacl vs Carbo/Pacl)</td>
<td></td>
<td>7.1 vs 4.4 m</td>
<td>18.3 vs 12</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR 0.51</td>
<td>HR 0.69</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Jotte RM, ASCO 2018; Paz-Ares LG, ASCO 2018; Brahmer WCLC 2017; Ghandi L et al, NEJM 2018; Socinski MA et al. NEJM 2018; Cappuzzo ESMO 2018, Barlesi, ESMO 2018; Paz Ares, ESMO IO 2019
Other chemotherapy-free opportunities in frontline? CheckMate 227

Key Eligibility Criteria
- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing EGFR mutations or known ALK alterations
- No untreated CNS metastases
- ECOG PS 0–1

Stratified by SQ vs NSQ

Independent co-primary endpoints: NIVO + IPI vs chemo
- PFS in high TMB (≥10 mut/Mb) population
- OS in PD-L1 ≥ 1% population

Secondary endpoints (PD-L1 hierarchy):
- PFS: NIVO + chemo vs chemo in PD-L1 < 1%
- OS: NIVO + chemo vs chemo in PD-L1 < 1%
- OS: NIVO vs chemo in PD-L1 ≥ 50%

Database lock: July 2, 2019; minimum follow-up for primary endpoint: 29.3 months
CheckMate 227
OS With NIVO + IPI vs Chemo PD-L1 ≥ 1%

Minimum follow-up for primary endpoint: 29.3 months.
NIVO + IPI dosage was NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W). Subsequent systemic therapy was received by 35% of patients in the NIVO + IPI arm and 54% of patients in the chemo arm; subsequent immunotherapy was received by 6% and 43%, respectively.

a95% CI, 0.67–0.94.
OS With NIVO + IPI vs Nivo vs Chemo PD-L1 ≥ 1%
Looking at chemo-free opportunities

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (n = 396)</th>
<th>NIVO (n = 396)</th>
<th>Chemo (n = 397)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo</td>
<td>17.1</td>
<td>15.7</td>
<td>14.9</td>
</tr>
<tr>
<td>HR (vs chemo)a</td>
<td>0.79</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>CI</td>
<td>0.65–0.96b</td>
<td>0.75–1.04c</td>
<td></td>
</tr>
</tbody>
</table>

No. at risk
- NIVO + IPI: 396, 341, 295, 264, 244, 212, 190, 165, 153, 145, 129, 91, 41, 9, 1, 0
- NIVO: 396, 330, 299, 265, 220, 201, 176, 153, 139, 129, 115, 70, 36, 10, 2, 0
- Chemo: 397, 358, 306, 250, 218, 190, 166, 141, 126, 112, 93, 57, 22, 6, 1, 0
OS With NIVO + IPI and NIVO + Chemo vs Chemo in Patients With Tumor PD-L1 Expression < 1%
Chemotherapy (only) has still a role in palliation
Importance of being exposed to IO -> 15% long term survival?
Immunotherapy in 1L metastatic NSCLC

• Increasing evidence for different drugs, alone or with chemotherapy, even in tumors with low/no PD-L1 expression
• Currently, pembrolizumab is the only drug approved in first line in PD-L1 $\geq$50%
• Monotherapy is preferred for tumors with high PD-L1 and NO druggable driver mutations
Non Small Cell Lung Cancer

With identified actionnable driver

Stage IV
Precision oncology and targeted therapies for selected patients

**ALK (7%)**
- Crizotinib; Alectinib; Ceritinib; Lorlatinib; Brigatinib; Ensartinib

**EGFR other (4%)**

**MET (3%)**

**>1 mutation (3%)**

**HER2 (2%)**

**ROS1 (2%)**
- Crizotinib; Cabozantinib; Centinib; Lorlatinib; Entrectinib

**BRAF (2%)**
- Vemurafenib; Dabrafenib/Trametinib

**RET (2%)**

**NTRK1 (1%)**

**PIK3CA (1%)**

**MEK1 (<1%)**

**Unknown oncogenic driver detected (31%)**

**KRAS (25%)**

**EGFR sensitizing (17%)**
- Gefitinib; Erlotinib; Afatinib; Osimertinib; JNJ-372; U3-1402

**EGFR sensitizing**

**ALK**

**ROS1**

**BRAF**

**MET**

**HER2**

**RET**

**NTRK1**

**PIK3CA**

**MEK1**

Osimertinib frontline versus 1st generation EGFR TKI (gefitinib or erlotinib): FLAURA OS

Ramalingam, NEJM 2019
Targeting the «impossible» but frequent KRAS

- Novel small molecule that specifically and irreversibly inhibits KRAS\textsuperscript{G12C} by permanently locking it in an inactive GDP-bound state

Shokat, Nature 2013; Blackhall BJC 2019
• There were no dose-limiting toxicities in the 34 patients with NSCLC enrolled
• Twenty-seven of these patients remain on treatment
• 85% more than 2 previous lines
MRTX849 for tumors with G12C

All Evaluable Patients: Best Tumor Response* (N = 12)

- CRC: 5% SD, 1% SD
- App: 0% SD
- NSCLC: -1% SD
- NSCLC: -2% SD
- NSCLC: -7% SD
- NSCLC: -14% SD
- NSCLC: -21% SD
- NSCLC: PR†
- NSCLC: PR§
- NSCLC: PR†
- NSCLC: PR†

Maximum % Change from Baseline

<table>
<thead>
<tr>
<th>Dose</th>
<th>150 mg (QD)</th>
<th>300 mg (QD)</th>
<th>600 mg (QD)</th>
<th>600 mg (BID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Based on local radiographic scans every 6 weeks using RECIST 1.1 criteria
† Confirmed response (1st scan: -37%, 2nd scan: -47%); † Response yet to be confirmed (on study but only 1 scan)
§ Patient had confirmed PR post data cut-off (1st scan: -33%, 2nd scan: -43%)
○ Patient on study (off study patients: 1 progressive disease, 1 global deterioration of health, 1 patient withdrawal of consent)

Data cut-off date: 11-Oct-2019
Targeted therapy

- Use best treatment first
  - We still need randomized trials for sequencing
  - Brain metastases remain an issue
  - PROs are amazingly important
- We can treat some of the resistant tumors
  - Rebiopsy at progression is systematically relevant
- Development is fast
  - Approval and reimbursements are lagging behind
  - Better drugs and new targets will come
Thanks for your kind attention