Immune checkpoint inhibitors in NSCLC

Rolf Stahel
University Hospital of Zürich

Zürich, November 3, 2017
What can we learn from the clinical experience of second line immunotherapy of advanced NSCLC?

• The observation of durable remissions in patients with metastatic NSCLC progressing after chemotherapy suggests a small proportion of patients might be cured by single agent immune checkpoint inhibition.

• Second line therapy with single agent immune checkpoint inhibitors (nivolumab, pembrolizumab or atezolizumab):
  • Provides a survival advantage over chemotherapy
  • Is associated with fewer side effects and better quality of life

• The optimal duration of treatment in patients responding to immune checkpoint inhibitors remains to be determined.

• There is potential in the combination with with radiotherapy.

• Immune checkpoint inhibitors have activity against CNS metastases.
Five-year follow-up from the CA209-003 study of nivolumab in previously treated advanced NSCLC: Overall survival

54% pretreated with 3-5 therapies, 17% confirmed responses
Of the 16 pts surviving 5 years, 12 had a PR, 3 SD and 1 PD as best response

Brahmer, AACR 2017
Five-year follow-up from the CA209-003 study of nivolumab in previously treated advanced NSCLC: Outcome and subsequent treatment of the 16 long term survivors

- 12/16 patients remain without evidence disease progression
- 4 patients had subsequent therapy
  - 1 had surgical resection alone (and remains with no evidence of disease)
  - 1 had surgery followed by systemic therapies
  - 2 had systemic therapies

Brahmer, AACR 2017
Checkmate 017 and 057: 2-years update of OAS (no biomarker selection)
Checkmate 017 and 057: 2-years update of PFS

Horn, JCO 2017
KEYNOTE 10: Pembrolizumab versus doxetaxel in 2nd line NSCLC (≥1% of tumor cells PD-L1 positive)

Herbst, ESMO Asia 2015, Lancet 2016
OAK: A randomized phase III study comparing atezolizumab with docetaxel in advanced NSCLC

PHASE III OAK STUDY DESIGN

Primary Endpoints (first 850 enrolled patients):
- OS in the ITT population
- OS in patients with PD-L1 expression on ≥1% TC or IC

Secondary Endpoints: ORR, PFS, DoR, Safety

OVERALL SURVIVAL, ITT (N = 850)

OS BY PD-L1 EXPRESSION

Barlesi, ESMO 2016
Less toxicity with immune checkpoint inhibitors in second line comparative studies

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Check-mate 17</td>
</tr>
<tr>
<td>N</td>
<td>59</td>
</tr>
<tr>
<td>Doc</td>
<td>87</td>
</tr>
<tr>
<td>All</td>
<td>63</td>
</tr>
<tr>
<td>3-5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
EQ-5D utility index: Mean scores over time while on treatment

Higher scores indicate better health status.

Only time points that had PRO data available for ≥5 patients in either treatment arm are plotted on the graph.

Reck, ECCO-ESMO 2015
Association between immune-related side effects and better outcome?

- June 2015: Pleomorphic carcinoma RUL, with nodal and bone metastases
- July-August 2015: Chemotherapy
- September 2015: Progressive disease, palliative RUL resection

09/2015  11/2015  03/2017

RT, followed by 2 cycles of nivolumab, stopped because of pneumonitis
Safety of retreatment with immune checkpoint inhibitors after treatment related toxicity?

38 patients receiving renewed treatment after interruption because of immune related adverse event:

<table>
<thead>
<tr>
<th>Pts who had the toxicity below as the culprit irAE</th>
<th>Rate of irAE occurrence (same/new irAE) after retreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>33% (2/6)</td>
</tr>
<tr>
<td>Rash</td>
<td>40% (2/5)</td>
</tr>
<tr>
<td>Colitis</td>
<td>57% (4/7)</td>
</tr>
<tr>
<td>Arthralgia/Myalgia</td>
<td>80% (4/5)</td>
</tr>
</tbody>
</table>

- 2 treatment-related deaths due to pneumonitis and colitis
- 8% (3/38) objective responses
CheckMate 153: Randomized results of continuous vs 1-Year fixed-duration nivolumab in patients with advanced NSCLC
CheckMate 153: Randomized results of continuous vs 1-Year fixed-duration nivolumab in patients with advanced NSCLC

PFS from randomization

OS from randomization

<table>
<thead>
<tr>
<th>Median, months (95% CI)</th>
<th>PFS rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous tx</td>
<td>NR (NR)</td>
</tr>
<tr>
<td>1-year tx</td>
<td>10.3 (6.4, 15.2)</td>
</tr>
</tbody>
</table>

HR: 0.42 (95% CI: 0.25, 0.71)

<table>
<thead>
<tr>
<th>Median, months (95% CI)</th>
<th>OS rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous tx</td>
<td>NR (NR)</td>
</tr>
<tr>
<td>1-year tx</td>
<td>23.2 (23.2, NA)</td>
</tr>
</tbody>
</table>

HR: 0.63 (95% CI: 0.33, 1.20)

Spigel, ESMO 2017
CheckMate 153: Randomized results of continuous vs 1-Year fixed-duration nivolumab in patients with advanced NSCLC

PFS from randomization

<table>
<thead>
<tr>
<th>CR/PR</th>
<th>Median, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous tx</td>
<td>NR (NR)</td>
</tr>
<tr>
<td>1-year tx&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.6 (4.8, NA)</td>
</tr>
</tbody>
</table>

HR: **0.45** (95% CI: 0.24, 0.85)

<table>
<thead>
<tr>
<th>SD</th>
<th>Median, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous tx</td>
<td>NR (5.6, NA)</td>
</tr>
<tr>
<td>1-year tx&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9.6 (4.5, 12.6)</td>
</tr>
</tbody>
</table>

HR: **0.44** (95% CI: 0.17, 1.09)

Spigel, ESMO 2017
Previous radiotherapy and the clinical activity of pembrolizumab in the treatment of NSCLC: A secondary analysis of the KEYNOTE-001 phase 1 trial

![Graphs showing progression-free survival and overall survival with and without radiotherapy](image-url)
Pembrolizumab for patients with melanoma or NSCLC and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial

Goldberg, Lancet Oncol 2016
Intracranial response to nivolumab in NSCLC patients with untreated or progressing CNS metastases

- 5 patients: 1 CR 1 PR to nivolumab alone
What can we learn from the biomarker experience of immunotherapy of advanced NSCLC?

- PD-L1 expression is an – albeit imperfect - biomarker with predictive value in advanced NSCLC
- There is a relationship between the neo-antigen load and the likelihood of response to immune checkpoint inhibition
- Clonal neo-antigens, but not subclonal neo-antigens, are associated with durable clinical benefit
- Tumor mutation load is likely to be come next biomarker introduced in clinical practice
- EGFR muted and ALK rearranged NSCLC have a low mutation burden and are not good candidates for immunotherapy
A prospective, multi-institutional, pathologist-based assessment of 4 immunohistochemistry assays for PD-L1 expression in NSCLC

28-8 antibody on the Dako Link 48 platform
22c3 antibody on the Dako Link 48 platform
SP142 antibody on the Ventana Benchmark platform,
E1L3N antibody on the Leica Bond platform

Rimm, JAMO Oncol 2017
KEYNOTE 10: Pembrolizumab versus doxetaxel in 2nd line NSCLC (≥1% of tumor cells PD-L1 positive)

OAK: A randomized phase III study comparing atezolizumab with docetaxel in advanced NSCLC

Baas, ASCO 2016

Barlesi, ESMO 2016
KEYNOTE 10: Pembrolizumab versus doxetaxel in 2nd line NSCLC (≥1% of tumor cells PD-L1 positive)

Baas, ASCO 2016

OAK: A randomized phase III study comparing atezolizumab with docetaxel in advanced NSCLC

Barlesi, ESMO 2016
Poplar: T-effector and interferon signature

Fehrenbacher, Lancet Oncol 2016
Mutational load and outcome of immune checkpoint inhibitor therapies in NSCLC

DBC: Durable clinical benefit; NBC: No durable clinical benefit

Rizvi, Science 2015; McGranaham, Science 2016
Impact of tumor mutation burden on the efficacy of first-line nivolumab in advanced NSCLC: PFS by TMB subgroup and PD-L1 expression

<table>
<thead>
<tr>
<th>TMB and PD-L1 Subgroup</th>
<th>No. at Risk</th>
<th>Months</th>
<th>PFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High TMB, PD-L1 ≥50%</td>
<td>16 13 10 8 8 6 2 0 0 32 24 13 12 7 5 2 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High TMB, PD-L1 1–49%</td>
<td>31 17 16 13 8 6 2 1 0 28 18 9 3 2 2 2 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/medium TMB, PD-L1 ≥50%</td>
<td>41 21 12 6 2 2 1 0 0 41 30 14 10 5 4 2 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/medium TMB, PD-L1 1–49%</td>
<td>70 33 18 9 7 5 1 1 1 53 35 23 13 10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Peters, AACR 2017
Tumor mutational burden in blood is associated with improved atezolizumab efficacy in 2L+ NSCLC (POPLAR and OAK)

Interaction $P = 0.75$

Gandara, ESMO 2016
**Checkpoint inhibitors in metastatic EGFR-mutated NSCLC - a meta-analysis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight</th>
<th>Hazard Ratio [95% CI]</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR wild-type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Checkmate 057</td>
<td>26.0%</td>
<td>0.66 [0.51, 0.86]</td>
<td></td>
</tr>
<tr>
<td>Keynote 010</td>
<td>52.0%</td>
<td>0.66 [0.55, 0.80]</td>
<td></td>
</tr>
<tr>
<td>POPLAR</td>
<td>11.0%</td>
<td>0.70 [0.47, 1.04]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>89.0%</td>
<td>0.66 [0.56, 0.76]</td>
<td></td>
</tr>
<tr>
<td>EGFR mutant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Checkmate 057</td>
<td>6.0%</td>
<td>1.18 [0.69, 2.00]</td>
<td></td>
</tr>
<tr>
<td>Keynote 010</td>
<td>3.8%</td>
<td>0.88 [0.45, 1.70]</td>
<td></td>
</tr>
<tr>
<td>POPLAR</td>
<td>1.1%</td>
<td>0.99 [0.28, 3.40]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>11.0%</td>
<td>1.05 [0.70, 1.55]</td>
<td></td>
</tr>
</tbody>
</table>

*Favors PD1/PDL1 inhibitor vs. Favors docetaxel*

Lee, JTO 2017
What are the developments using immune checkpoint inhibitors is first line

- The response rate with single immune checkpoint inhibitions in unselected patients is lower as standard chemotherapy
- Pembrolizumab has been approved as first line treatment for patients with NSCLC expression PD-L1 in 50% or more of tumor cells
- Combinations inhibitors of the PD-1/PD-1 axis with chemotherapy or CTLA-4 inhibitors show encouraging results in unselected patients
- The use of immune checkpoint inhibitors in earlier stages of disease (neoadjuvant, consolidation after radio-chemotherapy, adjuvant after complete resection) is under investigations
<table>
<thead>
<tr>
<th>PD-L1 Cutoffs:</th>
<th>CheckMate 012</th>
<th>KN-001</th>
<th>BIRCH</th>
<th>Durva (NCT01693562)</th>
<th>JAVELIN Solid Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50% (n=12)</td>
<td>50</td>
<td>58.3</td>
<td>29</td>
<td>15.4</td>
<td>50</td>
</tr>
<tr>
<td>≥25% (n=10)</td>
<td>44</td>
<td>17.4</td>
<td>27</td>
<td>21.4</td>
<td>12.2</td>
</tr>
<tr>
<td>≥1% (n=14)</td>
<td>28</td>
<td>10</td>
<td>29</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&lt;1% (n=144)</td>
<td>14</td>
<td>19</td>
<td>11</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>TC3 or IC3</td>
<td>23</td>
<td>26</td>
<td>27</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>TC2/3 or IC2/3</td>
<td>28</td>
<td>19</td>
<td>29</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>All patients (N=52)</td>
<td>14</td>
<td>17.4</td>
<td>10</td>
<td>18.7</td>
<td>12.2</td>
</tr>
</tbody>
</table>

ORR by PD-L1 expression levels in first line NSCLC with single agent PD-1 or PD-L1 directed antibody

ORR (%)
Phase 3 PD1/PD-L1 inhibition in 1L advanced NSCLC

**Nivolumab**
- **CHECKMATE 227**: Treatment-naïve or recurrent NSCLC, N=1980
  - Primary endpoint: OS, PFS
- **CHECKMATE 026**: Treatment-naïve non-squamous NSCLC, PD-L1+ NSCLC, N=895
  - Primary endpoint: OS, PFS
- **KEYNOTE-042**: Treatment-naïve non-squamous NSCLC, PD-L1+ NSCLC, N=1240
  - Primary endpoint: OS
- **KEYNOTE-024**: Treatment-naïve non-squamous NSCLC, PD-L1+ NSCLC, N=305
  - Primary endpoint: OS

**Pembrolizumab**
- **KEYNOTE-189**: Treatment-naïve non-squamous NSCLC, N=540
  - Primary endpoint: PFS
- **KEYNOTE-111**: Stage IV squamous NSCLC, N=420
  - Primary endpoint: OS
- **KEYNOTE-130**: Stage IV squamous NSCLC, N=1200
  - Primary endpoint: OS
- **KEYNOTE-131**: Stage IV squamous NSCLC, N=1200
  - Primary endpoint: OS
- **KEYNOTE-150**: Stage IV squamous NSCLC, N=1200
  - Primary endpoint: OS

**Durvalumab**
- **MYSTIC**: Advanced NSCLC, N=675
  - Primary endpoint: PFS and OS
- **NEPTUNE**: First-line metastatic NSCLC, N=800
  - Primary endpoint: OS

**Atezolizumab**
- **Impower 110**: Stage IV non-squamous PD-L1+ NSCLC, N=460
  - Primary endpoint: OS
- **Impower 111**: Stage IV squamous PD-L1+ NSCLC, N=450
  - Primary endpoint: OS
- **Impower 130**: Stage IV non-squamous NSCLC, N=550
  - Primary endpoint: OS
- **Impower 131**: Stage IV non-squamous NSCLC, N=1200
  - Primary endpoint: OS
- **Impower 150**: Stage IV non-squamous NSCLC, N=1200
  - Primary endpoint: OS

**Key Findings**
- Neg. PFS
- Pos. OS
- Neg. PFS, OS pending
CheckMate 026: A phase 3 trial of nivolumab vs investigator's choice of platinum-based doublet chemotherapy as first-line therapy for stage IV/recurrent PD-L1 positive NSCLC

**Phase 3 CheckMate 026 Study Design:**
Nivolumab vs Chemotherapy in First-line NSCLC

- **Key eligibility criteria:**
  - Stage IV or recurrent NSCLC
  - No prior systemic therapy for advanced disease
  - No EGFR/ALK mutations sensitive to available targeted inhibitor therapy
  - ≥1% PD-L1 expression
  - CNS metastases permitted if adequately treated at least 2 weeks prior to randomization

- **Randomize 1:1**
  - Nivolumab 3 mg/kg IV Q2W, n = 271
  - Disease progression or unacceptable toxicity

- **Tumor scans Q6W until wk 48 then Q12W**

- **Chemotherapy (histology dependent)**
  - Maximum of 6 cycles, n = 270

- **Disease progression**

- **Crossover nivolumab (optional)**

- **Stratification factors at randomization:**
  - PD-L1 expression (<5% vs ≥5%)
  - Histology (squamous vs non-squamous)

- **Primary endpoint:** PFS (≥5% PD-L1+)
  - Secondary endpoints:
    - OS
    - ORR

- **At risk:**
  - 211
  - 186
  - 156
  - 133
  - 118
  - 98
  - 49
  - 4
  - 0
  - 0

- 1-year OS rate, %
  - Nivolumab: 56.3
  - Chemotherapy: 53.6
  - HR = 1.02 (95% CI: 0.80, 1.30)

- **OS (≥5% PD-L1+)**

- **CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC**

- **Median OS, months**
  - Nivolumab: 14.4 (95% CI: 11.7, 17.4)
  - Chemotherapy: 13.2 (95% CI: 10.7, 17.1)

- **All randomized patients (≥5% PD-L1+): HR = 1.07 (95% CI: 0.86, 1.33)**

Socinski, ESMO 2016
KEYNOTE-024: Pembrolizumab vs platinum-based chemotherapy as first-Line therapy for advanced NSCLC with a PD-L1 TPS $\geq 50\%$

**KEYNOTE-024 Study Design (NCT02142738)**

- **Key Eligibility Criteria**
  - Untreated stage IV NSCLC
  - PD-L1 TPS $\geq 50\%$
  - ECOG PS 0-1
  - No activating EGFR mutation or ALK translocation
  - No untreated brain metastases
  - No active autoimmune disease requiring systemic therapy

- **Pembrolizumab**
  - $200\text{ mg IV Q3W}$ (2 years)

- **Platinum-Douplet Chemotherapy**
  - (4-6 cycles)

- **PD-L1 Screening**
  - 1934 patients entered screening
  - 1729 submitted samples for PD-L1 assessment
  - 1653 samples evaluable for PD-L1

- **End Points**
  - Primary: PFS (RECIST v1.1 per blinded, independent central review)
  - Secondary: OS, ORR, safety
  - Exploratory: DOR

*Reck, ESMO 2016*
KEYNOTE-024: Pembrolizumab vs platinum-based chemotherapy as first-Line therapy for advanced NSCLC with a PD-L1 TPS ≥50%
KEYNOTE-024: Pembrolizumab vs platinum-based chemotherapy as for advanced NSCLC Updated results

Disposition

305 patients randomly allocated

- Pembrolizumab
  - 154 allocated
  - 154 treated
  - 23 ongoing
  - 77 completed treatment
  - 114 discontinued
  - 67 progressive disease
  - 30 AEs
  - 7 death
  - 7 patient withdrawal
  - 2 complete response
  - 1 physician decision

- Chemotherapy
  - 151 allocated
  - 150 treated
  - 2 ongoing
  - 27 completed treatment
  - 121 discontinued
  - 76 progressive disease
  - 19 AEs
  - 5 death
  - 5 patient withdrawal
  - 11 physician decision

Disposition of Study Treatment

305 patients randomly allocated

- Pembrolizumab
  - 154 allocated (ITT)
  - 154 treated
  - Median (range) treatment duration: 7.9 mo (1 d to 28.8 mo)
  - 114 discontinued

- Chemotherapy
  - 151 allocated (ITT)
  - 150 treated
  - Median (range) treatment duration: 35.6 mo (1 d to 30.5 mo)
  - 121 discontinued

Median follow up: 25.2 mo

Data cut: July 16, 2017

Brahmer, WCLC 2017
KEYNOTE-024: Pembrolizumab vs platinum-based chemotherapy for advanced NSCLC: Updated results

Overall Survival: Updated Analysis

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>73</td>
<td>0.63</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>96</td>
<td>(0.47–0.86)</td>
</tr>
</tbody>
</table>

P = 0.002

Median (95% CI)
- Pembrolizumab: 30.0 mo (18.3 mo–NR)
- Chemotherapy: 14.2 mo (9.8 mo–19.0 mo)

Brahmer, WCLC 2017
KEYNOTE-024: Pembrolizumab vs platinum-based chemotherapy for advanced NSCLC: Updated results

### Duration of Response
By RECIST v1.1 Per Blinded, Independent Central Review

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab (N = 154)</th>
<th>Chemotherapy (N = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response, n</td>
<td>70</td>
<td>45</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>45.5 (37.4–53.7)</td>
<td>29.8 (22.6–37.8)</td>
</tr>
<tr>
<td>Difference, % (95% CI)</td>
<td>14.9 (4.3–25.3)</td>
<td>P = 0.0031*</td>
</tr>
<tr>
<td>Median Time to Response, mo (range)</td>
<td>2.1 (1.4–14.5)</td>
<td>2.2 (1.8–10.3)</td>
</tr>
<tr>
<td>Censored duration of response, n</td>
<td>52</td>
<td>16</td>
</tr>
</tbody>
</table>

*Nominal P value; *"* indicates the response duration is censored.
NR, not reached.
Data cutoff: July 10, 2017.
TREATMENT ALGORITHM FOR STAGE IV SCC

Stage IV SCC

Never or former light smoker (< 15 pack/year)

Molecular test (ALK/EGFR)

Molecular test negative

PD-L1 TPS ≥ 50%, ECOG PS 0–1, no untreated brain metastases: Pembrolizumab [I, A; MCBS 5]

Molecular test positive

Targeted therapy
Combination therapies: Early results in first line therapy of advanced NSCLC

- Randomized phase-2 study of first line chemotherapy with or without pembrolizumab (no restriction regarding PD-L1 expression)
  - *Langer, Lancet Oncol 2016*

- NSCLC cohorts treated in first line with nivolumab alone or nivolumab combined with ipilimumab according to PD-L1 expression
  - *Hellmann, Lancet Oncol 2016*
  - *CheckMate 227*
Randomized phase-2 study of carboplatin and pemetrexed with or without pembrolizumab as first line therapy of advanced NSCLC: Keynote-21 Cohort G: Updated results

**KEYNOTE-021 Cohort G**

**Key Eligibility Criteria**
- Untreated stage IIIb or IV non-small cell lung cancer (NSCLC)
- No activating EGFR mutation or ALK translocation
- Provision of a sample for PD-L1 assessment
- ECOG PS 0-1
- No untreated brain metastases
- NoILD or pneumonitis requiring systemic steroids

**End Points**
Primary: ORR (RECIST v1.1 per blinded, independent central review)
Key secondary: PFS
Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

**Disposition of Patients**
- 219 patients screened
- 123 patients randomly allocated
- Pembrolizumab + Chemotherapy
  - 89 allocated
  - 89 treated
  - 60 of 89 cycles pemetrexed (68%)
- Pembrolizumab alone
  - 34 allocated
  - 34 treated
  - 42 of 34 cycles pemetrexed (66%)
- 35 crossed over to pembrolizumab on study
- 15 received anti–PD-L1/L1 outside of crossover


Borghaei, ESMO2017
Randomized phase-2 study of carboplatin and pemetrexed with or without pembrolizumab as first line therapy of advanced NSCLC: Keynote-21 Cohort G: Updated results

**Overall Survival**

- **ORR, % (95% CI)**
  - Pembrolizumab + PC: 56.7 (Δ24.8%, 95% CI: 7.2%–40.9%) with \( P = 0.0029^a \)
  - PC Alone: 31.7

- **Median (95% CI)**
  - NR (22.8–NR)
  - NR (20.9–14.9–NR)

- **Events, n/N**
  - Pembrolizumab + PC: 20/80^a
  - PC alone: 31/83^a

- **HR (95% CI)**
  - Pembrolizumab + PC vs. PC alone: 0.59 (0.34–1.05)
  - \( P = 0.03^p \)

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*Borghaei, ESMO2017*
Updated Results From KEYNOTE-021 Cohort G

Overall Survival

Median (95% CI)
NR (22.8–NR)
20.9 (14.9–NR)

Borghaei, ESMO2017
Neoadjuvant nivolumab in early stage resectable NSCLC

| Histopathologic Response (N=17)* (% residual viable tumor) |
|---------------|-----|
| <10%          | 38  |
| 10-50%        | 13  |
| >50%          | 50  |

<table>
<thead>
<tr>
<th>Pathologic downstaging from Pre-treatment Clinical Stage (N=17)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

*Only resected patients included for histopathologic response and downstaging exploratory analyses

Forde, ESMO 2016

63yo M, ex-smoker, adeno, PD-L1 2%+, <10% viable tumor at resection
NICOLAS - A feasibility trial evaluating nivolumab consolidation after standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B NSCLC (amendment 1)

**Study design:**
- Multicentre, single-arm phase II trial.
- ETOP sponsored

**Primary Endpoint:**
- Grade ≥3 pneumonitis

**Sample Size:**
- 43 patients

**Screening, eligibility and enrolment**

**Stage IIIA/B NSCLC**

**Investigator’s choice**

**Radiotherapy**

**Nivolumab:**
- 480mg Q4W up to 1 year
- 240mg Q2W, 8 doses

**Whole body FDG-PET**

**CT scans year 1:** every 9 weeks
**year 2:** every 12 weeks
**beyond 2 years:** every 6 months...

... until PD

Amendment 2: Expansion to 73 patients U(concurrent strata) for efficacy analysis
PACIFIC: Consolidation durvalumab for 1 year after chemoradiotherapy of stage III NSCLC

- 713 pts with stage III NSCLC chemo-radiotherapy
- 2:1 durvalumab 10 mg/kg Q2w for 12 months or placebo

No. of Events/Total No. of Patients | Median PFS (95% CI) | 12-Mo PFS (95% CI) | 18-Mo PFS (95% CI)
--- | --- | --- | ---
Durvalumab | 214/476 | 16.8 (13.0–18.1) mo | 55.9 (51.0–60.4) % | 44.2 (37.7–50.5) %
Placebo | 157/237 | 5.6 (4.6–7.8) mo | 35.3 (29.0–41.7) % | 27.0 (19.9–34.5) %

Paz-Ares, ESMO 2017; Antonia, NEJM 2017
PEARLS: Pembrolizumab adjuvant therapy after complete resection of stages IB-IIIA NSCLC

Study design:
Multicentre, randomized, placebo controlled phase III trial.  
- MSD sponsored  
- EORTC coordinated  
- ETOP as collaborative group

Co-primary endpoint:  
- DFS in the PD-L1 strong sub-group  
- DFS in the overall population

Sample Size:  
- 1380 randomized patients