Non-Small Cell Lung Cancer (NSCLC) Regulatory – Industry perspective

CHALLENGES FOR THE APPROVAL OF ANTI-CANCER IMMUNOTHERAPEUTIC DRUGS
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Disclosure

- Employment: currently employed by Bristol-Myers Squibb as head of regulatory EU

- The views expressed in this presentation are personal based on my experience and do not necessarily reflect the views of Bristol-Myers Squibb
Outline

• Lung cancer and I-O
  – Immune checkpoint inhibition

• BMS Experience - nivolumab in NSCLC
  – Approved indication – pretreated Squamous NSCLC
  – Regulatory path to approval

• Non-squamous NSCLC

• Key takeaways for ongoing/future development
  – Future study design – immune biomarkers exploration
  – Combinations of I-O agents
  – Concluding remarks
Immunotherapy for Lung Cancer

Immunotherapy

Active
*Designed to act on the immune system itself*

- Antigen-dependent
  - Enhancing immune cell function
    - Cytokines
  - Therapeutic vaccines
    - TG4010
    - Tergenpumacel-L
    - Racotumomab
    - L-BLP25
- Antigen-independent
  - Modulate T-cell function
    - Immune checkpoint inhibition
      - CTLA-4 inhibition
      - PD-1 inhibition
      - PD-L1 inhibition

Passive (adoptive)
*Designed to act at tumor; immune-based mechanism*

- Antitumor monoclonal antibodies
- Adoptive
  - Adoptive cell transfer
  - Bavituximab
  - EGFR inhibition

Select examples of immune checkpoint inhibitors under evaluation for lung cancer \(^a\)

<table>
<thead>
<tr>
<th>Target</th>
<th>Antibody</th>
<th>Development stage</th>
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<tbody>
<tr>
<td></td>
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<td>Phase 1</td>
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<tr>
<td>PD-1</td>
<td>Nivolumab (BMS-936558)</td>
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<td>Pembrolizumab (MK-3475)</td>
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<td>PD-L1</td>
<td>Durvalumab (MEDI-4736)</td>
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<td>Atezolizumab (MPDL3280A)</td>
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<td>Avelumab (MSB0010718C)</td>
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<td>CTLA-4</td>
<td>Ipilimumab (+nivolumab)</td>
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<td></td>
<td>Tremelimumab (+durvalumab) (^b)</td>
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\(^a\)Only agents under evaluation in studies specifically for NSCLC or SCLC are shown; antibodies directed against other immune checkpoint molecules are under evaluation; \(^b\)Also under evaluation for mesothelioma. www.clinicaltrials.gov. Accessed June, 2015.
Nivolumab – anti-PD-1 mAb
New pathway against Cancer

- **Opdivo (nivolumab):** I-O medicinal product, HuMAb PD-1 inhibitor, approved in EU in 2015:
  - “OPDIVO as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
  - OPDIVO is indicated for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.”

- Comprehensive clinical development program across multiple tumour types
  - **Survival benefit** demonstrated in several tumour types
Nivolumab – Lung Cancer

- Major Clinical Development Program:
  - **Non-small cell lung cancer (NSCLC):** dedicated Ph. 3 studies (Overall Survival) to populations of different histology in patients failing prior treatment for metastatic disease: *Squamous (SQ) and Non-Squamous (NSQ)*
    - Close interactions with HAs and multiple CHMP Scientific Advice have been of major value
    - Nivolumab activity expected in principle to be independent from histology
    - With evolving Ph 1 data (higher ORR in SQ NSCLC) and high unmet medical need in squamous population, BMS decided to conduct independent Ph 3 studies for SQ and NSQ NSCLC, supported by CHMP SA

- Across lines of therapy, monotherapy, combination regimens
  - Optimization of posology and most effective combinations – ongoing efforts
Nivolumab lung cancer: OS in clinical studies

**Phase 1 Data**

*CA209-003*

Median OS = 9.9 months

- 2-year OS rate = 24%
- 3-year OS rate = 18%

**Phase 2 Data**

*Checkmate 063*

Median OS = 8.1 months

- 1-year OS rate = 39%
- 18-mo OS rate = 27%

**Phase 3 Data**

*CheckMate 017: Squamous*

Median OS Nivo = 9.2 months

- 18-mo OS rate = 28%
- 18-mo OS rate = 13%

*CheckMate 057: NonSquamous*

Median OS Nivo = 12.2 months

- 1-yr OS rate = 51%
- 1-year OS rate = 39%

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Nivolumab – MAA

- **Initial MAA**: focused on patient population metastatic SQ-NSCLC after prior chemotherapy (in parallel to MAA – Melanoma)
  - Recognized by EMA and EU Community as area of high and urgent unmet medical need, very limited treatment options
  - Ph. 2 (CA209063) and Ph. 1 study
  - Ph. 3 (CA209017) confirmatory
    - Primary objective was met, based on Interim Analysis: superiority in OS for nivolumab vs. Docetaxel
  - Very close collaboration with EMA and Rapporteurs – shared sense of urgency
Nivolumab – SQ NSCLC

- Pivotal Phase 3 trial: CA209017
  - OS robust primary endpoint
  - Early stopping for superiority - **clinically relevant difference in OS for whole population, regardless of tumour PD-L1 status**
  - Modest correlation between OS and PFS (not unexpected for I-O agents)

<table>
<thead>
<tr>
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<th>Nivolumab (n=135)</th>
<th>Docetaxel (n=137)</th>
<th>HR</th>
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</thead>
<tbody>
<tr>
<td><strong>Median OS, months</strong></td>
<td>9.2</td>
<td>6.0</td>
<td>HR = 0.59 (0.44, 0.79); <em>P</em> = 0.0002</td>
</tr>
<tr>
<td><strong>Median PFS, months</strong></td>
<td>3.5</td>
<td>2.8</td>
<td>HR = 0.62 (0.47, 0.81); <em>P</em> = 0.0004</td>
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<tr>
<td><strong>ORR, %</strong></td>
<td>20</td>
<td>9</td>
<td><em>P</em> = 0.008</td>
</tr>
<tr>
<td><strong>Median DOR, months</strong></td>
<td>NR</td>
<td>8.4</td>
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- Safety:
  - In general consistent with characterized safety profile (MAA melanoma studies), some ADRs (e.g. pulmonary) higher incidence in NSCLC likely due to the locally elicited immune response
  - Safety profile mostly commonly associated with **immune-related adverse reactions – SmPC risk minimization guidance, Patient: Alert Card.**
  - Safety profile favorable versus docetaxel
    - Less frequent treatment-related AEs (any grade, 59%; grade 3–5, 8%; no grade 5 events) than docetaxel (any grade, 87%; grade 3–5, 58%), both hematologic and non-hematologic toxicities

- Commitment to continue exploration of biomarkers value to predict the efficacy of nivolumab
Nivolumab data suggest similar activity in squamous and non-squamous NSCLC

- **CheckMate 057: non-squamous**
  - Nivolumab
  - Docetaxel
  - OS (1-yr) = 51%
  - OS (1-yr) = 39%
  - HR = 0.73 (96% CI: 0.59, 0.89) $P = 0.0015$

- **CheckMate 017: squamous**
  - Nivolumab
  - Docetaxel
  - OS (1-yr) = 42%
  - OS (1-yr) = 24%
  - HR = 0.62 (0.48, 0.81); $P = 0.0004$

**Patient characteristics were similar in both studies**

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Select on-going phase 3 studies with immune checkpoint inhibitors in pretreated, advanced NSCLC

**Pembrolizumab**

**KEYNOTE-010**

- *2nd-line PD-L1+ NSCLC*  
  - Pembrolizumab low dose Q3W
  - Pembrolizumab high dose Q3W
  - Docetaxel
  - Primary endpoints: OS, Safety

**Durvalumab**

**ARCTIC**

- *3rd-line PD-L1+/− NSCLC*  
  - (PD-L1+) durvalumab vs SOC chemotherapy
  - (PD-L1−) durvalumab + tremelimumab vs SOC chemotherapy
  - Primary endpoints: OS, PFS

**Atezolizumab**

**OAK**

- *2nd-line NSCLC*  
  - Atezolizumab
  - Docetaxel
  - Primary endpoint: OS

**Avelumab**

**Javelin Lung 200**

- *2nd-line PD-L1+ NSCLC*  
  - Avelumab
  - Docetaxel
  - Primary endpoint: OS

**SOC=standard of care.**

Presently and Going forward

- Identify factors that may impact patient outcome with immune checkpoint inhibitors
  - Patient characteristics; mutational status; histology; role of PD-L1 expression/other immune biomarkers

- Further understanding of role of biomarkers in the tumour and tumour environment will guide most effective treatment therapies
  - Different role / impact according to tumour type and line of therapy?

- Important to have Product Information that provide data and adequate recommendations / precautions to guide physicians to most optimal clinical assessment for individual patients
  - Sub-group analysis very relevant

- NSCLC in earlier lines of therapy may benefit further from combination regimens
  - Synergy of complementary immune pathways / other treatment modalities
  - Guidelines not yet fully addressing all development challenges
Concluding Remarks

- **Nivolumab:**
  - **Patient centric clinical development**
    - Ph. 1 data & multiple CHMP SA led to innovative clinical development plan
    - pre-treated Met. Lung: 2 phase 3 studies initiated in parallel / histology
  - **MAA procedure**
    - very close collaboration on the regulatory pathway with HAs and EC – shared recognition of unmet need
      - MAA submitted in accordance with art. 82.1 or Reg. (EC) 724/2004

- **Value of OS in I-O**

- **Safety:** immune-related adverse reactions (most resolved with appropriate medical therapy or withdrawal)
  - SmPC clear guidance in several sections & Alert Card for patients

- **Biomarkers**
  - **PD-L1 predictive value:** clear role not yet defined, not only in Lung but across tumour types in pre-treated Metastatic Lung cancer B/R+ in all comers!
  - **Biomarker exploration** beyond PD-L1 is needed:
    - Including other immune parameters, eg tumor-infiltrating immune cells, immune-gene signatures
      - PAM (in line with previous CHMP SA)
      - IION (academic network: International Immuno-Oncology Network)

- **Close & early collaboration with all stakeholders** (patients, academia, regulators, HTA/payers, policy makers)

- **Future - Combination regimens in earlier line of disease**