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

CHALLENGES FOR THE APPROVAL OF ANTI-CANCER IMMUNOTHERAPEUTIC DRUGS

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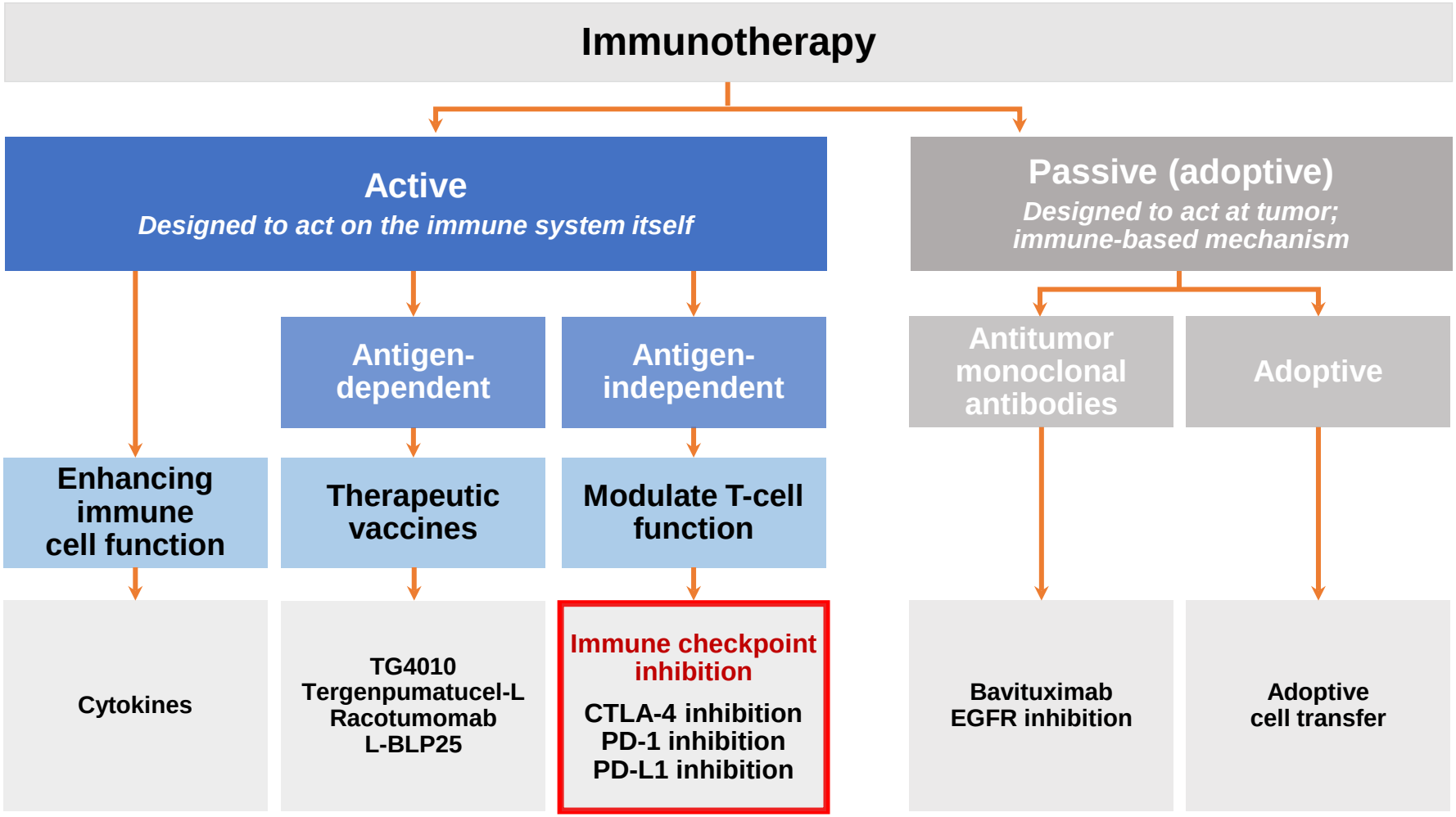
Disclosure

- 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

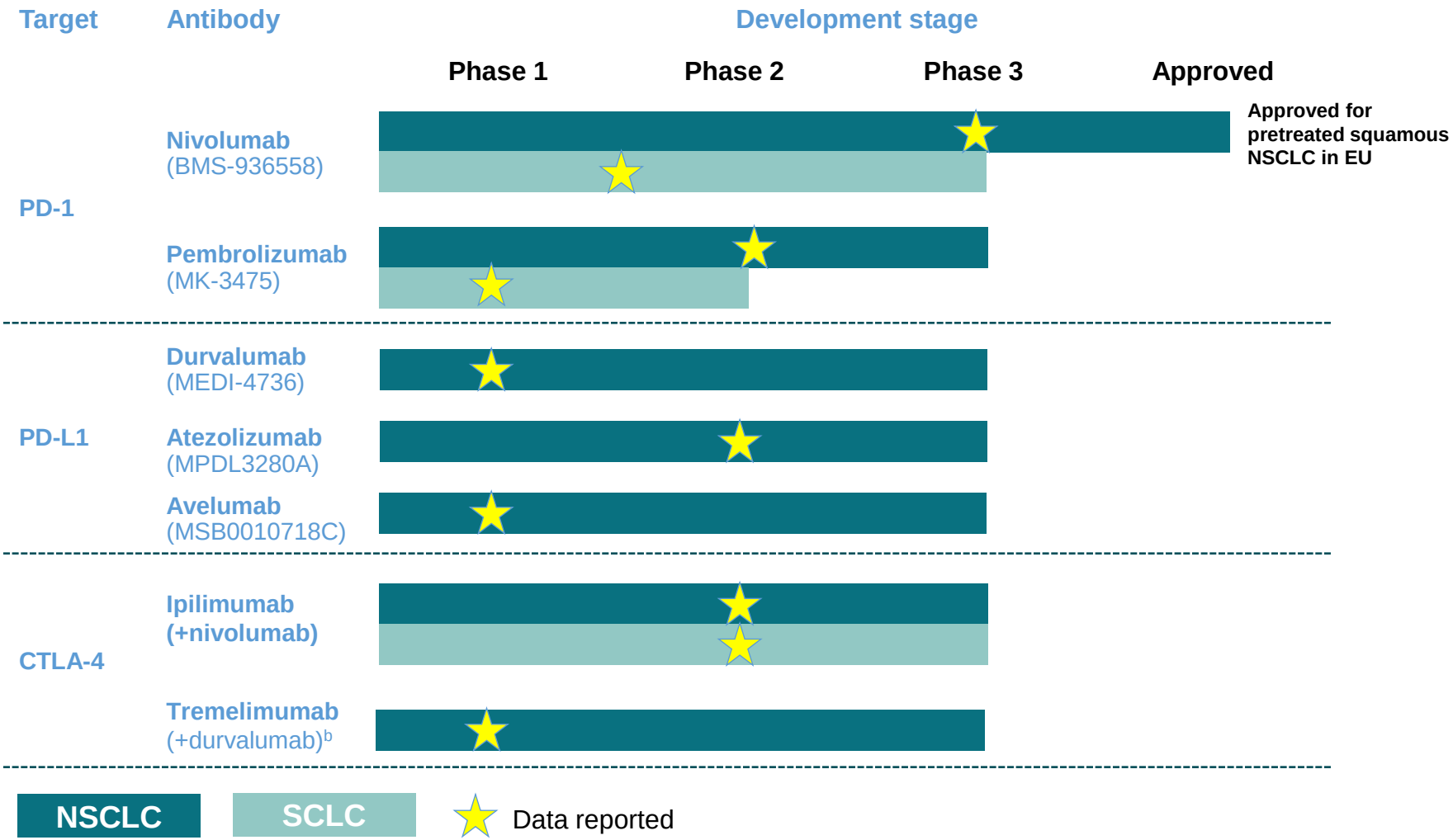
- Lung cancer and I-O
  - Immune checkpoint inhibition
- BMS Experience - nivolumab in NSCLC
  - Approved indication – pretreated Squamous NSCLC
  - Regulatory path to approval
- Non-squamous NSCLC
- Key takeaways for ongoing/future development
  - Future study design – immune biomarkers exploration
  - Combinations of I-O agents
  - Concluding remarks

Immunotherapy for Lung Cancer



www.clinicaltrials.gov. Accessed June 2015;
NCCN Guidelines. Non-small cell lung cancer. v3.2014; Peters S, et al. *Ann Oncol*. 2012;23:vii56–vii64.

Select examples of immune checkpoint inhibitors under evaluation for lung cancer[a]



[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.

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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

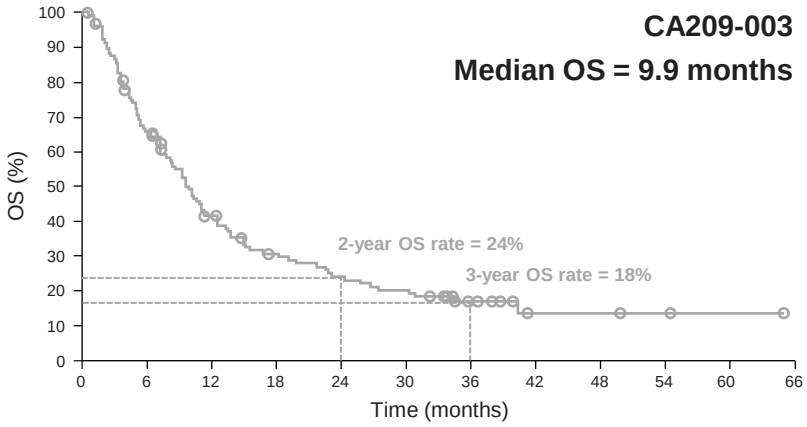
Nivolumab – Lung Cancer

- **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

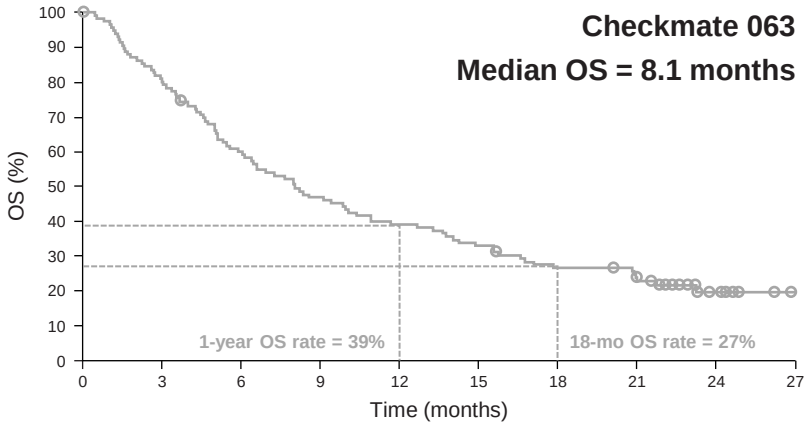
- **Across lines of therapy, monotherapy, combination regimens**
  - Optimization of posology and most effective combinations – ongoing efforts

Nivolumab lung cancer: OS in clinical studies

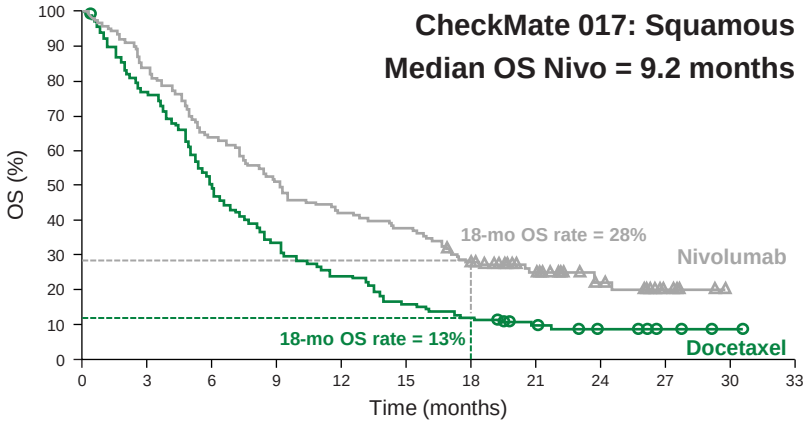
Phase 1 Data[1]

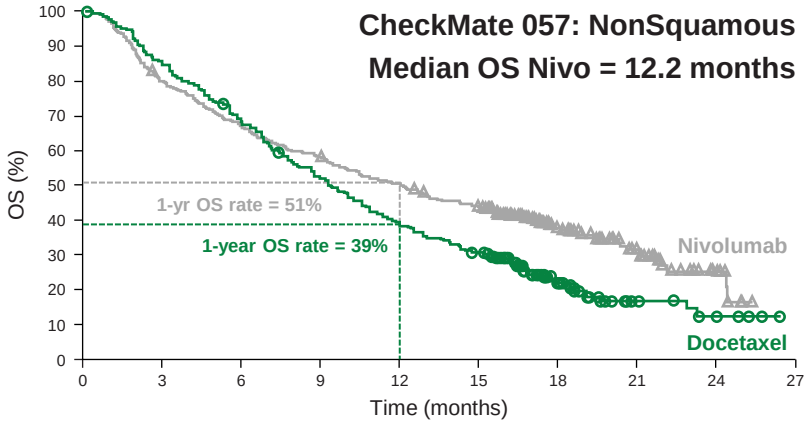


Phase 2 Data[2]



Phase 3 Data[3,4]





1. Gettinger S, et al. Poster presented at CMSTO 2014. 2. Horn L, et al. Presented at WCLC 2015, Abstract 828.
3. Reckamp K, et al. Presented at WCLC 2015, Abstract 736. 4. Paz-Ares L, et al. Presented at ASCO 2015, Abstract LBA109.

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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

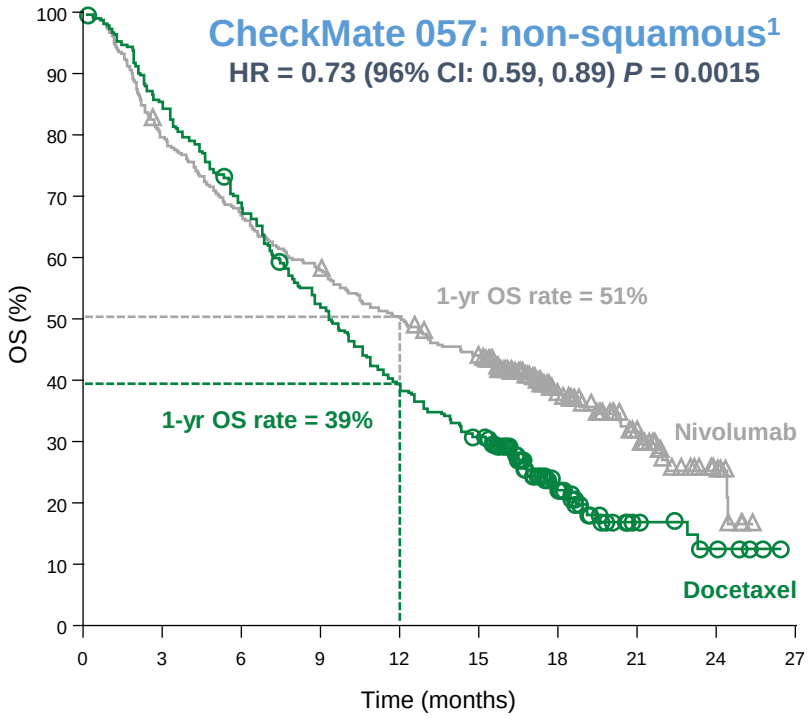
Nivolumab – SQ NSCLC

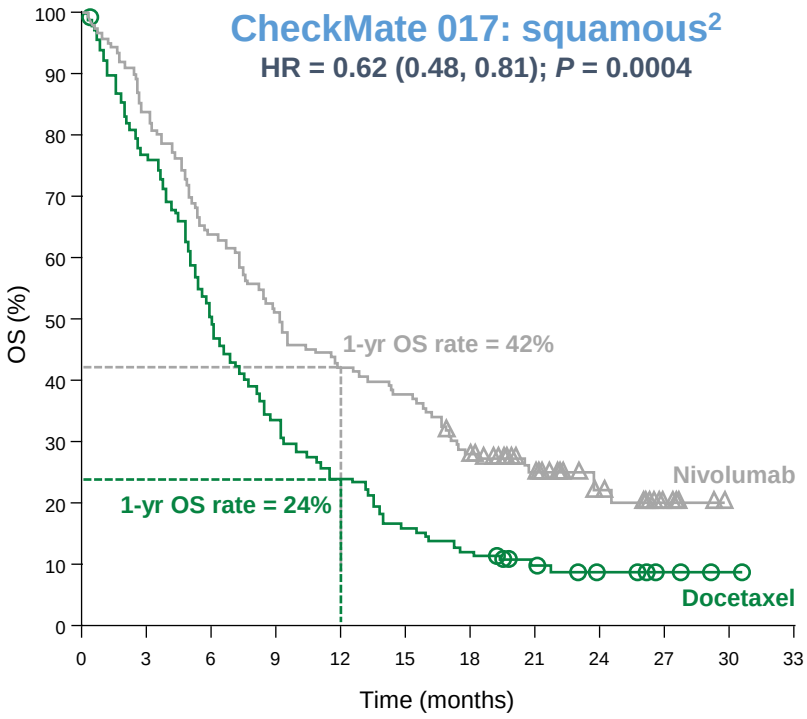
- **Pivotal Phase 3 trial: CA209017**
  - OS robust primary endpoint
  - Early stopping for superiority - **clinically relevant difference in OS for whole population,** regardless of tumour PD-L1 status
  - Modest correlation between OS and PFS (not unexpected for I-O agents)

	Nivolumab (n=135) 3mg/kg	**Docetaxel** (n=137) 75mg/m2	**HR**
Median OS, months	9.2	6.0	HR = 0.59 (0.44, 0.79); *P* = 0.0002
Median PFS, months	3.5	2.8	HR = 0.62 (0.47, 0.81); *P* = 0.0004
ORR, %	20	9	*P* = 0.008
Median DOR, months	NR	8.4	

- 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 – NSQ NSCLC



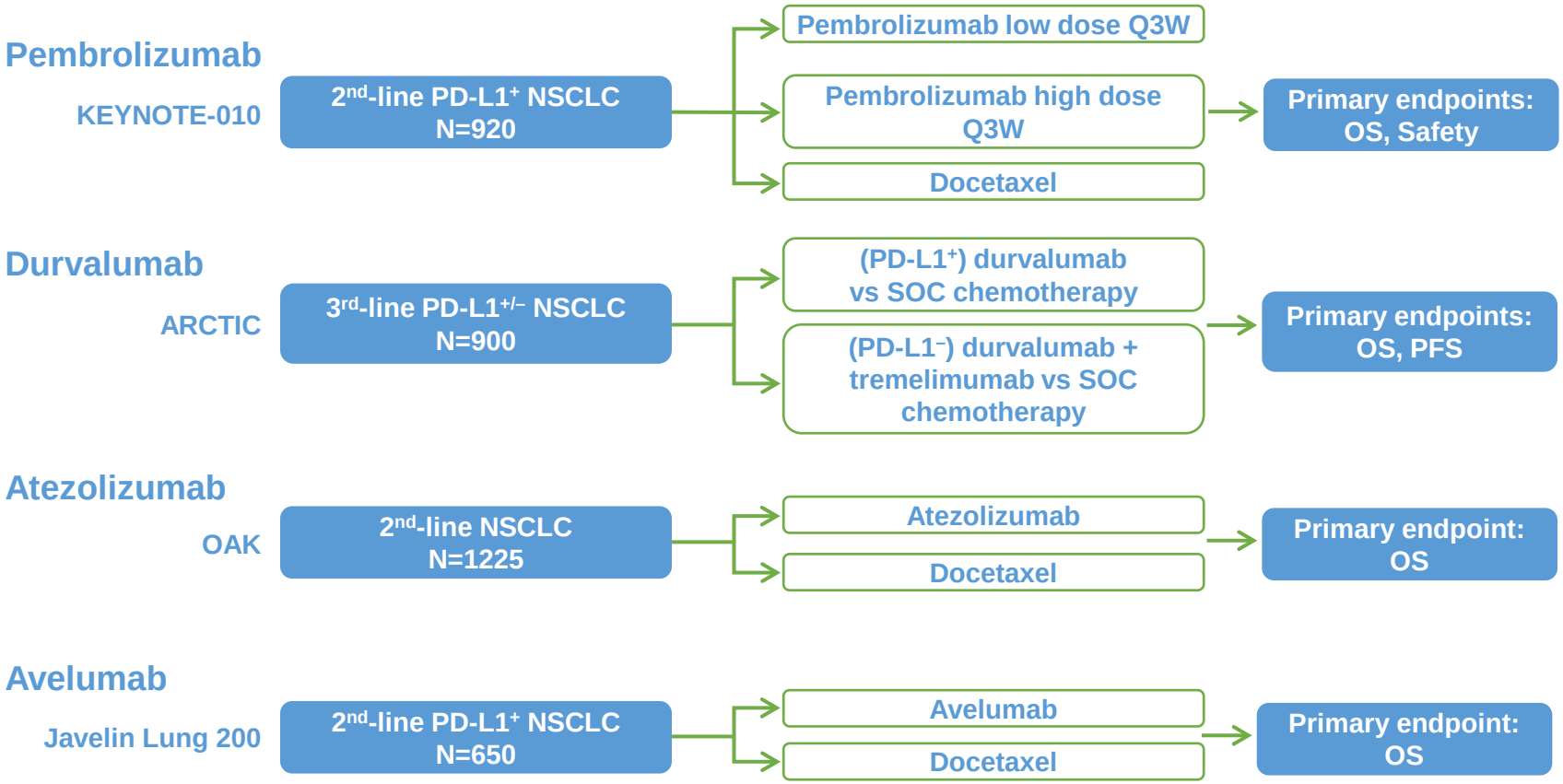


Patient characteristics were similar in both studies

Nivolumab data suggest similar activity in squamous and non squamous NSCLC

1. Paz-Ares L, et al. Presented at ASCO 2015, Abstract LBA109. 2. Reckamp K, et al. Presented at WCLC 2015, Abstract 736.

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



SOC=standard of care.

ClinicalTrials.gov. http://www.clinicaltrials.gov/. Accessed August 2015.

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***