EARLY ACCESS TO MEDICINES SCHEME
Industry experience: Case study

Keytruda® granted the first positive EAMS Scientific Opinion

Joanna Maitland Smith, UK Regulatory Affairs
Merck Sharp & Dohme Limited

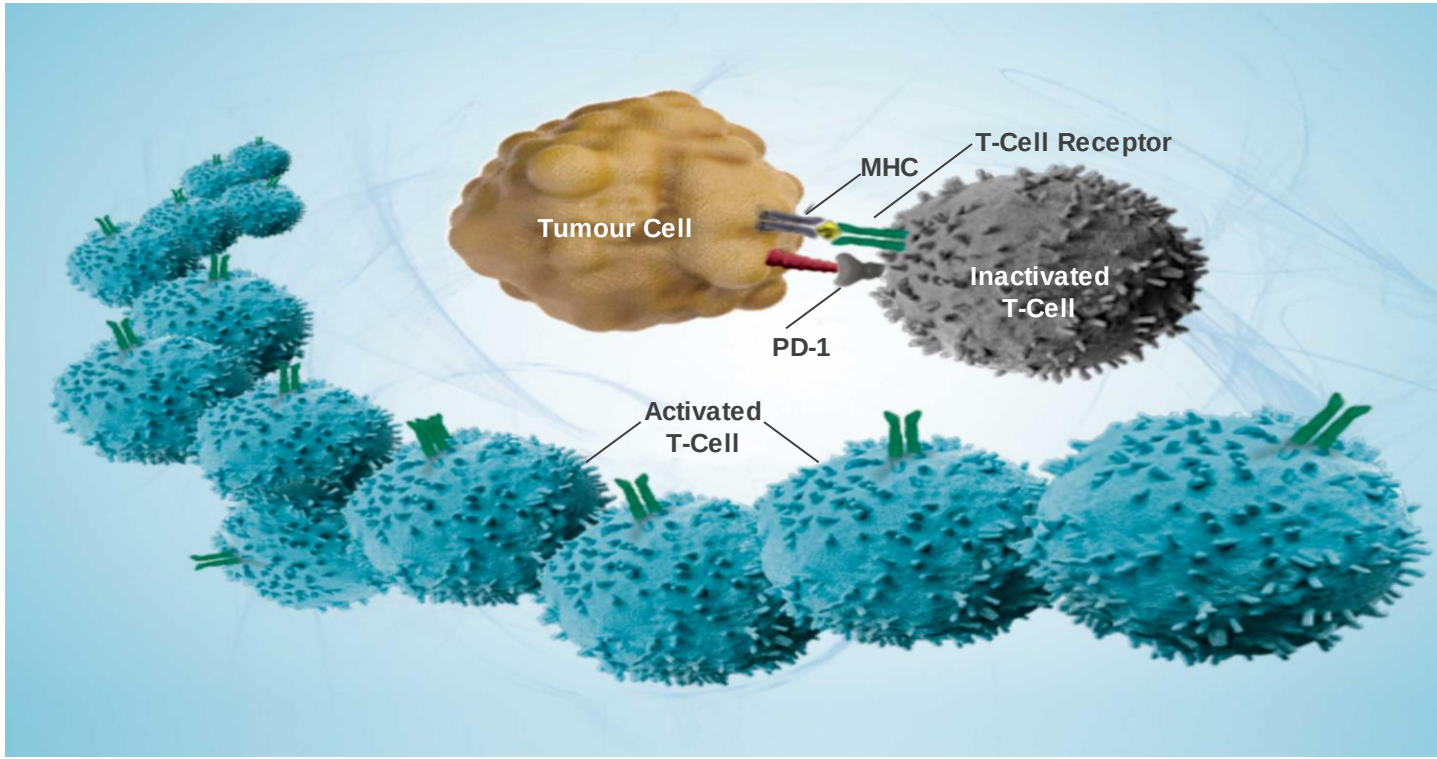
BIA/MHRA Conference May 4 2016

MSD

EAMS for pembrolizumab

- Presubmission
- Preparing the application for melanoma
- Review and approval
- Next Steps- EAMS for NSCLC
- Summary and learnings

The PD-1 pathway: inhibits the effector phase of T-cell activity



PD-1 is a cell surface co-inhibitory receptor expressed on T-cells which inactivates antigen specific T-cells in the tumour microenvironment[1–4]

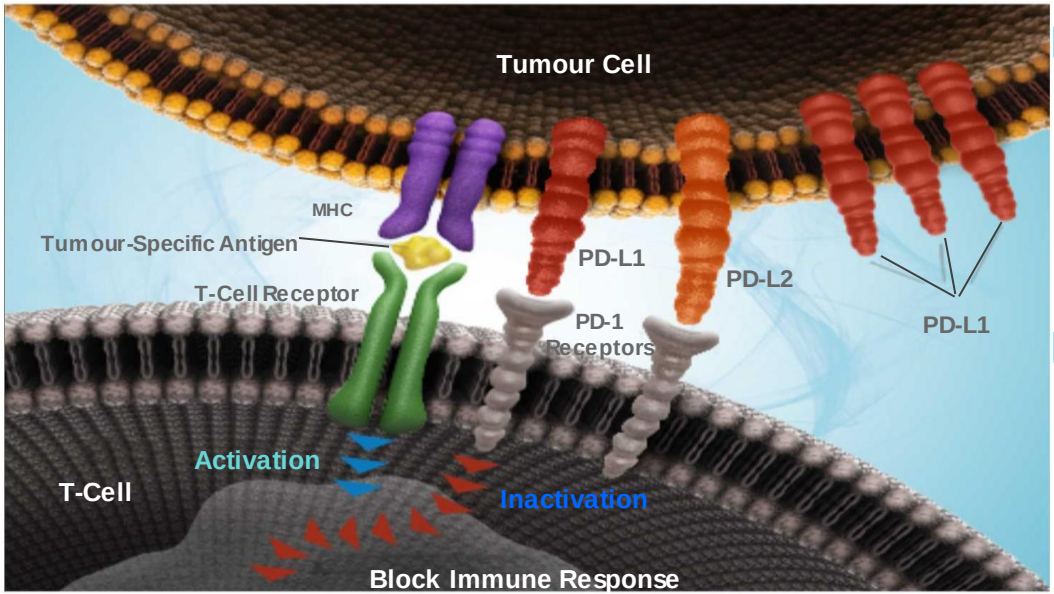
Its normal role is to down-regulate T-cell activity in peripheral tissues and limit collateral tissue damage during the immune response[1–4]

MHC: major histocompatibility complex; PD-1: programmed death receptor 1.

1. Quezada SA, Peggs KS. *Br J Cancer* 2013;108:1560–65; 2. Pardoll DM. *Nat Rev Cancer* 2012;12:252–64; 3. Ribas A. *N Engl J Med* 2012;366:2517–9; 4. Keir ME *et al. Annu Rev Immunol* 2008;26:677–704.

MSD

Tumour cells may evade immune surveillance by exploiting the PD-1 checkpoint pathway



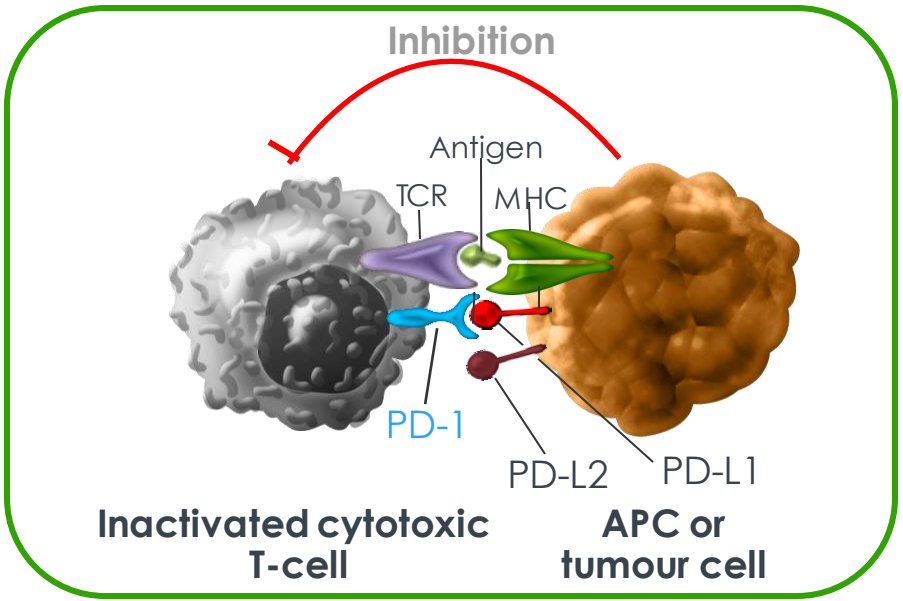
- Tumour cells may block immune responses via the PD-1 immune checkpoint pathway by expressing the dual PD-1 ligands, PD-L1 and PD-L2[1,2]
- PD-L1 and PD-L2 engage the PD-1 receptor on T-cells, inactivate T-cell signaling, proliferation and effector function to allow tumour cells to evade the immune response[1,3]

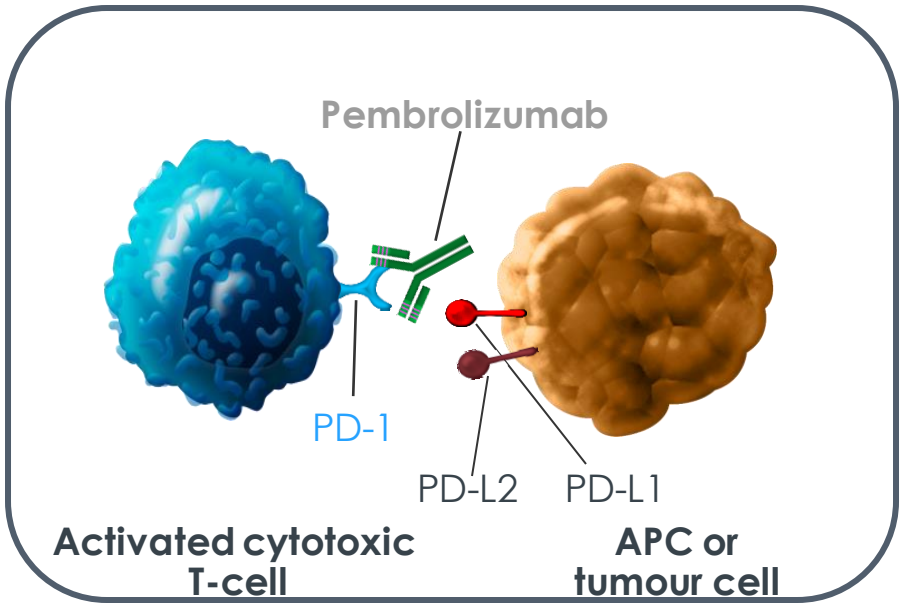
PD-1: programmed death receptor 1; PD-L1: programmed death ligand 1; PD-L2: programmed death ligand 2.

1. Freeman G *et al. PNAS* 2008;105:10275–6; 2. Zou W, Chen L. *Nat Rev Immunol* 2008;8:467–77; 3. Rozali EN *et al. Clin Dev Immunol* 2012;2012:656340; Pardoll DM. *Nat Rev Cancer* 2012;12:252–64.

MSD

PD-1 blockade with pembrolizumab[1,2]





APC: antigen-presenting cell; MHC: major histocompatibility complex; PD-1: programmed death receptor 1; PD-L1: programmed death ligand 1; PD-L2: programmed death ligand 2; TCR: T-cell receptor.

1. Pardoll DM. *Nat Rev Cancer* 2012; 12: 252–264.
2. KEYTRUDA® (pembrolizumab) Summary of Product Characteristics (SPC). July 2015. Merck Sharp & Dohme Limited, UK.

MSD

Pembrolizumab EAMS Starting off….1

- Mar 2014 MHRA announced EAMS: guidance to be available in April
- Immediate discussions at MSD UK -pembrolizumab ideal candidate
- Idea was put to HQ colleagues
  - **Questions:**
    - How was this different to a global Early Access Programme being implemented concurrently?
    - Data requirements and how much work to submit?
    - Concern about resource competition with ongoing MA filing preparation
  - **Justifications:**
    - Ideal candidate – fulfilled criteria for unmet medical need
    - Earlier patient access with defined risk benefit profile
    - Credibility and value of product
    - Opportunity to partner with MHRA on new process.
    - Opportunity to partner with other stakeholders- NICE, NHSE to reduce access timelines.

MSD

Pembrolizumab EAMS Starting off….2

- 07Apr14 MHRA published guidance
- Secured internal agreement to discuss with MHRA
- Telecon held at end of April
  - Indications – melanoma, NSCLC
  - Timelines both PIM and SO – joint mtg possible?
  - Status of MA application (programme too advanced?)
- April – Aug 2014: **many** internal and external stakeholder discussions
- MSD UK Challenge: to ensure HQ groups aligned on local discussions, support needed and provision of approval to proceed.
- 22Aug14 – application for PIM and for Presub meeting submitted.
- MHRA advised MSD to notify NHS, NICE and DH of submission.
- Meanwhile MA application for melanoma submitted June 2014 to EMA

MSD

Making the submission….1

- Face to Face meeting 25Sep14
  - Suitability for PIM designation confirmed -content of dossier main discussion
  - EAP already in place- discussions about the documentation, data collection and AE reporting for EAMS
  - Labelling – what to use as a basis?
  - RMP, risk minimisation requirements & AE reporting
  - Indication - broad or restricted?
  - Timelines - Target submission end October.

PIM designation granted 10 October 2014

MSD

Making Submission….2

- Majority of work for SO submission in UK office with HQ review and approval
- MHRA agreed to accept MA summaries
- Main challenges
  - Labelling –EU SPC, CCDS, FDA label?
  - RMP- what version and in line with UK EAMS label.
  - Physician pack documents – suitable for EAMS
  - PV arrangements
  - Timelines, workload and many stakeholders internally
- **Filed SO application 24Oct2014**

MSD

The review

- Day 45 prelim SO on 17Dec14: responses due 01Jan15.
  - Questions from review extensive
    - Clinical clarifications during review
    - Formal list of 22 Questions
    - Including CMC, Benefit/Risk, RMP, PV system, labelling,
    - Some questions the same as from EU file review
- Changed from 75 to 90 day procedure- responses due by 16 Jan 2015
- Issues around consistency with MA procedure
  - Day 120 questions for EU file being answered in parallel
  - MHRA flexible on accepting later submission of RMP and labelling

SO approval and beyond

- **SO granted 09Mar15**
  - Later than anticipated but still meaningful for patients
  - Over 500 patients supplied from Mar15 prior to MA grant
- Parallel activity with NICE, NHSE and DoH
- Collaboration resulted in accelerated NICE review and reduced implementation period of NICE guidance.
  - NICE recommendation Sept15
  - Keytruda routinely available through NHS for 2L treatment from Oct15

EAMS application for NSCLC

- PIM submission 11Nov15, Approval 24Nov15
- MHRA presubmission meeting 19Nov15
- SO submission 4Dec15
- Approval 10Mar16: 75 day procedure
- Challenges
  - Labelling and RMP - No EU filing at the time for NSCLC
  - hybrid physician and patient info and hybrid RMP
  - **Companion diagnostic**
- Day 45 Questions: 11 around RMP, clarifications and more details required plus labelling changes.
- First patient treated end Apr16

Summary and Learnings

- Work load is sizeable – don't underestimate it
- Engage senior internal leadership properly
  - Resource allocation and alignment to other priorities
- Educate stake holders internally, with sound rationale
- Committed team both UK and HQ
  - Timelines are challenging- need to prioritise
- Do as much of the work as possible locally if competing priorities for HQ
- Consistency of documentation can be a challenge
- PV system and RMP are critical

MSD

Pembrolizumab EAMS

Thankyou for your attention