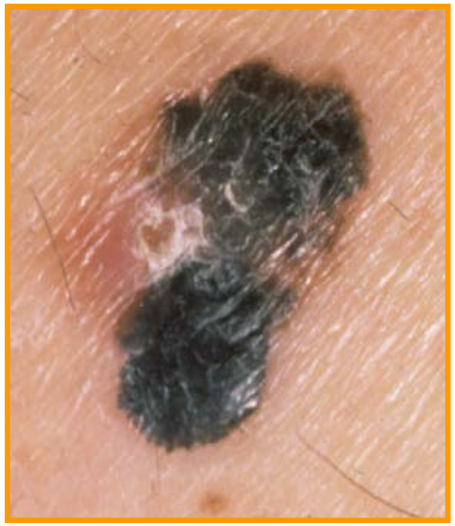
KEYTRUDA® (pembrolizumab) Melanoma Lessons Learnt

EMA-CDDF JOINT MEETING
Challenges for the approval of anti-cancer immunotherapeutic drugs

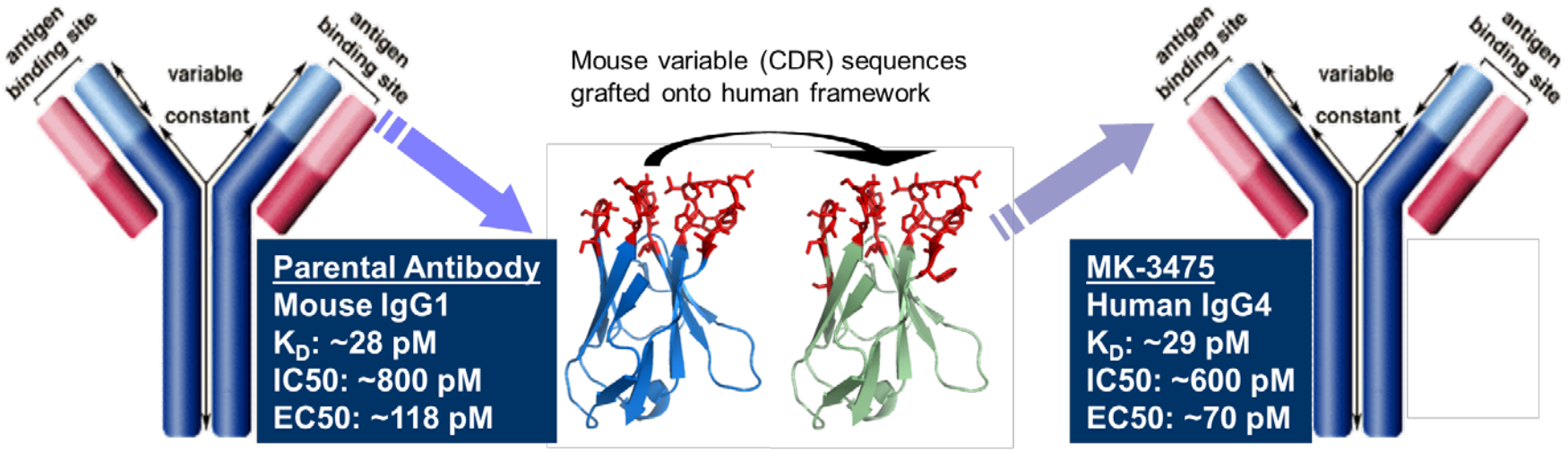
4 February 2016

Melanoma: A Disease Model for Immuno-Oncology

- Malignant tumor of melanocytes
- ~ 200,000 new cases annually and increasing worldwide.
- Progress with BRAF and Mek inhibitors for BRAF mutant melanoma
- Model tumor type for development of new immunotherapies
- Anti-CTLA-4 antibody ipilimumab approved in EU in 2011
- Anti-PD-1 antibodies pembrolizumab and nivolumab approved in EU in 2015



Pembrolizumab is a Humanized IgG4, High-Affinity Anti-PD-1 Blocking Antibody

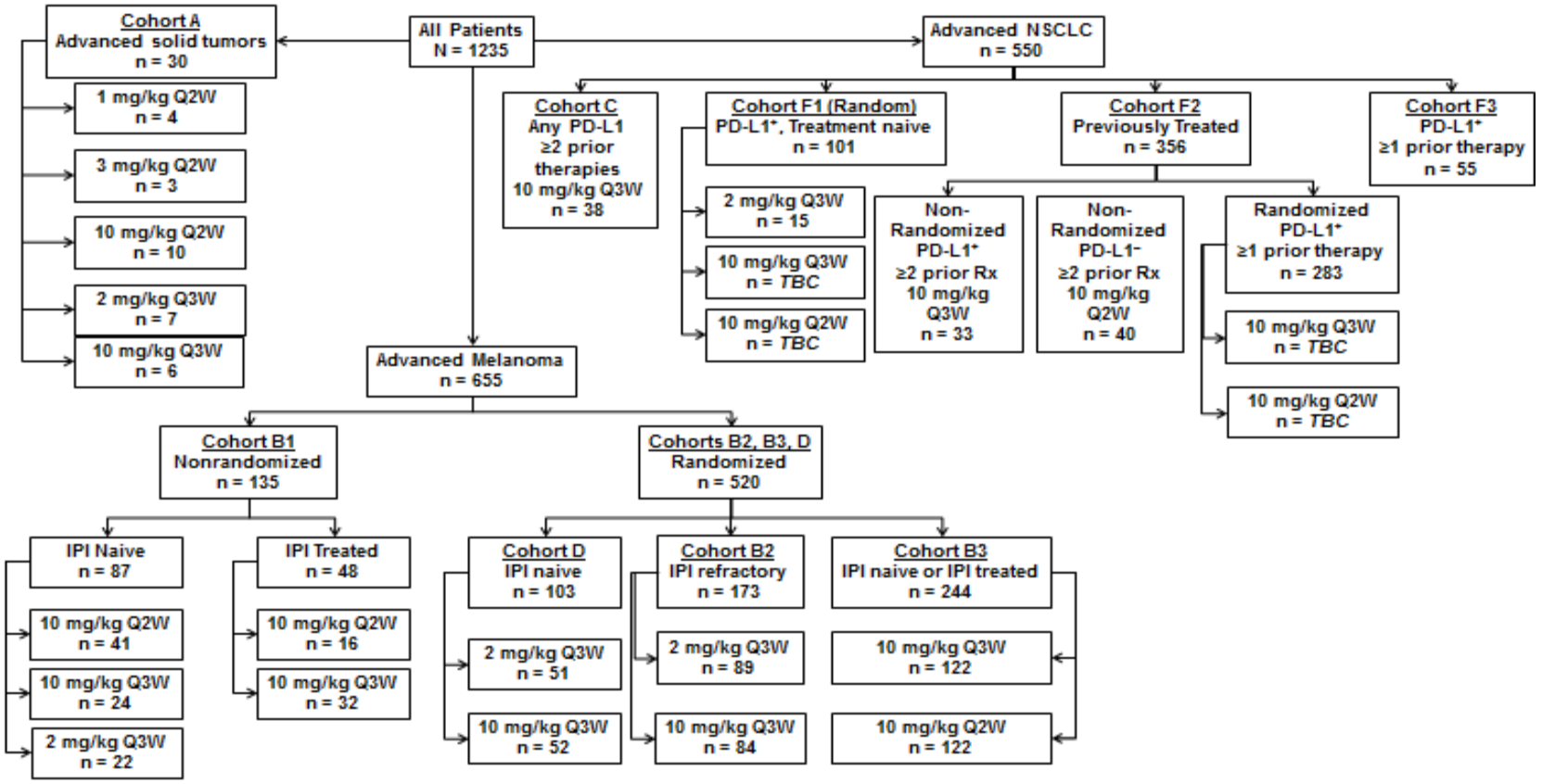


- No cytotoxic (ADCC/CDC) activity
- Pharmacokinetics supportive of dosing every 2 weeks (Q2W) or every 3 weeks (Q3W)
- Low occurrence of anti-drug antibodies and no impact on pharmacokinetics

Presented by: Antoni Ribas ASCO 2013

KEYNOTE-001 First in Human to Registration

- From a small Phase 1-the study expanded to a 655-melanoma and 550 NSCLC patient multi-part study

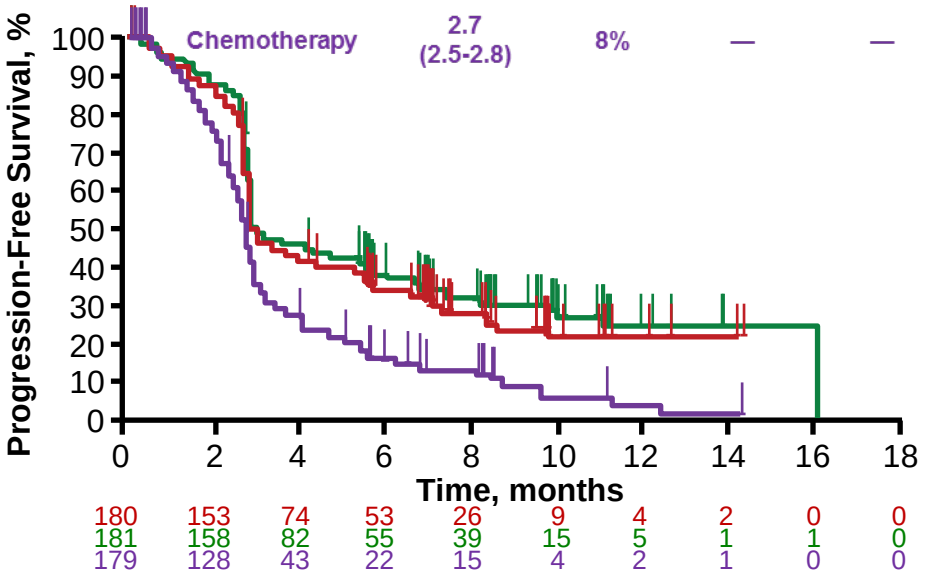


US Approval: Melanoma

- Grant of Breakthrough Therapy Designation Jan 2013
- Rolling submission initiated Jan 2014
- File accepted and priority review granted May 2014
- Accelerated Approval received in Sept 2014
  - indicated for unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor
  - Based on 173 IPI-refractory patients
  - Overall Response rate 24% and durable
  - Safety profile acceptable

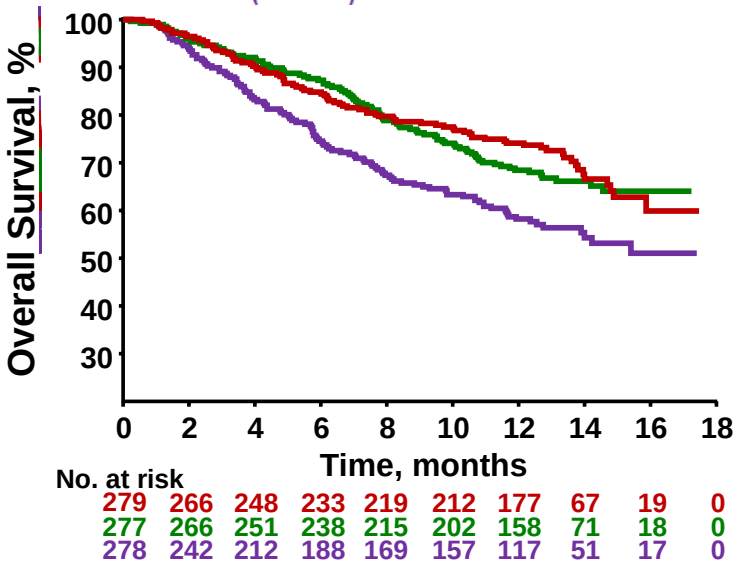
Melanoma: Phase 3 Trials Supported Full Approval December 2015

Arm	Median (95% CI), mo	Rate at 9 mo	HR (95% CI)	*P*
Pembro 2 Q3W	2.9 (2.8-3.8)	24%	0.57 (0.45-0.73)	<0.0001
Pembro 10 Q3W	2.9 (2.8-4.7)	29%	0.50 (0.39-0.64)	<0.0001
Chemotherapy	2.7 (2.5-2.8)	8%	—	—



Adapted from presentation by Antoni Ribas SMR 2014

Treatment Arm	Median (95% CI), mo	Rate at 12 mo	HR (95% CI)	*P*
Pembro Q2W	NR (NR-NR)	74.1%	0.63 (0.47-0.83)	0.00052
Pembro Q3W	NR (NR-NR)	68.4%	0.69 (0.52-0.90)	0.00358
Ipi	NR (12.7-NR)	58.2%	—	—

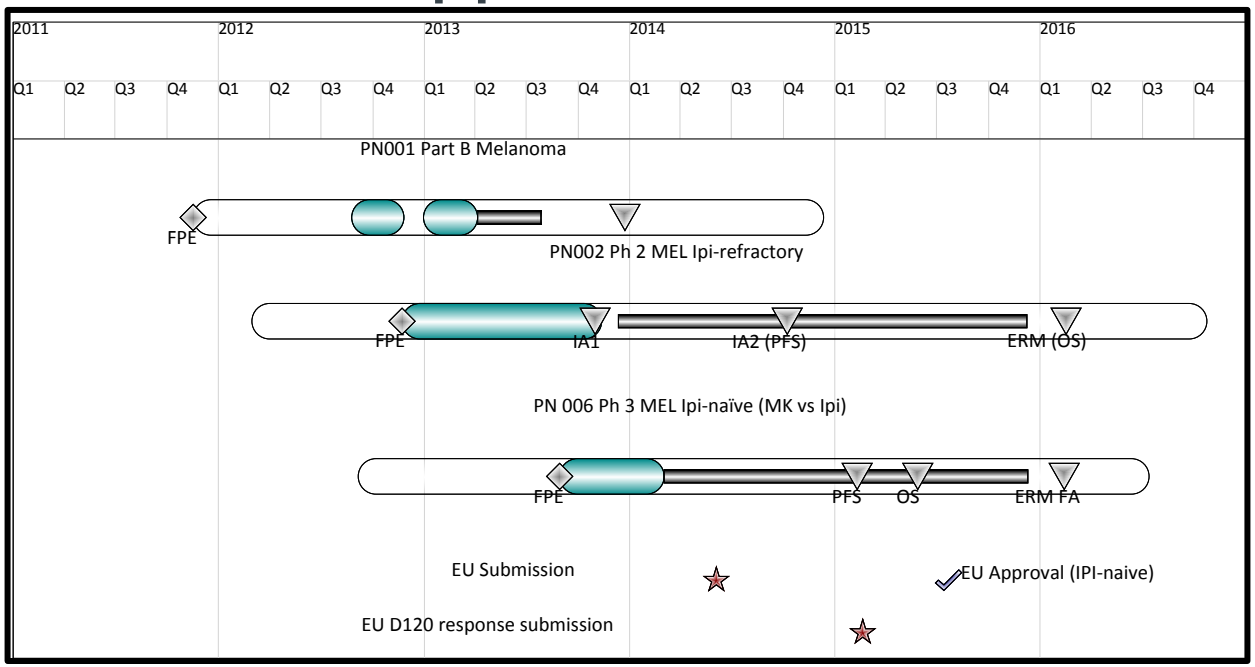


Adapted from presentation by Antoni Ribas, AACR 2015

Indication statement updated:

KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma

EU Approval - Melanoma



- Approval in a broad indication
  - Pembrolizumab as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults
- Full approval based on P001, P002 & P006
  - Efficacy on sub-populations (BRAF, PD-L1) also included in label

Differences in US & EU Approval Timelines

- US: Accelerated approval based on KN001 cohort B2
  - Narrow indication Sep 2014

vs.

- EU: Full approval based on KN001, KN002, KN006
  - Broad indication, 10.5 months later, July 2015

Explore new pathways in EU (PRIME, Adaptive Pathways) to accelerate approval and access to patients for new drugs/new indications

Pseudoprogression in Melanoma

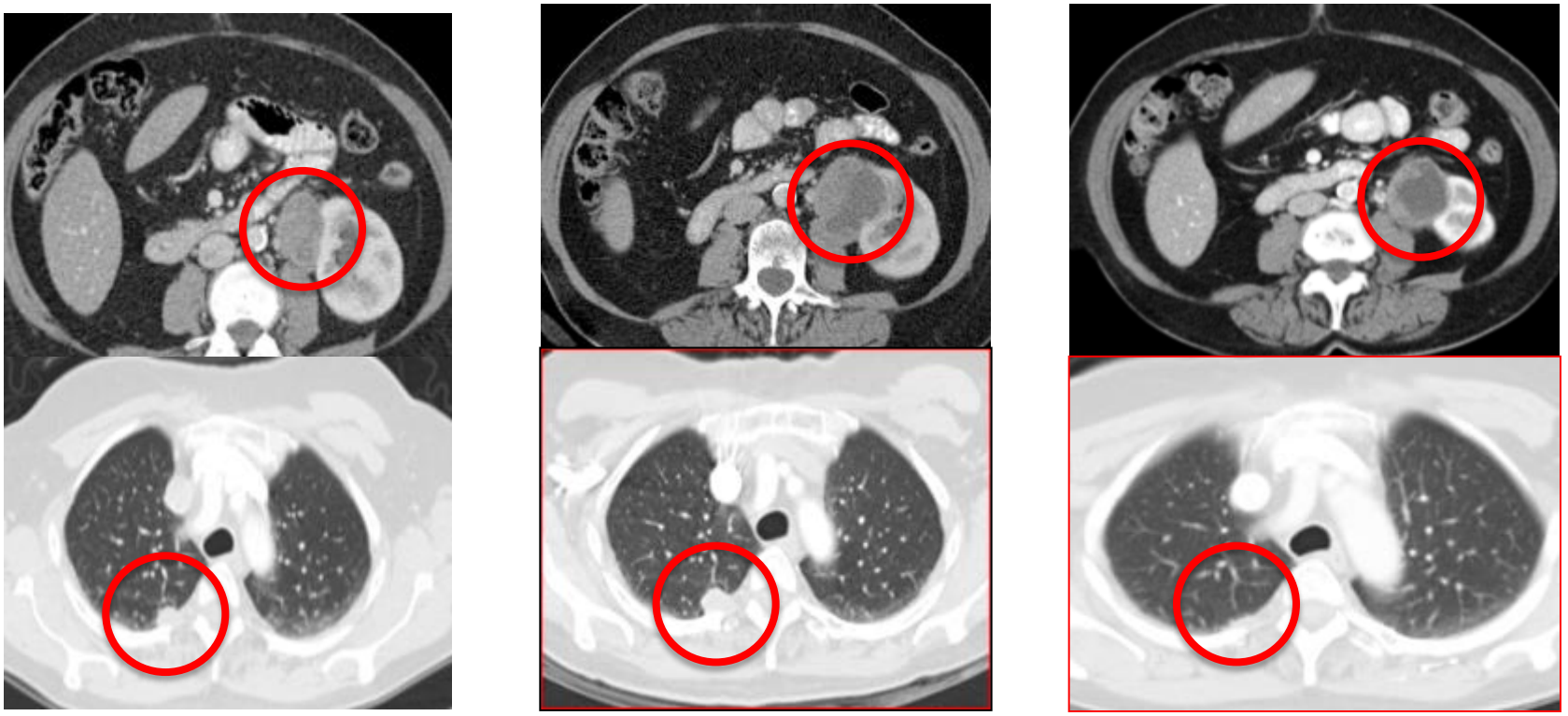
- Pseudo-progression:
  - Initial progression followed by response observed in melanoma patients treated with pembrolizumab
  - Also observed with anti–CTLA-4 and anti–PD-L1 therapy
  - RECIST 1.1 does not capture all the clinical benefit of an immunotherapy
- Immune-related response criteria (irRC) developed
  - Captures additional response patterns beyond RECIST 1.1
  - Allows investigators to make treatment decisions closer to real world practice

Assessment of Response in KEYNOTE-001 and Identification of Pseudoprogression

- Imaging performed every 12 weeks
  - RECIST v1.1 by central review for assessing response
  - irRC by investigator review for patient management
- Retrospective analysis of imaging per centrally review irRC conducted to identify
  - Early pseudoprogression: ≥25% increase in tumor burden at week 12 not confirmed as PD on the 2 following assessments
  - Delayed pseudoprogression: ≥25% increase in tumor burden at any assessment after week 12 not confirmed as PD at next assessment
  - Melanoma patients followed by imaging for ≥28 weeks (n = 327)

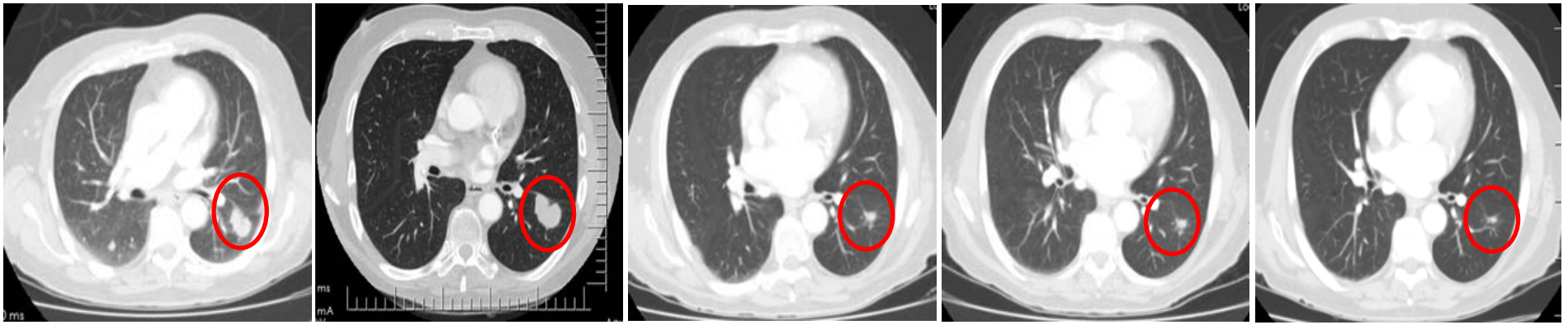
•Analysis cutoff date: October 2014.

Early Pseudoprogression: Patient (IPI-N) With Advanced Melanoma Treated With Pembrolizumab Melanoma (KEYNOTE-001)



•[a]Unconfirmed at this assessment (initial observation).
•Case courtesy of R. Dronca, Mayo Clinic, Rochester, MN.

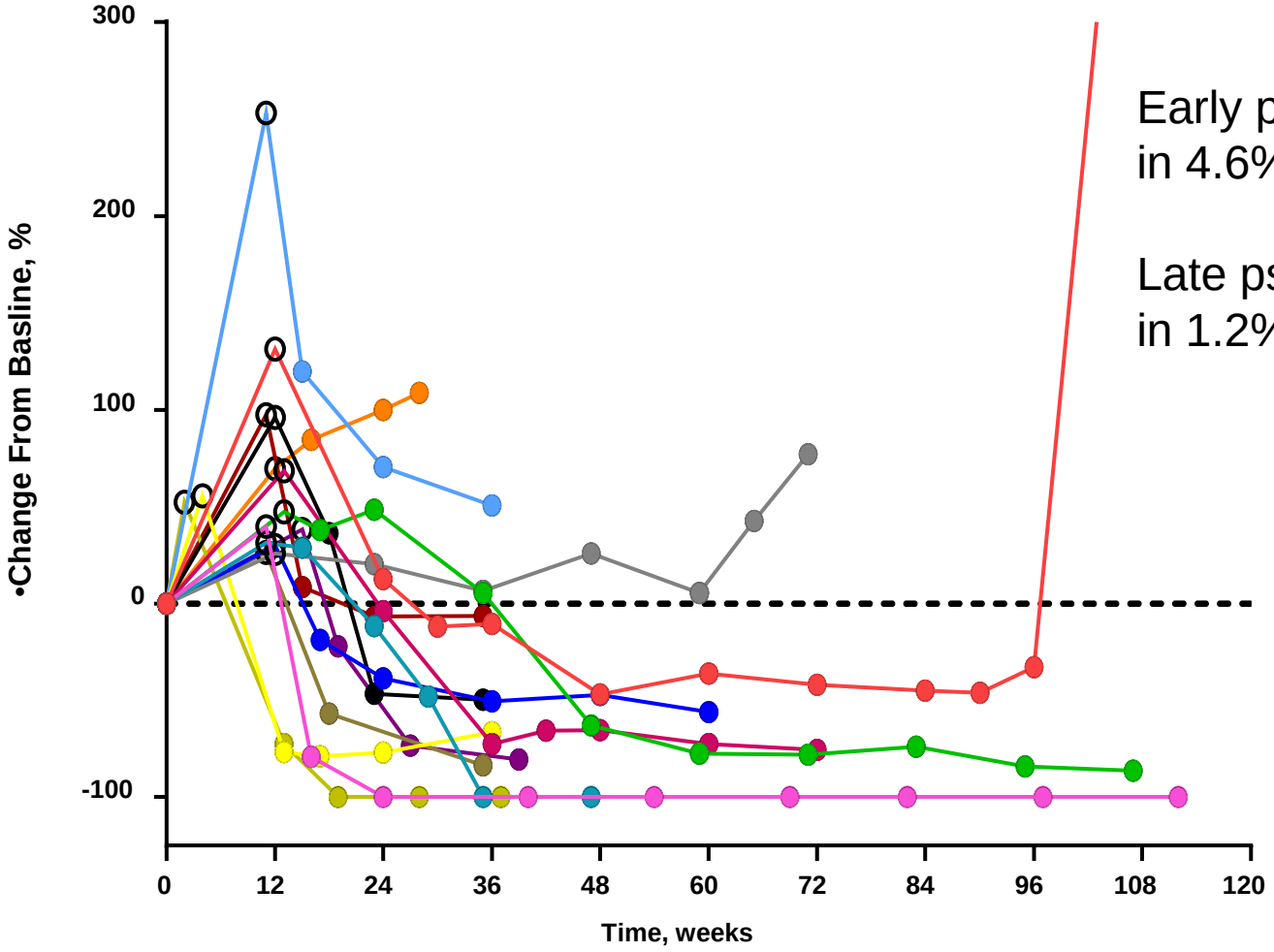
Early Pseudoprogression: Melanoma (KEYNOTE-001)



Baseline:	Week 4:	Week 16:	Week 24:	Week 60:
TL left lung	SOD 17% ↑ **SD by RECIST 1.1** SPD 55.5% ↑ **irPD by irRC**	SOD 55% ↓ **PR by RECIST 1.1** SPD 84.9% ↓ **irPR by irRC**	TL 55% ↓ **PR by RECIST 1.1** SPD 86.3% ↓ **irPR by irRC**	TL 49% ↓ **PR by RECIST 1.1** SPD 84.9% ↓ **irPR by irRC**

TL=target lesion; SOD=sum of diameters; SPD=sum of the products of diameters.

Early Pseudoprogression (irRC, Central Review)



Early pseudoprogression in 4.6%

Late pseudoprogression in 1.2%

•Circles represent times of radiologic assessment. Open circles represent the time at which the 25% threshold for pseudoprogression was crossed.
•Analysis cutoff: October 2014

Atypical Response Text in EU-SmPC

4.2 Posology and method of administration

Posology

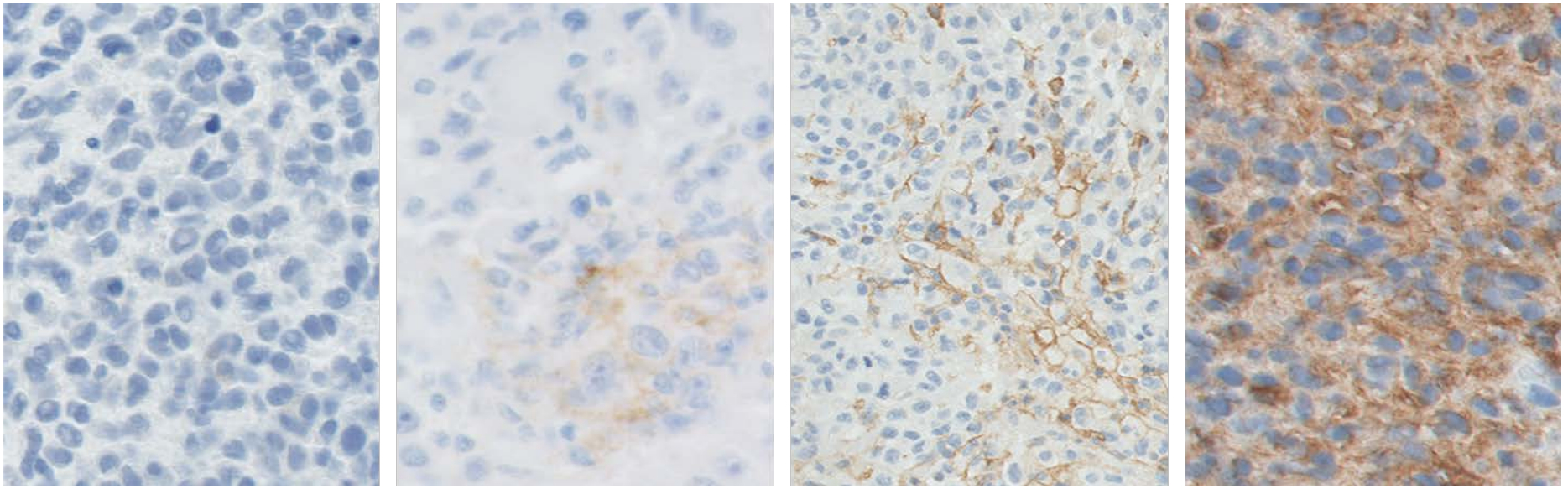
The recommended dose of KEYTRUDA is 2 mg/kg administered intravenously over 30 minutes every 3 weeks. Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity.

Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Biomarker Development in Melanoma: PD-L1 by IHC

- Tested using the Merck-DAKO 22C3 antibody test
  - Positive cutpoint of 1% for melanoma based on training and validation sets in Keynote-001
  - ORR:
    - Unselected 40%
    - PD-L1 positive 49%
    - PD-L1 negative 13%
  - Applied to KN-002 retrospectively and KN-006 prospectively

Examples of PD-L1 Melanoma Sample Immunohistochemical Staining



PD-L1–Negative

PD-L1–Positive

- PD-L1 positivity was defined as staining in ≥1% of tumor cells or inflammatory cells if present in tumor nests

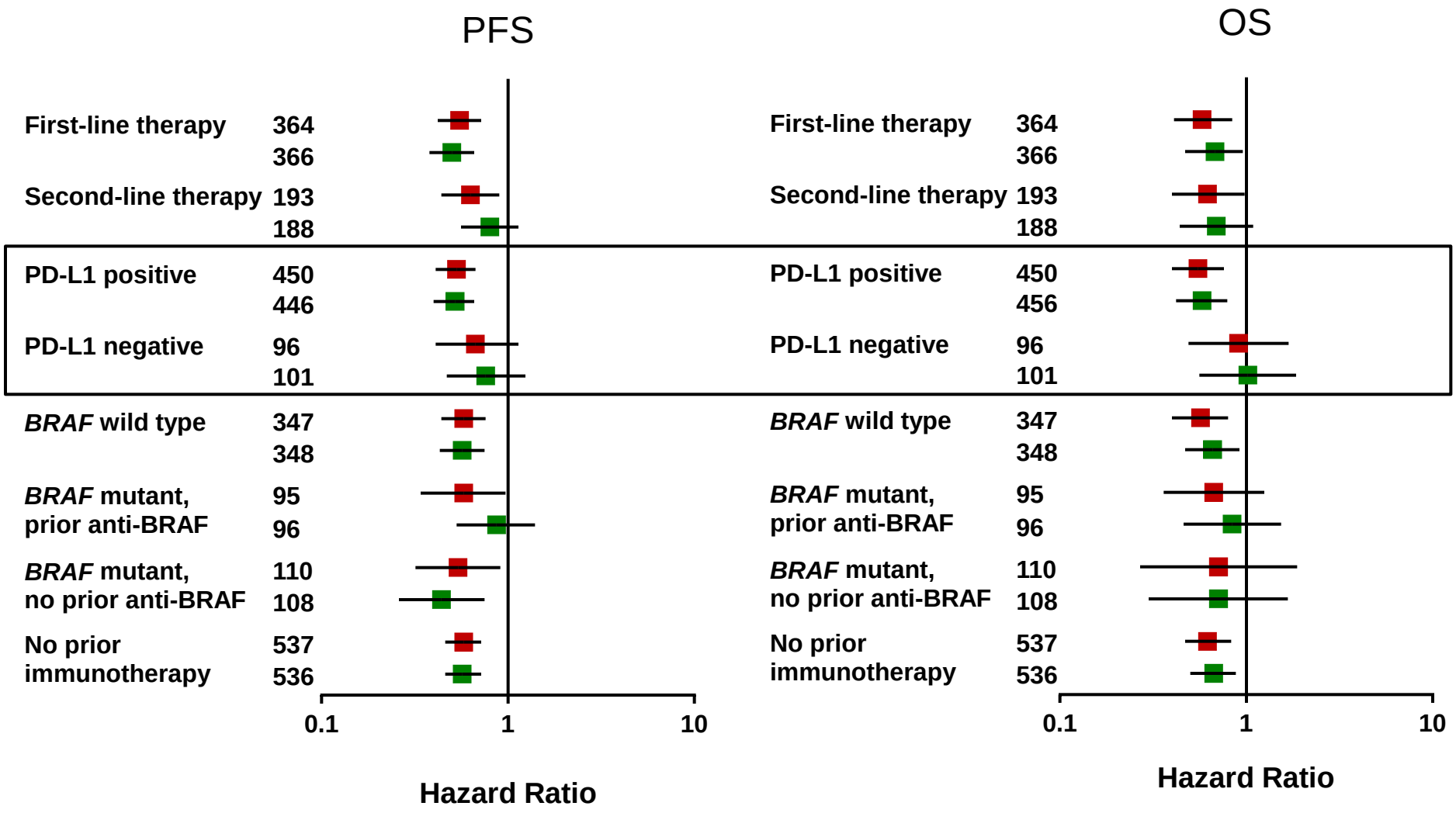
Summary of Efficacy Data from KN002 and KN006 in PD-L1 Subgroups (from EU-SmPC)

	KN006				KN002			
	Pembro*		IPI		Pembro*		Chemo	
PD-L1	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg
PFS HR	0.53	0.73	---	---	0.52	0.60	---	---
OS HR	0.56	0.95	---	---	0.82	0.77	---	---
ORR (%)	37	18	12	11	26	15	4	8

*pooled treatment arms

- PD-L1 prevalence 69-82% in KN002 and KN006
- Pembrolizumab treatment effect present in PD-L1 positive and negative patients

Keynote-006: Efficacy in PD-L1 Subgroups



Biomarker Development in Melanoma

- PD-L1 expression by IHC as a biomarker:
  - High overall prevalence of PD-L1 positivity
  - Clinically benefit seen in meaningful numbers of PD-L1 negative patients
  - No clinical utility in patient selection for pembrolizumab monotherapy
  - May have a role in selecting combination therapies over monotherapy

Post Authorization Measure on Biomarkers in EU

- Post-authorization measure:
  - The value of biomarkers to predict the efficacy of pembrolizumab should be further explored
    - Additional biomarkers other than PD-L1 expression status by IHC (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy
    - More information regarding archival vs fresh tissue and pre vs post treatment regarding expression of PD-L1 in the ongoing melanoma studies
- For new indications clearly establish clinical utility of PD-L1 or new generation biomarkers