

Challenges of Anti-Cancer Immunotherapy Development- Industry Perspective

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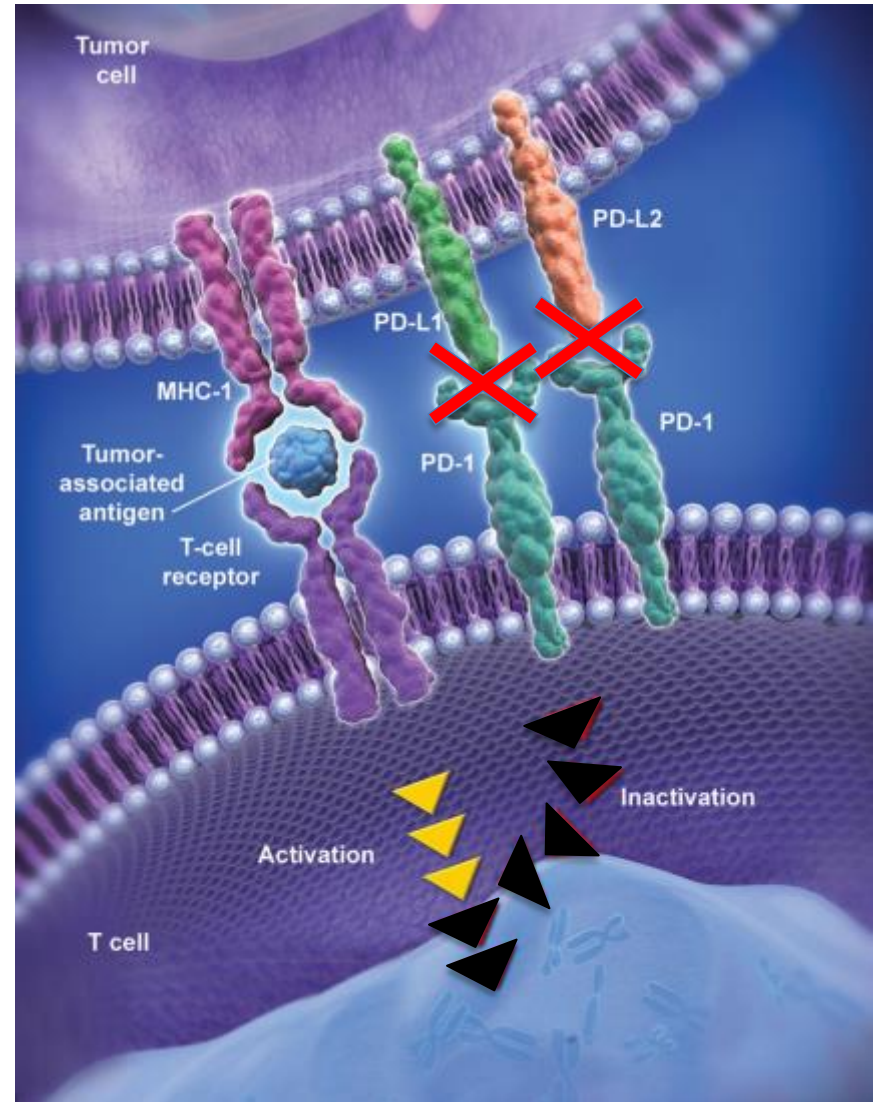
Merck Sharp & Dohme

Key Challenges

- Unique mechanism of action and increasing commercial availability create a challenge for use of traditional efficacy endpoints to assess clinical benefit
- Biomarkers predictive of efficacy have been identified, but similar to other biomarkers used in cancer, are not completely accurate in identifying responders and non-responders

PD-1 and PD-L1/L2 Pathway

- PD-1 is an immune checkpoint receptor
- Binding of PD-1 by its ligands PD-L1 or PD-L2 leads to downregulation of T-cell function
- This mechanism is usurped by many tumors
- PD-1 blockade through mAb therapy can restore and reveal effective anti-tumor immunity



Topalian et al. *N Engl J Med.* 2012.
Garon et al. *N Engl J Med.* 2015.
Robert et al. *Lancet.* 2014.

PFS in Assessing Clinical Benefit

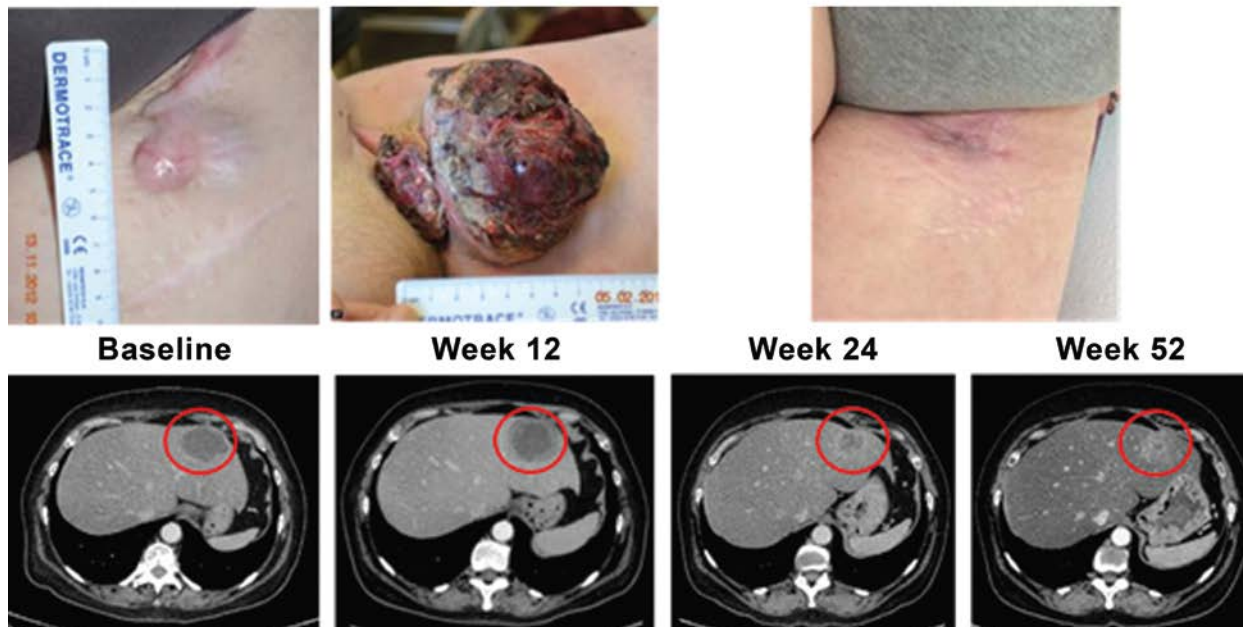
- PFS may provide a more reliable assessment of clinical benefit than OS in certain scenarios
 - Crossover may confound OS comparison in a randomized study
 - OS effect may be diluted by multiple effective subsequent treatments
- PFS may not always indicate clinical benefit
 - Delay in disease progression may be offset by toxicity
- **With increasing availability of highly effective immunotherapies and the resulting potential for crossover, PFS will likely become an increasingly important endpoint for assessing clinical benefit**

Progression by RECIST vs “irRECIST”

- RECIST may “overcall” progression events for immunotherapy drugs, confounding PFS calculations
 - “new lesions” may represent immune cell infiltration rather than increased mass of tumor cells
 - Supported by biopsies of post-treatment metastatic lesions
- Regulators and IRBs have allowed treatment beyond RECIST progression in clinical studies, but PFS by “irRECIST” is not a recognized regulatory endpoint
- Little data on use of “irRECIST” for calculation of PFS with non-immunotherapy standard-of-care treatments
 - Investigators may not be willing to continue treatment with non-immunotherapy treatments beyond RECIST progression
- However, with recent and upcoming approvals, both arms of a randomized study may involve immunotherapy
 - **“irPFS” may be important in assessing benefit in such studies**

Example of Progression by RECIST, Followed by Response

A

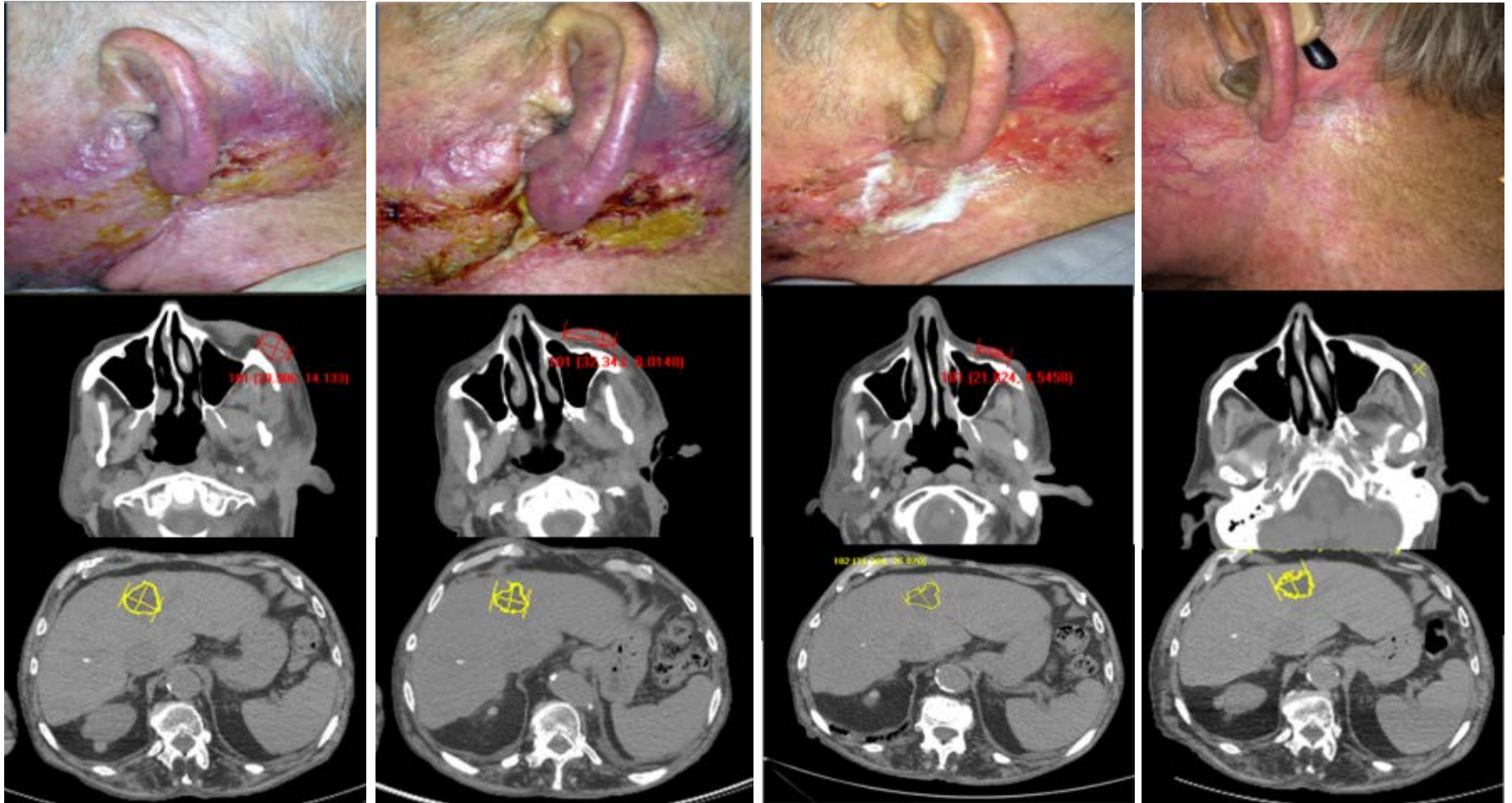


Pembrolizumab-treated melanoma patient

Among 592 patients with melanoma who survived ≥ 12 weeks, 84 (**14%**) patients experienced progressive disease per RECIST v1.1 but non-progressive disease per irRC

Hodi, et al., JCO 2016, in press

Not Unique to Melanoma: Pembrolizumab-Treated Head and Neck Cancer Patient



Baseline:
Extensive skin infiltration
and liver metastasis

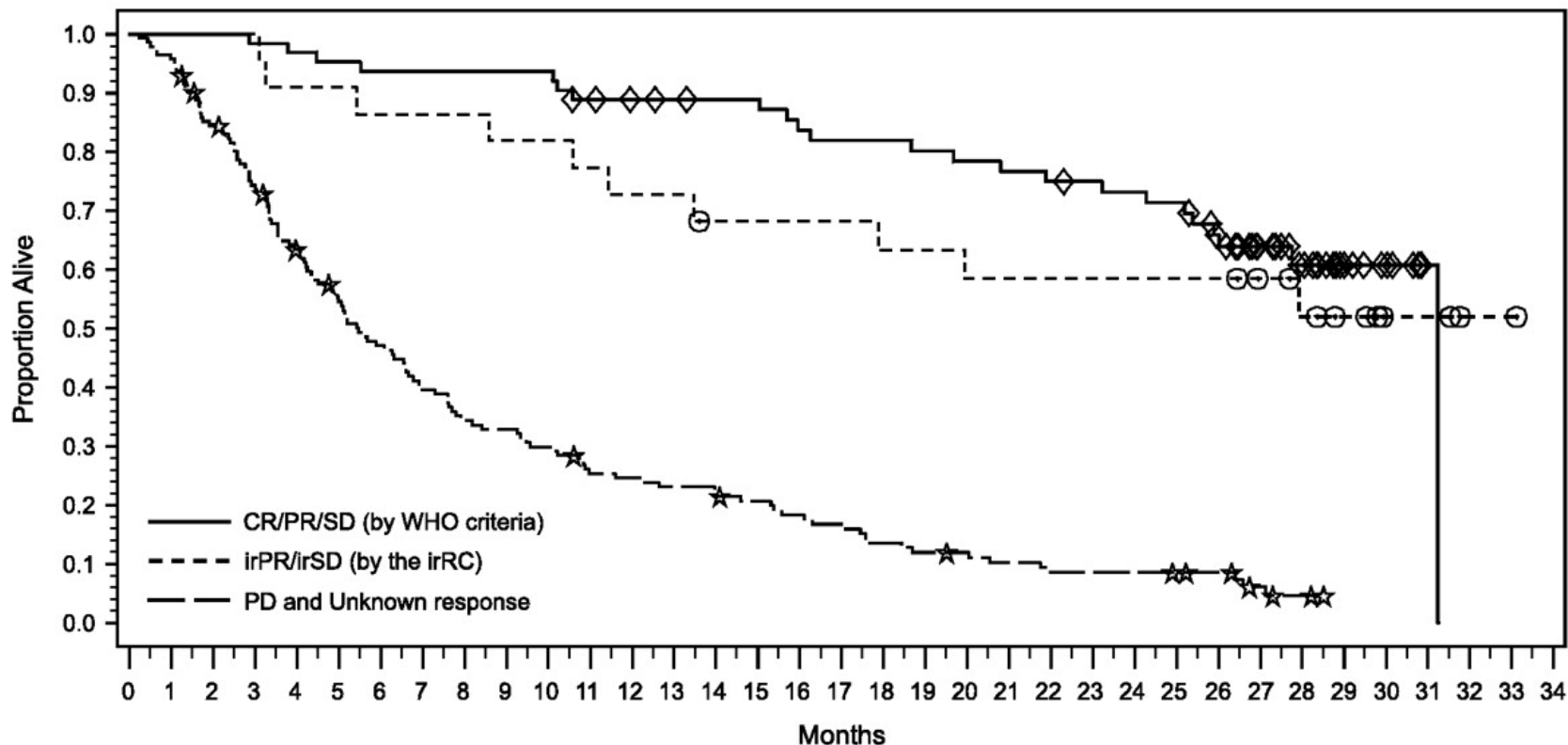
Month 1:
Marked local edema,
hospital admission
Week 8 CT: **PD** by RECIST 1.1
due to non-target

Month 3:
Clinical improvement
Week 12 CT: Stable disease

Month 6:
Skin disease near CR
Week 40 CT
head lesion almost resolved,
liver lesion
unchanged

Case courtesy of Dr. Tanguy Seiwert

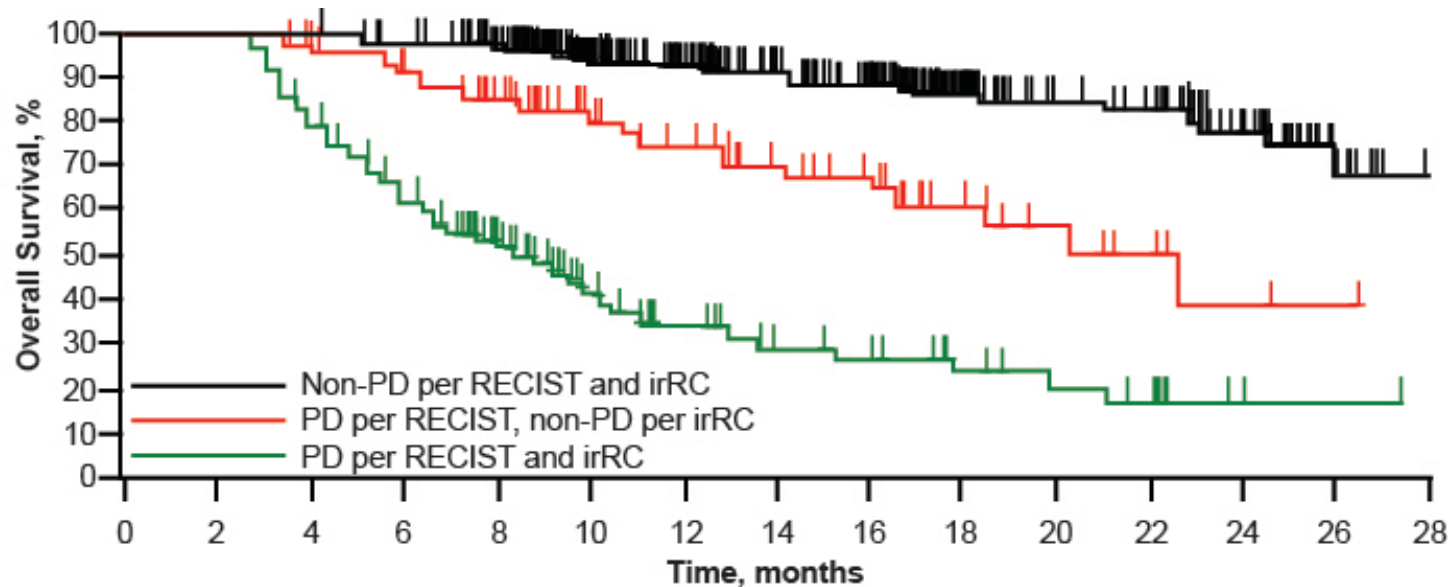
Association of OS with irRC vs RECIST Progression Criteria – Ipilimumab Melanoma



Subjects at Risk

CR/PR/SD	63	63	63	62	61	60	59	59	59	59	59	55	53	52	51	51	48	47	47	46	45	44	43	42	41	40	34	24	18	10	6	1	0	0	0
irPR/irSD	22	22	22	22	20	20	19	19	19	18	18	17	16	16	14	14	14	14	13	13	12	12	12	12	12	12	12	10	8	6	3	3	1	1	0
PD/Unkown	142	136	118	102	86	73	63	53	46	44	40	33	32	30	28	26	23	21	17	15	14	12	10	10	10	9	8	4	2	0	0	0	0	0	0

Association of OS with irRC vs RECIST Progression Criteria – Pembrolizumab Melanoma



n at risk

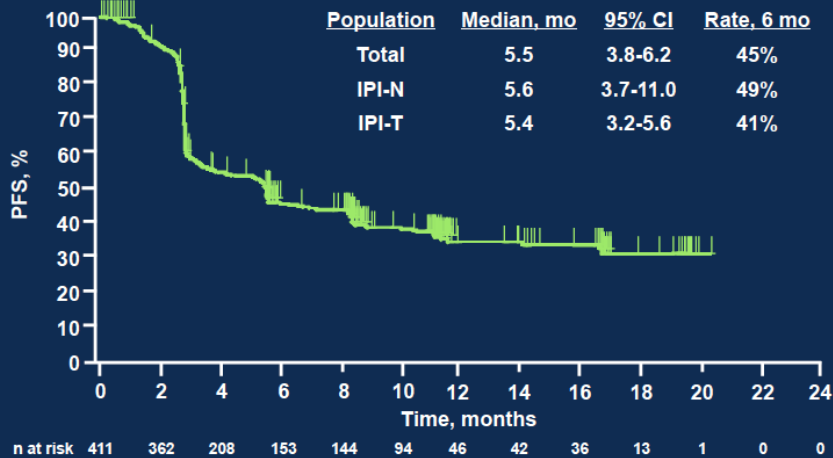
Non-PD per RECIST and irRC	331	331	329	321	301	219	192	159	136	79	60	55	31	8	0
PD per RECIST, non-PD per irRC	84	84	79	71	60	44	37	28	22	13	9	6	3	2	1
PD per RECIST and irRC	177	177	139	109	75	48	33	23	20	15	10	8	1	1	0

Melanoma Pembrolizumab (ASCO 2014)

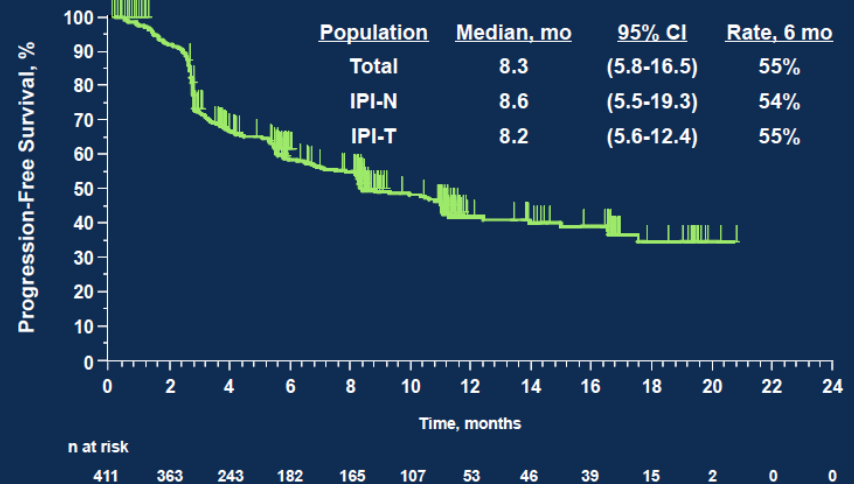
RECIST by independent review, irRC by investigator

n=411

Kaplan-Meier Estimate of PFS per RECIST 1.1, Independent Central Review



Kaplan-Meier Estimate of PFS per irRC, Investigator Review



Median PFS (mo)

RECIST

5.5

6 mo PFS

45%

irRC

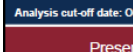
8.3

55%



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Using Biomarkers (Companion Diagnostics) to Select Patients for Treatment

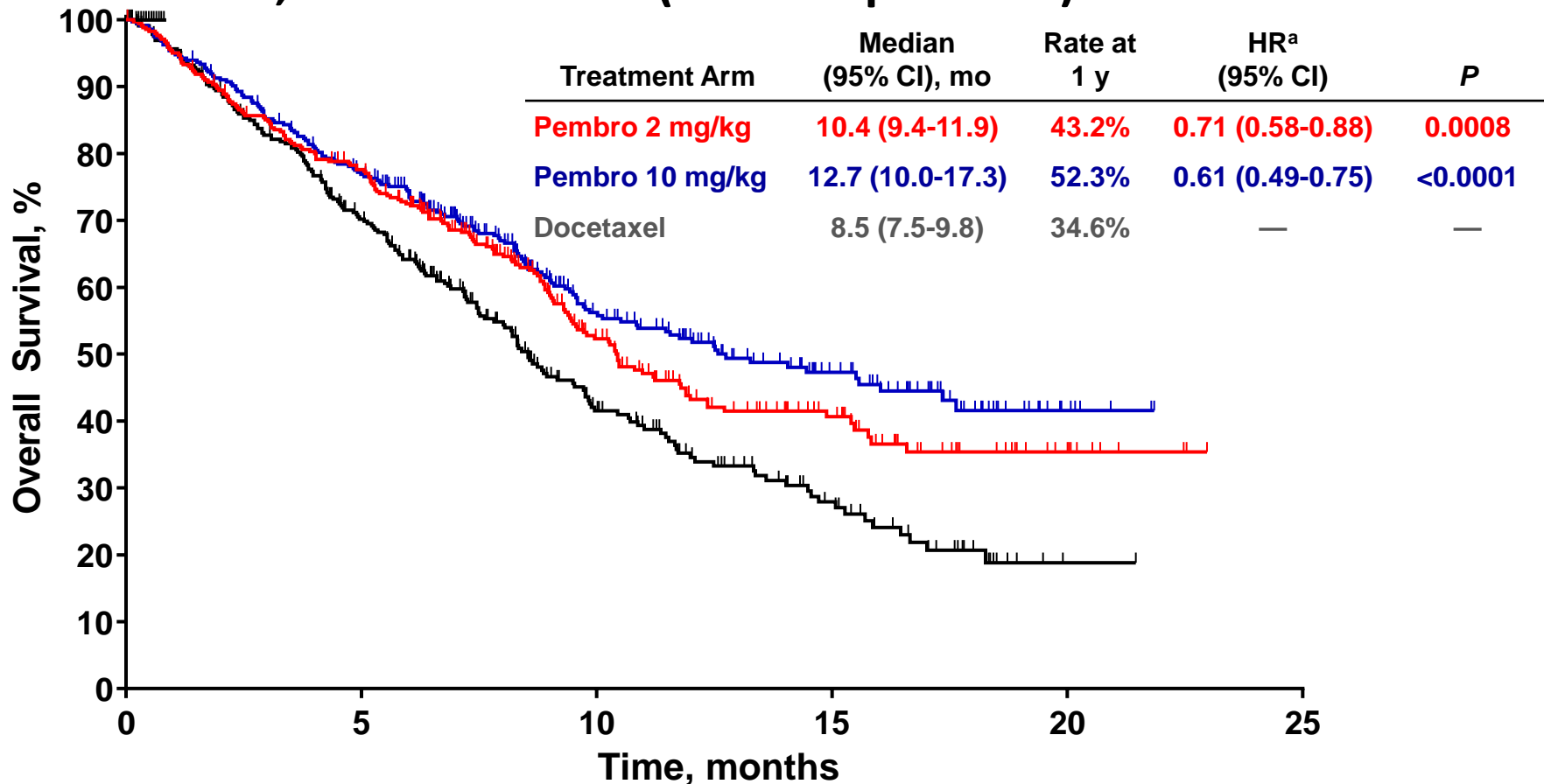
- Histology is an imperfect biomarker that is used to select cancer patients for treatment
- “No test is perfect, but some tests are useful”
 - Imperfect HER2 IHC test allowed rapid development of an effective treatment for breast cancer patients
 - PD-L1 IHC test allowed accelerated development of PD-1 targeting in lung cancer
 - Companion diagnostics may be used to select among treatment options, vs excluding patients from an immunotherapy treatment
- Companion diagnostic development typically lags behind therapeutics, creating scientific and regulatory complexity
- Several biomarkers for PD-1 targeting agents have been identified that are predictive for efficacy, including PD-L1 protein expression, RNA signatures, and MSI/DNA mutation burden

Clinical Utility of PD-L1 Expression in Lung Cancer

- PD-L1 expression predicts survival outcome in lung cancer patients treated with PD-1 antibodies
 - In a pembrolizumab randomized study in 2L NSCLC, a survival benefit vs docetaxel was observed in patients with $\geq 1\%$ PD-L1 tumor staining (Herbst, et al, Lancet 2015)
 - In a randomized study in 2L non-squamous NSCLC, survival was similar in patients with PD-L1-negative tumors treated with nivolumab vs docetaxel (Borghaei, et al, NEJM 2015)

Pembrolizumab vs Docetaxel in Previously Treated NSCLC Patients

OS, PD-L1 TPS $\geq 1\%$ (Total Population)

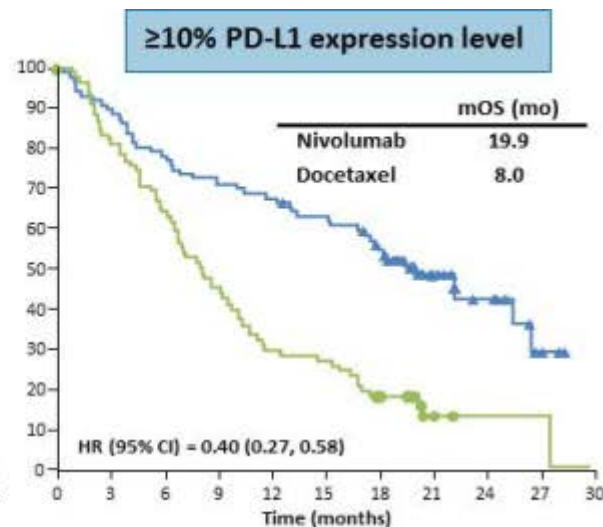
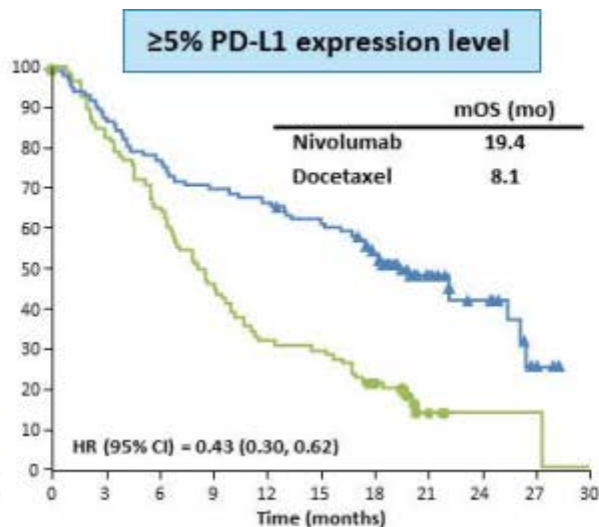
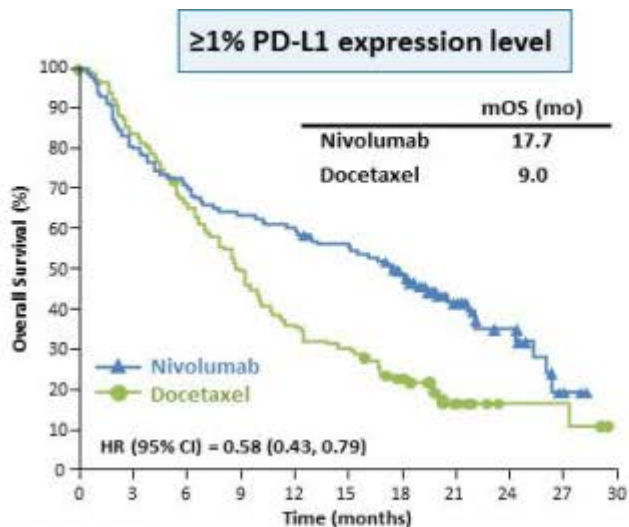


344	259	115	49	12	0
346	255	124	56	6	0
343	212	79	33	1	0

^aComparison of pembrolizumab vs docetaxel.

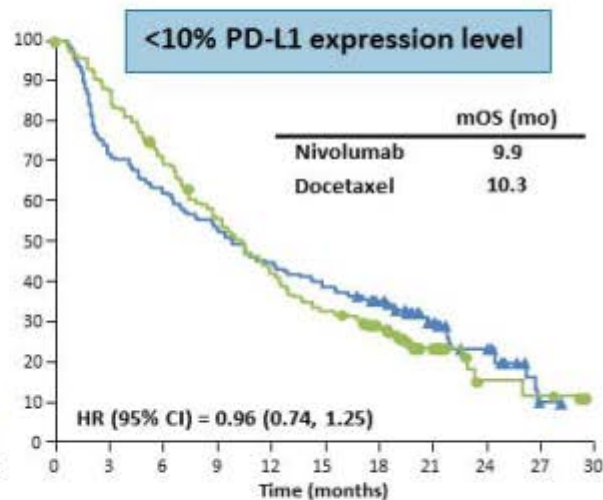
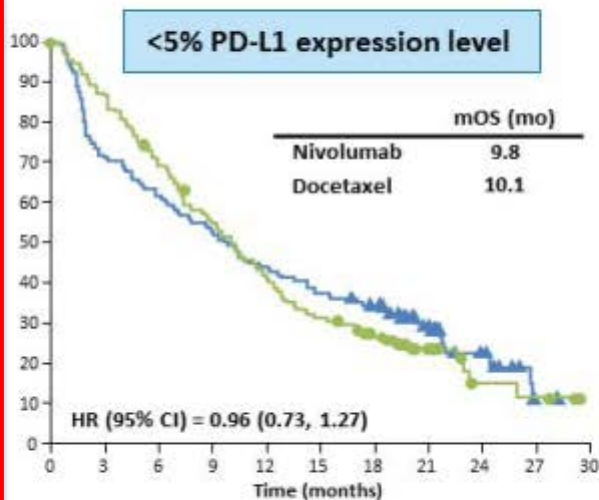
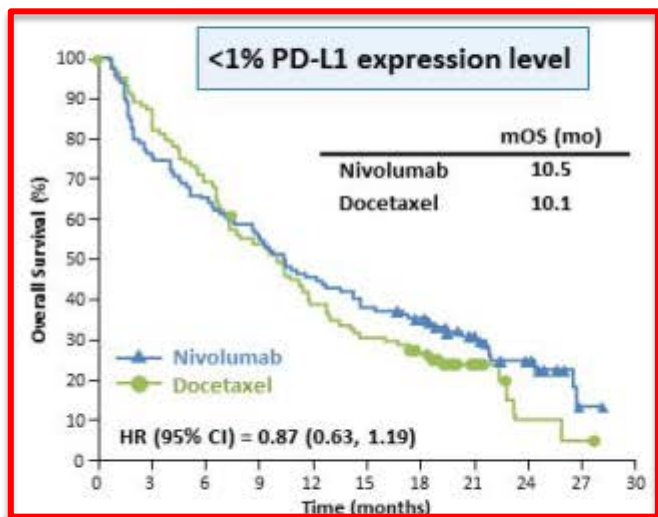
Analysis cut-off date: September 30, 2015.

Nivolumab vs Taxotere in Previously Treated Non-Squamous NSCLC Patients: OS by PD-L1 Status



Number of patients at risk

Nivolumab	123	99	87	78	74	68	56	24	13	3	0	95	83	73	66	63	58	47	20	12	3	0	86	77	67	61	58	53	44	19	11	3	0
Docetaxel	123	102	80	61	44	37	24	8	3	3	0	86	70	55	39	27	28	17	4	1	1	0	79	63	50	35	23	21	13	3	1	1	0



Number of patients at risk

Nivolumab	108	82	70	61	49	41	36	23	13	1	0	136	98	84	73	60	51	45	27	14	1	0	145	104	90	78	65	56	48	28	15	1	0
Docetaxel	101	87	69	53	38	30	24	11	2	1	0	138	119	94	75	55	42	31	15	4	3	0	145	126	99	79	59	46	35	16	4	3	0

Summary

- PFS Kaplan-Meier curves (and median PFS) for immunotherapies may be different when assessed by RECIST vs “irRECIST”
 - Patients with progression by RECIST but non-progression by irRC criteria have similar survival outcomes compared to patients with non-progression by RECIST
 - A uniform definition of “irRECIST” is needed
 - Analyses of immunotherapies across various cancer types are needed
- While not a perfect test, clinical utility of PD-L1 protein expression has been established in NSCLC
 - Additional predictive biomarkers involving RNA and DNA are under development – it remains to be determined whether these will have superior clinical utility relative to PD-L1 expression