Immunomodulation with a Focus on the Clinical Development of PD-1/PD-L1 Inhibitors in Non-Small Cell Lung Cancer

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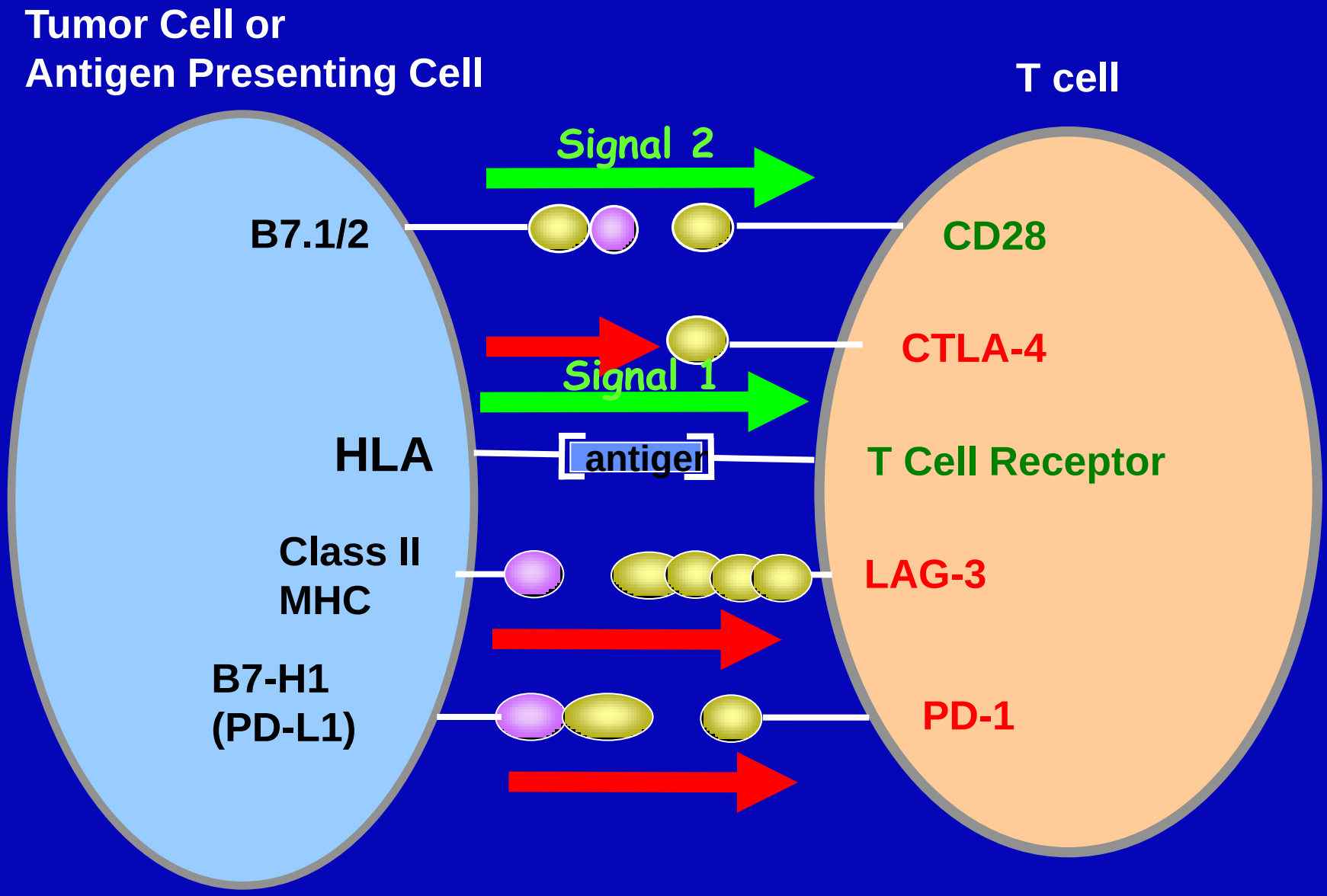
Disclosures

- Consultant/Advisory board member – BMS (Uncompensated), Merck (compensated)
- Institutional Research Support - BMS

Potential Mechanisms for Immune Evasion in Lung Cancer

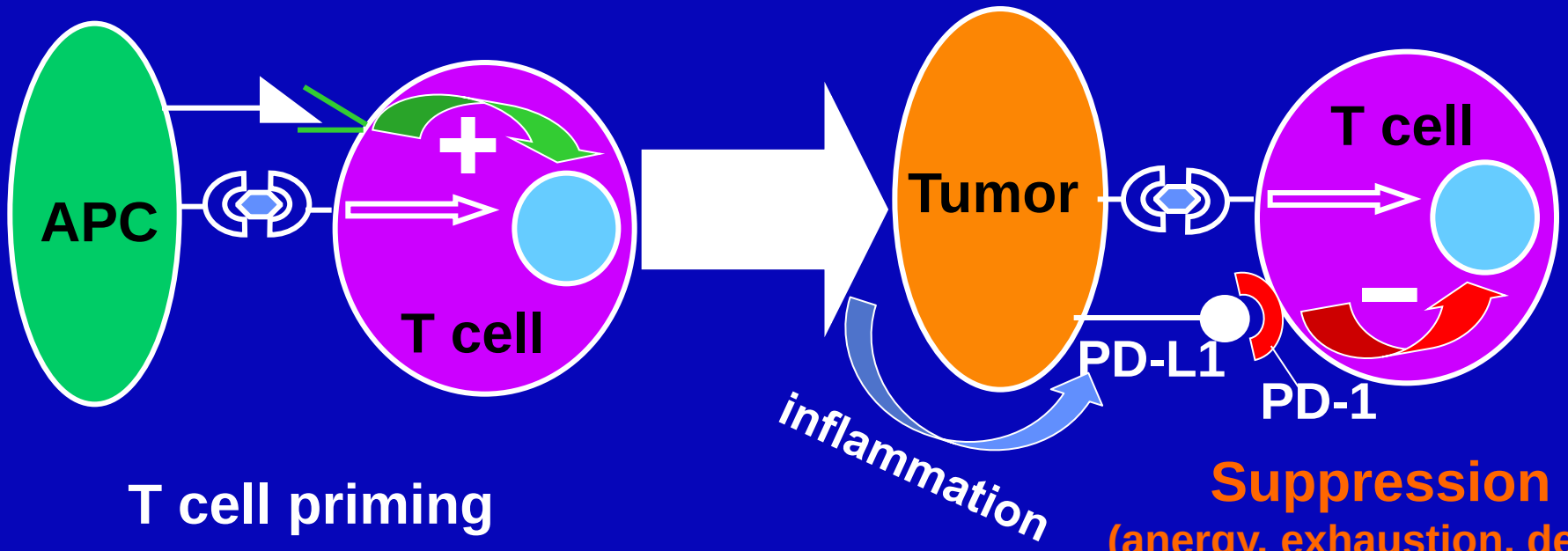
- Defective antigen presentation
- Immunosuppressive cell infiltrates - T reg and MDSCs
- Upregulation/secretion of immunosuppressive cytokines
- Checkpoint pathways

Immune Checkpoint Pathways



Others: ICOS, GITR, Tim-3

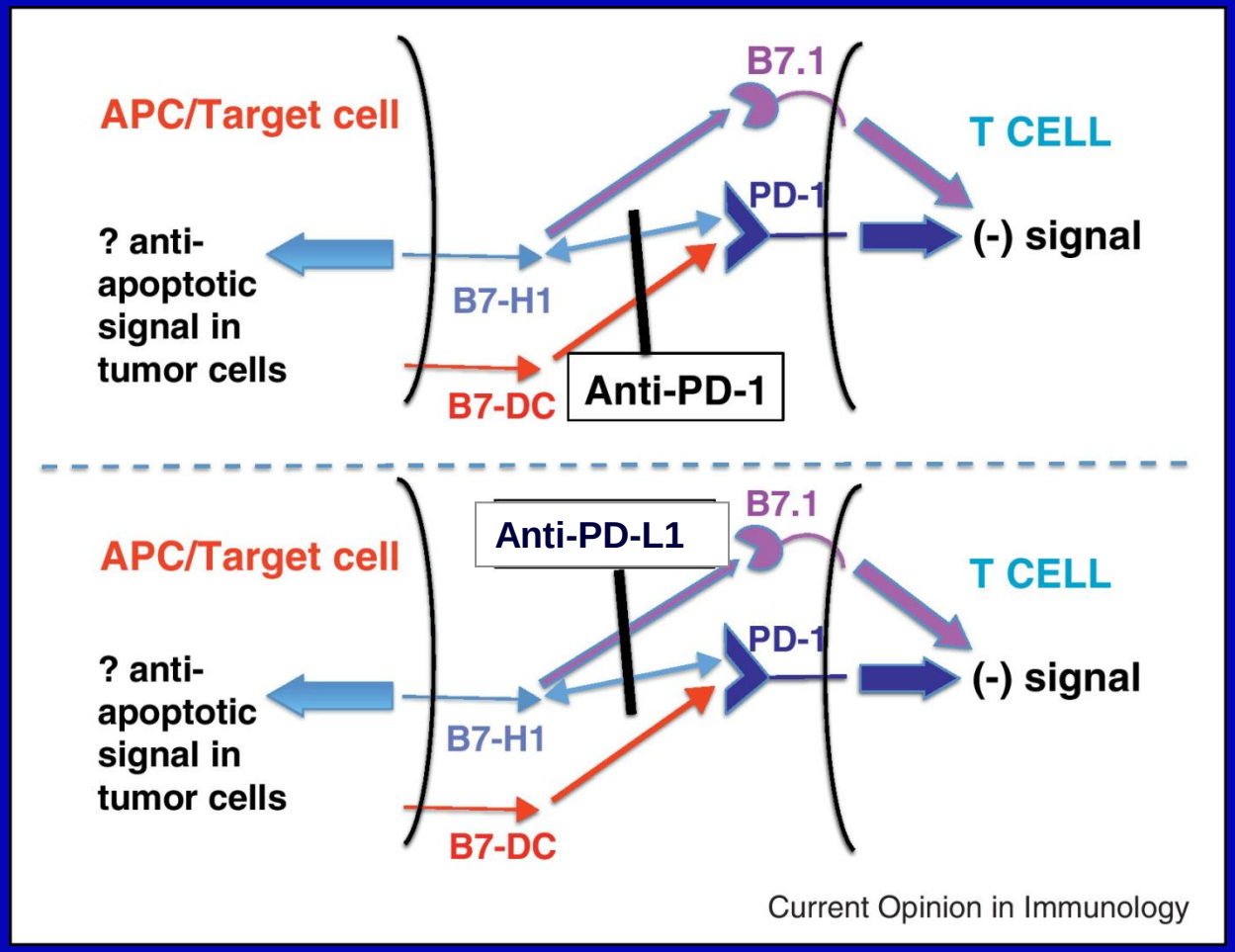
PD-1/PD-L1: Pathway: Tumor cells – T cells



- PD-L1 can be expressed on tumor cells either endogenously or induced by association with T cells (adaptive immune resistance)[1,2]
- In RCC, melanoma and other tumors, PD-L1 expression has been shown to be associated with adverse clinical/pathologic features, including[3]:
  - More aggressive disease
  - Shorter survival

[1]Topalian et al. *Curr Opin Immunol 2012,* [2]Taube JM, et al. *Science Transl Med.* 2012;4:127ra37. [3]Thompson RH, et al. *PNAS* 2004.

Potential Differences in PD-1 vs. PD-L1 Blockade



Topalian S et al Curr Opin Immunol 2012

Clinical Development of Inhibitors of PD-1 Immune Checkpoint

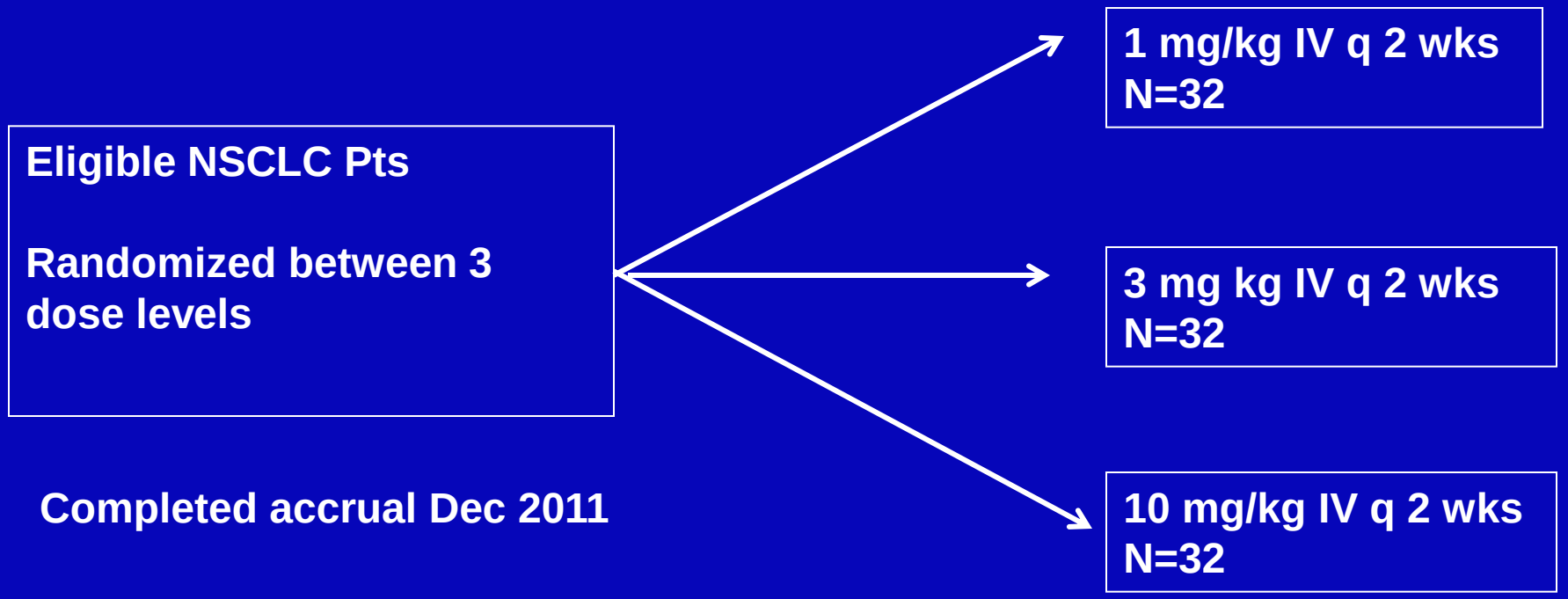
Target	Antibody	Molecule	Company	Development stage
PD-1	Nivolumab-BMS-936558	Fully human IgG4	Bristol-Myers Squibb	Phase III multiple tumors
	Pidilizumab CT-011	Humanized IgG1	CureTech	Phase II multiple tumors
	MK-3475	Humanized IgG4	Merck	Phase I-III
PD-L1	BMS-936559	Fully human IgG4	Bristol-Myers Squibb	Phase I
	MedI-4736	Engineered human IgG1	MedImmune	Phase I
	MPDL-3280A	Engineered human IgG1	Genentech	Phase I-III
	MSB0010718C	Human IgG1	EMD Serono	Phase I

Inhibitors of PD-1 – Phase I Trials

Antibody	Molecule	Dose/schedule tested	Eligible patients	Results
BMS-936558 (Nivolumab)	Fully human IgG4 mAb	1,3,10 mg/kg IV once every 2 wks in 8wk cycles	N= 304 MEL, RCC, NSCLC, CRC, Prostate Ca	No MTD identified
MK-3475	Humanized IgG1 mAb	1,3,10 IV once every 2 or 3 wks in 6 wk cycles	N= 140+ Solid tumors	No MTD identified

Topalian S et al NEJM 2012: Ribas A et al NEJM 2013

Nivolumab (Anti-PD-1) Phase I Trial: Expansion Cohorts for NSCLC



Completed accrual Dec 2011

Current analysis for patients treated through July 2012

129 patients with NSCLC were evaluable for safety and clinical activity

Efficacy of Nivolumab Monotherapy in Patients with NSCLC

Dose mg/kg	ORR[a,b] % (n/N)	Estimated Median DOR Weeks (Range)	Stable Disease Rate ≥24 Wks % (n/N)	Median PFS Months (95% CI)	Median OS Months (95% CI)
All doses	17.1 (22/129)	74.0 (6.1+, 133.9+)	10.1 (13/129)	2.3 (1.9, 3.7)	9.9 (7.8, 12.4)
1	3.0 (1/33)	63.9 (63.9, 63.9)	15.2 (5/33)	1.9 (1.8, 3.6)	9.2 (5.3, 11.1)
3	24.3 (9/37)	74.0 (16.1+, 133.9+)	8.1 (3/37)	1.9 (1.7, 12.5)	14.9 (7.3, NE)
10	20.3 (12/59)	83.1 (6.1+, 132.7+)	8.5 (5/59)	3.6 (1.9, 3.8)	9.2 (5.2, 12.4)

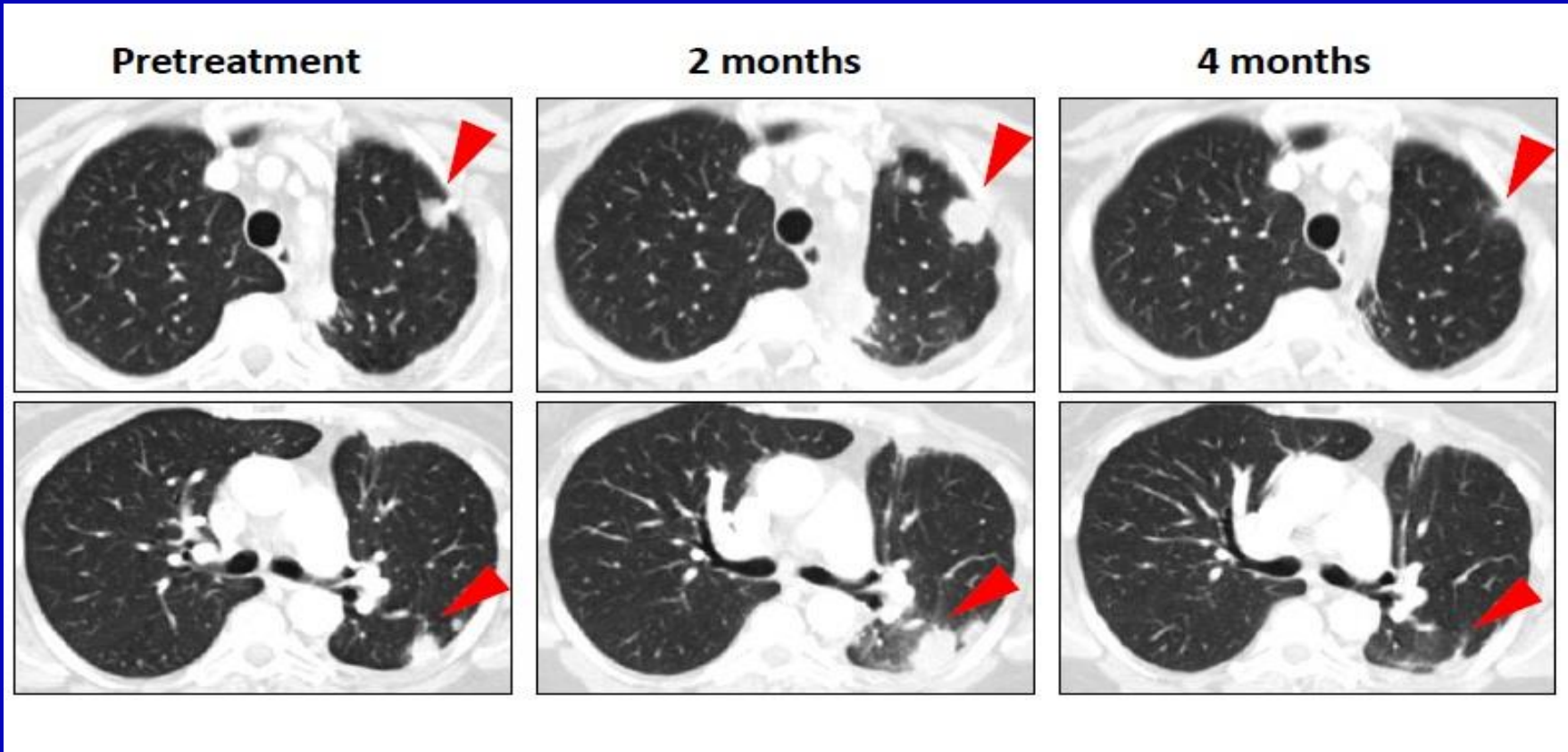
CI = confidence interval; DOR = duration of response; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

[a]Tumors and responses were assessed after each cycle per modified RECIST v1.0.

[b]All efficacy analyses based on data collected as of September 2013

- Durable responses were observed; responses are ongoing in 45% of patients (10/22)
- Higher ORRs observed at 3 and 10 mg/kg nivolumab doses relative to 1 mg/kg dose
- Rapid responses; 50% of patients (11/22) demonstrating response at first assessment (8 weeks)
- 7/16 responders who discontinued for reasons other than disease progression responded for ≥16 wks; 6/7 remain in response
- Similar response rates in both squamous and nonsquamous histologies
- 6 patients with unconventional “immune-related” responses were not included as responders

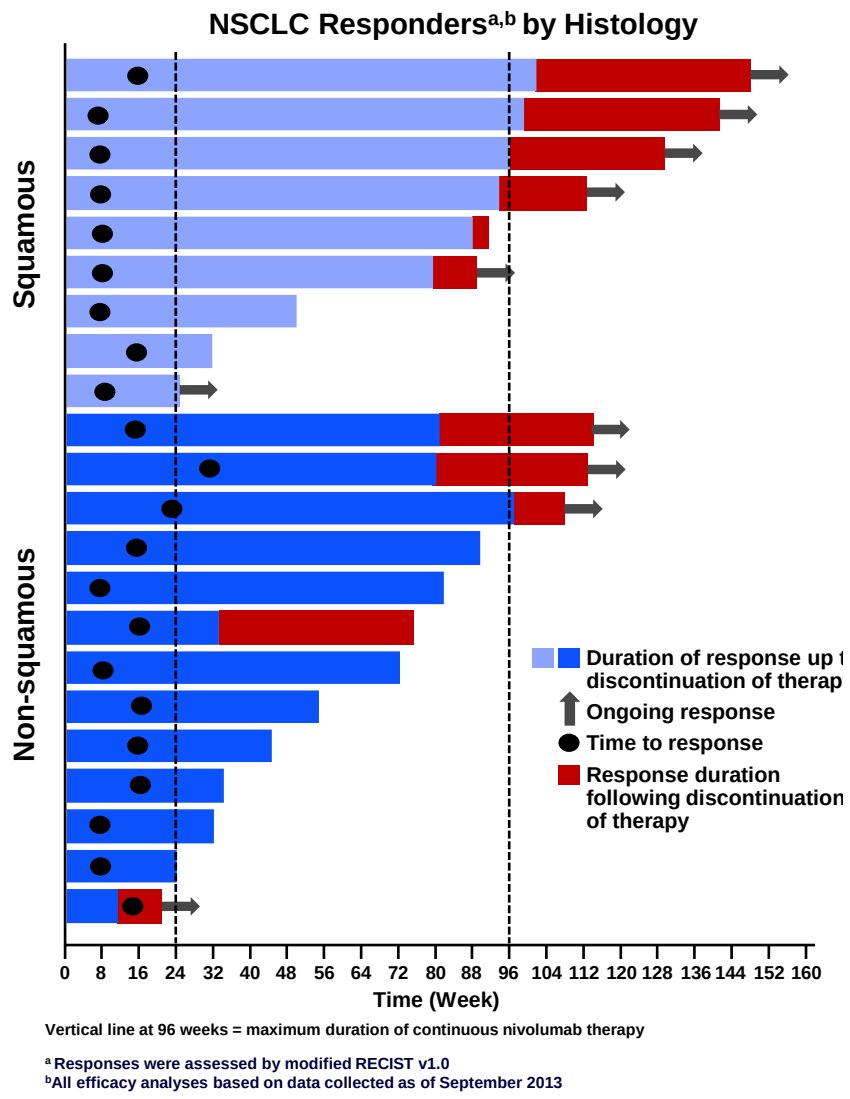
Response of Metastatic NSCLC (Nivolummab, 10mg/kg)



- Initial progression in pulmonary lesions of a NSCLC patient with non-squamous histology was followed by regression
- Dx ‘04, EGFR mutation +; Rx Gem/carbo, erlotinib, erlotinib + LBH589 (trial for T790 mutation), and lastly pemetrexed

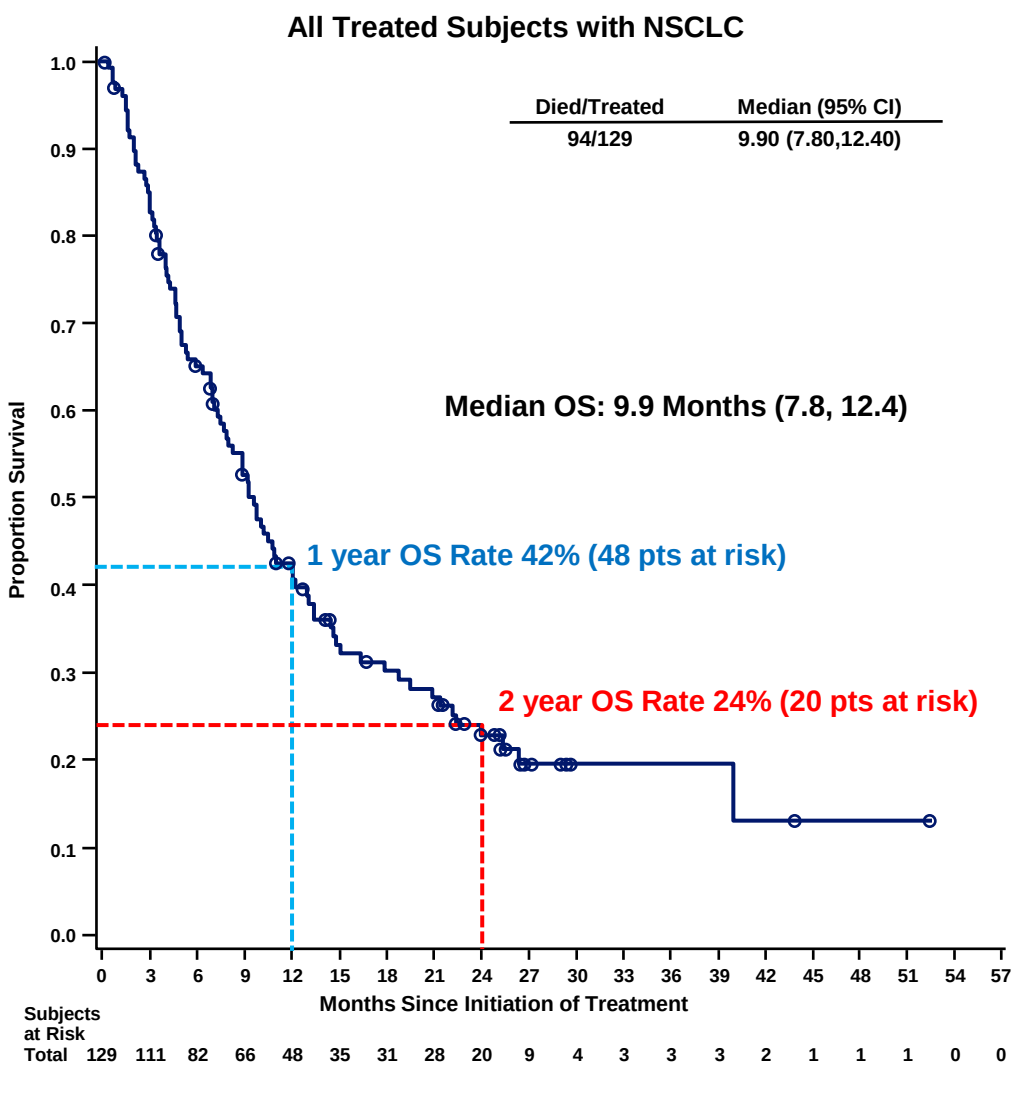
S Antonia, Moffitt Cancer Center

Nivolumab in NSCLC: Duration of Response and Overall Survival



Vertical line at 96 weeks = maximum duration of continuous nivolumab therapy

[a] Responses were assessed by modified RECIST v1.0
[b] All efficacy analyses based on data collected as of September 2013



MK-3475: Phase I Trial

MK-3475 - antibody binds to PD-1

Part A – Dose escalation

- 3+3 design 1, 3, and 10 mg/kg
  - IV every 2 or 3 wks
- Advanced solid tumors
- Well tolerated – No Dose Limiting Toxicities, low grade fatigue, itching, breathlessness
- Activity – 2 Partial Responses (PR) melanoma, 1 PR NSCLC

Part B – NSCLC expansion cohort

- 10 mg/kg q 3 wks
- 33 pts
- Response Rate – 21%
- Similar for squamous and nonsquamous

Ribas A et al ASCO 2013 , Garon E et al WCLC 2013

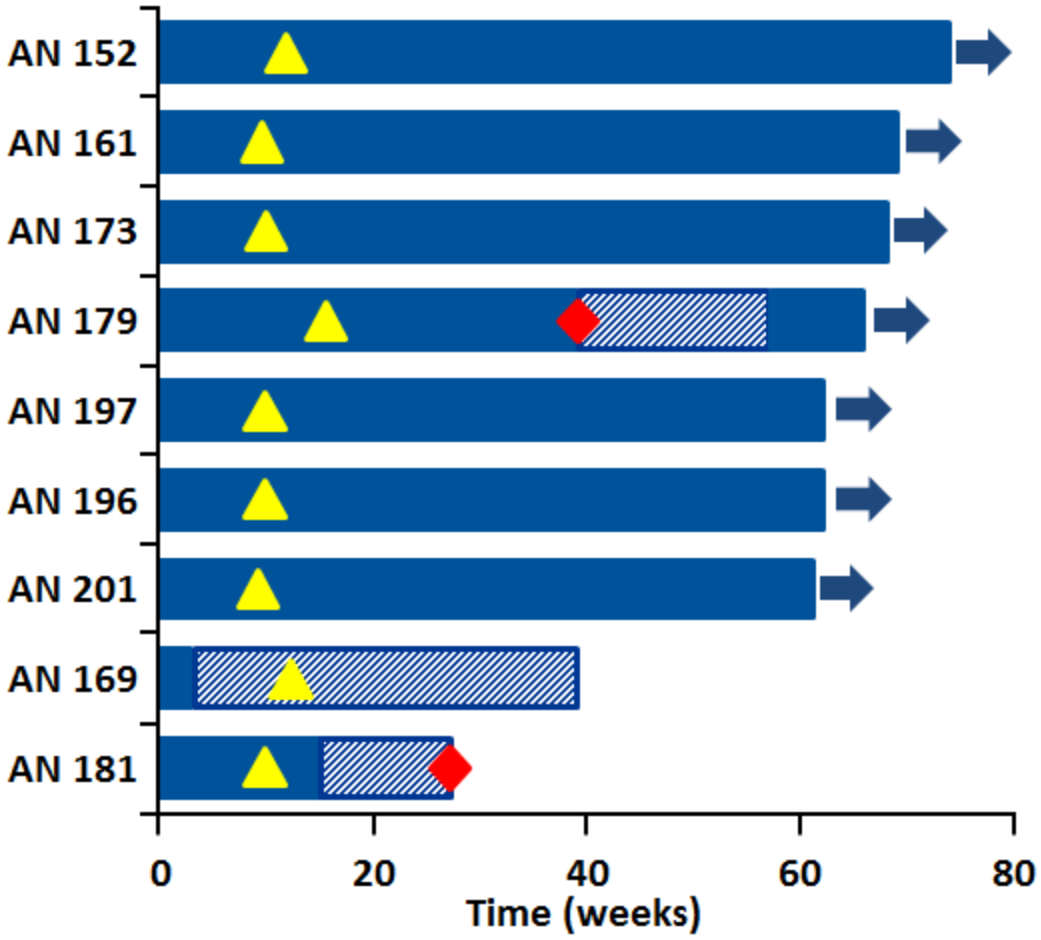
MK-3475: NSCLC Clinical Activity

Subgroup	irRC, Investigator Review			RECIST v1.1, Independent Review			
	N	ORR, n (%) [95% CI]	Median PFS, wk (95% CI)	N	ORR,* (%), [95% CI]	Median PFS, wk (95% CI)	Median OS, wk (95% CI)
All	38	9 (24%) [11%, 40%]	9.1 (8.3, 17.4)	33	7 (21%) [9%, 39%]	9.7 (7.6, 17)	51 (14, NR)
Non-squamous	31	7 (23%) [10%, 41%]	9.1 (8.3, 17.0)	26	4 (16%) [4%, 35%]	10.3 (7.6, 17)	35 (14, NR)
Squamous	6	2 (33%) [4%, 78%]	23.5 (2.7, NR)	6	2 (33%) [4%, 78%]	15.2 (1.4, NR)	NR (2.7, NR)

Characteristics- 42% Male, 58% ECOG 1, 66% Former and Current smokers, 16% Squamous, 61% PD-L1 positive tumors

Garon E et al WCLC 2013

MK-3475 Responders Have Prolonged Duration of Response

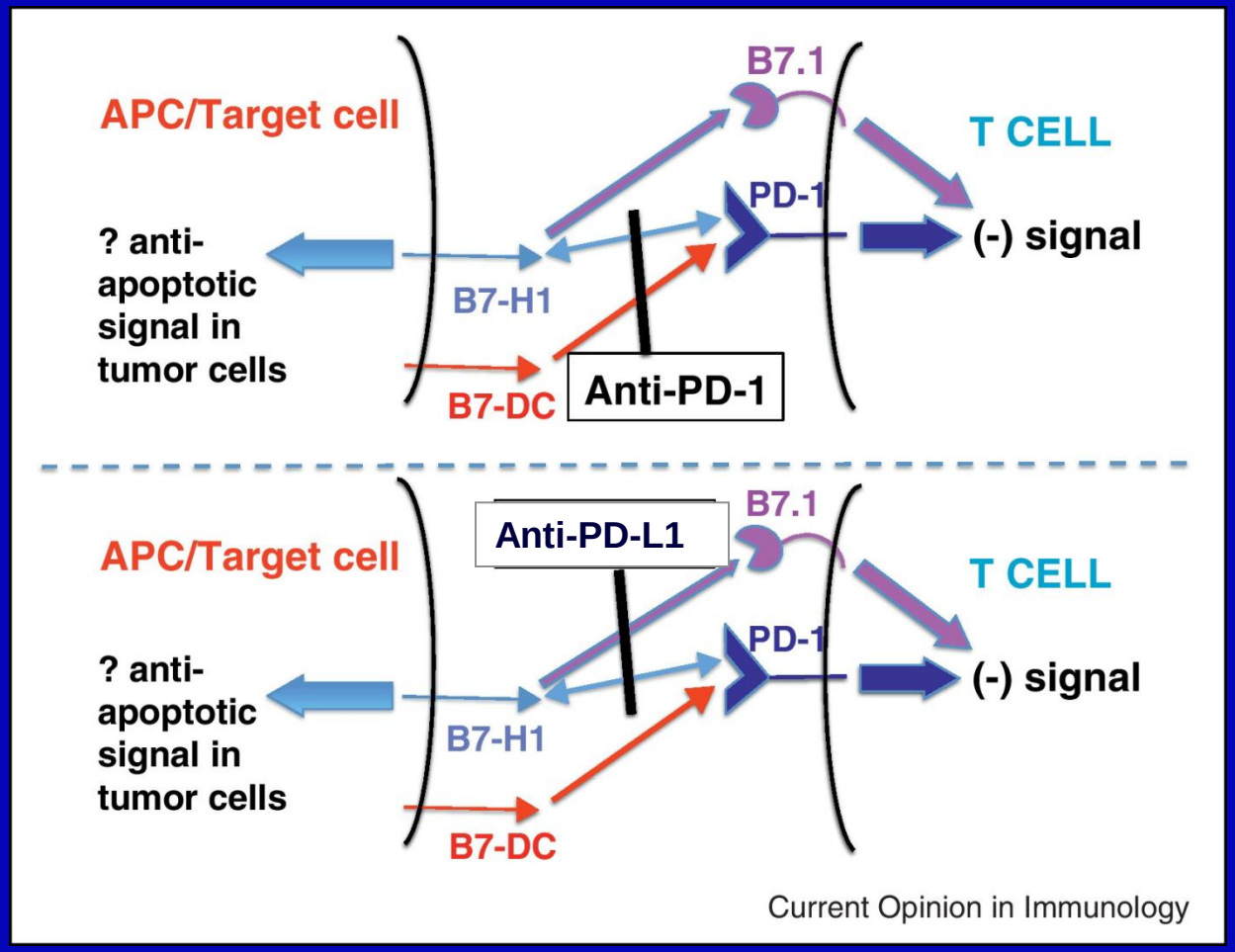


- 7/9 responders on treatment at time of analysis
- Median PFS of responders not reached at 62 weeks
- AN 179: stopped MK for local therapy to brain metastasis; MK resumed based on continued systemic response
- AN 169: after 1 dose, MK stopped for unrelated grade 4 hypercalcemia; response maintained without further treatment; per protocol, follow-up ceased at 39 weeks

On therapy
Confirmed response
Off therapy
Progression
Therapy continuing

Garon E et al WCLC 2013

Potential Differences in PD-1 vs. PD-L1 Blockade



Topalian S et al Curr Opin Immunol 2012

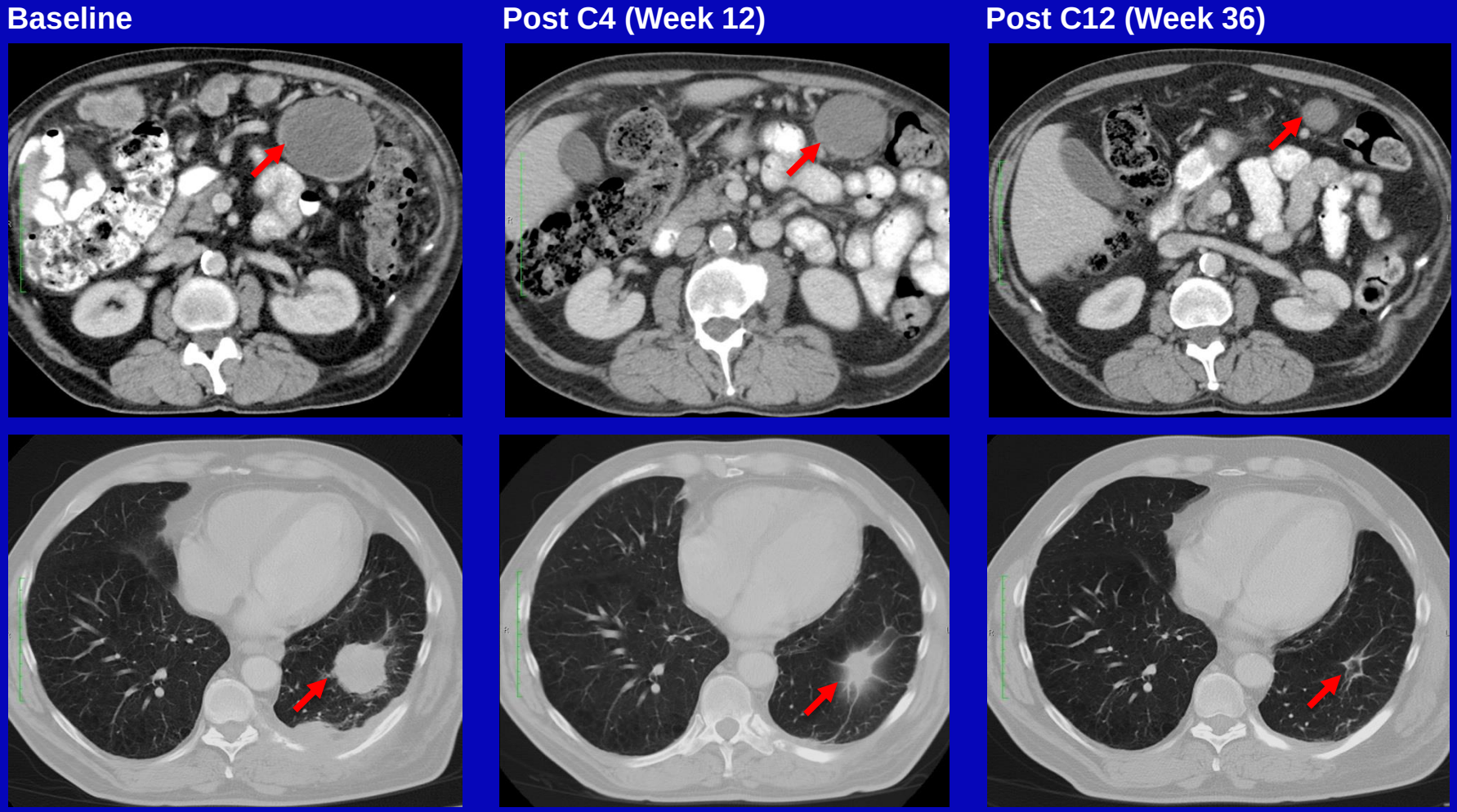
Inhibitors of PD-L1 – Activity in NSCLC

Antibody	# of evaluable NSCLC	RR (%)	SD rate at 24 wks	PFS rate at 24 wks
BMS-936559	49	10%*	12%	31%
Nonsquamous	36	11%	8%	26%
Squamous	13	8%	23%	43%
MPDL-3280A	53	23%^	17%	45%
Nonsquamous	42	21%	17%	44%
Squamous	11	27%	18%	46%

^Recist 1.1 used, *Recist 1.0 used

Brahmer J et al NEJM 2012: Soria J et al ECC 2013

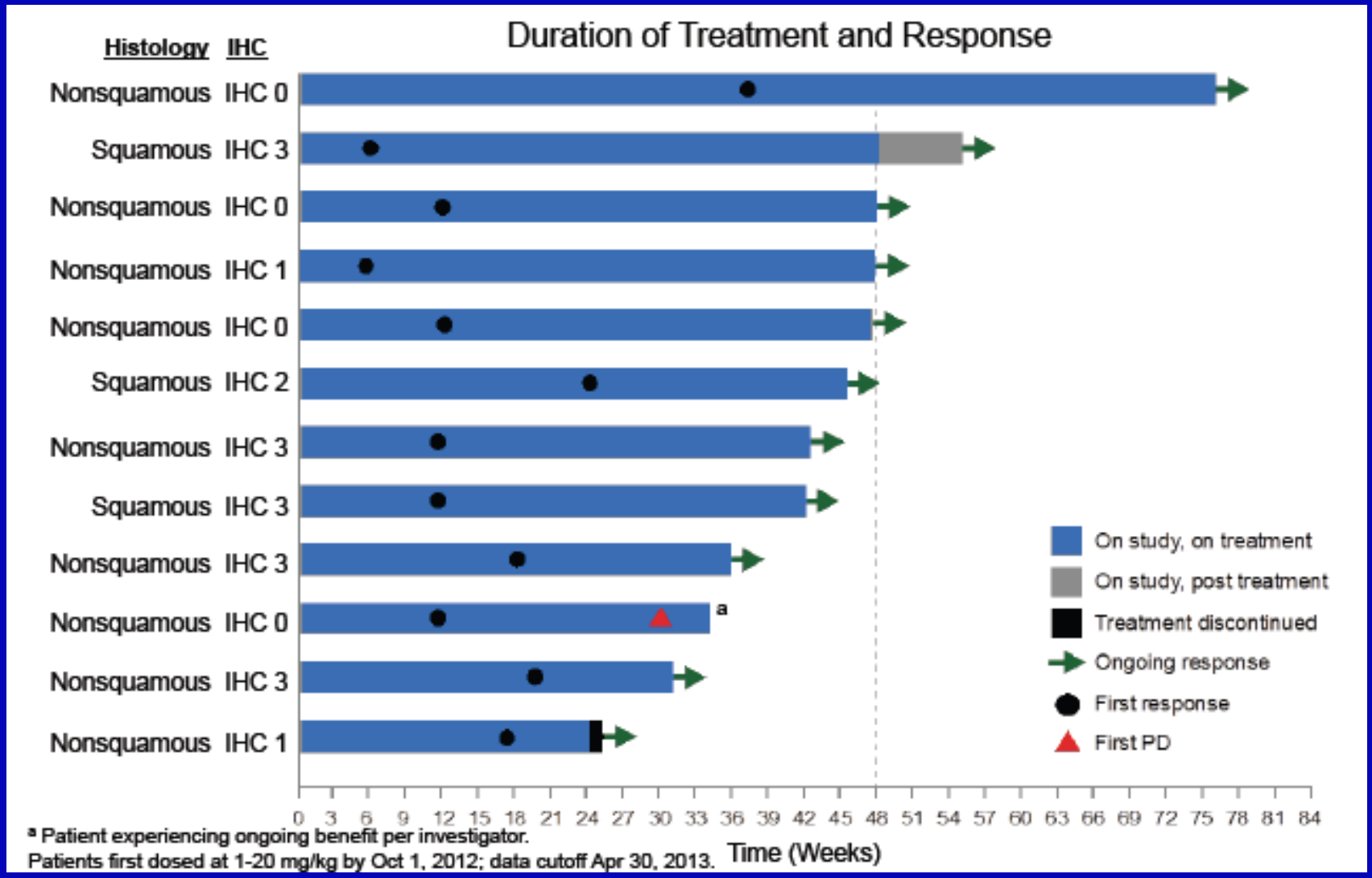
Clinical Activity of MPDL3280A in NSCLC (Adeno)



62-year-old male, pretreated including carboplatin + paclitaxel, bevacizumab + erlotinib, pemetrexed, PD-L1 positive

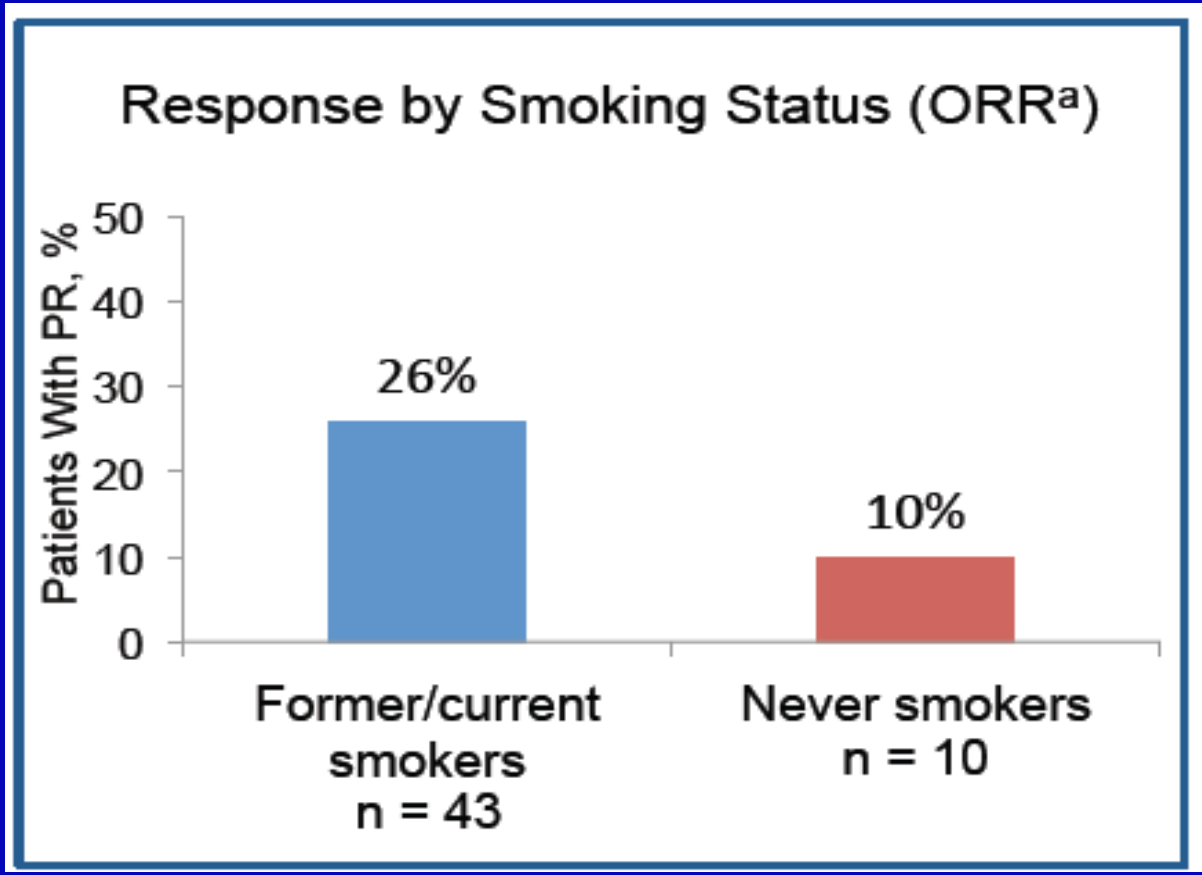
Spigel D, et al ASCO 2013

MPDL-3280A: Duration of Response



Soria J et al ECC 2013

MPDL-3280A: Response by Smoking History in NSCLC Patients



Maybe due to the fact that people with a smoking history have a higher mutation rate which could be associated with increased immune recognition or response.

Soria J et al ECC 2013

Summary of PD-1/PD-L1 blockade immune-mediated toxicities

- **Common:**
  - **Fatigue**
  - **Rash – maculopapular and pruritus**
    - **topical treatments**
  - **Diarrhea/colitis**
    - **initiate steroids early, taper slowly**
  - **Hepatitis/liver enzyme abnormalities**
  - **Infusion reactions**
  - **Endocrinopathies – Thyroid, adrenal, hypophysitis**
- **Infrequent – pneumonitis**
- **Grade 3 and 4 toxicities uncommon**

Topalian S et. al. NEJM 336, 2455-65, 2012, Patnaik, A, ASCO 2012, Brahmer J et. al. NEJM 2012, Herbst R et. al. ASCO 2013

PD-1 Checkpoint Inhibition - Toxicities

Agent & Population, N	Rx related AE - All & Grade 3/4	Most common Rx related AE	Select AE All Grade & Grade 3/4	Pneumonitis rate
Nivolumab NSCLC - 129	71% 14%	Fatigue - 24% ↓ appetite -10% Diarrhea - 10%	53% 5%	All – 6% Gr 3/4 - 2% 2 deaths
MK3475 NSCLC - 38	53% 2%	Rash– 21% Pruritis – 18% Fatigue – 16%	NR	All – 2% (1-grade 2) No Grade 3-5
BMS-936559 Phase I -207	61% 9%	Fatigue -16% Infusion rxn – 10% Diarrhea – 9%	39% 5%	All – 1% No Grade 3-5
MPDL-3280A NSCLC - 85	66% 11%	Fatigue – 20% Nausea – 14% ↓ appetite – 10%	NR 1%	All – NR No Grade 3-5

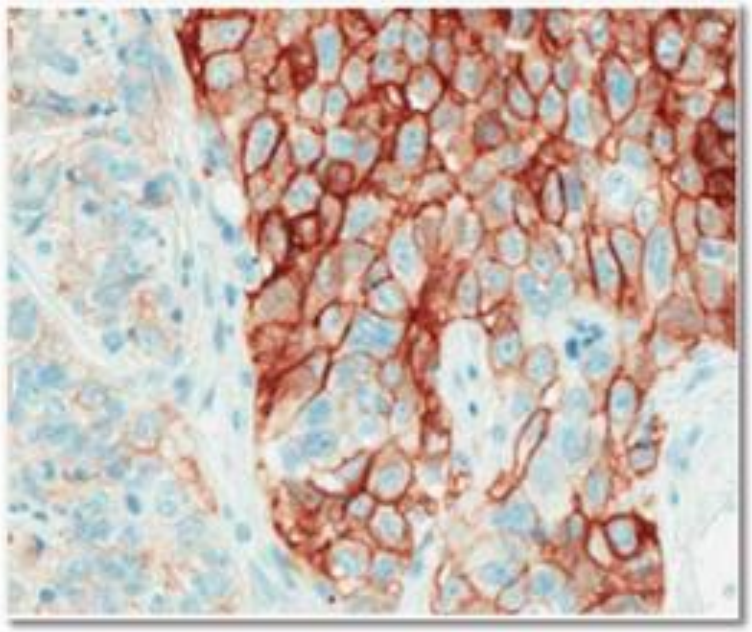
Slight differences may be due to mechanism of action OR trial maturity and number of treated patients

Brahmer et al ASCO 2013, Patnaik A et al ASCO 2012, Ribas A et al ASCO 2013, Brahmer et al NEJM 2012, Soria J et al ECC 2013

Current Trials of PD-1 Pathway Inhibitors

- MPDL-3280A – PD-L1 positive disease
- MPDL-3280A – PD-L1 antibody versus taxotere in the second line treatment setting
- MK-3475 – Taxotere versus anti-PD-1 antibody in the second line treatment setting
- MK-3475 – Single agent
- Nivolumab – First line trial in metastatic disease
- Other Phase I trials – MEDI-4736, Combination trials
- Phase 3 trials of Nivolumab vs. Taxotere have completed enrollment

PD-L1 testing



Positive PD-L1 staining in lung cancer
(GNE/Roche PD-L1 IHC)

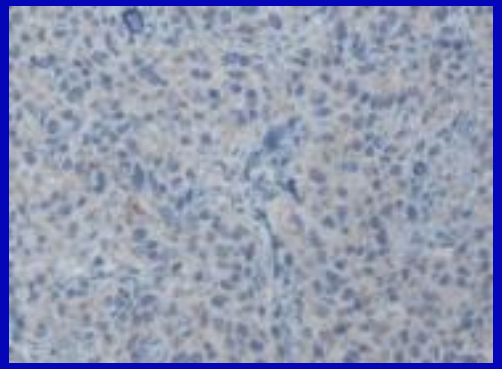
Tumor Type	Estimated PD-L1 Prevalence (≈ %)*
NSCLC (SCC)	50
NSCLC (adeno)	45

Expression of PD-L1: Required for Clinical Response to PD-1 Blockade

B7-H1 staining patterns (clone 5H1)

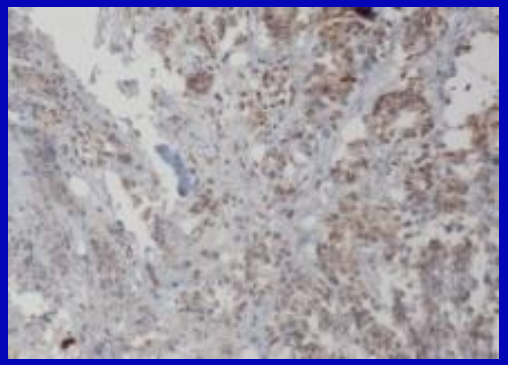
MDX-1106-01:
9 JHU pts
with
pre-Rx
biopsies

Negative



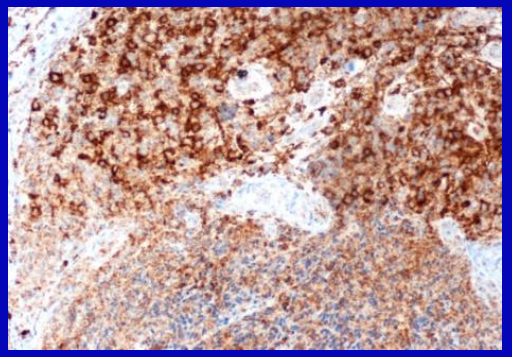
0/1 responders

Cytosolic



0/4 responders

Membranous



3/4 responders

J. Taube and S. Topalian, Brahmer J et al JCO 2010

Objective Response Rates by PD-L1 Expression in Patients with Solid Tumors

Rx Antibody	Testing Method	N	PD-L1 Positive RR	PD-L1 Negative RR
Nivolumab Topalian 2013	Manual staining – 5H1 5% cutoff Tumor staining	49	13/31 42%	0/18 0%
Nivolumab Grosso 2013	Dako automated 5% cutoff Tumor staining	38	7/17 41%	3/21 14%
MPDL3280A Herbst 2013	Automated Genentech Roche Dx IHC 1% cutoff Tumor immune cell staining	103	13/36 36%	9/67 13%

Topalian S et al ASCO 2013, Grosso J et al ASCO 2013, Herbst R et al ASCO 2013

MPDL-3280A Phase I – NSCLC PD-L1 Staining and Response

Diagnostic Population[a] (n = 53)	ORR[b] % (n/n)	PD Rate % (n/n)
IHC 3	**83%** (5/6)	**17%** (1/6)
IHC 2 and 3	**46%** (6/13)	**23%** (3/13)
IHC 1/2/3	**31%** (8/26)	**38%** (10/26)
All Patients[c]	**23%** (12/53)	**40%** (21/53)

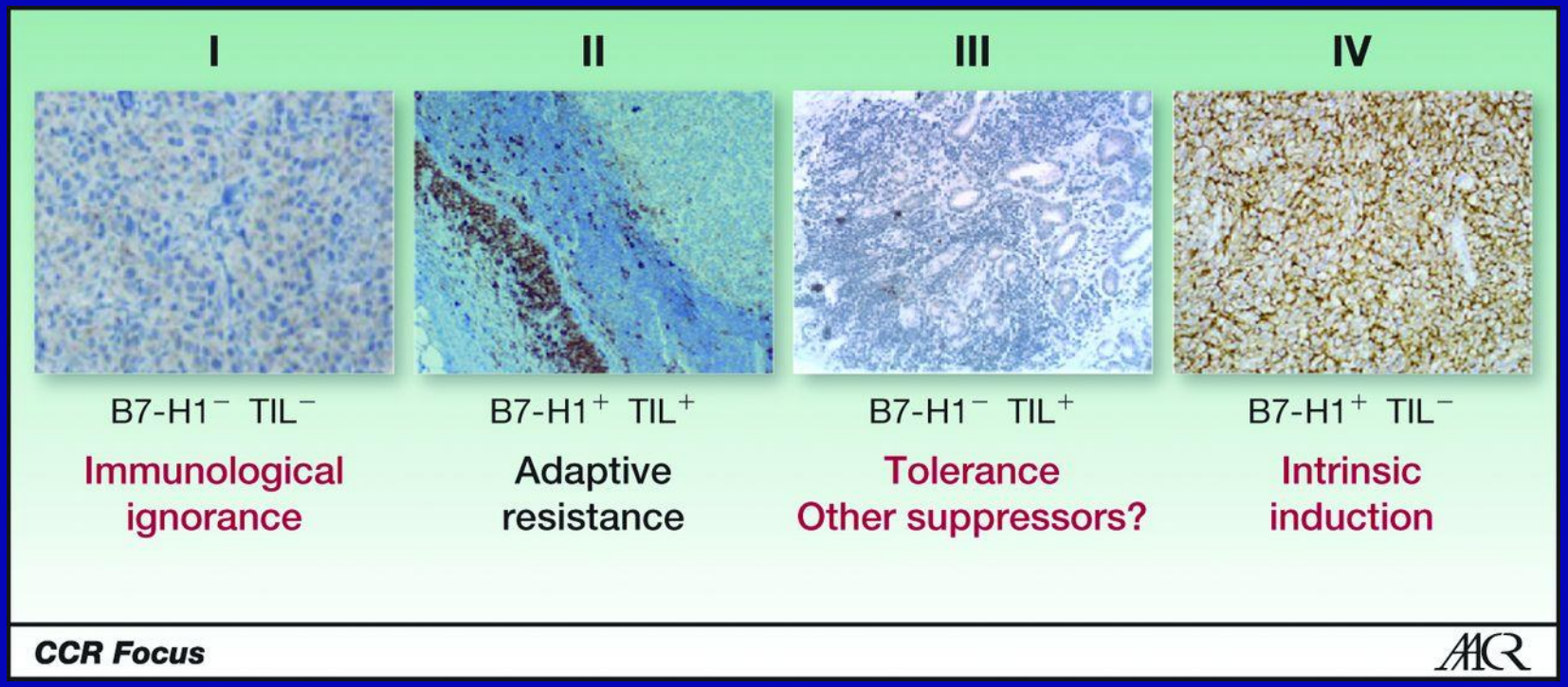
[a] IHC 3: ≥ 10% tumor immune cells positive for PD-L1 (IC+); IHC 2 and 3: ≥ 5% tumor immune cells positive for PD-L1 (IC+); IHC 1/2/3: ≥ 1% tumor immune cells positive for PD-L1 (IC+); IHC 0/1/2/3: all patients with evaluable PD-L1 tumor IC status.
[b] ORR includes investigator-assessed unconfirmed and confirmed PR.
[c] All patients includes patients with IHC 0/1/2/3 and 7 patients have an unknown diagnostic status.
Patients first dosed at 1-20 mg/kg by Oct 1, 2012; data cutoff Apr 30, 2013.

Soria J et al ECC 2013

Questions Regarding PD-L1 testing

- Assay limitations
  - Requirement to assess membrane B7-H1 protein (IHC)
  - Differing commercially available antibodies
  - What is important? Tumor vs. Stroma or Both?
- Archived versus fresh biopsy – How old of a biopsy is too old?
- Heterogeneity in expression within tumor tissue – Did you biopsy the right spot?
- Is the presence and composition of TILS required?
- Is PD-L1 positivity a Predictor of response and / or Prognostic?

PD-L1 (B7-H1) Expression and Inflammation: Implications for Mechanisms and Therapy



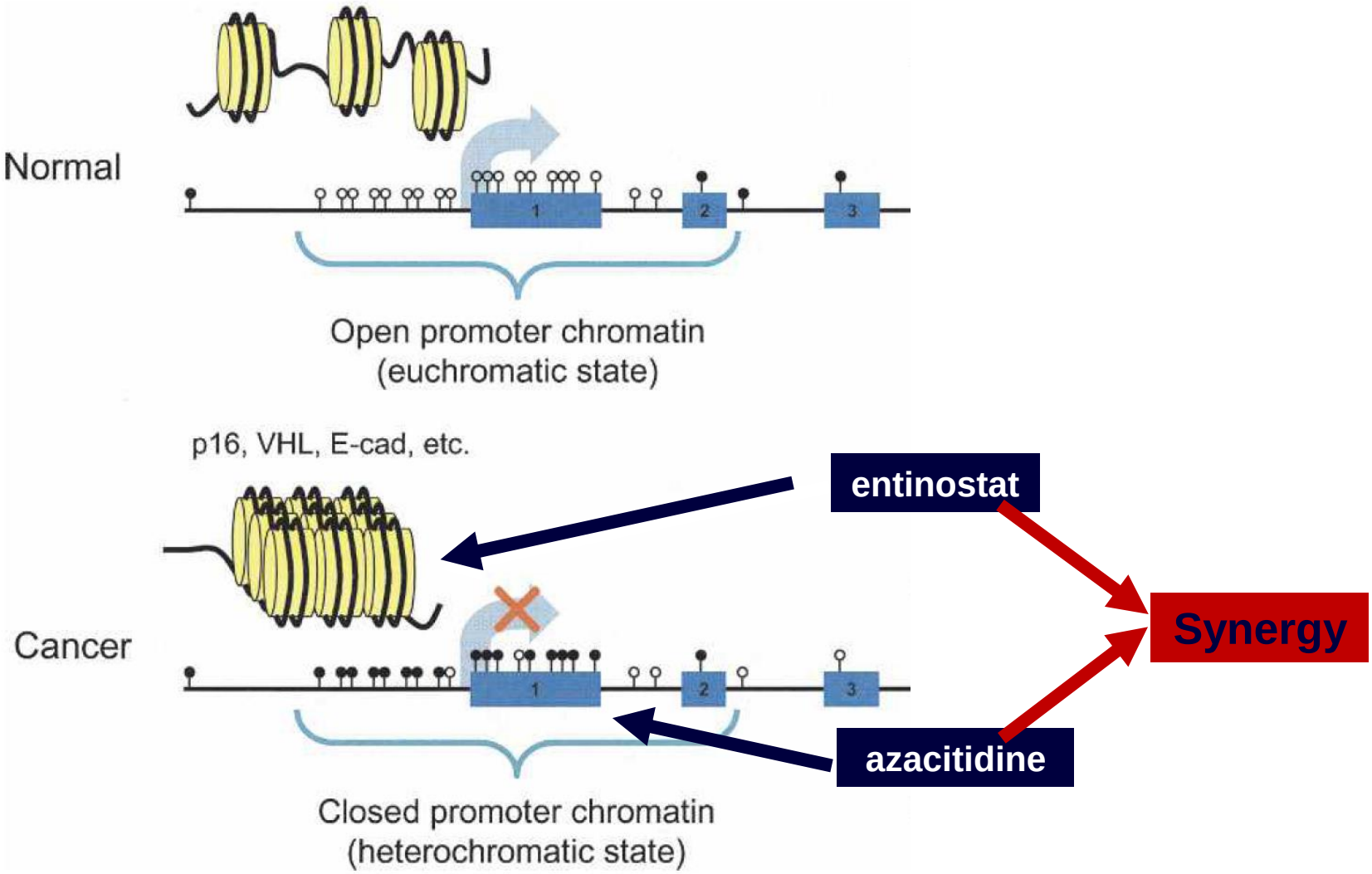
***Implications for combination therapy with other checkpoint inhibitors, chemotherapy, targeted therapy, and vaccines**

Sznol M , and Chen L Clin Cancer Res 2013;19:1021-1034

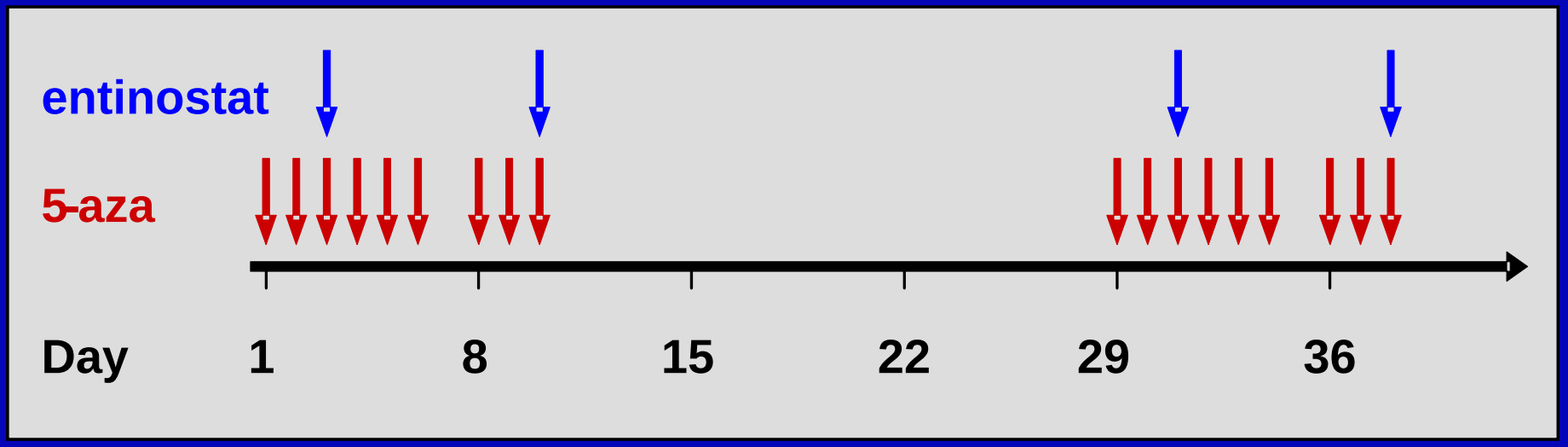
Combinations with PD-1 Checkpoint Inhibitors

- Other co-inhibitory pathways
  - CTLA-4, TIM-3, LAG-3
- Co-stimulatory pathways
  - OX40, 4-1BB, GITR
- Standard of care
  - Chemotherapy, TKI, XRT
- Cancer vaccines
- Epigenetic therapy

Combination epigenetic therapy



Epigenetic lung cancer study - trial schema

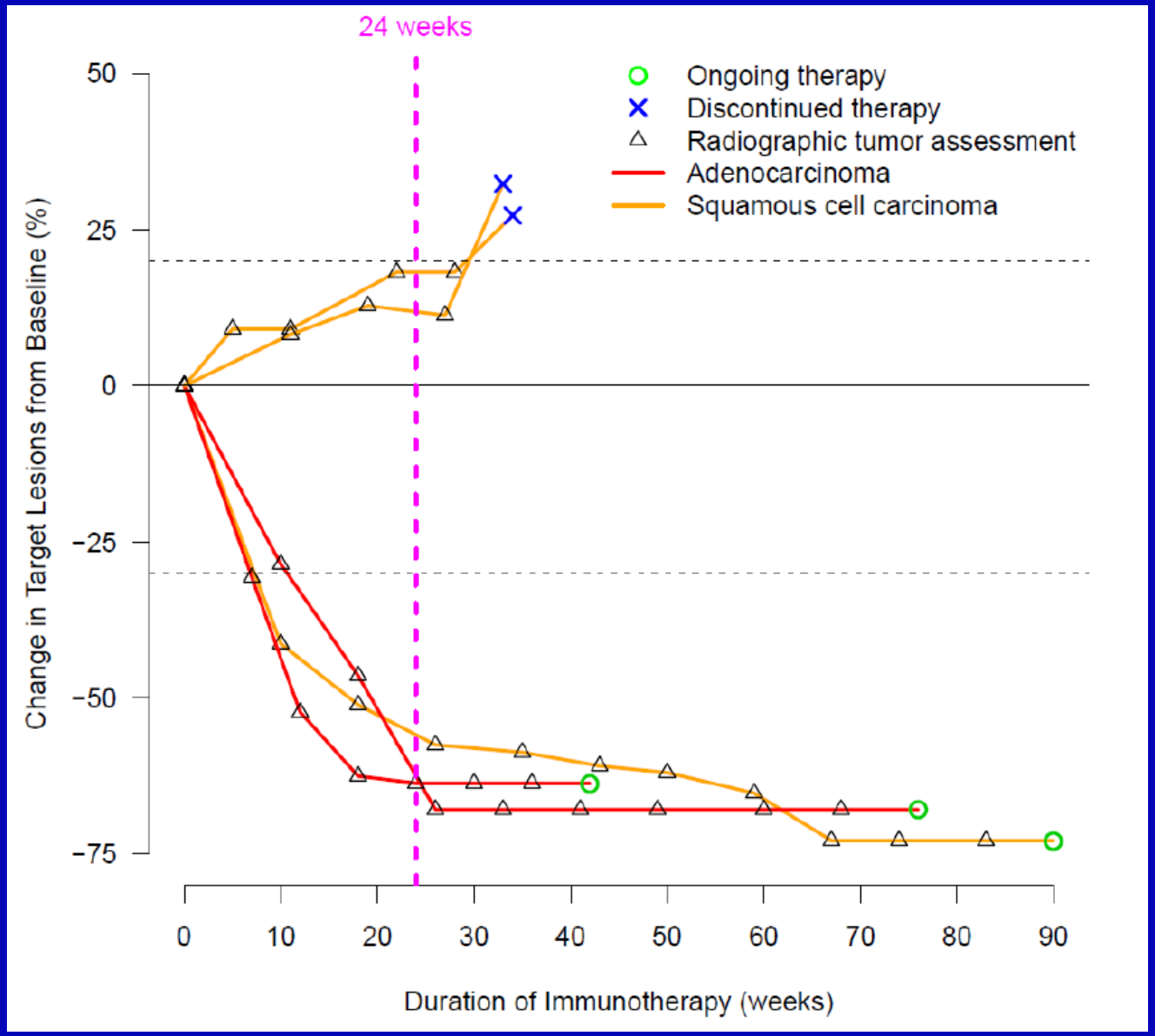


- Single-arm phase II
- Simon two-stage design
- 5AC dosing = 40 mg/m^2 SQ daily on days 1-6 and 8-10
- Entinostat dosing = 7 mg PO days 3 & 10
- Cycle length = 28 days
- 3% RR, Median Survival 8.6 months

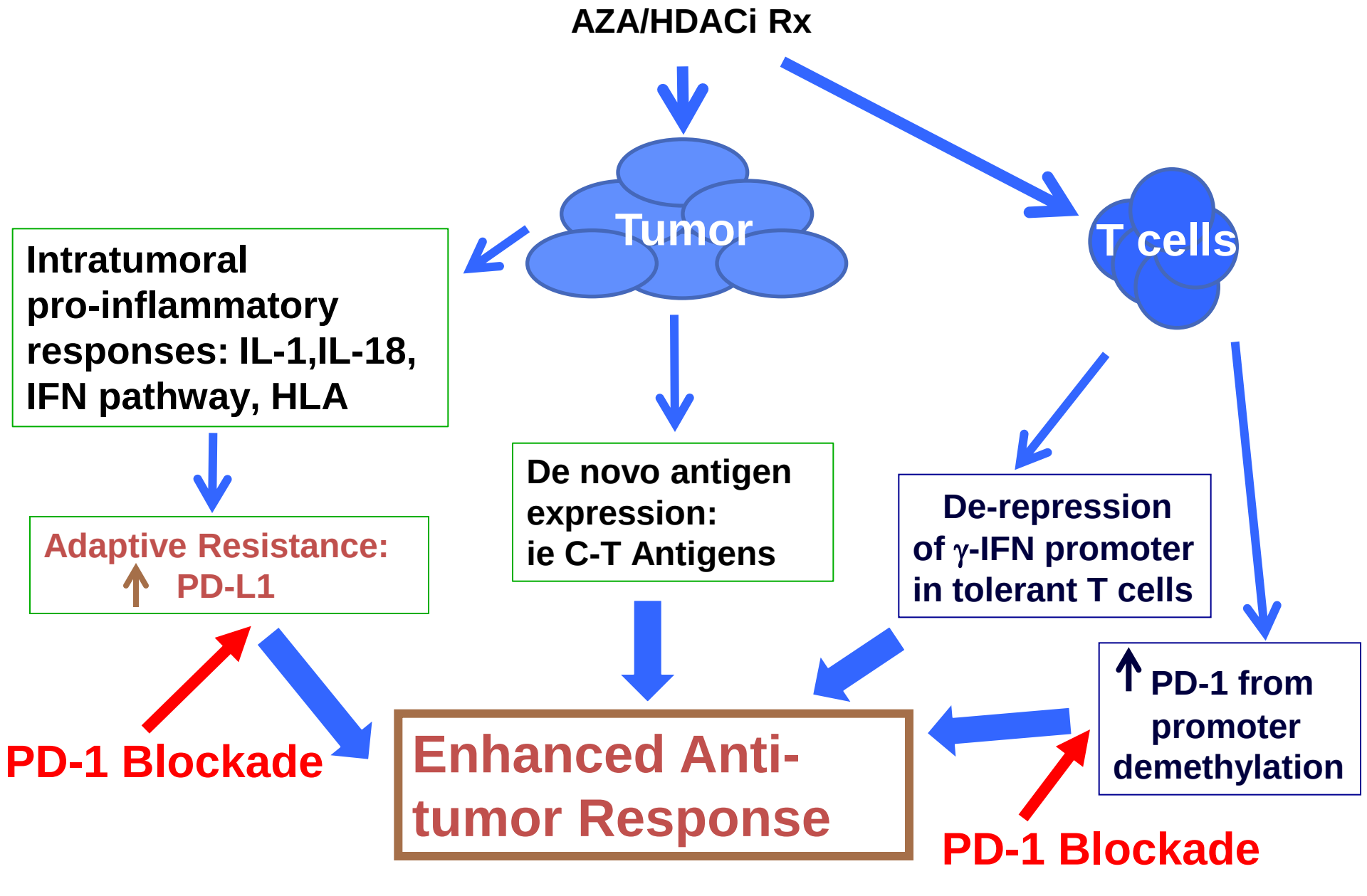
Juergens R et al Cancer Disc 2011

STAND UP TO CANCER

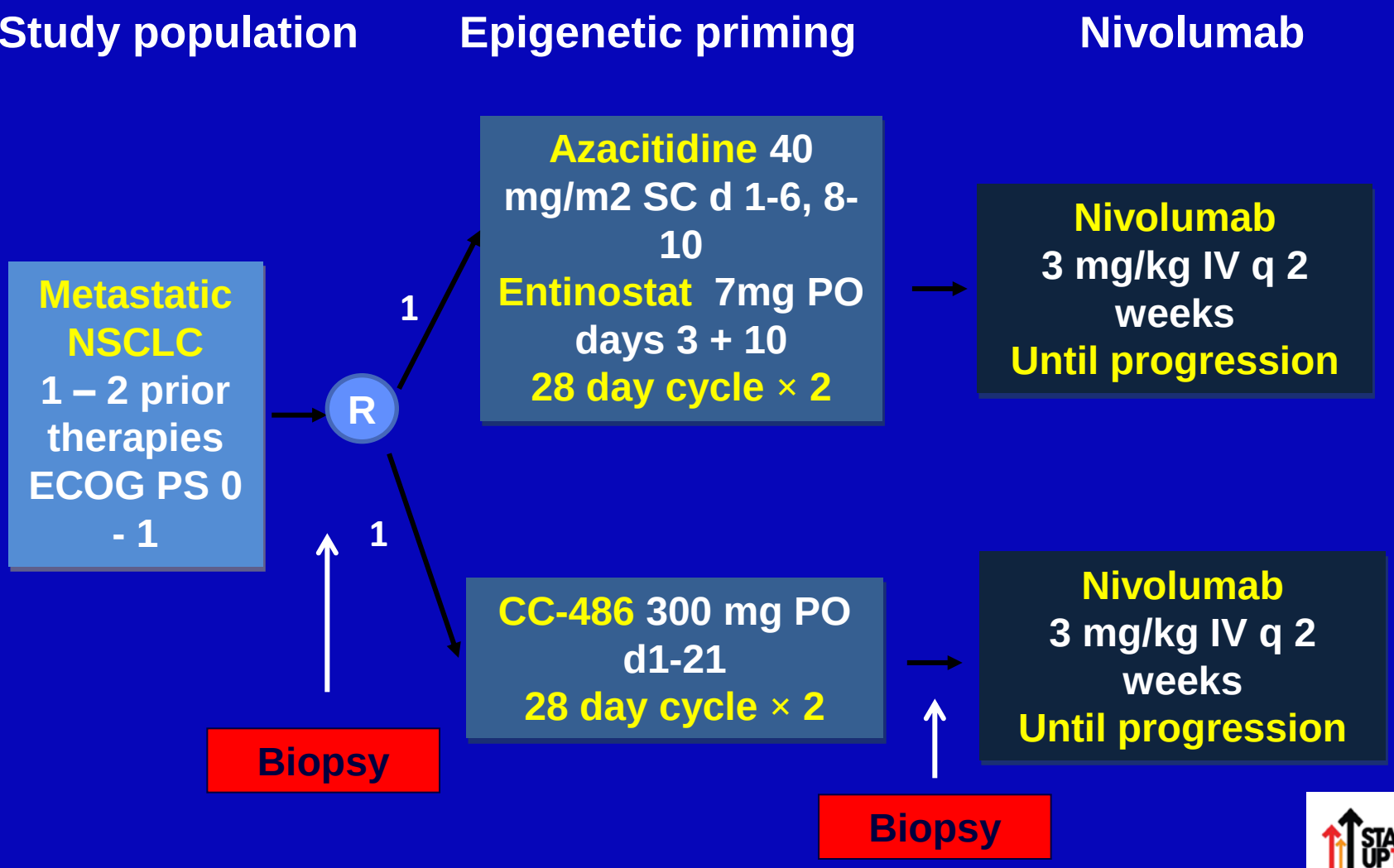
Immunotherapy After Epigenetic Therapy



Synergy between Epigenetic Modulation and PD-1 pathway blockade - Unleashing the Perfect Storm against Tumors



Epigenetic Priming Study Design



Conclusions

- PD-1/PD-L1 checkpoint inhibitors have promising activity in NSCLC
- Checkpoint inhibitors have a unique set of side effects consistent with the immune mechanism of action.
- Patient selection (biomarker) is being evaluated
- Randomized studies are ongoing
- The future of immunotherapy in NSCLC may be in determining the mechanism of immune evasion in each patient

Acknowledgements

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