Harnessing the Immune System via Checkpoint Blockade

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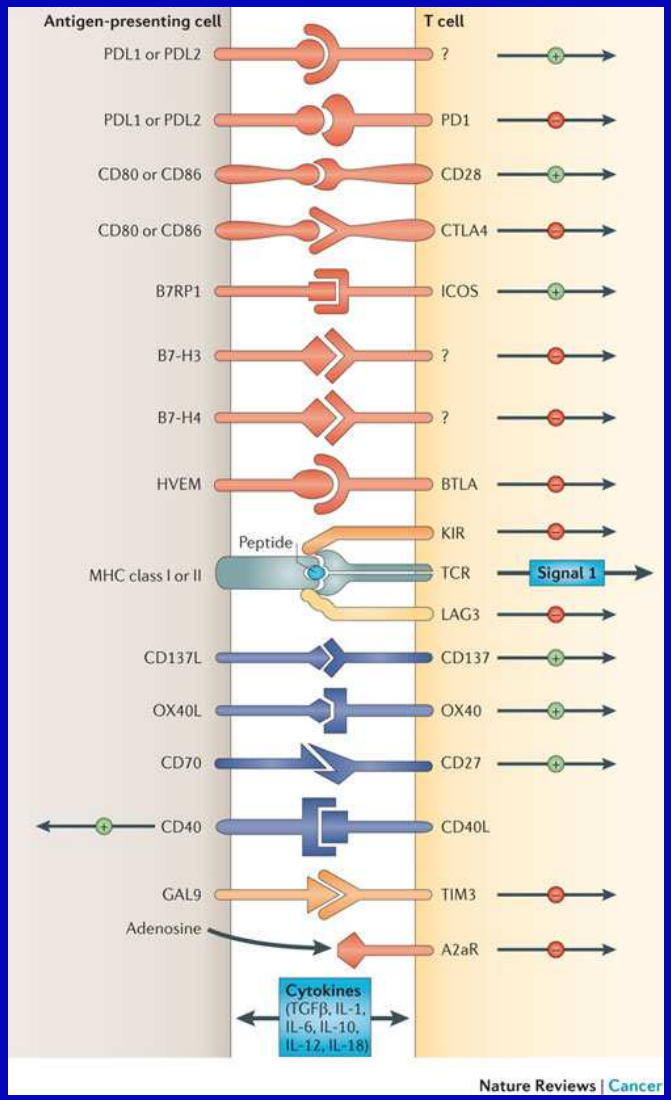
Disclosures

- Bristol Myers Squibb
  - Advisory Board member – uncompensated
  - Institutional Research Support
- Merck
  - Advisory Board member - compensated

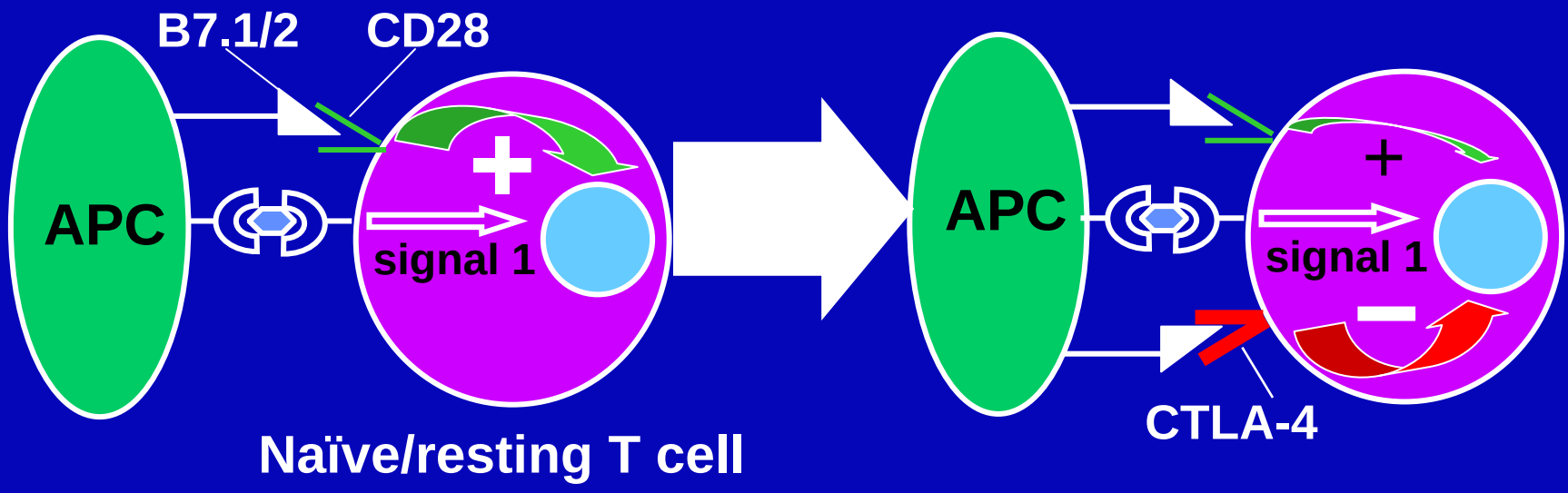
Regulation of T Cell Responses Via Multiple Co-Stimulatory and Inhibitory Interactions

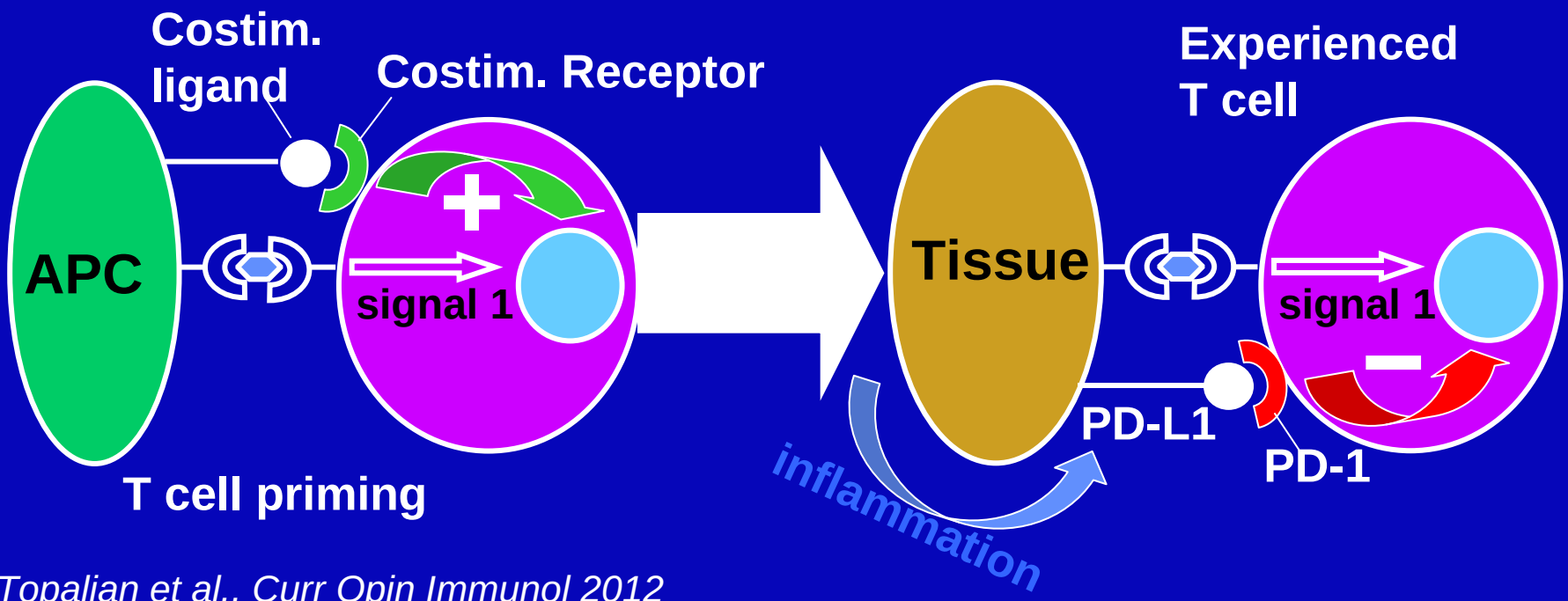


- T cell response to antigen is mediated by peptide-MHC recognized by TCR (first signal – specificity)
- B7 family of membrane-bound ligands bind both co-stimulatory and inhibitory receptors (second co-stimulatory signal)

Pardoll DM Nature Rev Cancer 12, 252, 2012

CTLA-4 vs. PD-1: Distinct Immune Checkpoints





Topalian et al., Curr Opin Immunol 2012

Comparison of CTLA-4 versus PD-1

CTLA-4 Pathway

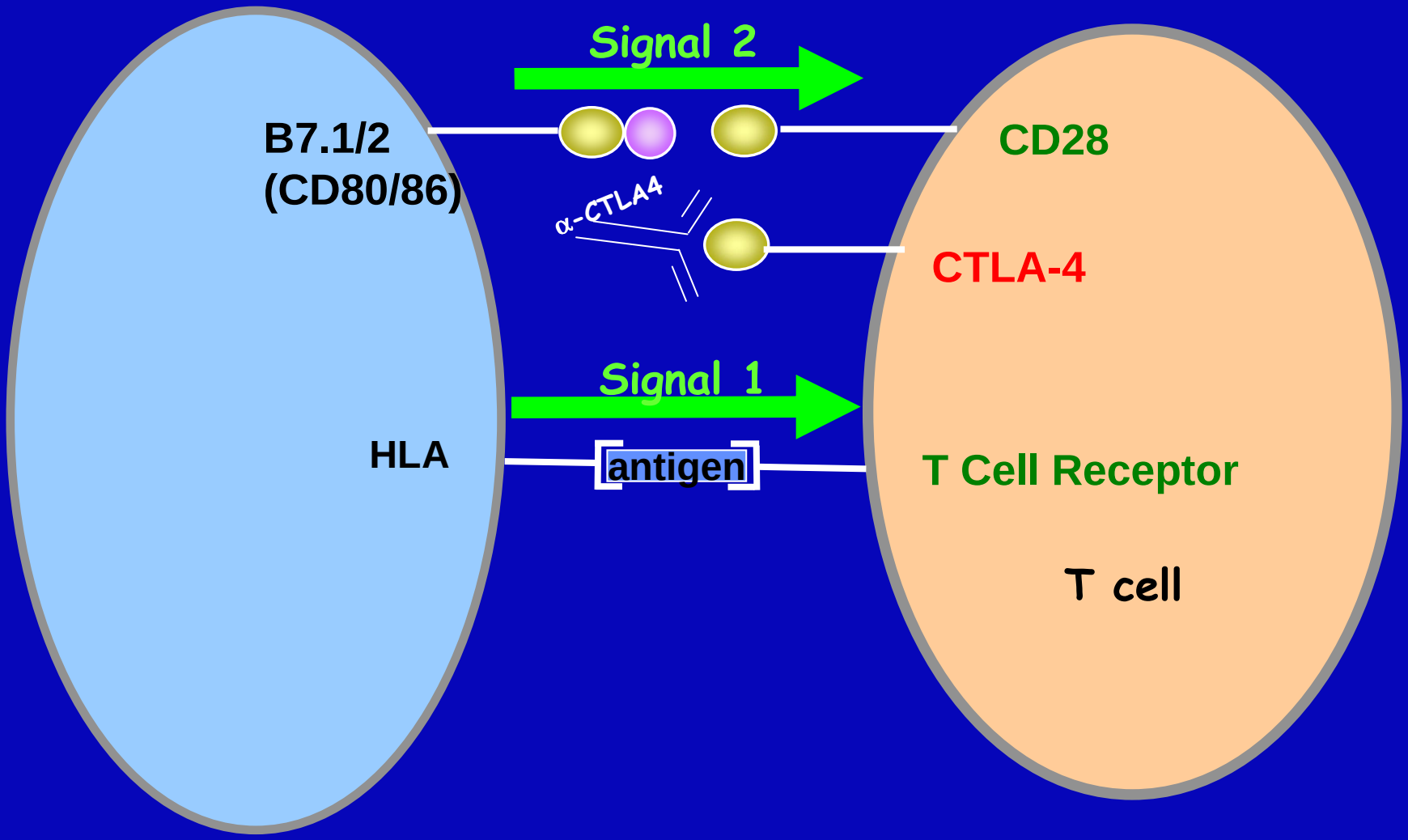
- Exclusively on T cells
- Ligands – CD 80 & 86
- Ligands only expressed on APCs
- CTLA-4 deficient mice suffer early, fatal autoimmune syndrome
- Blockade enhances proliferation of CD4 and CD8 T cells with increase in ratio to regulatory T cells

PD-1 Pathway

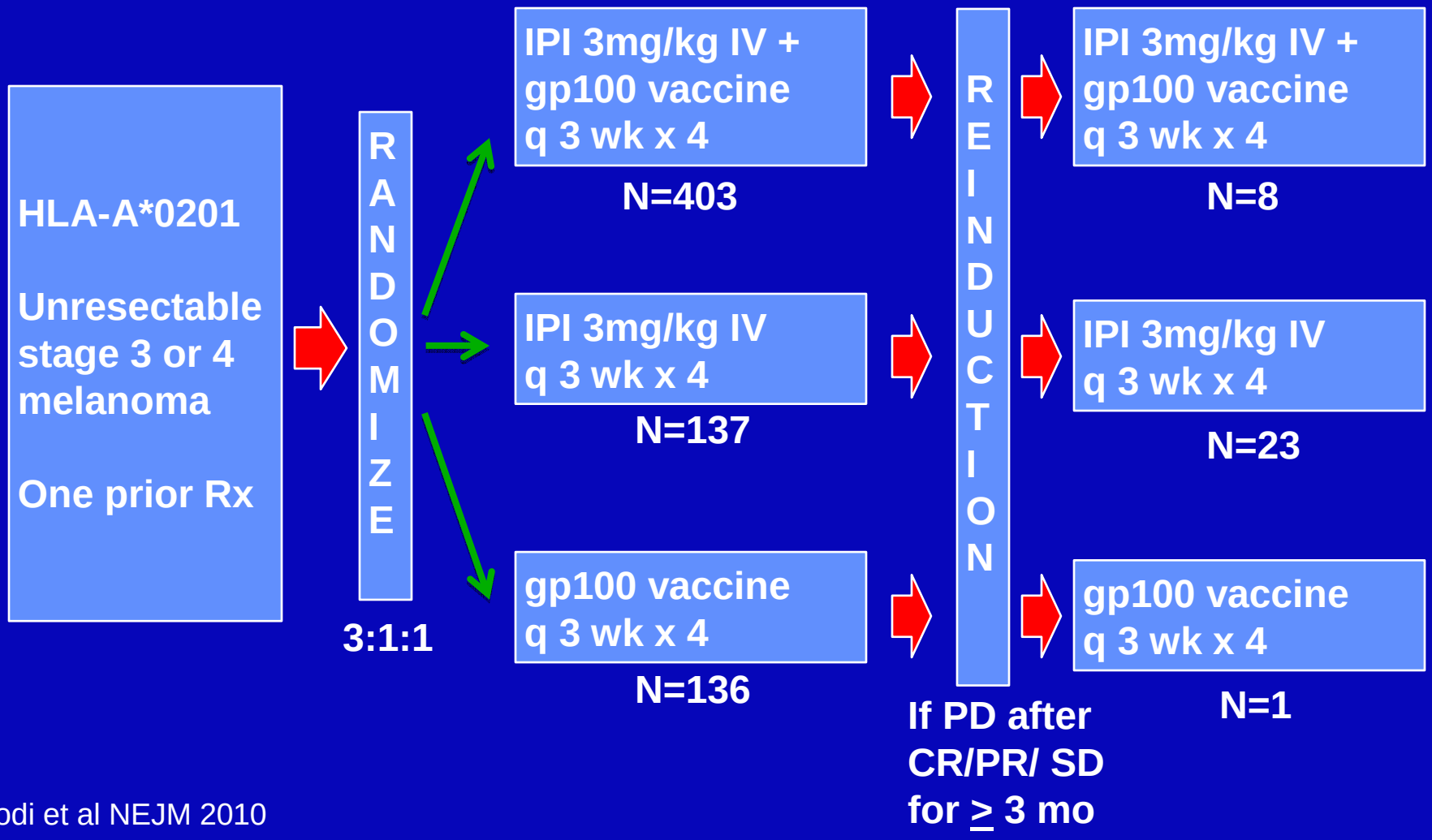
- On T, B and NK cells
- Ligands - PD-L1 & PD-L2
- Ligand expressed on APCs and tumor cells
- PD-1 deficient mice develop strain-specific autoimmunity late in life
- Blockade enhances CD8 Tcells greater than CD4 with increase of CD8 to T regs & cytotoxicity of CD8

Greenwald et al Ann Rev Immunol 23:515(2005), Chambers et al. Ann Rev Immunol 19:565 (2001), Dong et al Nat Med 8:793 (2002), Curran et al Proc Natl Acad Sci 107:4275 (2010), Pilon-Thomas et al. J Immunol 184:3442 (2010)

Blocking the Immune Checkpoint
CTLA-4 - Ipilimumab



Phase 3 Trial of Ipilimumab in Patients with Previously Treated Melanoma



Hodi et al NEJM 2010

Phase 3 Trial of Ipilimumab in Patients with Previously Treated Melanoma

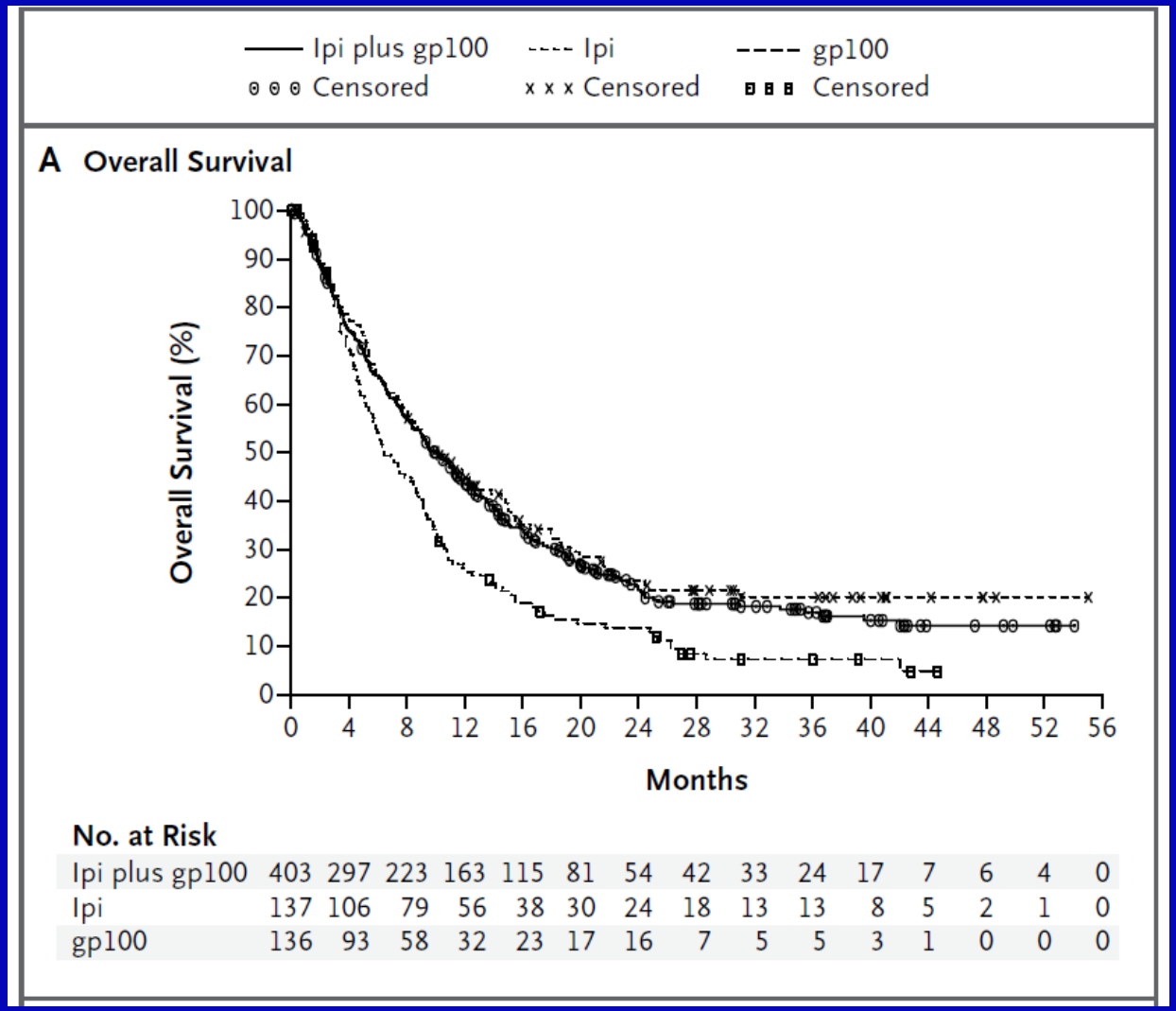
Treatment	BORR	Median OS	2 yr OS	HR
Ipi + gp 100	5.7%	10 mo	21.6%	0.68 p<0.001 to gp100
Ipi	10.9%	10.1 mo	23.5%	0.66 p=0.003 to gp 100
gp100	1.5%	6.4 mo	13.7%	

- **Most common toxicities – Rash and diarrhea**
- **Grade 3 / 4 immune related toxicities – 10-15%**
- **14 deaths, 7 due to immune related toxicites**

BORR – best overall response rate, OS=overall survival

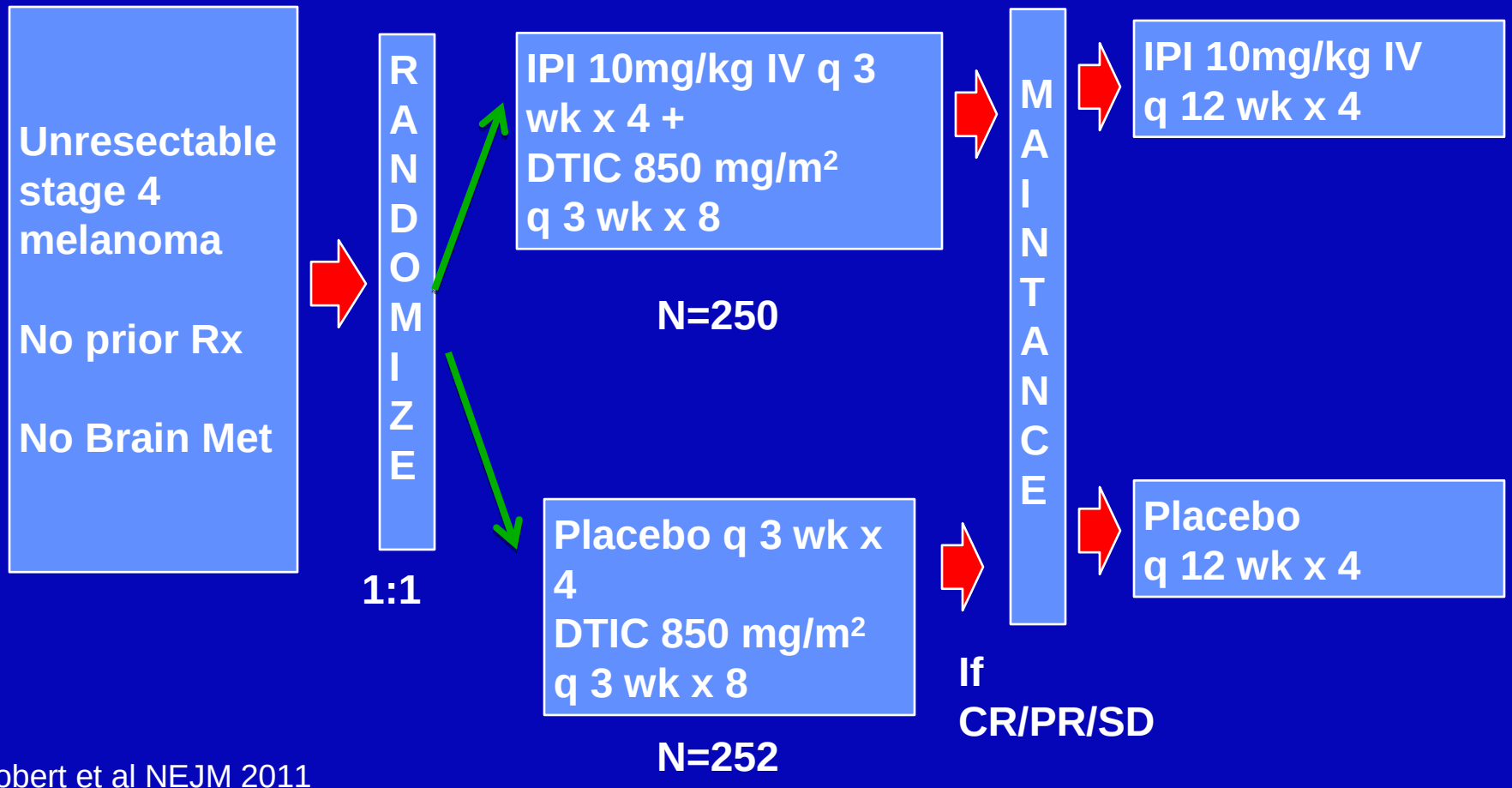
Hodi et al NEJM 2010

Ipilimumab: Survival Benefit in Metastatic Melanoma



Hodi et. al. *NEJM* 2010

Phase 3 Trial of DTIC +/- Ipilimumab in Patients with Advanced Melanoma



Robert et al NEJM 2011

Phase 3 Trial of DTIC +/- Ipilimumab in Patients with Melanoma

Treatment	BORR	Median OS	2 yr OS	HR
DTIC + Ipi	15.2%	11.2 mo	28.5%	0.72 p<0.001
DTIC	10.3%	9.1 mo	17.9%	

- **Most common toxicities – Rash, diarrhea, and elevated LFTs**
- **Grade 3 / 4 immune related toxicities – 38.1% vs 4.4%**
- **Most common grade 3 /4 immune related toxicity - Hepatitis**
- **Drug related discontinuation rate – 34% vs 4%**
- **No deaths**

BORR – best overall response rate, OS=overall survival

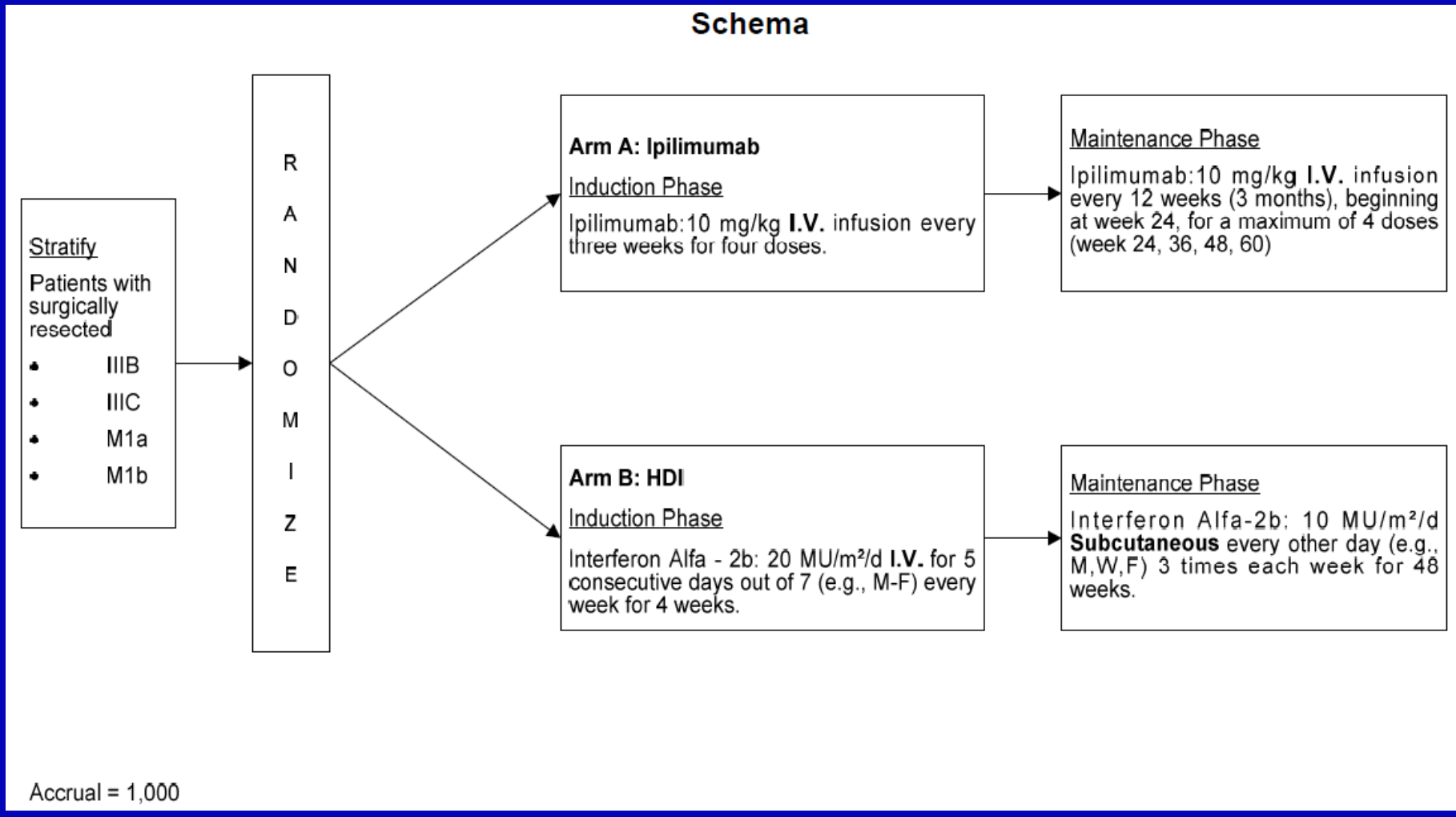
Robert et al NEJM 2011

Ipilimumab Toxicity Management

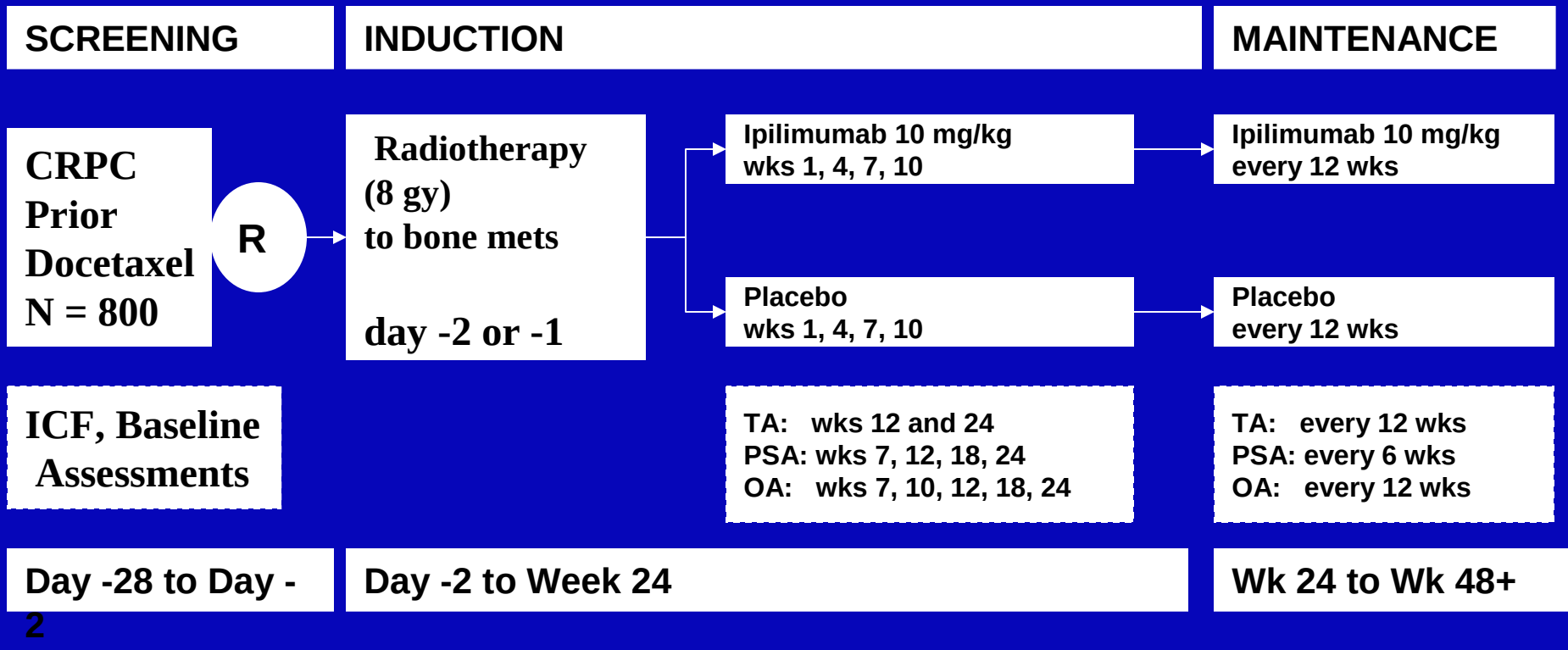
- **Grade 1 – supportive care & close observation**
- **Symptomatic Grade ≥ 2 – hold treatment**
  - **Consider moderate dose steroids (prednisone 0.5 to 1.0 mg/kg)**
  - **Taper over 4 weeks**
  - **Retreat if ≤ grade 1, prednisone tapered to ≤ 7.5 mg**
- **Grade ≥ 3**
  - **Permanently stop ipilimumab (except dermatologic)**
  - **Consider high dose steroids (prednisone 1-2 mg/kg or methylprednisone 1g IV daily)**
  - **Supportive care, specialist consultation**
  - **Additional immunosuppressive therapy – infliximab or mycophenolate**

Weber JS et. al. JCO 30:2691-7, 2012,
Kaehler KC et. al . Seminars in Oncology, 37(5), October 2010

E1609 Schema



Randomized, Double-Blind, Phase III Trial Comparing Ipilimumab vs. Placebo Following Radiotherapy in Subjects with Castration Resistant Prostate Cancer that Have Received Prior Treatment with Docetaxel (CA184-043)



TA = tumor assessment
PSA = prostate specific antigen
OA = outcome assessment

Completed Accrual 1/2012

Ongoing Phase III Trials of Ipilimumab in Lung Cancer

Squamous cell Subtype only

R

- Carbo–paclitaxel*-placebo
- Carbo-paclitaxel*-Ipilimumab

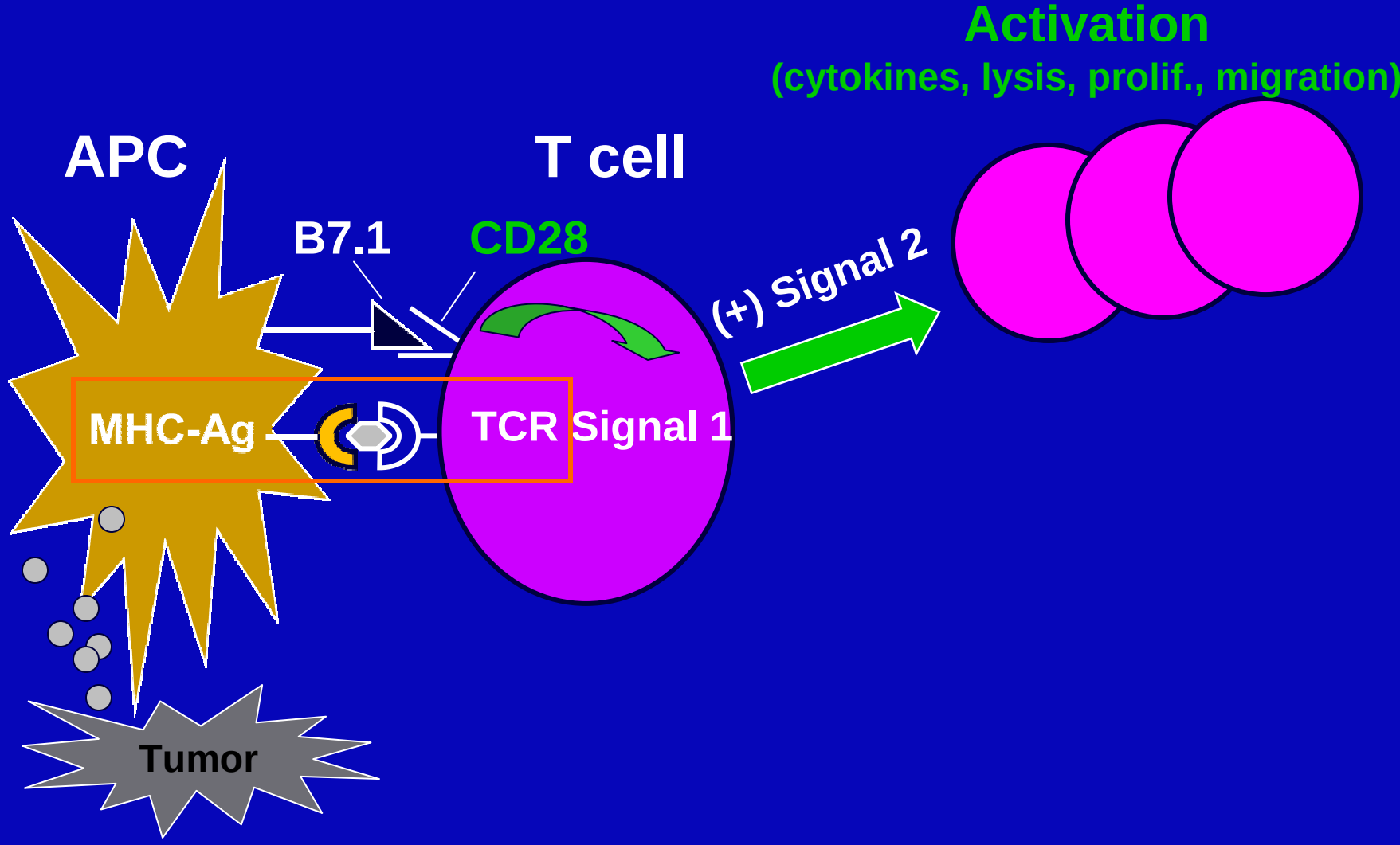
Small cell lung cancer

R

- Carbo–etoposide - placebo
- Carbo-etoposide - ipilimumab

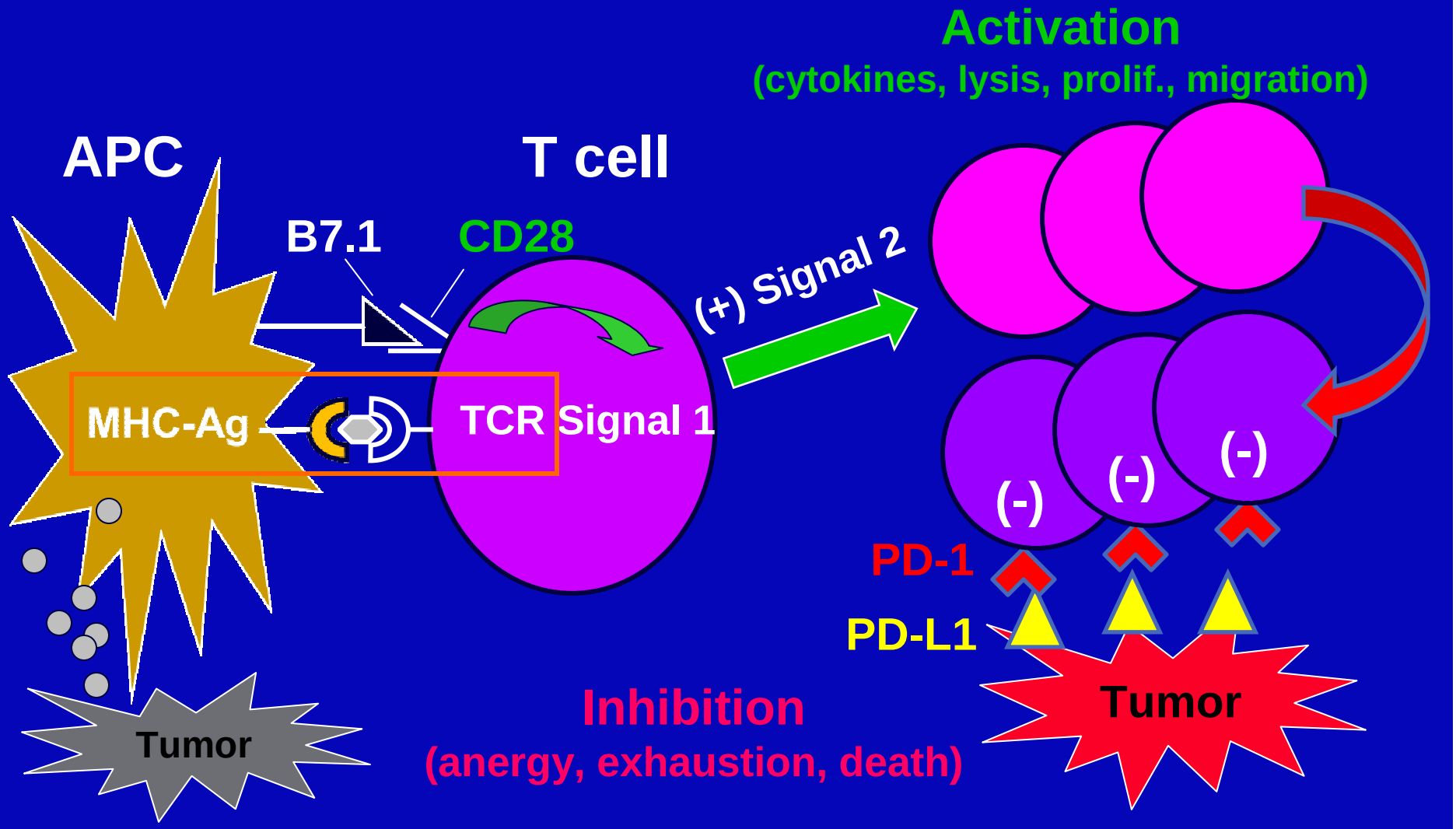
*Carboplatin (AUC 6); paclitaxel (175 mg/m2); ipilimumab (10 mg/kg q3w)

Role of PD-1 in Suppressing Antitumor Immunity



Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

Role of PD-1 in Suppressing Antitumor Immunity



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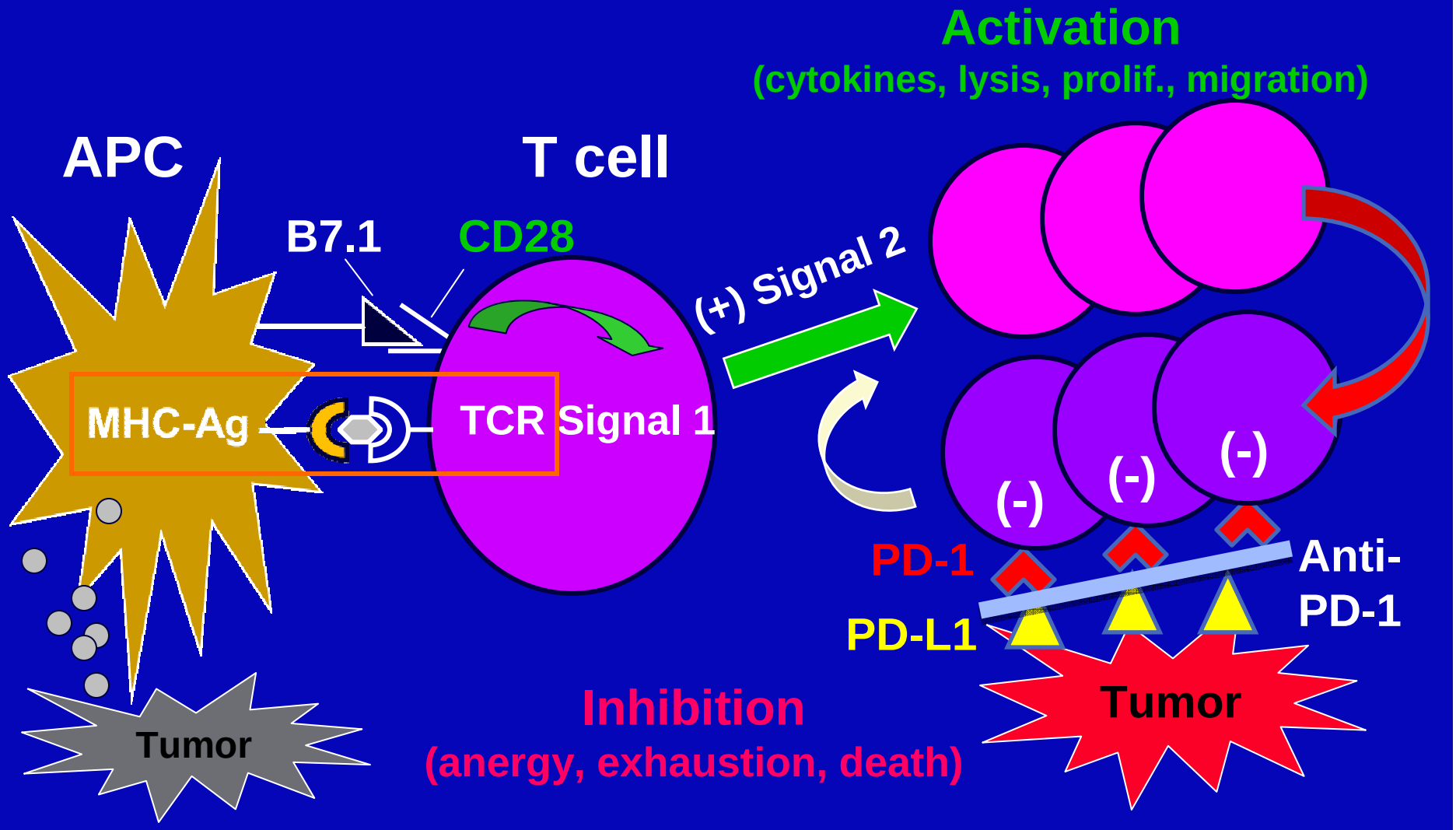
Role of PD-1 in Suppressing Antitumor Immunity

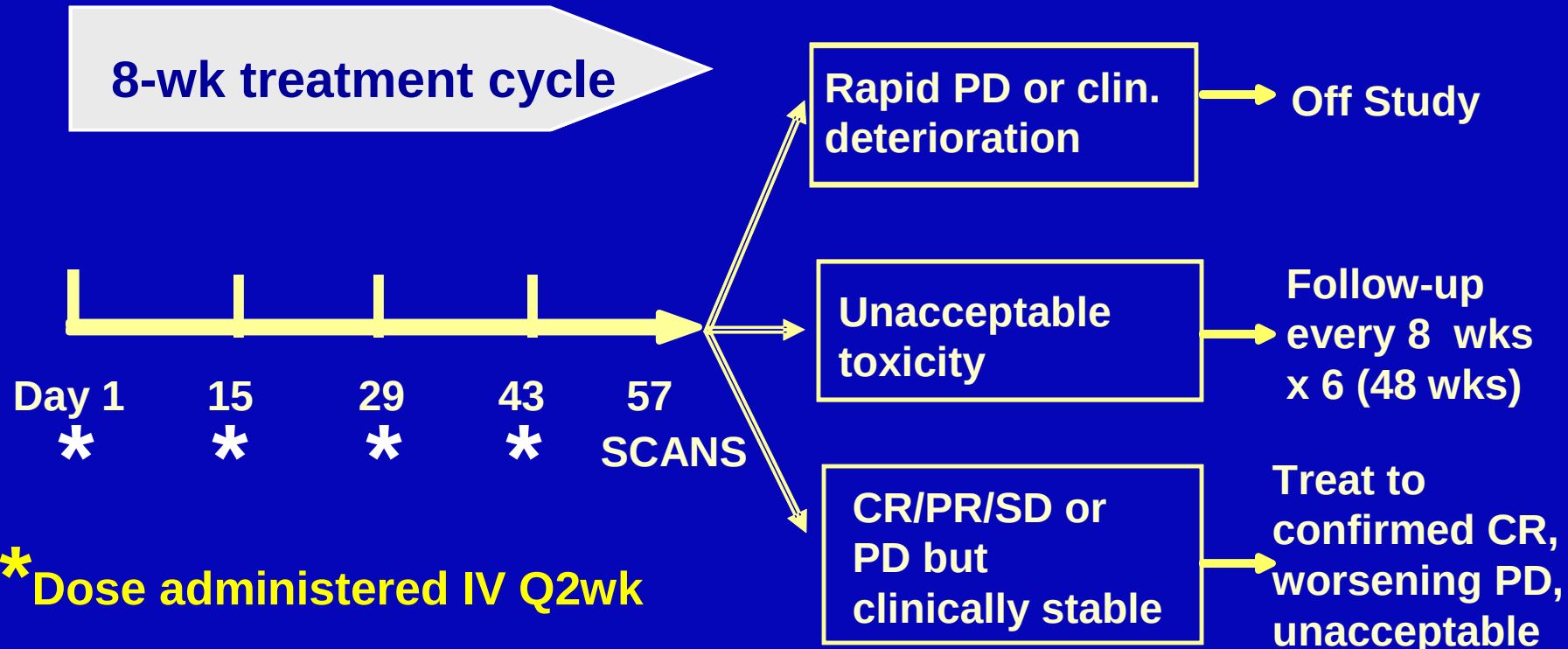


Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

Clinical Development of Inhibitors of PD-1 Immune Checkpoint

Target	Antibody	Molecule	Company	Development stage
PD-1	Nivolumab/ BMS-936558/ MDX-1106/ ONO-4538	Fully human IgG4 mAb	Bristol-Myers Squibb	Phase III multiple tumors
	Pidilizumab CT-011	Humanized IgG1 mAb	CureTech	Phase II multiple tumors
	Lambrolizumab MK-3475	Humanized IgG4 mAb	Merck	Phase I-II
PD-L1	BMS-936559/ MDX-1105	Fully human IgG4 mAb	Bristol-Myers Squibb	Phase I
	MedI-4736	Fully human IgG1 mAb	MedImmune	Phase I
	MPDL-3280A	Fully human IgG1 mAb	Genentech	Phase I-II

Nivolumab Study Design: Phase I Multi-Dose Regimen



*Dose administered IV Q2wk

Eligibility: Advanced MEL, RCC, NSCLC, CRC, or CRPC with PD after 1-5 systemic therapies

Topalian S et al NEJM 2012

Safety of Nivolumab-Multi-dose Phase I Trial

- 220 (72%) patients experienced drug-related AEs
  - Fatigue (26%), rash (14%), diarrhea (12%), and pruritus (10%) were the most common
  - Grade 3–4 AEs were experienced by 15% of patients
  - 18/304 (6%) patients discontinued treatment because of drug-related AEs
- AEs of special interest (AEOSI), defined as AEs with a potential immune-related etiology, were observed in 138 (45%) of study patients
  - Majority of AEOSI were low grade; 6% Grade 3–4
  - The most common AEOSI of any grade included rash (14%), diarrhea (12%), and pruritus (10%)
    - AEOSI occurring in ≤1% of patients included colitis, hepatitis, hypophysitis, and thyroiditis
- There were 3 (1%) deaths in patients with pneumonitis (2 NSCLC, 1 CRC)

Topalian S ESMO 2012

Clinical activity of Nivolumab

Tumor Type	Dose (mg/kg)	No. of Patients	ORR (CR/PR) No. of Patients (%)	SD ≥24 Weeks No. of Patients (%)
MEL	0.1–10	106	33 (31)	6 (6)
NSCLC	1–10	122	20 (16)	11 (9)
RCC	1 or 10	34	10 (29)	9 (27)

- 28 responses (16 MEL, 6 RCC, and 6 NSCLC) lasted ≥1 year among 54 patients with treatment initiation prior to 1 year
- 13 patients (4 MEL, 6 NSCLC, 3 RCC) demonstrated non-conventional patterns of response but were not included as responders

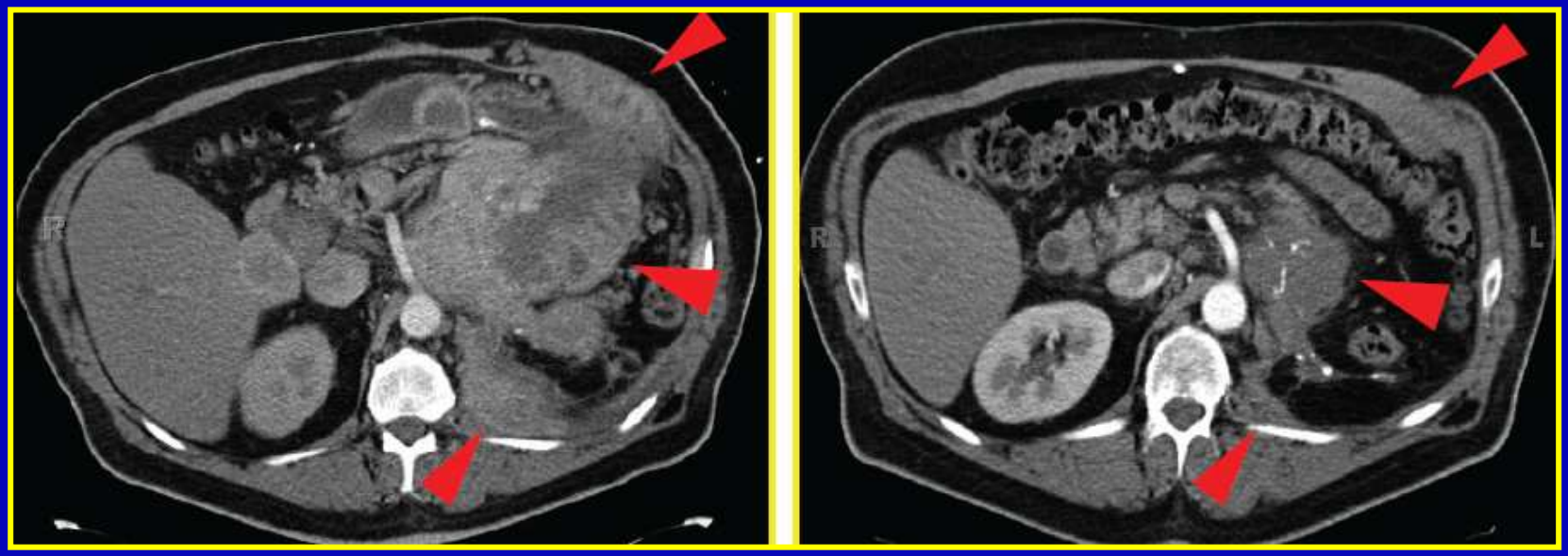
Topalian S ESMO 2012

Partial regression of metastatic RCC (Nivolumab, 1 mg/kg)

Case studies

- **57-year-old male patient**
- **Developed progressive disease following radical surgery and treatment with sunitinib, temsirolimus, sorafenib, and pazopanib**

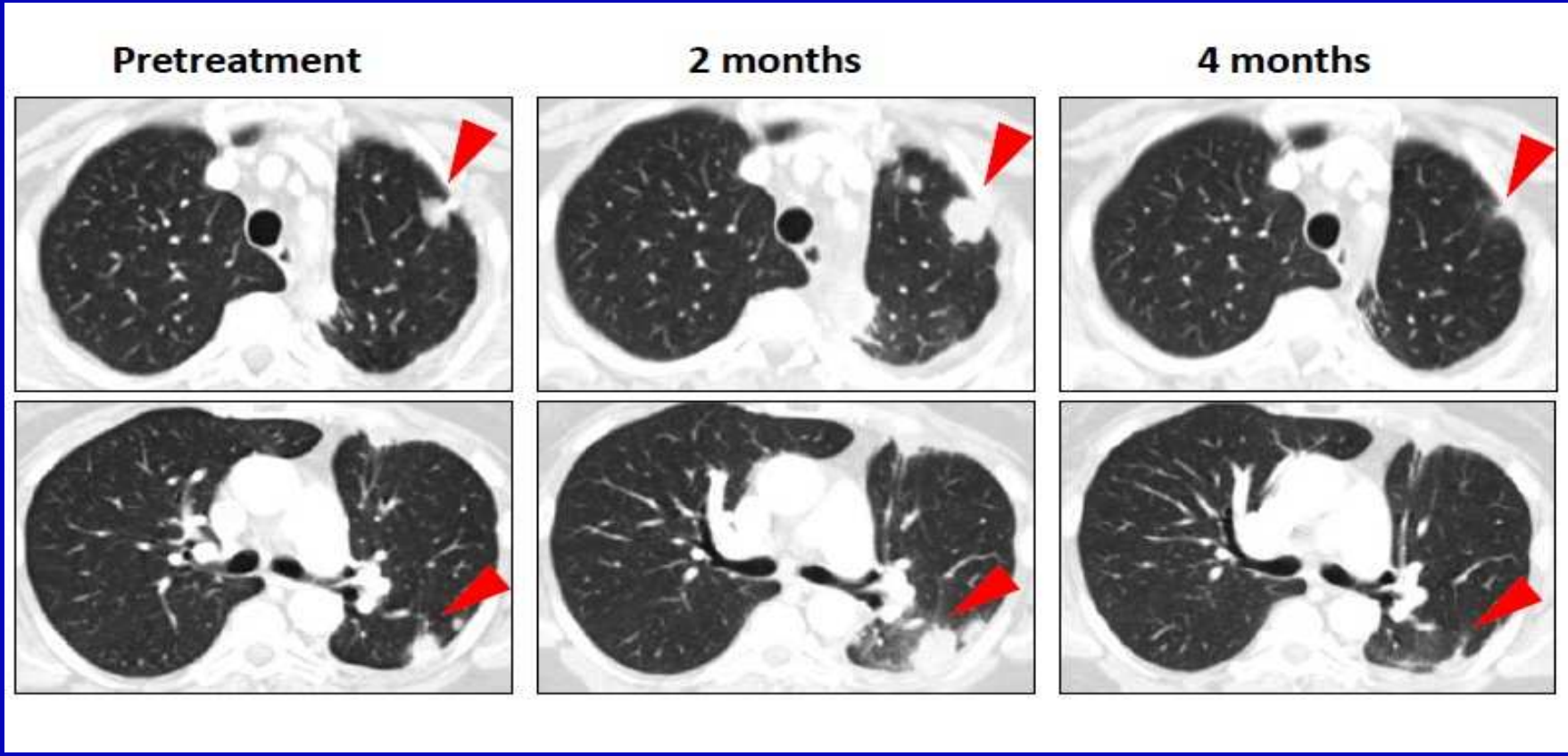
Pretreatment **6 Months**



RCC = renal cell cancer

McDermott D ESMO 2012

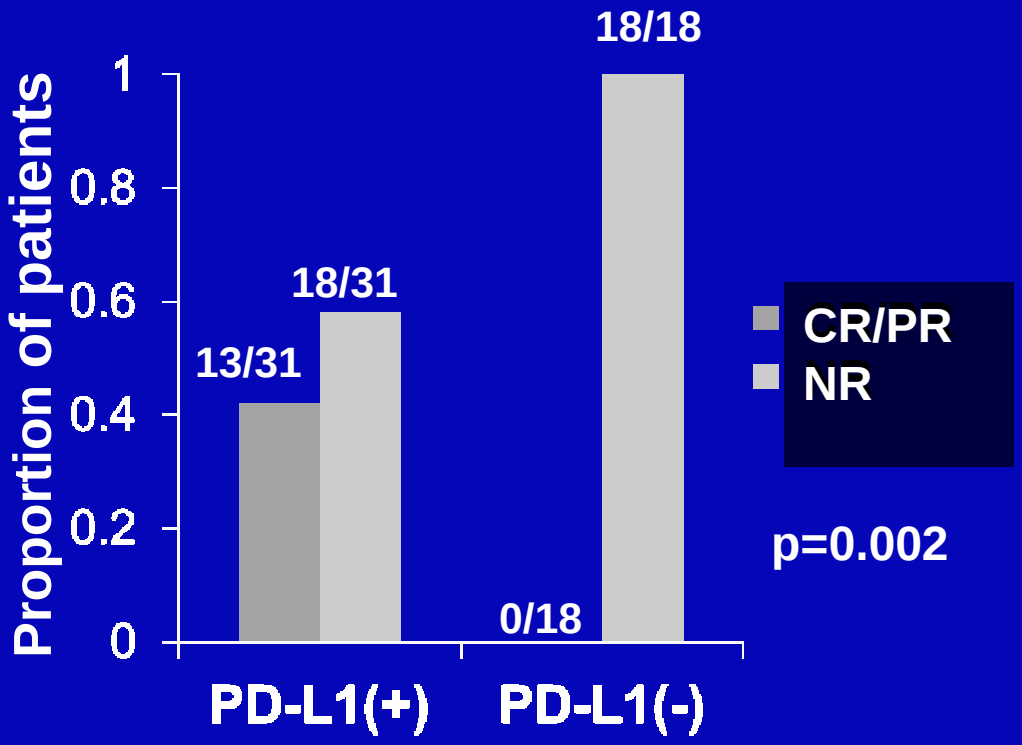
Response of Metastatic NSCLC (Nivolumab, 10mg/kg)



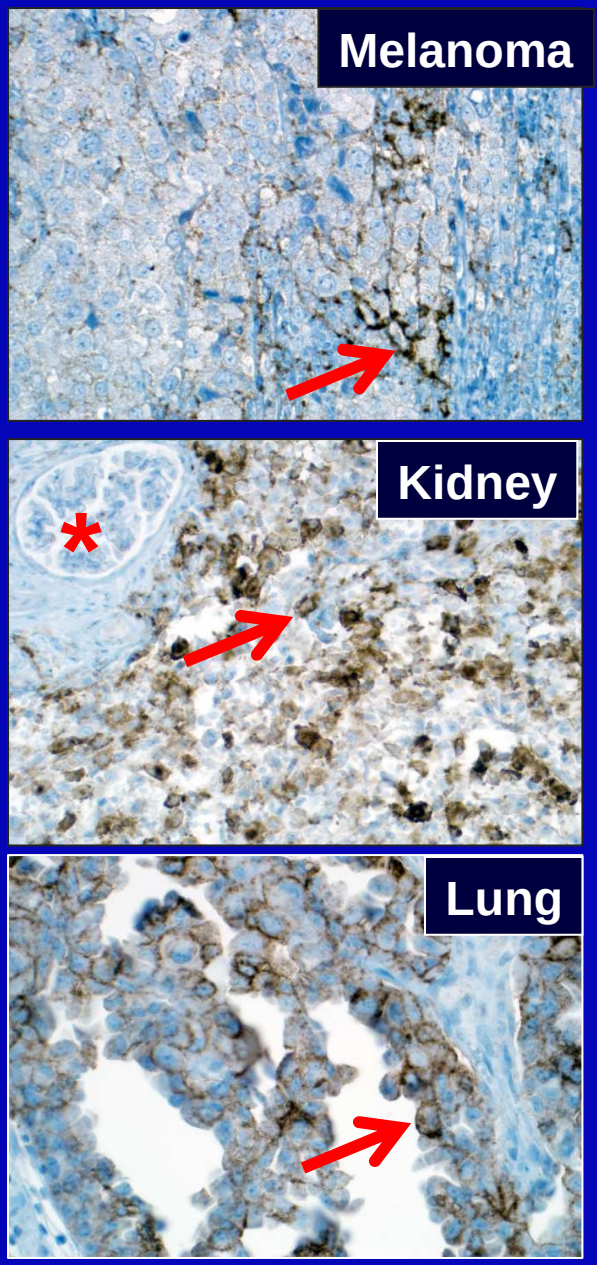
- Initial progression in pulmonary lesions of a NSCLC patient with non-squamous histology was followed by regression
- Dx ‘04, EGFR mutation +; Rx Gem/carbo, erlotinib, erlotinib + LBH589 (trial for T790 mutation), and lastly pemetrexed

S Antonia, Moffitt Cancer Center

Preliminary molecular marker studies: Correlation of PD-L1 expression in pretreatment tumor biopsies with clinical response to anti-PD-1



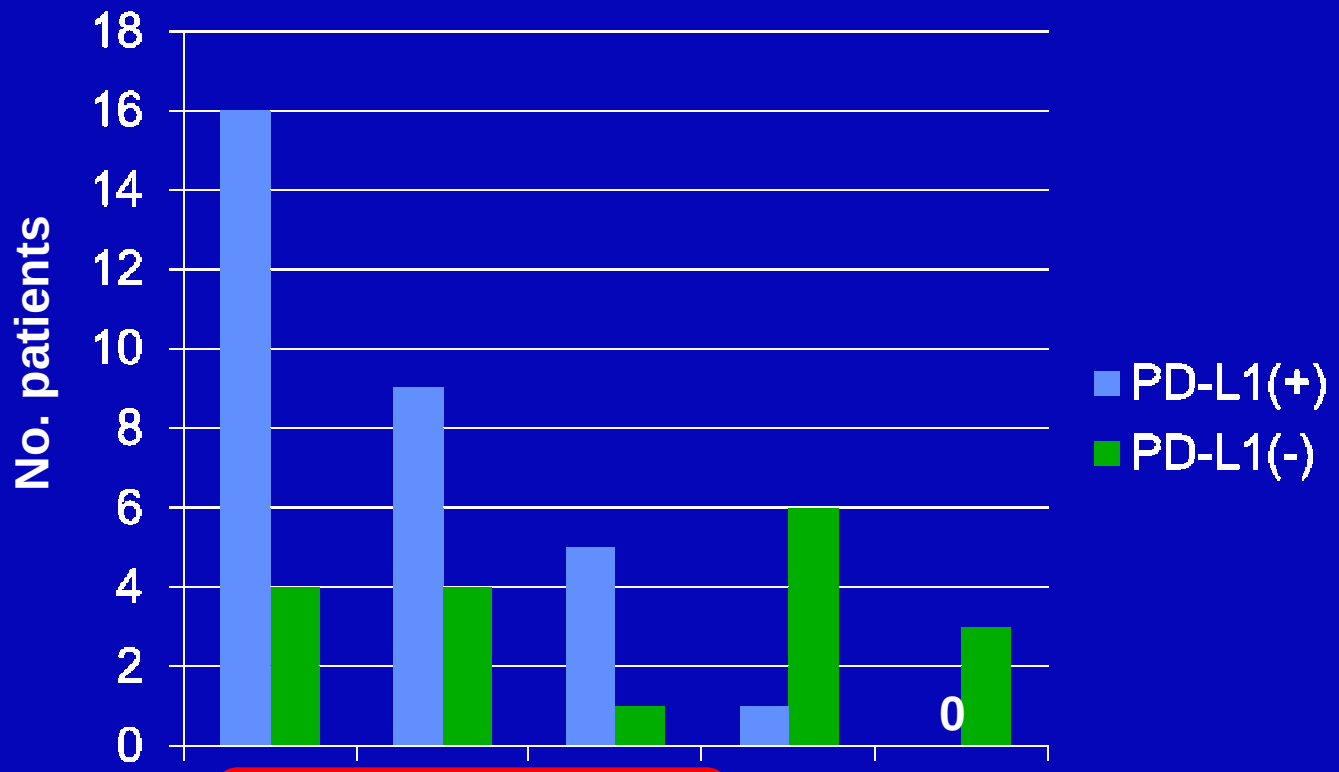
49 patients include 20 with melanoma,13 NSCLC, 7 colon, 6 kidney, and 3 prostate cancer.



* Normal renal glomerulus

Topalian S and Taube J personal communication 2013

Correlation of PD-L1 expression with tumor type in 49 patients treated with anti-PD-1



Patients were "PD-L1+" if ≥5% of tumor cells in *any* tumor biopsy expressed cell surface PD-L1, using mAb 5H1 and manual staining technique.

Topalian S and Taube J personal communication 2013

Nivolumab Ongoing Phase 3 Trials

- NSCLC
  - Nivolumab vs. Docetaxel in the 2nd line setting in patients with squamous cell carcinoma
  - Nivolumab vs. Docetaxel in the 2nd or 3rd line setting in patients with non-squamous cell
- RCC
  - Nivolumab vs. Everolimus who have received prior anti-angiogenic therapy
- Melanoma
  - Nivolumab vs. Nivo + Ipi vs. Ipi in untreated pts
  - Nivolumab vs. Physicians' Choice (taxol/carbo or dacarbazine) after Ipi progression
  - Nivolumab vs. Dacarbazine in untreated (outside-US)

MK-3475: Phase I Trial Design

MK-3475 - Humanized IgG4 antibody binds to PD-1

Part A – Dose escalation

- 3+3 design 1, 3, and 10 mg/kg
  - Administered every 2 or 3 weeks
- Advanced solid tumors

Part B – Melanoma expansion cohort

- Single arm, open label
- 2 mg/kg and 10 mg/kg
  - Administered every 2 or 3 weeks
- Advanced Melanoma
  - Naïve to Ipilimumab (IPI)
  - Previously treated with IPI

Hamid O et al Society of Melanoma 2012

MK-3475: Summary of Dose Escalation Phase

- MK-3475 is well tolerated at all dose levels tested - (1mg/kg, 3mg/kg, and 10 mg/kg; administered every 2 or 3 weeks):
  - No DLTs
  - Majority of AEs are Grade 1-2
    - Common AEs were fatigue, pruritus, dyspnea, and nausea
- Early evidence of anti-tumor activity
  - Two melanoma patients with confirmed partial responses by RECIST 1.1 at 3 mg/kg and 10 mg/kg
  - One NSCLC patient with unconfirmed partial response by RECIST 1.1 at 1 mg/kg

Hamid O et al Soc of Melanoma 2012

MK-3475: Preliminary Best Overall Response in Advanced Melanoma Patients

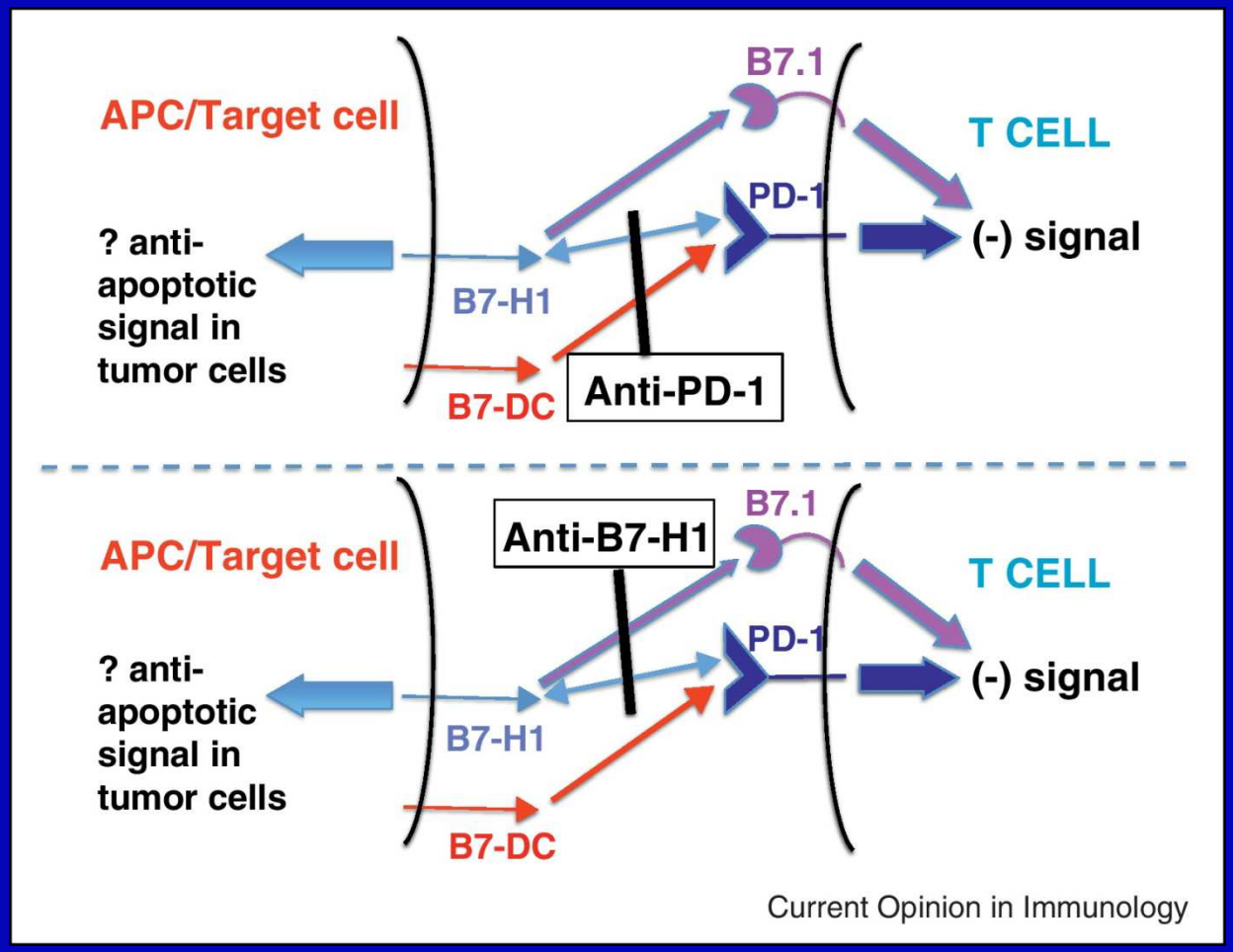
	Complete Response (N, 95% CI)	Objective Response (N, 95% CI)	Disease Control Rate (N, 95% CI)
All MEL N=83	5% (4; 2%-13%)	47% (39; 34%-56%)	60% (50; 48% - 70%)
IPI Naïve N=58	7% (4; 2%-18%)	50% (29; 35%-61%)	67% (39; 51%-76%)
IPI Treated N=25	0%	40% (10; 17%-59%)	44% (11; 24%-68%)

-All patients were dosed at 10 mg/kg
-7 Grade 3 / 4 immune related events including thyroid disease, pneumonitis, nephritis etc
-Disease control rate = objective response + stable disease

Randomized phase II trial for 2nd line therapy enrolling
– High dose vs. low dose vs. chemo

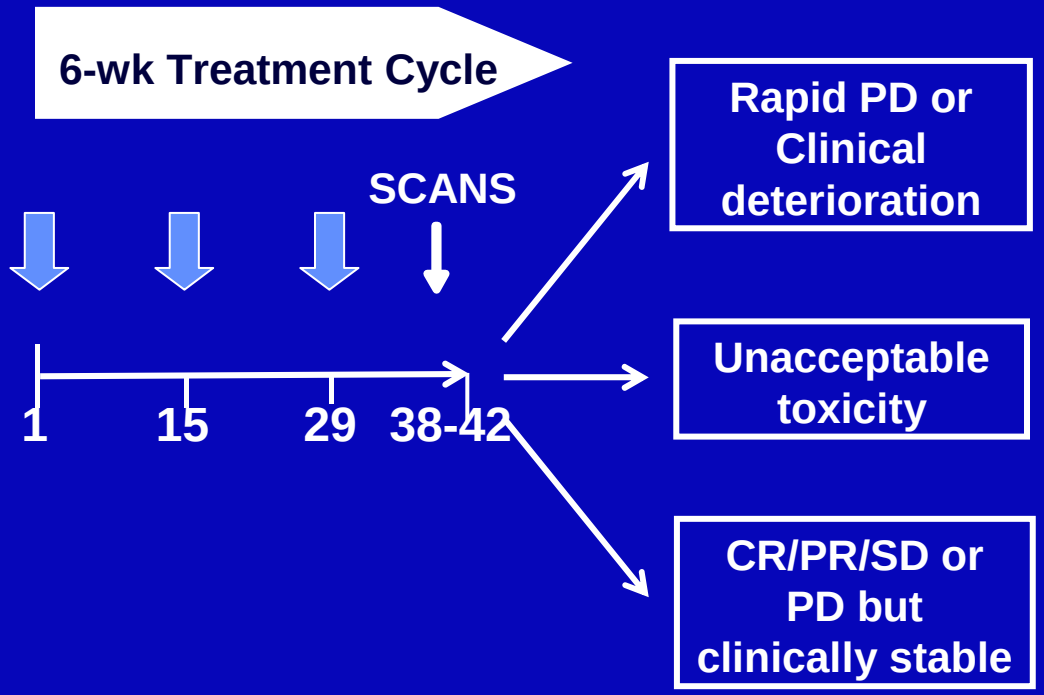
Hamid O et al Soc of Melanoma 2012

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



Topalian S et al Curr Opin Immunol 2012

Study Design: First-in-Human Trial of BMS-936559 (anti-PD-L1 Ab)



Rapid PD or Clinical deterioration → Off Study

Unacceptable toxicity → Follow-up

CR/PR/SD or PD but clinically stable → Treat to 16 cycles (96 wk total) → On-study follow-up for 12 mo → Optional: Retreatment at original dose for ≤12 mo if PD during follow-up

Dose administered IV, Q2wk in 6 wk cycles

Eligibility: Advanced MEL, NSCLC, RCC, CRC, Ovarian, Pancreatic, Breast, Gastric Cancers with PD; No previous T-cell therapy (CTLA-4, Anti-PD-1/L1)

Brahmer J et al NEJM 2012

BMS 936559 - Safety

- A maximum tolerated dose was not identified at doses up to 10 mg/kg
- There was no apparent relationship between drug dose and AE frequency in all treated patients
- Median duration of therapy was 12 weeks (range 2.0−111.1 weeks)
- 12 of 207 (6%) patients discontinued treatment due to a BMS-936559-related adverse event (AE)
- Drug-related AEs in 126 of 207 patients (61%)
  - Most AEs were low grade (grade 1/2 in 107 of 207 patients, 52%)
  - Grade 3/4 drug-related AEs in 19 of 207 patients (9%)
- No drug-related deaths

Brahmer J et al NEJM 2012

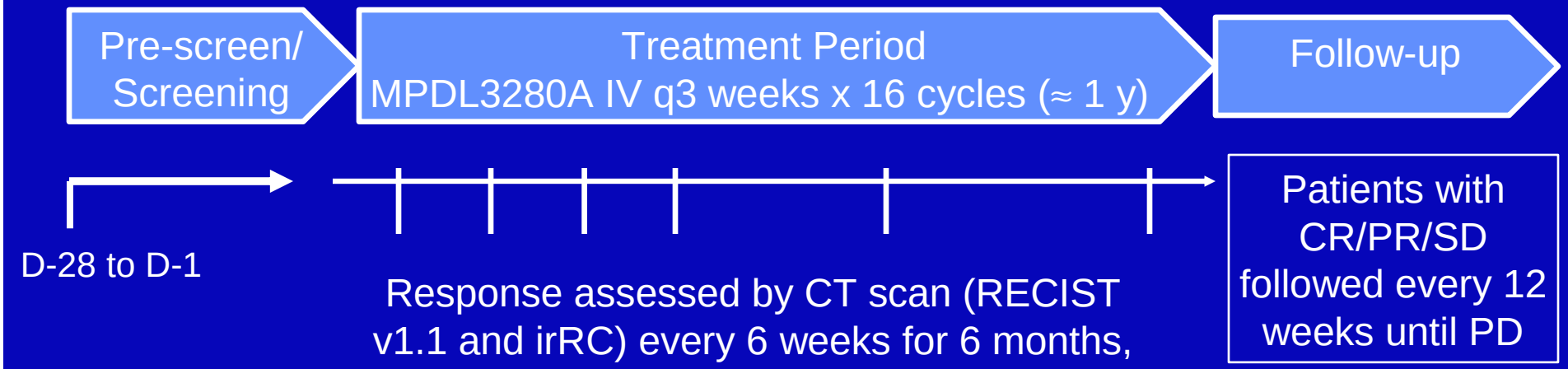
Clinical activity of BMS-936559 in 160 response-evaluable patients[a]

Tumor Type[b]	Dose (mg/kg)	No. Patients (N=160)	ORR[c] No. Patients (%)	Duration of Response Range, Months	SD≥24 Weeks No. Patients (%)	PFSR at 24 Weeks (%)
Melanoma	0.3-10	52	9 (17)[d]	2.8-23.5+	14 (27)	42
NSCLC	1-10	49	5 (10)	2.3+-16.6+	6 (12)	31
All Squamous		13	1 (8)	-	3 (23)	43
All Non-squamous		36	4 (11)	-	3 (8)	26
RCC	10	17	2 (12)	4-17	7 (41)	53
Ovarian	3 and 10	17	1 (6)	1.3+	3 (18)	22

[a] Response-evaluable patients who initiated treatment by August 1, 2011
[b] To date there have been no objective responses in patients with colorectal or pancreatic cancer; no patients with gastric or breast cancer were evaluable as of the date of data analysis
[c] ORR was assessed using modified RECIST v1.0 criteria
[d] Includes 3 CRs

Tykodi S SITC 2012, Brahmer J et al NEJM 2012

MPDL3280A, Anti-PD-L1: Phase I Schema



Key Eligibility Criteria

- *Incurable or metastatic solid tumor or hematologic malignancy*
- *Measureable disease per RECIST v1.1*
- *ECOG PS 0 or 1*

Gordon M et al AACR 2013

MPDL3280A: Phase I trial

- MPDL3280A safety and PK profile
  - Generally well tolerated
    - Most common side effects: fatigue, nausea and diarrhea
    - No dose-limiting toxicities up to 20 mg/kg
  - No MTD identified
- Activity observed in multiple solid tumor types, with responses continuing in all responders
- Expansion phases in NSCLC, melanoma, RC and other tumor types are ongoing
- Phase Ib trials in combination with bevacizumab, chemotherapy and vemurafenib are ongoing
- Phase II trials in NSCLC initiated

Conclusions

- Checkpoint inhibitors have promising anti-tumor activity
  - Ipilimumab is the first checkpoint inhibitor approved for use in cancer
- Checkpoint inhibitors have a unique set of side effects consistent with the immune mechanism of action
- Patient selection (biomarker) are being sought
- Phase 3 trials are ongoing