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Clinical Perspective: Immuno-Oncology

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Disclosures

- Ad hoc advisory board
  - Astra Zeneca, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, Genentech, Merck, Lilly.

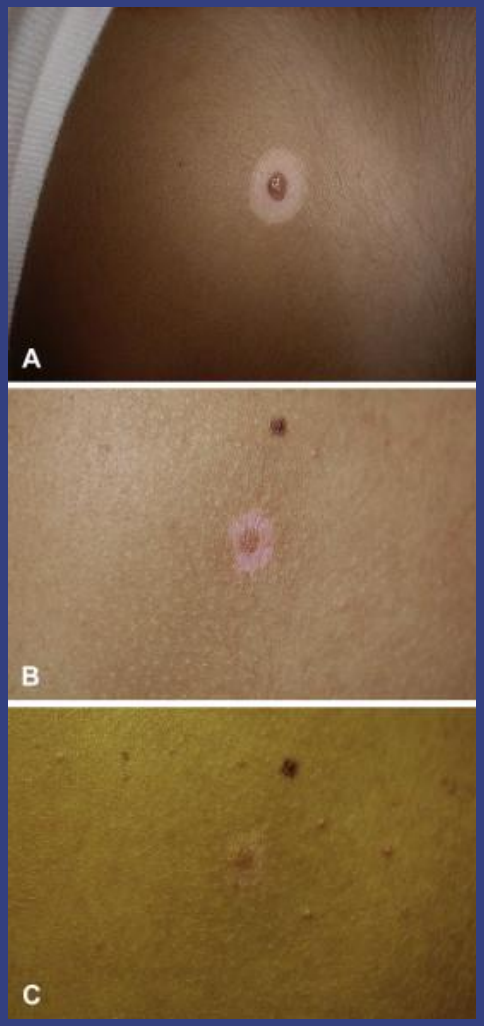
Outline

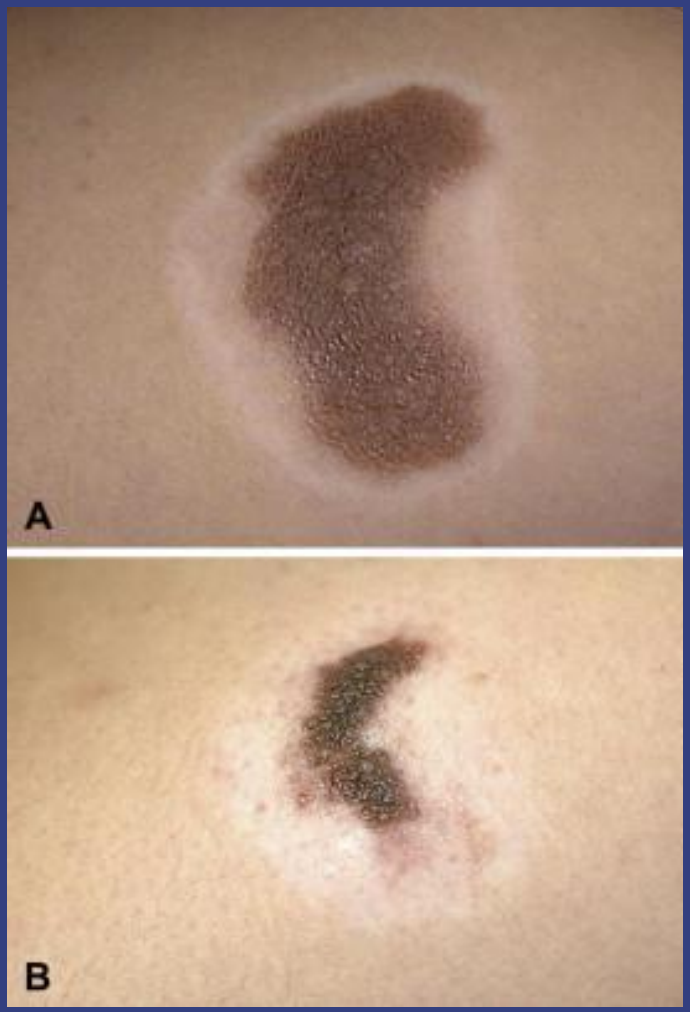
- Rationale
- Clinical Data
- Biomarkers
- Combination approaches
- Tolerability
- Future perspectives

Anti-tumor Immunity

- Major requisites
  - Recognition of tumor-related protein(s) as foreign
  - Mount an appropriate immune response
- Both steps involve a number of well-regulated events
- Failure of one or more steps aides tumor progression and metastasis

Halo Nevus



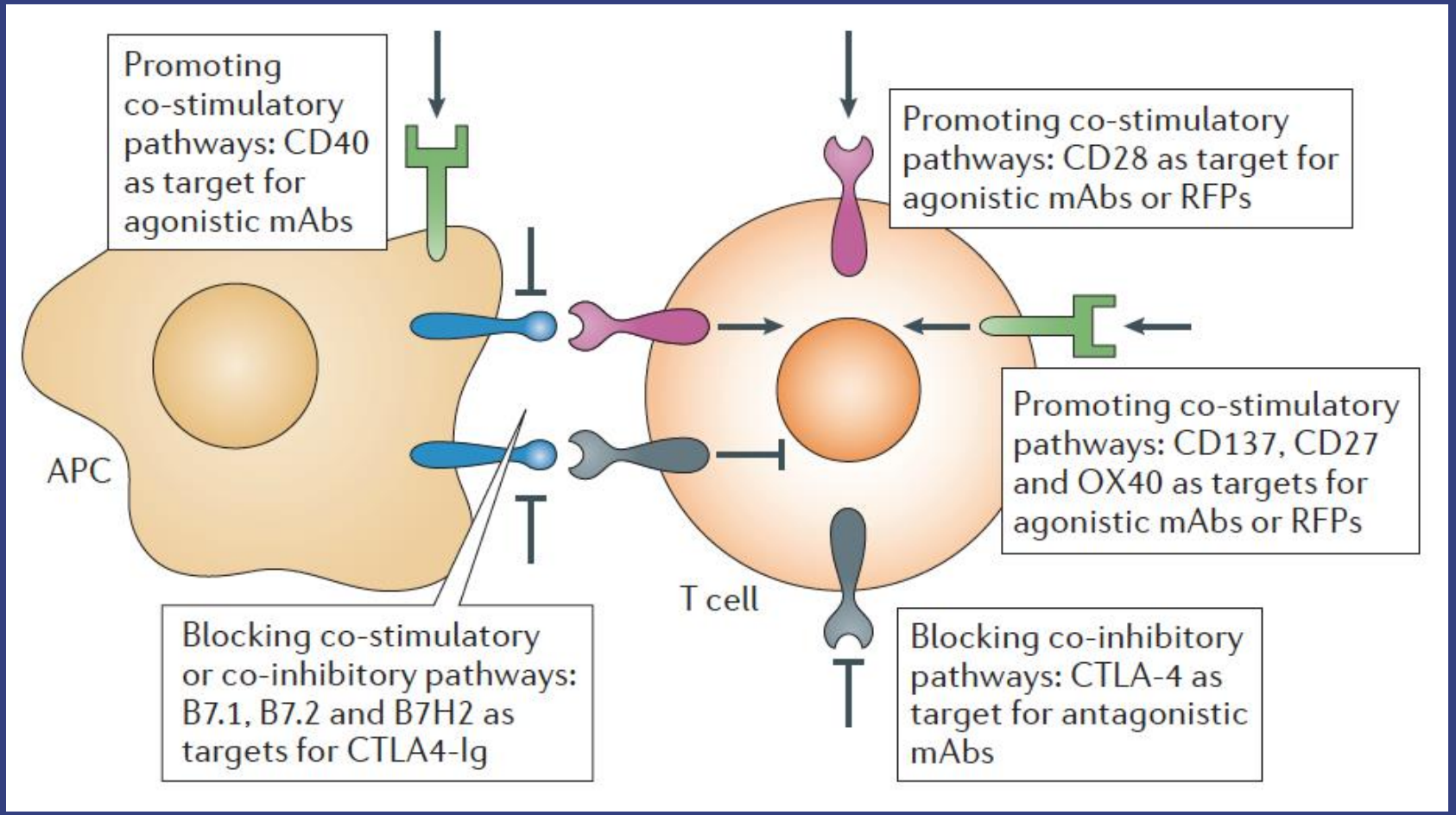


Aouthmany M, et al. *J Am Acad Dermatol.* 2012;67(4):582-286.

Key Components

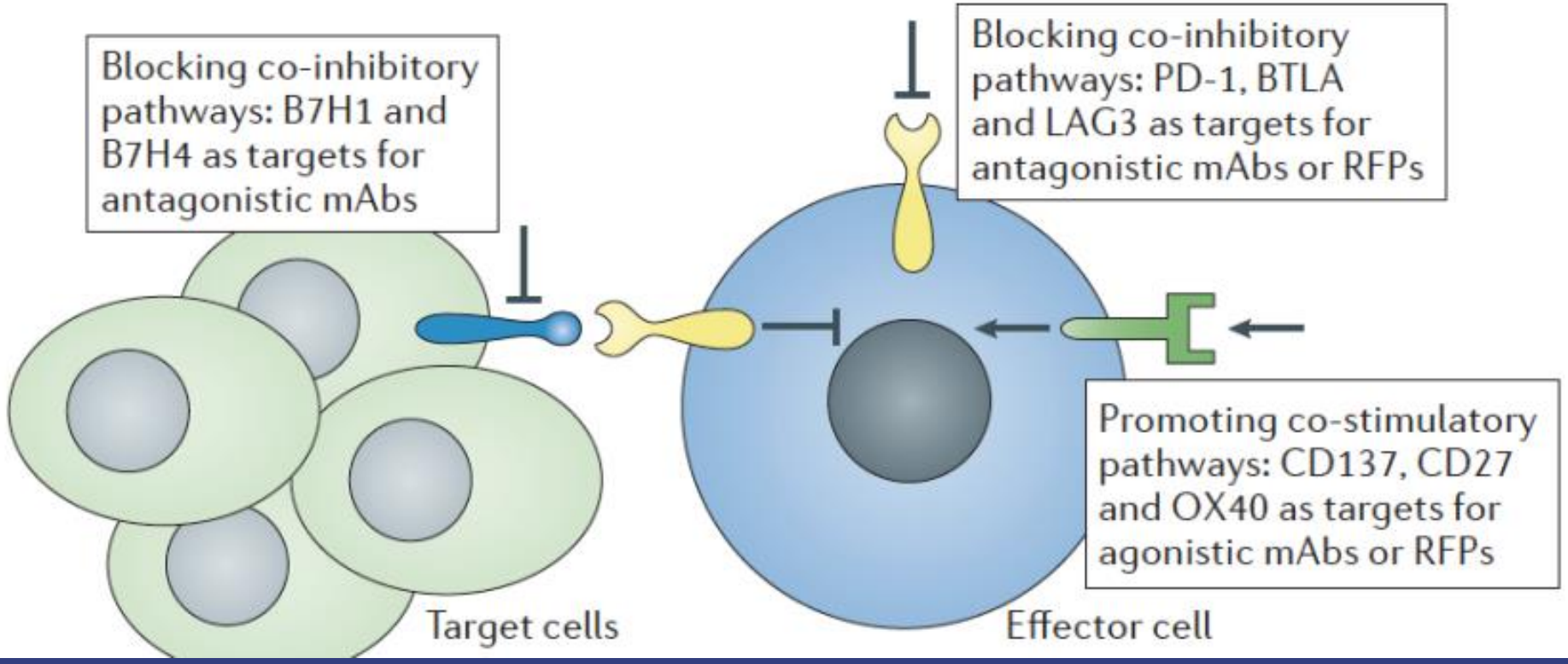
- Natural killer cells
- Dendritic cells
- Toll-like receptor
- T-lymphocytes
- Regulatory T-lymphocytes
- Chemokines
  - TGF Beta
  - IL-10

Immune Recognition



Yao S, et al. *Nat Rev Drug Discov.* 2013;12(2):130-146.

Antitumor Effects



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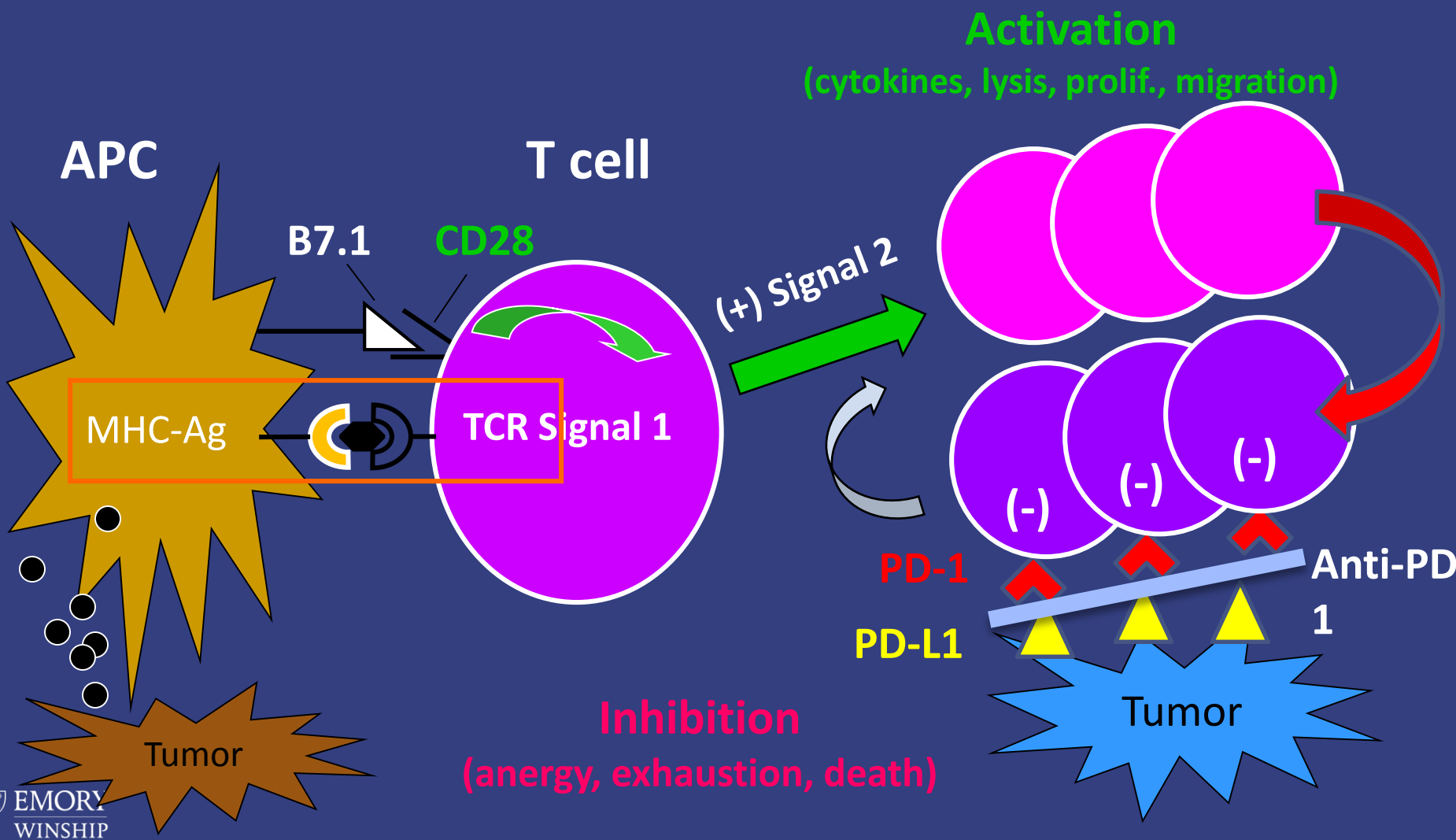
Yao S, et al. *Nat Rev Drug Discov.* 2013;12(2):130-146.

Basic Approaches

- Immunization
  - Utilize cancer vaccines to promote antitumor immunity
- Passive
  - Activated immune cells to enhance antitumor immunity
- Non-specific
  - Promote effector cells against tumor cells
  - Inhibit regulatory cells

Devita VT, et al. *Principles and Practice of Oncology*, 8th Edition. Lippincott, Williams, & Watkins. Philadelphia, PA.

Role of PD-1 in Suppressing Antitumor Immunity



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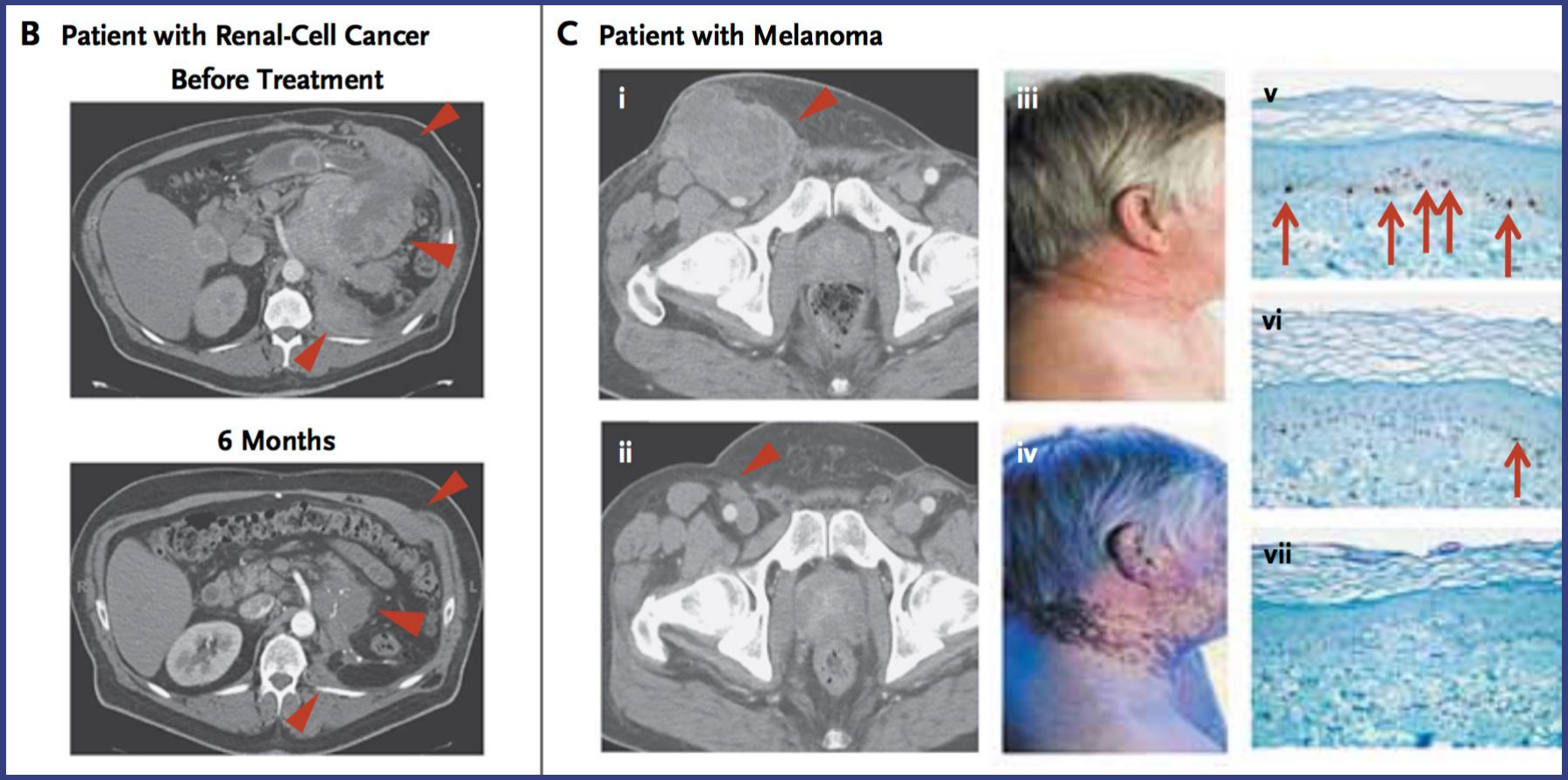
Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

ANTI- CANCER ACTIVITY OF IMMUNE CHECKPOINT INHIBITORS

Cancers Sensitive to Immune Checkpoint Inhibition

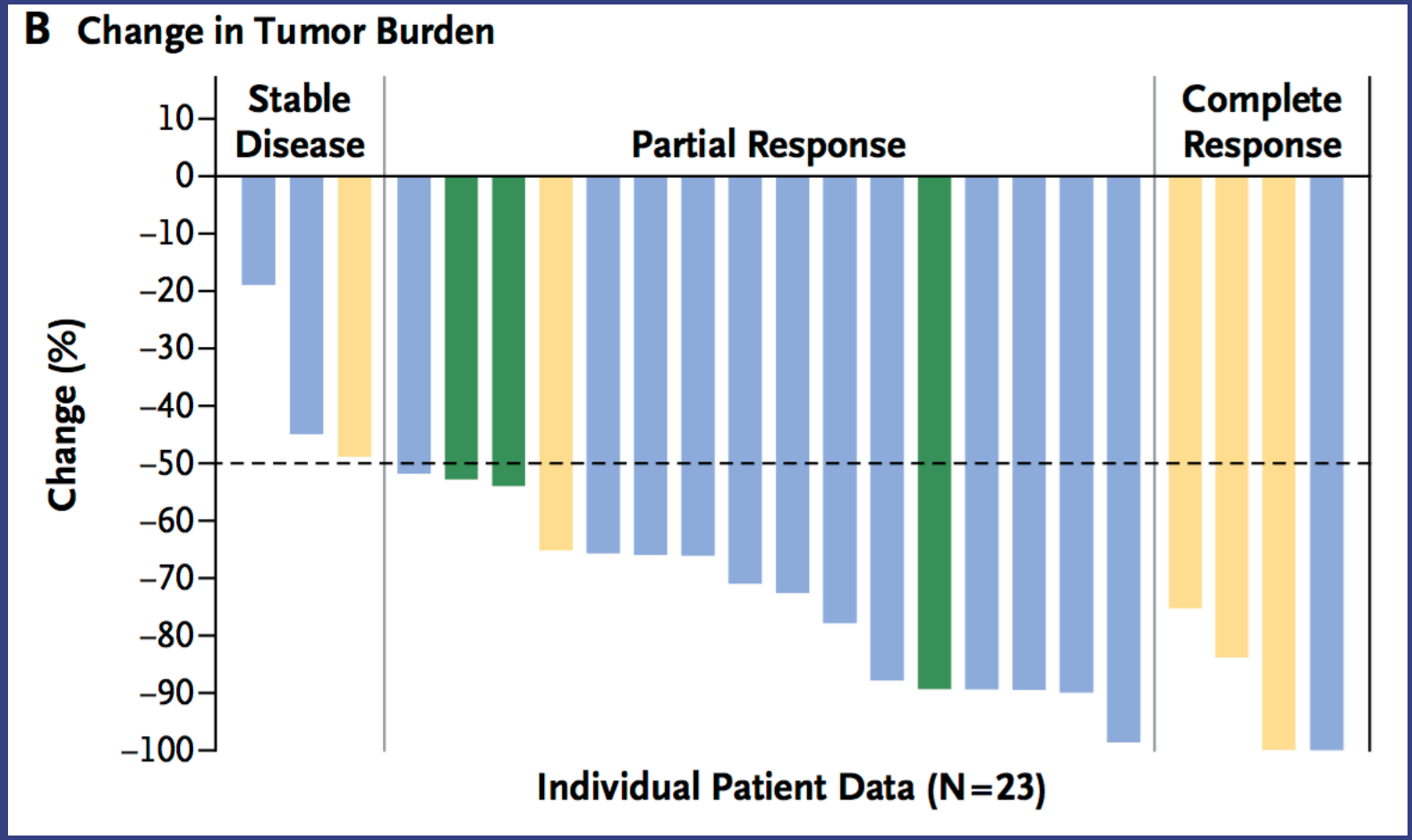
- Melanoma
- Lung cancer
- Bladder cancer
- Renal cell carcinoma
- Hodgkin's disease
- Hepatocellular carcinoma
- ……

Nivolumab: Phase I Evaluation



Topalian et al, N Engl J Med, 2012

Nivolumab in Relapsed/Refractory Hodgkin's Disease



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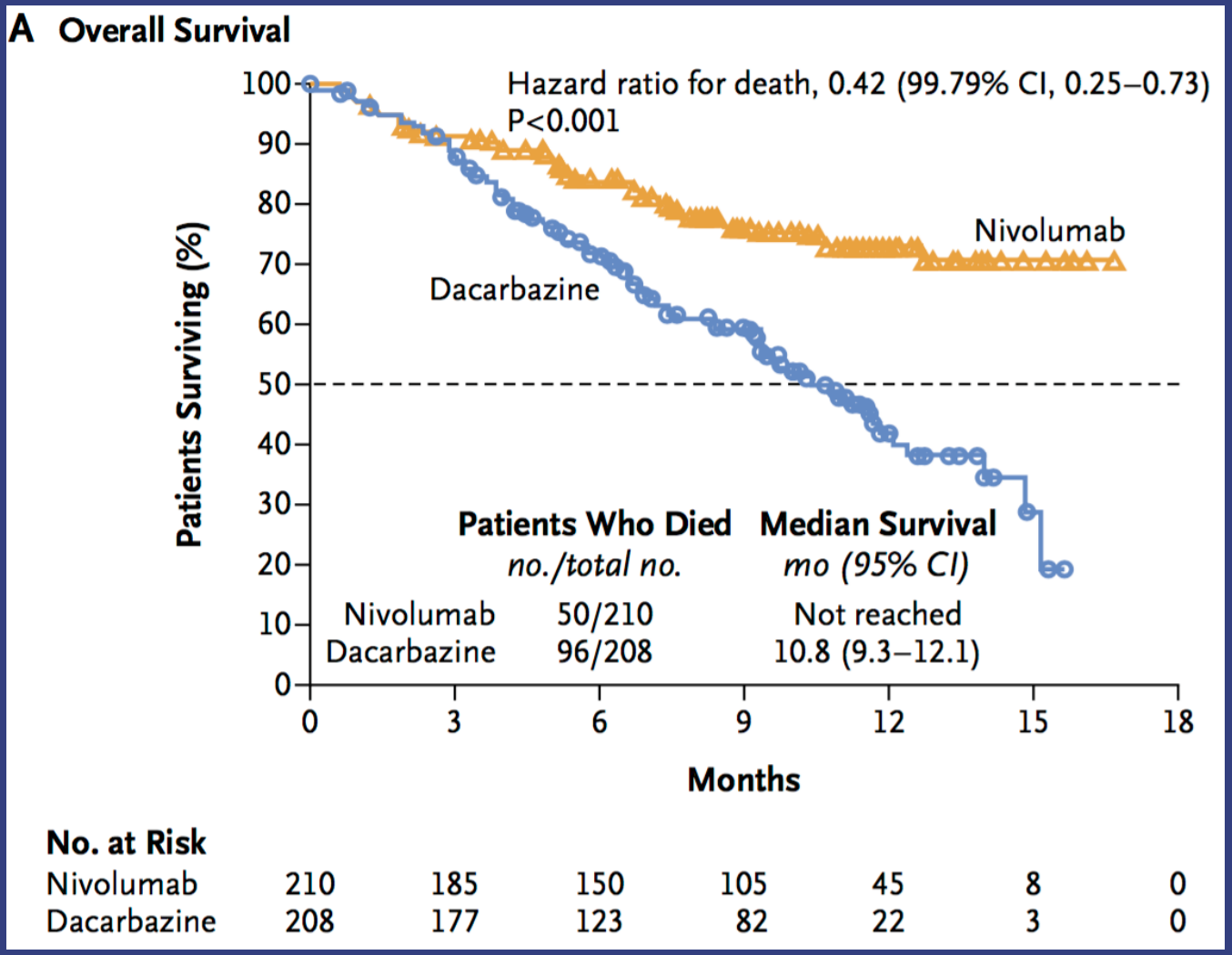
Ansell et al, N Engl J Med, 2015

Nivolumab Vs. Dacarbazine in Untreated Melanoma



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Robert et al, N Engl J Med, 2015

CheckMate 063: Nivolumab in Sq NSCLC

- Stage IIIB/IV SQ NSCLC
- ≥2 prior systemic therapies
- ECOG 0–1

(N = 140 screened)

→

Nivolumab 3 mg/kg IV Q2W until PD or unacceptable toxicity

(N = 117)

→

Endpoints

Primary:
- Confirmed ORR* (IRC assessed)

Secondary:
- Confirmed ORR* (investigator assessed)

Exploratory:
- Safety and tolerability
- PFS/OS
- PD-L1 expression and efficacy

* Further characterized by DOR

- Planned to treat approximately 100 patients
  - Expected ORR of 10–50%, with 20% maximum width of exact 2-sided 95% confidence interval
- Assessments (RECIST v1.1) performed at week 8 and Q6W
  - Initial data lock March 2014 (including investigator-assessed endpoints)
  - Updated data lock July 2014 for IRC endpoints, OS and safety (minimum follow-up 11 months)

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Rizvi et al, Lancet Oncology, 2014

Phase II: Clinical Activity of Nivolumab

	IRC Assessed (per RECIST v1.1)[a]
ORR, % (n) [95% CI]	15 (17) [9, 22]
Disease control rate, % (n)	40 (47)
Median DOR, months (range)	NR (2+, 12+)
Ongoing responders, % (n)	76 (13)
Median time to response, months (range)	3 (2, 9)
PFS rate at 1-year, % (95% CI)	20 (13, 29)
Median PFS, months (95% CI)	2 (2, 3)

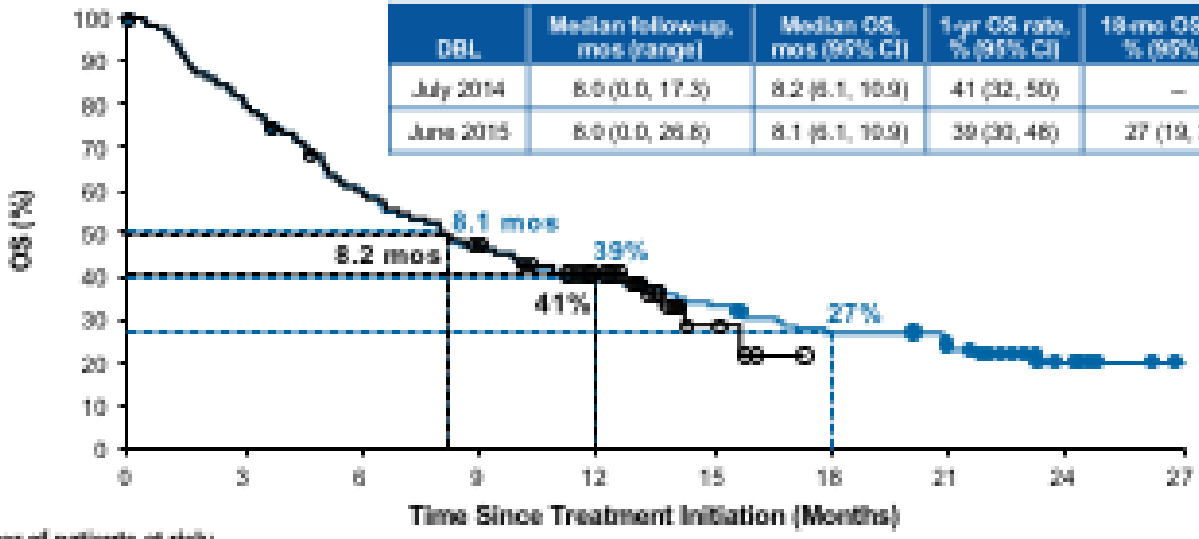
[a]July 2014 DBL
NR = not reached; DOR = duration of response; ORR = objective response rate; PFS = progression free survival

Ramalingam S et al CMSTO 2014

Efficacy

Overall Survival (All Treated Patients)

DBL	Median follow-up, mos (range)	Median OS, mos (95% CI)	1-yr OS rate, % (95% CI)	18-mo OS rate, % (95% CI)	Events, n/N
July 2014	8.0 (0.0, 17.5)	8.2 (6.1, 10.9)	41 (32, 50)	–	72/117
June 2015	8.0 (0.0, 26.8)	8.1 (6.1, 10.9)	39 (30, 48)	27 (19, 35)	90/117



Number of patients at risk:

July 2014 DBL	117	93	68	51	28	5	0	0	0	0
June 2015 DBL	117	93	69	54	45	35	30	24	6	0

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Nivolumab vs. Docetaxel in Previously Treated Squamous NSCLC

N = 272

Key Eligibility Criteria
- Stage IIIB/IV squamous NSCLC
- Measurable disease
- ECOG PS ≤ 1
- Multimodal therapy allowed; disease progression after one platinum doublet-based chemo
- Available tumor tissue sample

RANDOMIZ

1:1

Nivolumab 3 mg/kg IV Q2W until PD or unacceptable toxicity (N=135)

Docetaxel 75 mg/m^2 IV Q3W until PD or unacceptable toxicity (N= 137)

Endpoints
- Primary: OS
- Secondary: ORR, PFS, PDL1-efficacy association, safety, QoL

One pre-planned interim analysis for OS
- At the time of database lock, 199 deaths reported[a,b]
- Boundary for OS superiority: *P*<0.03

[a]Data base lock was December 15, 2014
[b]86% deaths required for final analysis

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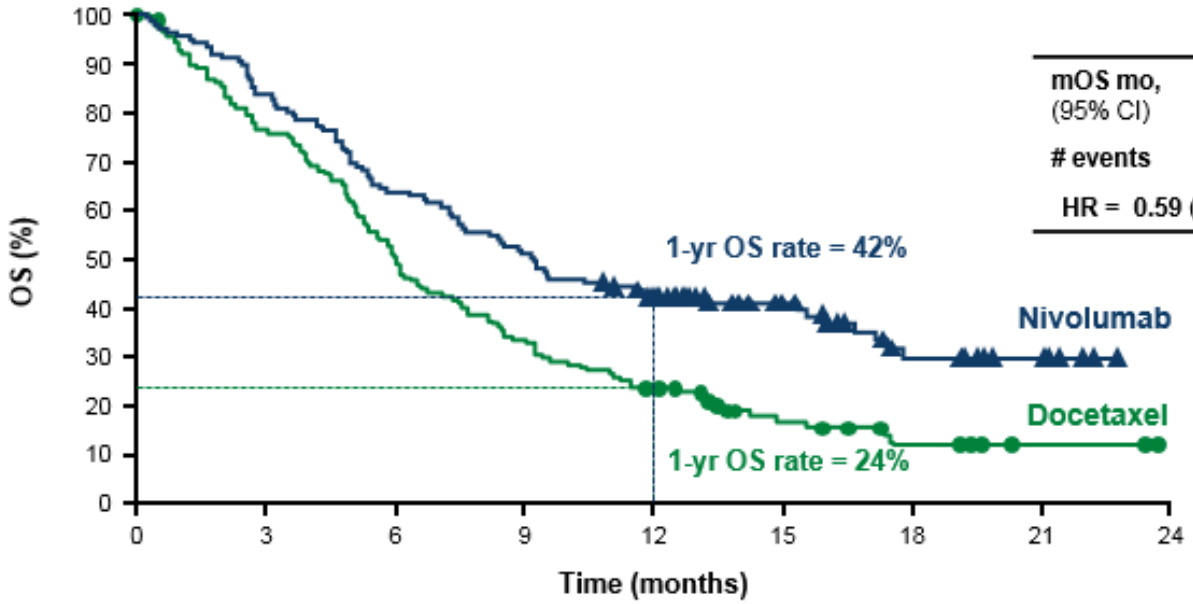
Brahmer et al, N Engl J Med, 2015

Phase 3 CheckMate 017: Nivolumab vs. Docetaxel in Previously Treated Squamous NSCLC: Efficacy (cont)

Overall Survival



	Nivolumab n = 135	Docetaxel n = 137
mOS mo, (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
# events	86	113

HR = **0.59** (95% CI: 0.44, 0.79), ***P*** = **0.00025**

Number of Patients at Risk

Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

Symbols represent censored observations

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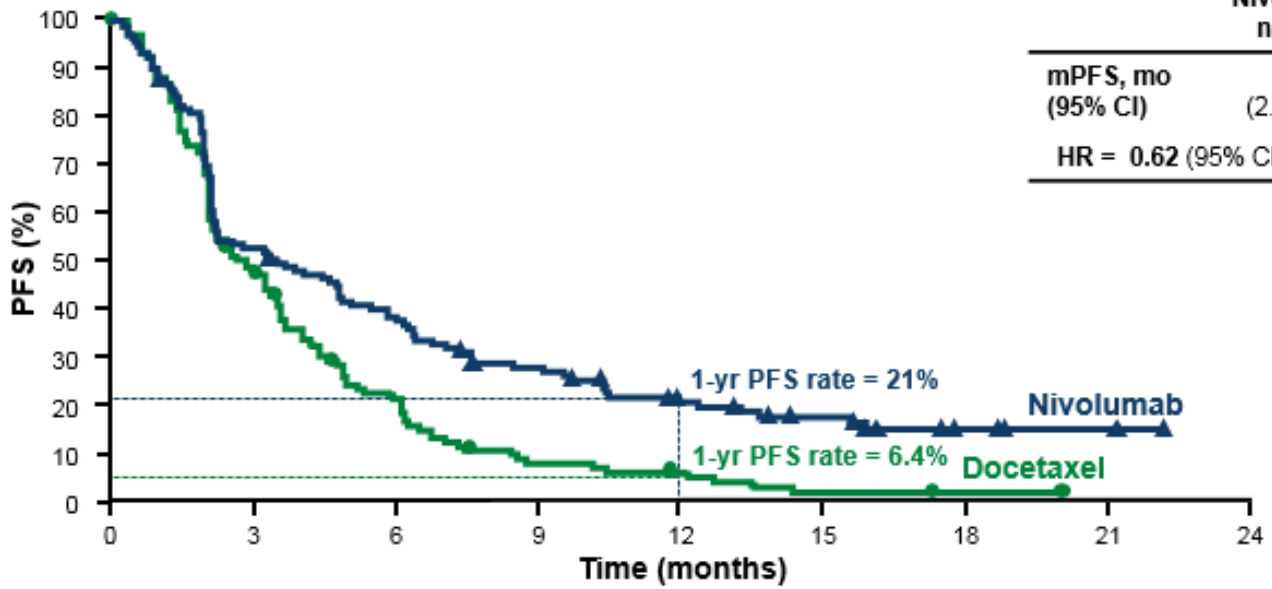
Phase 3 CheckMate 017: Nivolumab vs. Docetaxel in Previously Treated Squamous NSCLC: Efficacy (cont)

Progression-free Survival



	Nivolumab n = 135	Docetaxel n = 137
mPFS, mo (95% CI)	3.5 (2.1, 4.9)	2.8 (2.1, 3.5)

HR = **0.62** (95% CI: 0.47, 0.81); ***P*** = **0.0004**

Number of Patients at Risk

Nivolumab	135	68	48	33	21	15	6	2	0
Docetaxel	137	62	26	9	6	2	1	0	0

PFS per investigator.

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Nivolumab vs. Docetaxel in Advanced Non-Squamous NSCLC

N = 582

Key Eligibility Criteria
- Stage IIIB/IV NSCLC
- ECOG PS 0- 1
- Failed 1 prior platinum doublet
- Prior maintenance therapy allowed[a]
- Prior TKI therapy allowed for known ALK translocation or EGFR mutation
- Available tumor tissue sample

RANDOMIZ

1:1

Nivolumab 3 mg/kg IV Q2W until PD or discontinuation

Docetaxel 75 mg/m^2 IV Q3W until PD or discontinuation

Endpoints
- Primary: OS
- Secondary: ORR, PFS, PDL1 expression, disease-related symptom improvement rate

[a]Maintenance therapy included pemetrexed, bevacizumab, or erlotinib

- PD-L1 expression measured using DAKO/BMS automate IHC assay
  - Fully validated with analytical performance having met pre-determined acceptance criteria for precision, specificity, sensitivity and robustness

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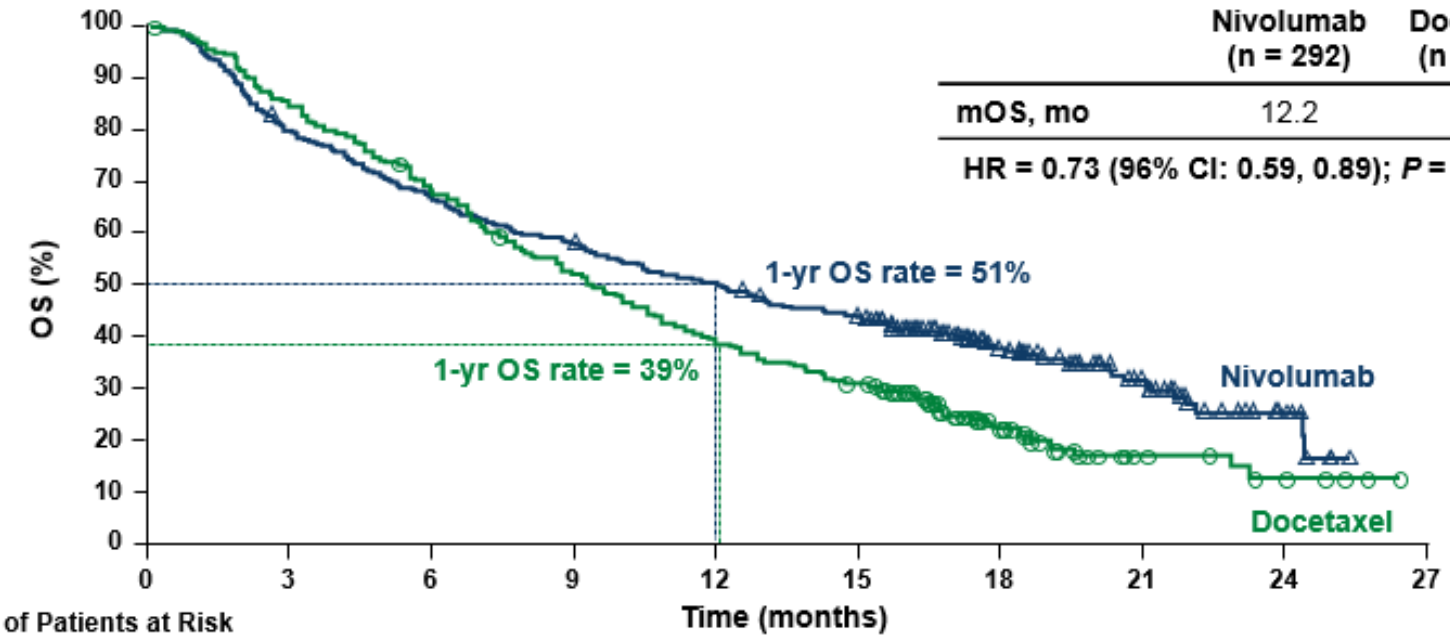
Borghaei et al, N Engl J Med, 2015

Nivolumab vs. Docetaxel in Advanced Non-Squamous NSCLC: Efficacy

Overall Survival



	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4

HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015

Number of Patients at Risk										
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Symbols represent censored observations.

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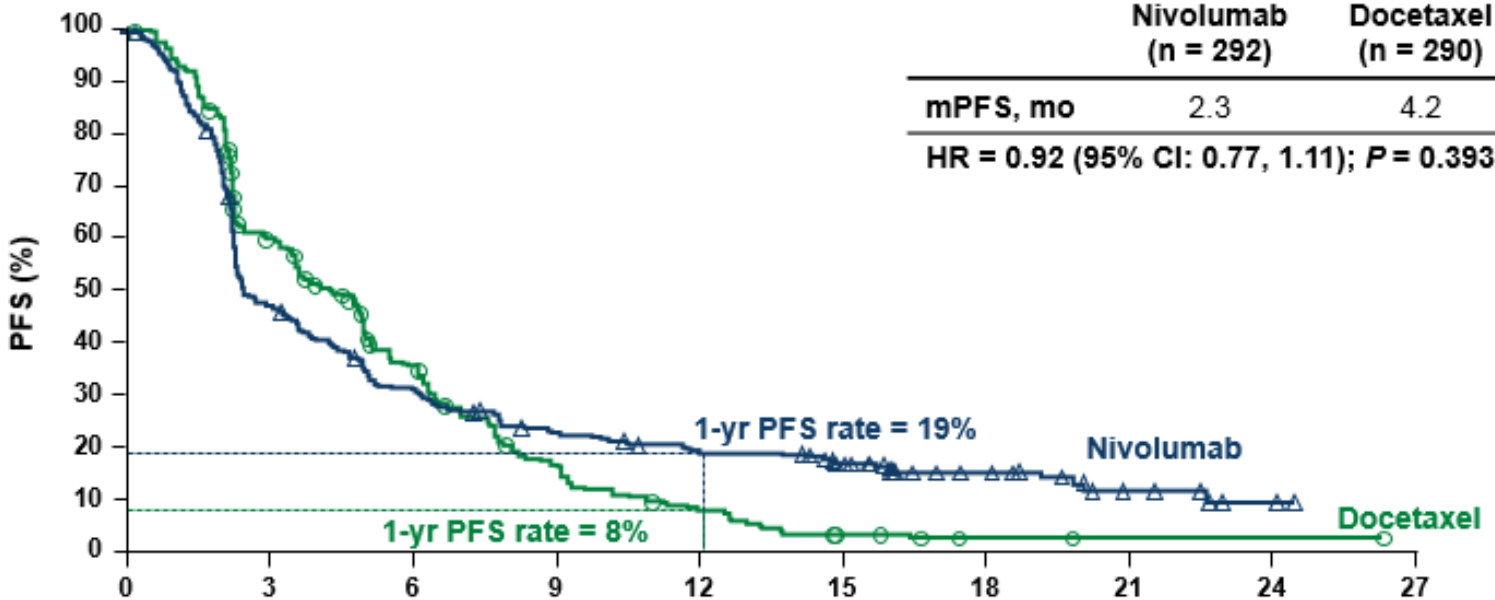
Phase 3 CheckMate 057: Nivolumab vs. Docetaxel in Advanced Non-Squamous NSCLC: Efficacy

Progression-free Survival



	Nivolumab (n = 292)	Docetaxel (n = 290)
mPFS, mo	2.3	4.2

HR = 0.92 (95% CI: 0.77, 1.11); *P* = 0.3932

Number of Patients at Risk										
Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

Symbols represent censored observations.

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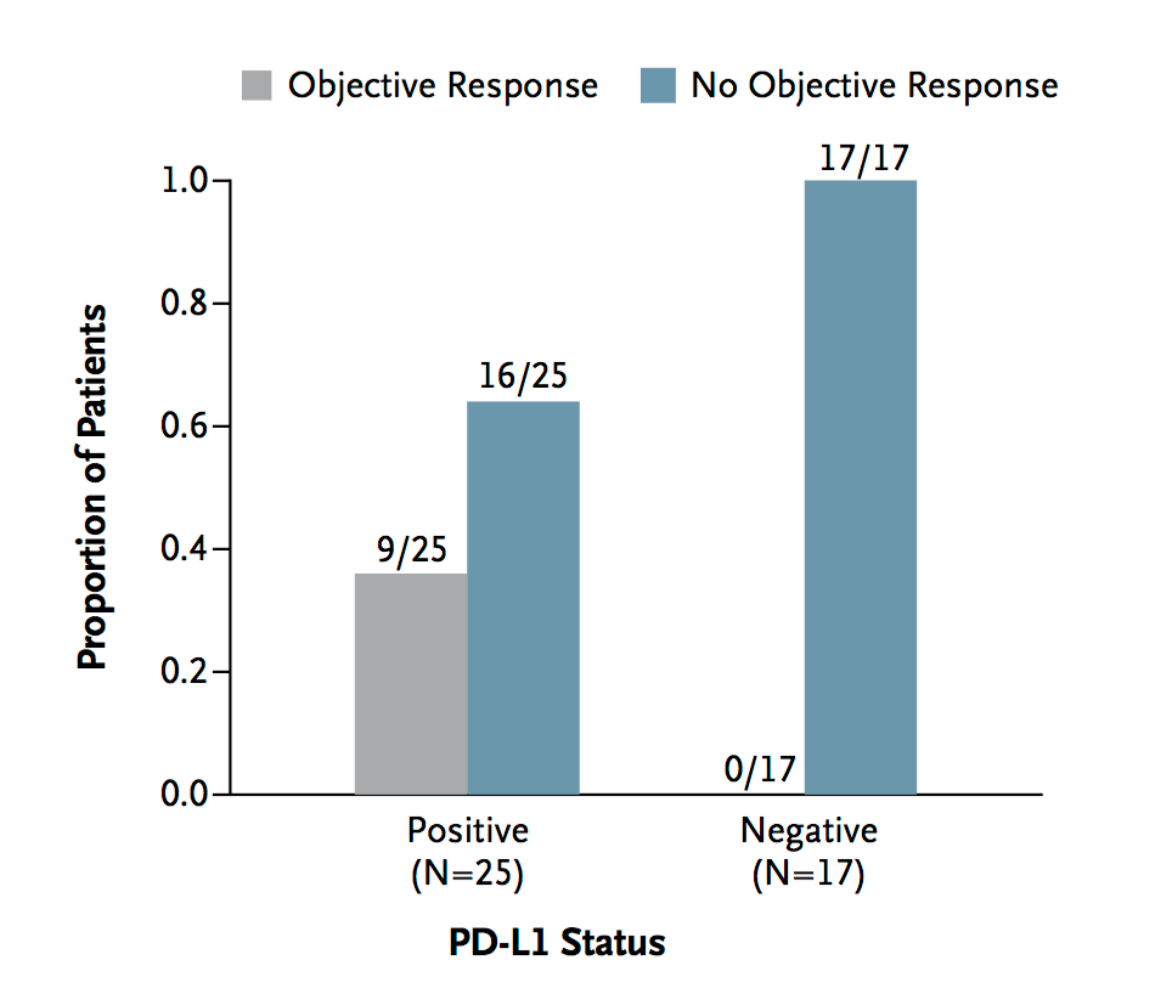
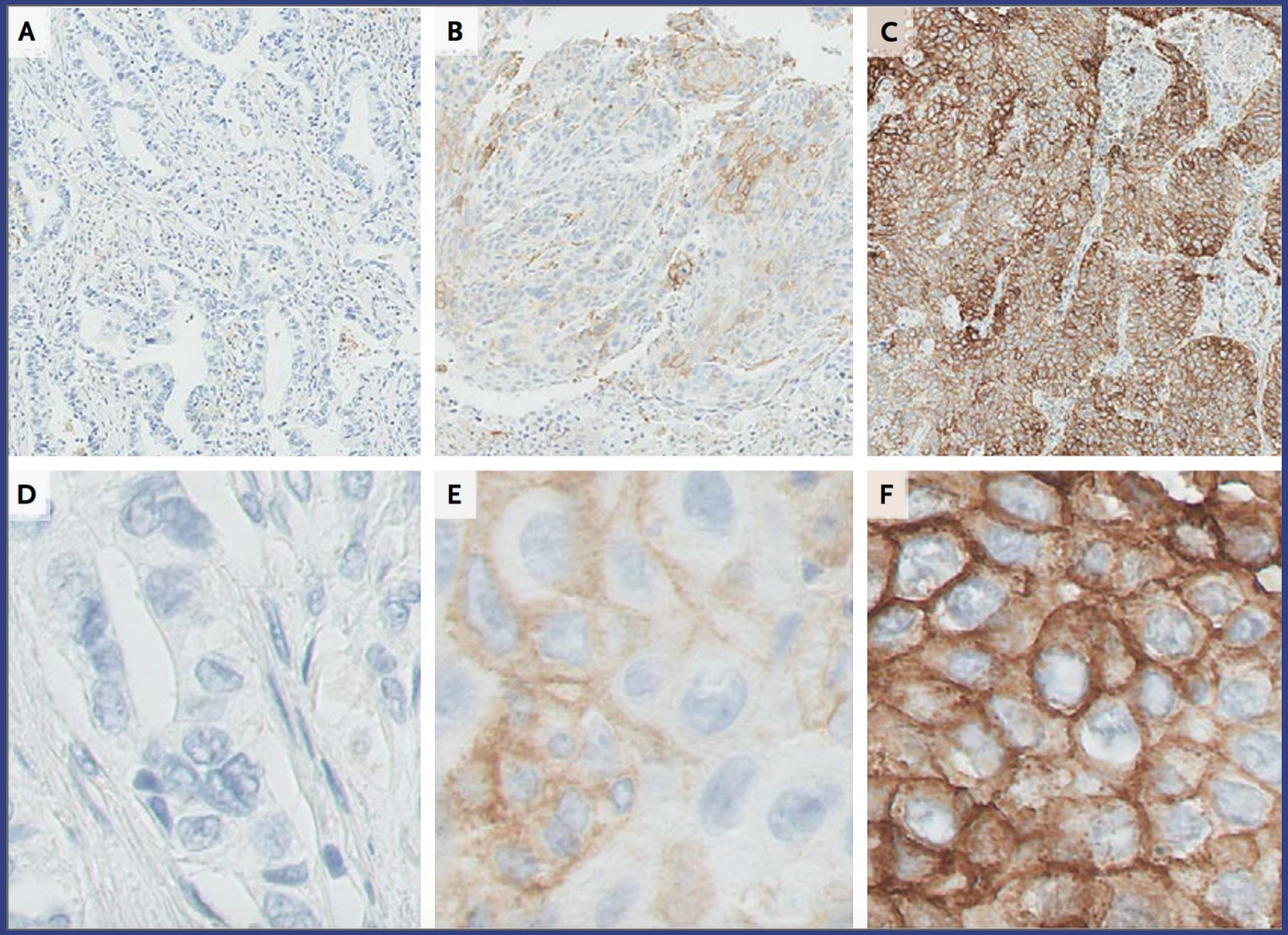
BIOMARKERS FOR PATIENT SELECTION

PDL-1 Expression as a Predictive Marker



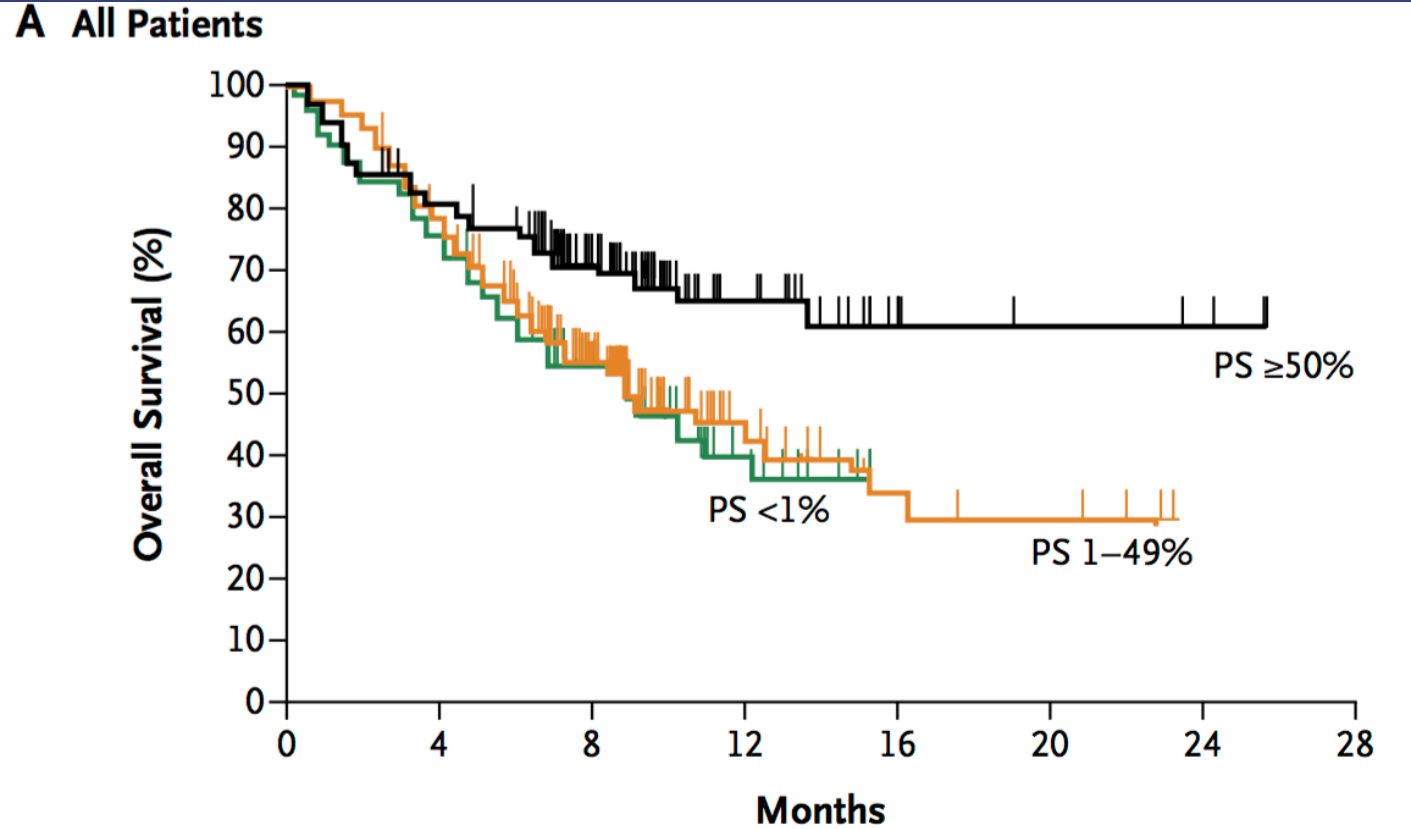
Topalian et al, N Engl J Med, 2012

PD-L1 Expression in NSCLC



Garon et al, N Engl J Med, 2015

Pembrolizumab in NSCLC: Efficacy by PD-L1 Expression



No. at Risk

PS ≥50%	119	92	56	22	5	4	3	0
PS 1–49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

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KEYNOTE-010 Study Design

Patients

- Advanced NSCLC
- Confirmed PD after ≥1 line of chemotherapy[a]
- No active brain metastases
- ECOG PS 0-1
- PD-L1 TPS ≥1%
- No serious autoimmune disease
- No ILD or pneumonitis requiring systemic steroids

R
1:1:1

- Pembrolizumab 2 mg/kg IV Q3W for 24 months
- Pembrolizumab 10 mg/kg IV Q3W for 24 months
- Docetaxel 75 mg/m^2 Q3W per local guidelines[c]

Stratification factors:

- ECOG PS (0 vs 1)
- Region (East Asia vs non-East Asia)
- PD-L1 status[b] (TPS ≥50% vs 1%-49%)

End points in the TPS ≥50% stratum and TPS ≥1% population

- Primary: PFS and OS
- Secondary: ORR, duration of response, safety

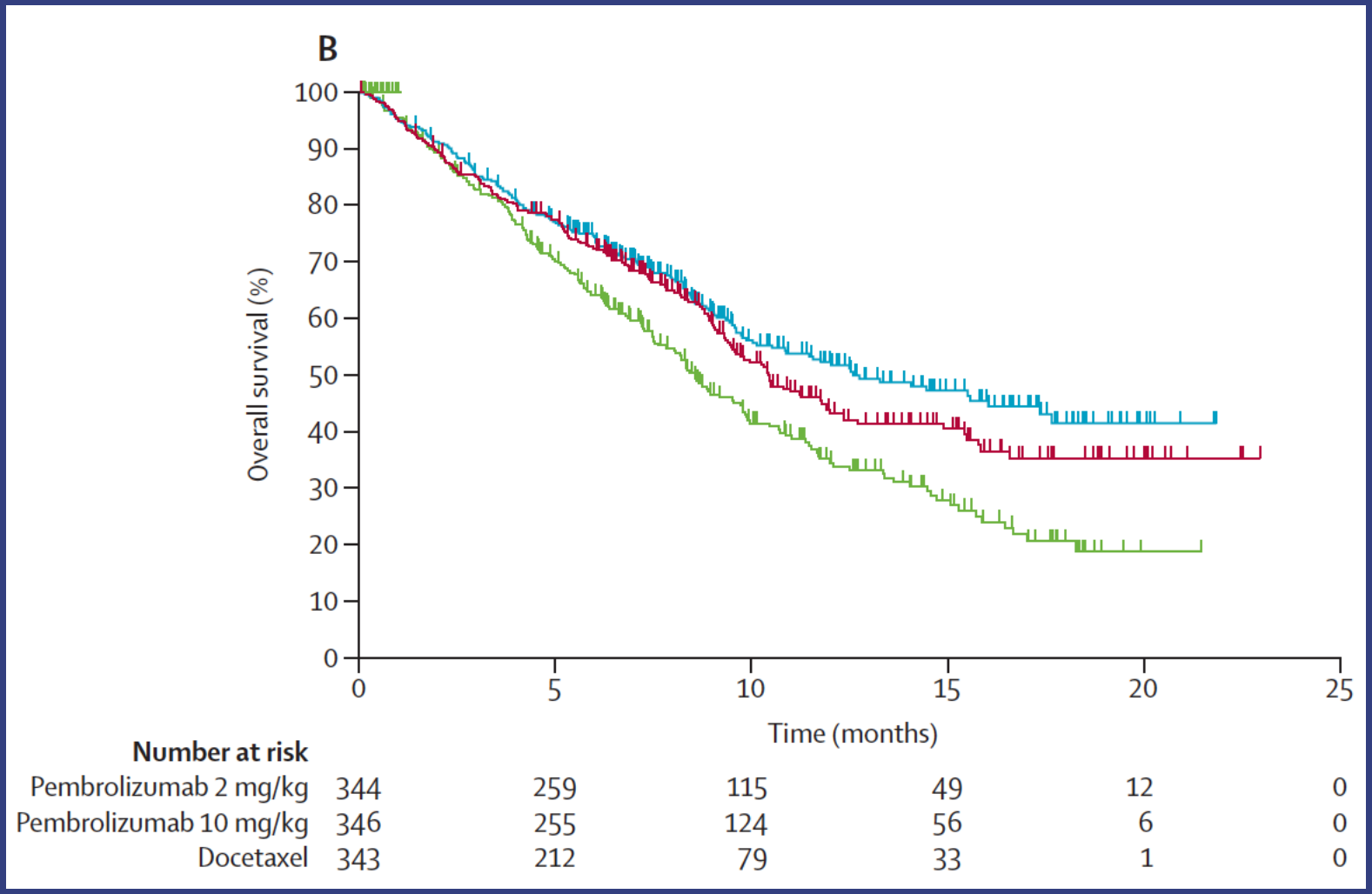
ClinicalTrials.gov, NCT01905657.

[a]Prior therapy must have included ≥2 cycles of platinum-doublet chemotherapy. An appropriate tyrosine kinase inhibitor was required for patients whose tumors had an *EGFR* sensitizing mutation or an *ALK* translocation.

[b]Added after 441 patients enrolled based on results from KEYNOTE-001 (Garon EB et al. *N Engl J Med*. 2015;372:2018-28).

[c]Patients received the maximum number of cycles permitted by the local regulatory authority.

Pembro Vs. Docetaxel in NSCLC: OS in All Patients



Number at risk						
Pembrolizumab 2 mg/kg	344	259	115	49	12	0
Pembrolizumab 10 mg/kg	346	255	124	56	6	0
Docetaxel	343	212	79	33	1	0

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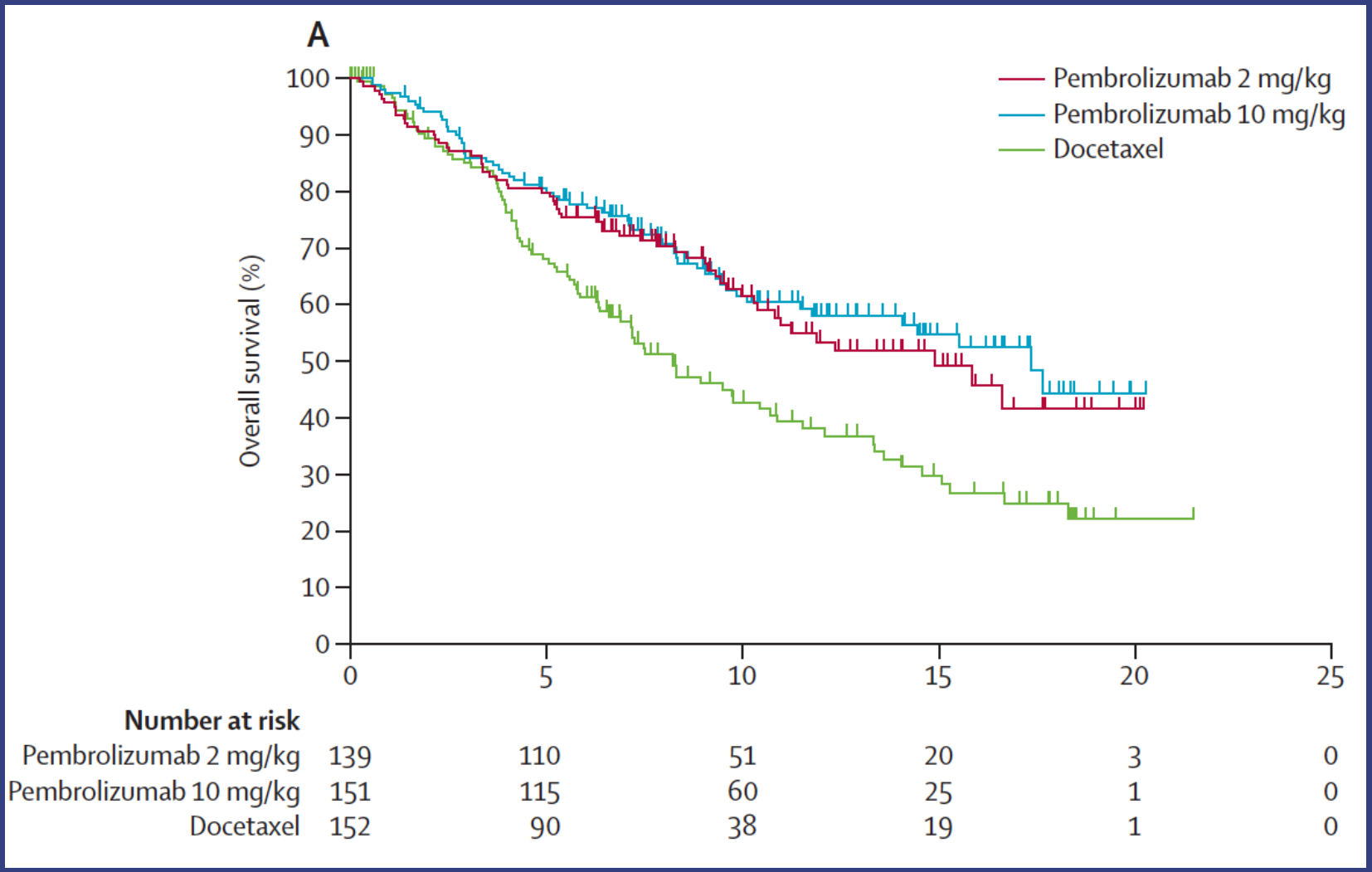
Herbst et al, Lancet, 2015

Pembro Vs. Docetaxel: OS in PD-L1 Positive Disease



Number at risk						
Pembrolizumab 2 mg/kg	139	110	51	20	3	0
Pembrolizumab 10 mg/kg	151	115	60	25	1	0
Docetaxel	152	90	38	19	1	0

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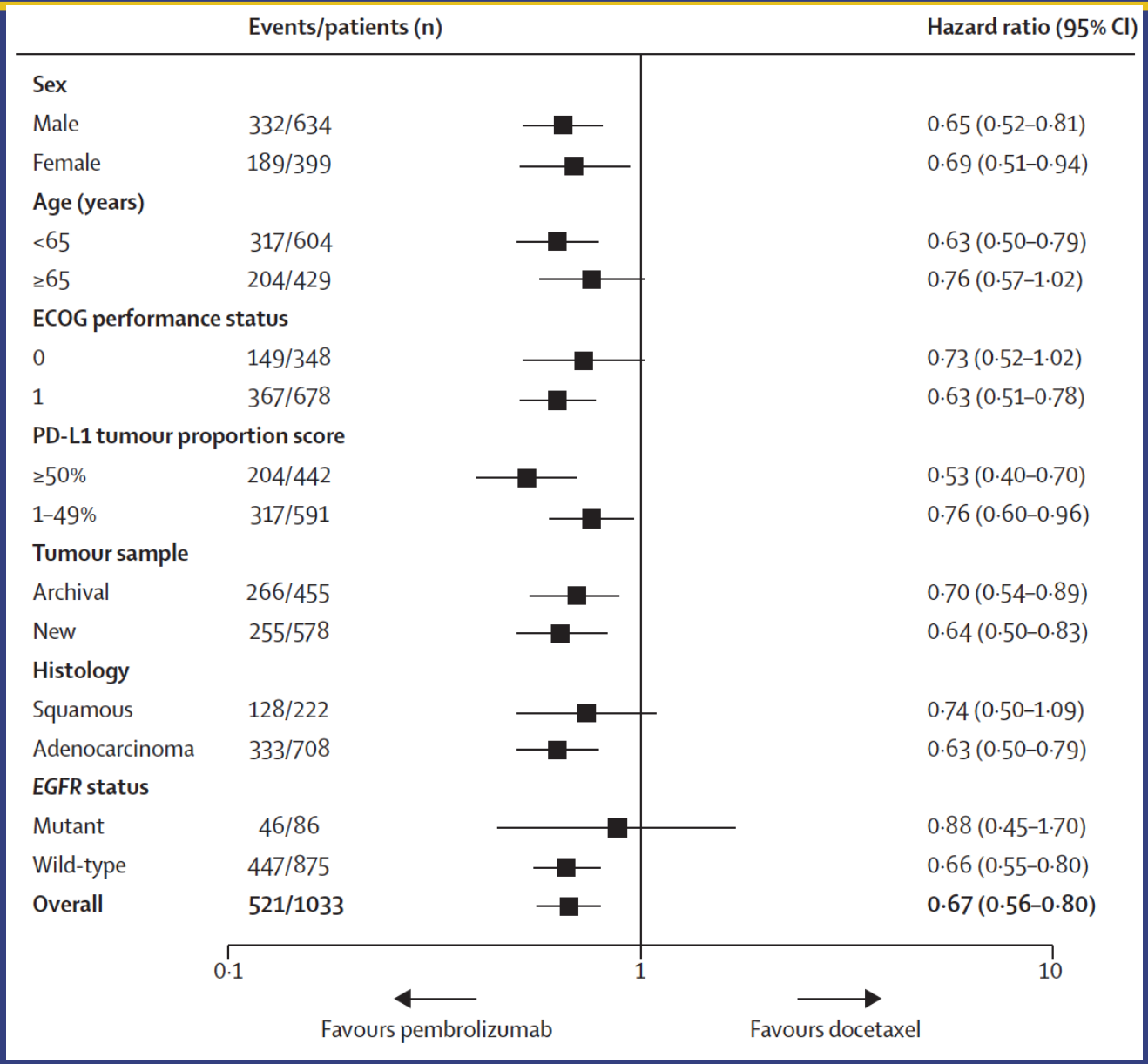
Herbst et al, Lancet, 2015

Pembro Vs. Docetaxel



Herbst et al, Lancet, 2015

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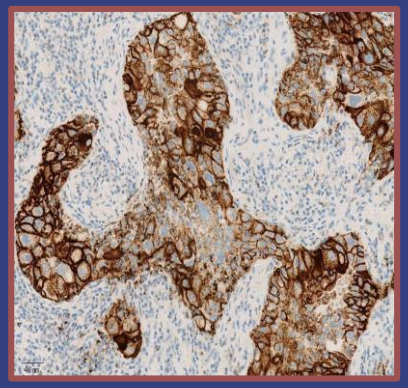
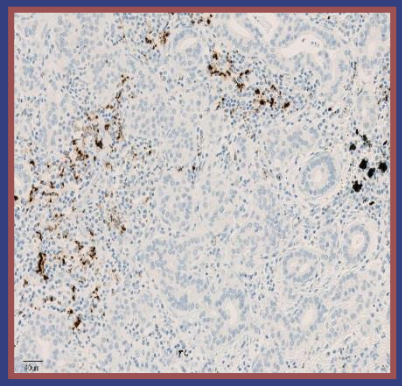
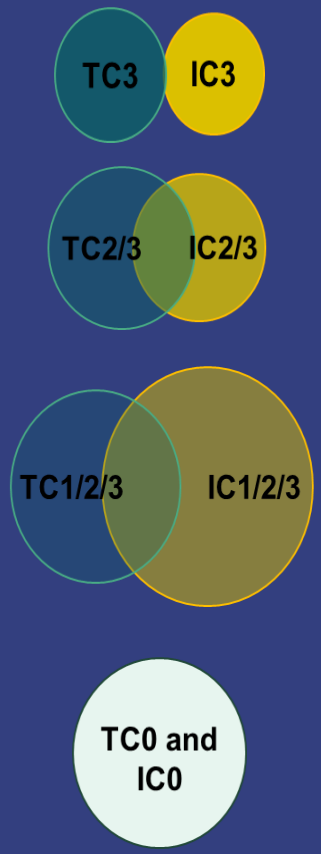
PD-L1 Expression on TC and IC is a Potential Predictive Biomarker for Atezolizumab in NSCLC



***Intrinsic* PD-L1 expression in tumor cells (TC)**



***Adaptive* PD-L1 expression in tumor-infiltrating immune cells (IC)**



PD-L1 expression levels and TC/IC overlap in POPLAR

- SP142 IHC assay is sensitive and specific for PD-L1 expression on both TC and IC.
- Distinct TC and IC sub-populations exist at each of four cutoff levels[a] (Gettinger SN et al. *J Clin Oncol.* 2015;33[suppl]: abstract 3015.)
- PD-L1 expression on TC and IC was independently predictive of response (Horn L et al. *J Clin Oncol.* 2015;33[suppl]: abstract 8029.)

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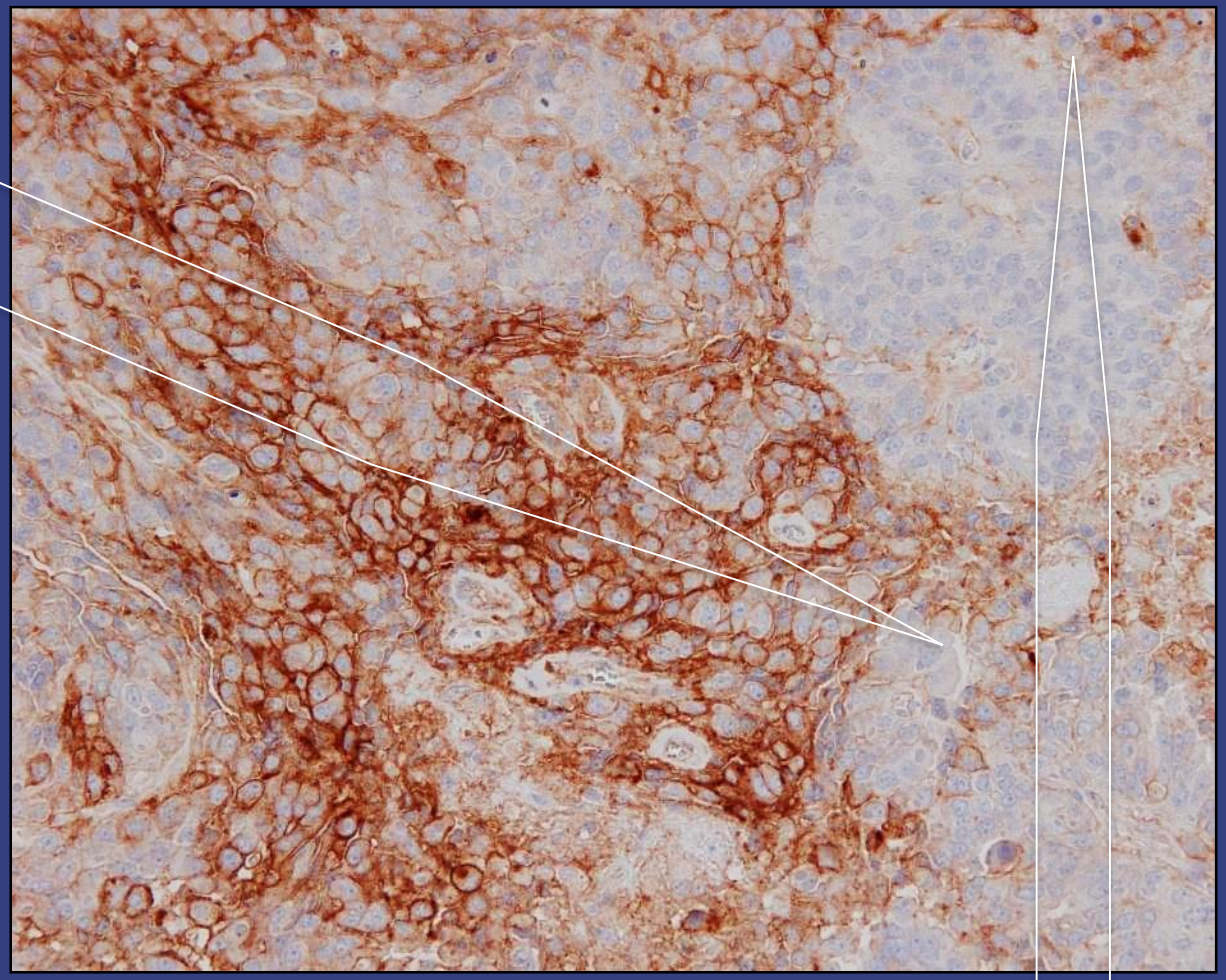
[a]TC scored as percentage of tumor cells and IC scored as percentage of tumor area. TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1+; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1+; TC1/2/3 or IC1/2/3 = TC or IC ≥ 1% PD-L1+; TC0 and IC0 = TC and IC < 1% PD-L1+, respectively.

Spira AI et al. *J Clin Oncol*. 2015;33(suppl): abstract 8010.

PD-L1 IHC: Expression Heterogeneity and Potential for Sampling Error



Biopsy Core 1

Biopsy Core 2

18g needle = 800 µm

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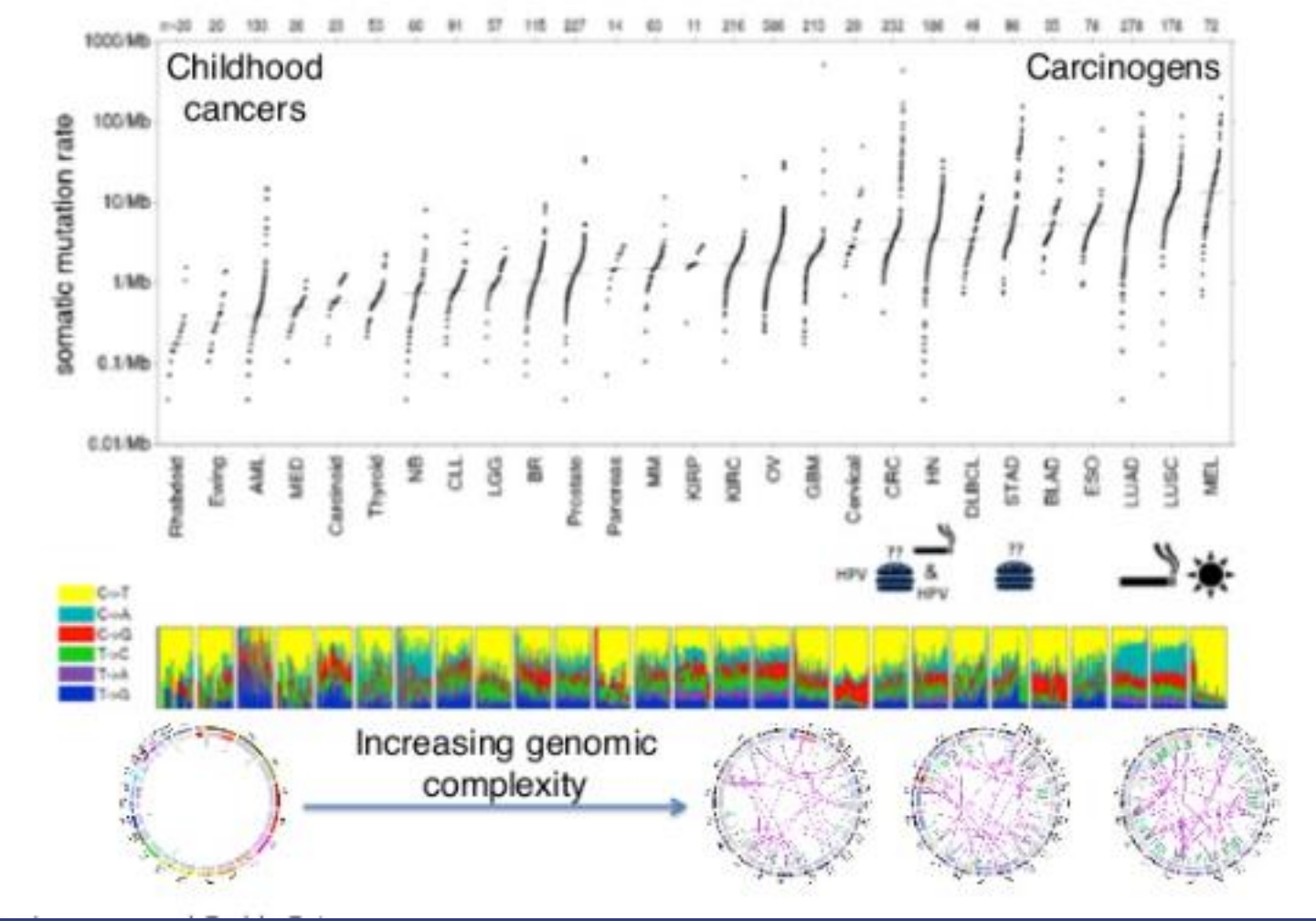
PD-L1 Assays for Immune Checkpoint Inhibitors

	Pembrolizumab Merck	Nivolumab Bristol-Myers Squibb	MPDL3280A Roche/Genentech	MEDI4736 AstraZeneca
PD-L1 Assay	• Prototype or clinical trial IHC assay (22C3 Ab)[1]	• Dako automated IHC assay (28-8 Ab)[3,4]	• Ventana automated IHC assay	• 1st generation or Ventana automated IHC BenchMark ULTRA) assay (Ventana PD-L1 (SP263) clone)[7,8]
Sample Source and Collection	• Surface expression of PD-L1 on tumor specimen* • Ph I: Fresh tissue • Ph II/III: Archival or fresh tissue[2]	• Surface expression of PD-L1 on tumor cells* • Archival[4] or fresh tissue	• Surface expression of PD-L1 on TILs[5] • Archival or fresh tissue	• Surface expression of PD-L1 on TILs • PhI: Fresh tissue
Definition of Positivity†	**IHC Staining:** • Strong vs weak expression[2] • PD-L1 expression required for NSCLC for enrollment[2] • Note that one arm of KEYNOTE 001 trial requires PD-L1- tumors[1] **Tumor PD-L1 expression:**[1] • ≥50% PD-L1+ cut-off: 32% (41/129) • 1-49% PD-L1+ cut-off: 36% (46/129)	**IHC Staining:** • Strong vs weak expression[3,4] • Patients not restricted in PD-L1 status in 2nd- & 3rd-line[4] • Ph III 1st-line trial in PD-L1+[3] **Tumor PD-L1 expression:**[4] • 5% PD-L1+ cut-off: 49% (33/68)[4]	**IHC Staining intensity (0, 1, 2, 3):** • IHC 3 (≥10% PD-L1+): Ph III trial[5] • IHC 2,3 (≥5% PD-L1+)[5] • IHC 1,2,3 (≥1% PD-L1+)[5] • IHC 1, 0, or unknown • PD-L1 expression required for NSCLC for enrollment **TIL PD-L1 expression:**[5,6] • IHC 3 (≥10% PD-L1+): 11% (6/53) • PD-L1 low (IHC 1, 0): 75% (40/53)	**IHC Staining intensity:** • Not presented to date[7,8,9] **TIL PD-L1 expression:** • Not presented to date[7,8,9]

Mutational Burden in Cancer



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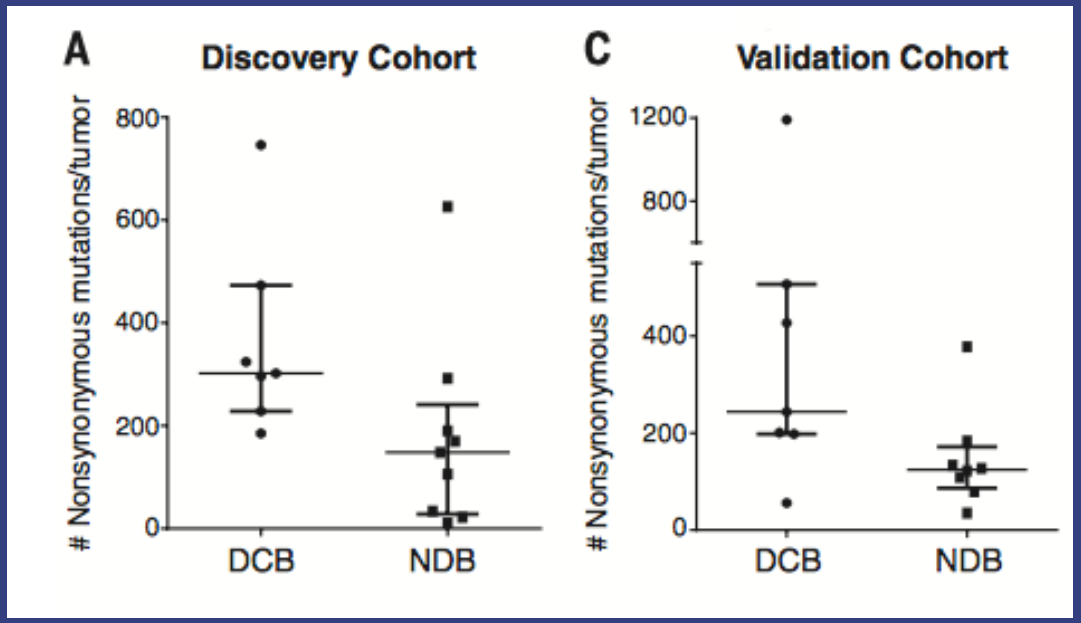
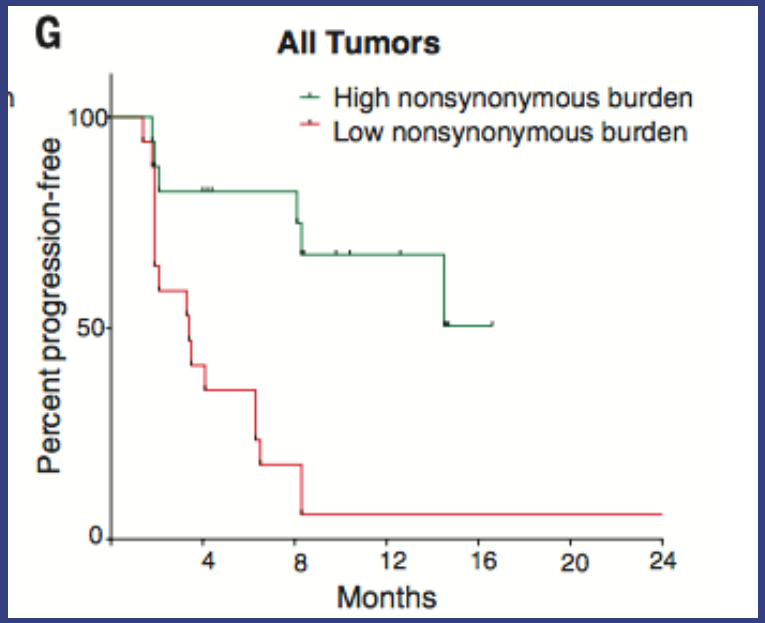
Mutational Burden as Biomarker





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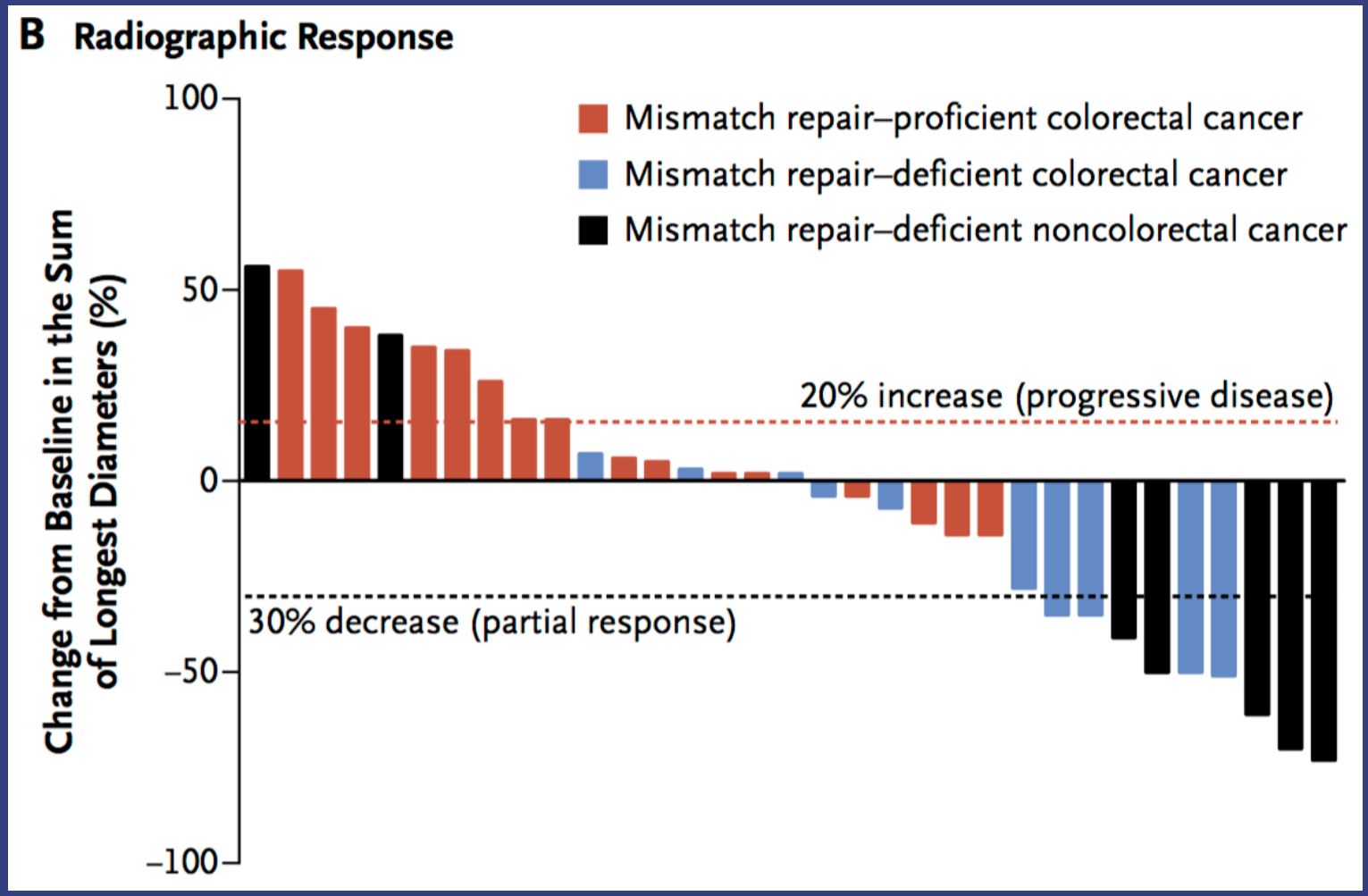
Rizvi et al, Science, 2015

MMR Deficiency as Predictive Marker



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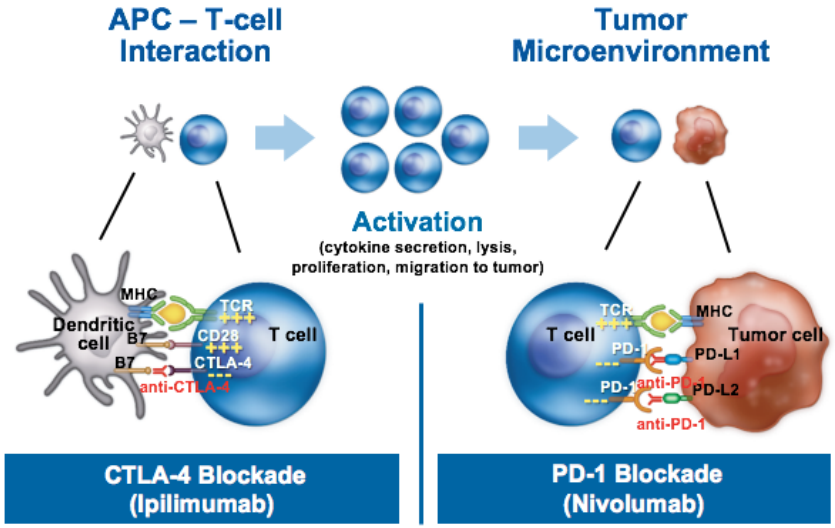
Le DT et al, N Engl J Med, 2015

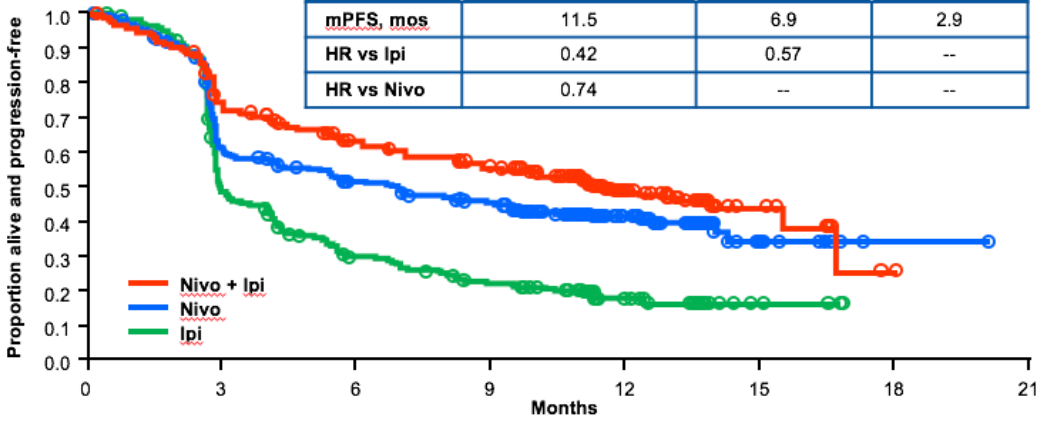
COMBINATION APPROACHES

Rationale for Combined CTLA-4 and PD-1 Blockade in NSCLC



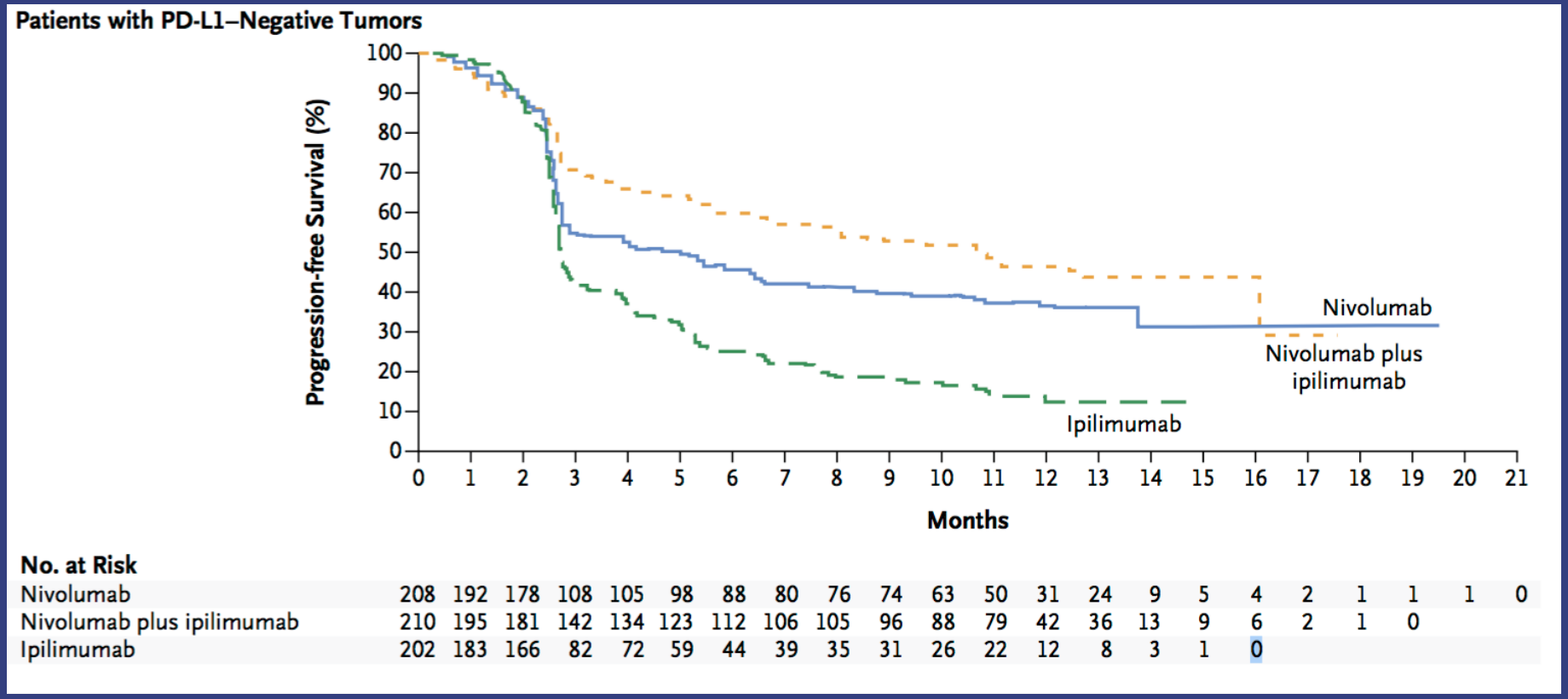
PFS with nivo or nivo plus ipi vs ipi alone in previously untreated advanced MEL[12]

	Nivo + Ipi (N=314)	Nivo (N=316)	Ipi (N=315)
mPFS, mos	11.5	6.9	2.9
HR vs Ipi	0.42	0.57	--
HR vs Nivo	0.74	--	--



- Nivolumab and ipilimumab enhance T-cell antitumor activity through distinct but complementary mechanisms[5–8]
- Preclinical data suggest synergy with dual CTLA-4 and PD-1 blockade vs either agent alone[9]
  - Increased proliferation of effector CD8+ and CD4+ T cells and decreased intratumoral T-regulatory cells vs single pathway blockade
- Clinical experience with nivolumab plus ipilimumab demonstrate
  - Deep and durable responses in previously treated advanced MEL and SCLC[10,11]
  - 2-year OS of 79% in patients with previously treated advanced MEL[11]

Nivolumab + Ipilimumab in Melanoma



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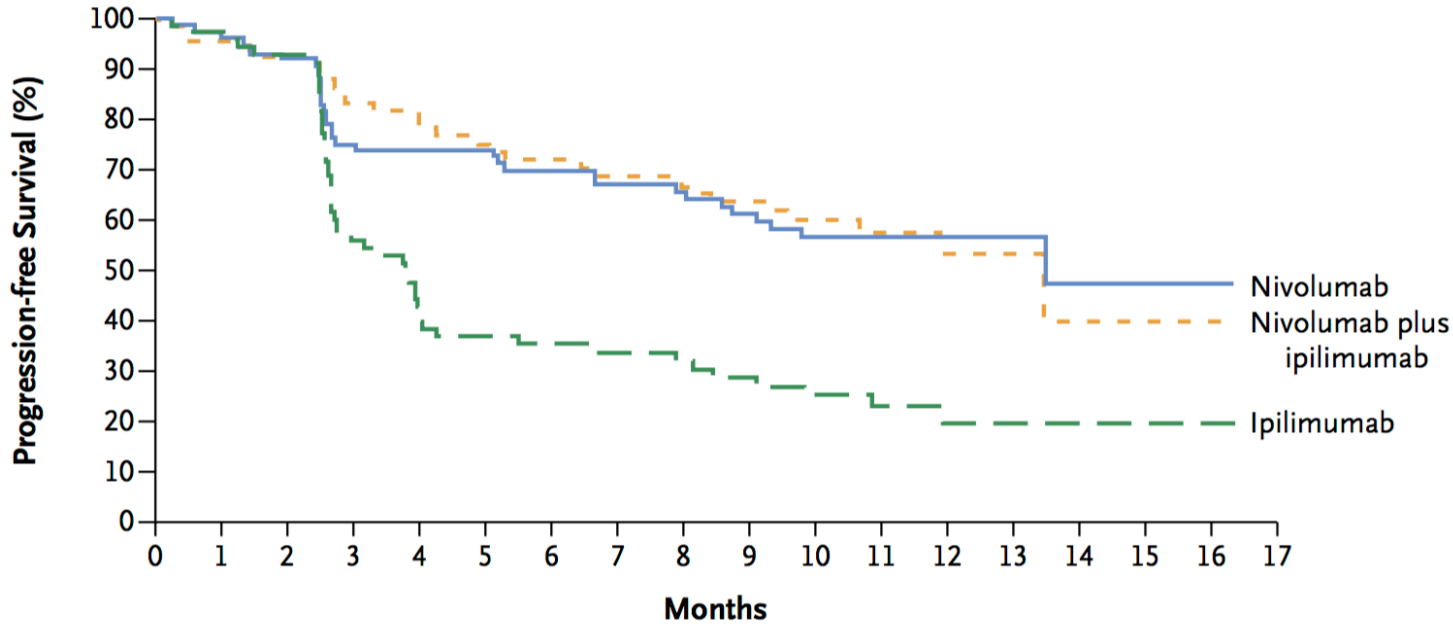
Larkin et al, N Engl J Med, 2015

Nivolumab + Ipilimumab in Melanoma

Patients with PD-L1–Positive Tumors



No. at Risk

Nivolumab	80	76	71	57	56	54	51	49	49	43	38	32	16	13	5	4	2	0
Nivolumab plus ipilimumab	68	63	61	53	52	47	44	42	42	39	34	24	16	12	3	1	1	0
Ipilimumab	75	69	66	40	33	24	22	21	21	17	16	15	9	6	3	2	2	0

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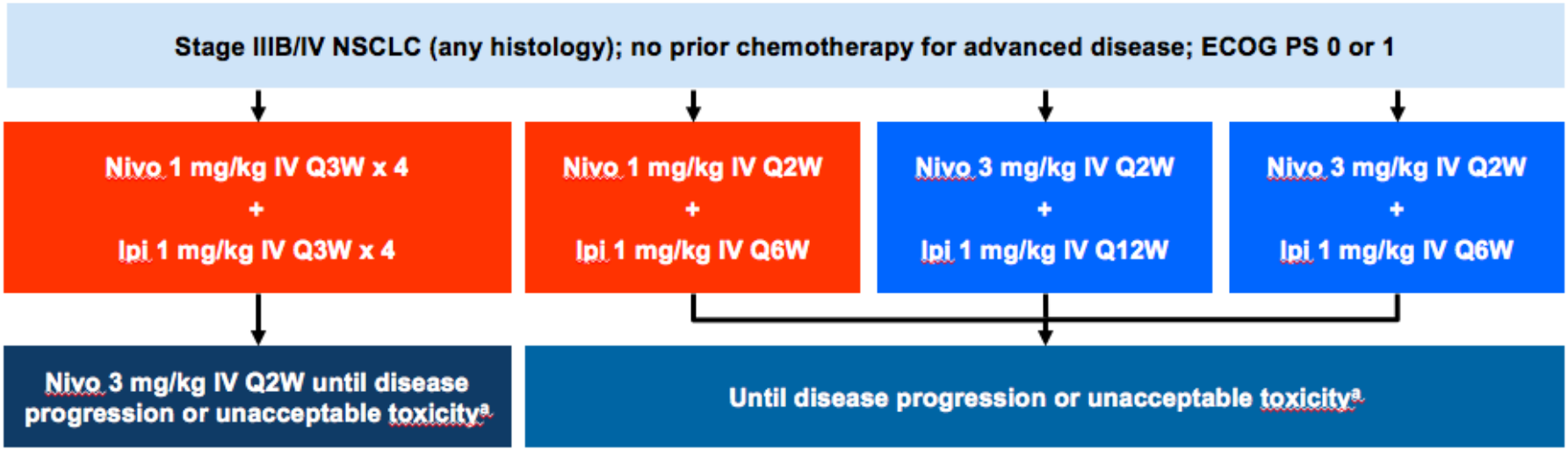
Larkin et al, N Engl J Med, 2015

CheckMate 012 Design



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Rizvi et al. WCLC 2015

Efficacy by PDL-1 Expression

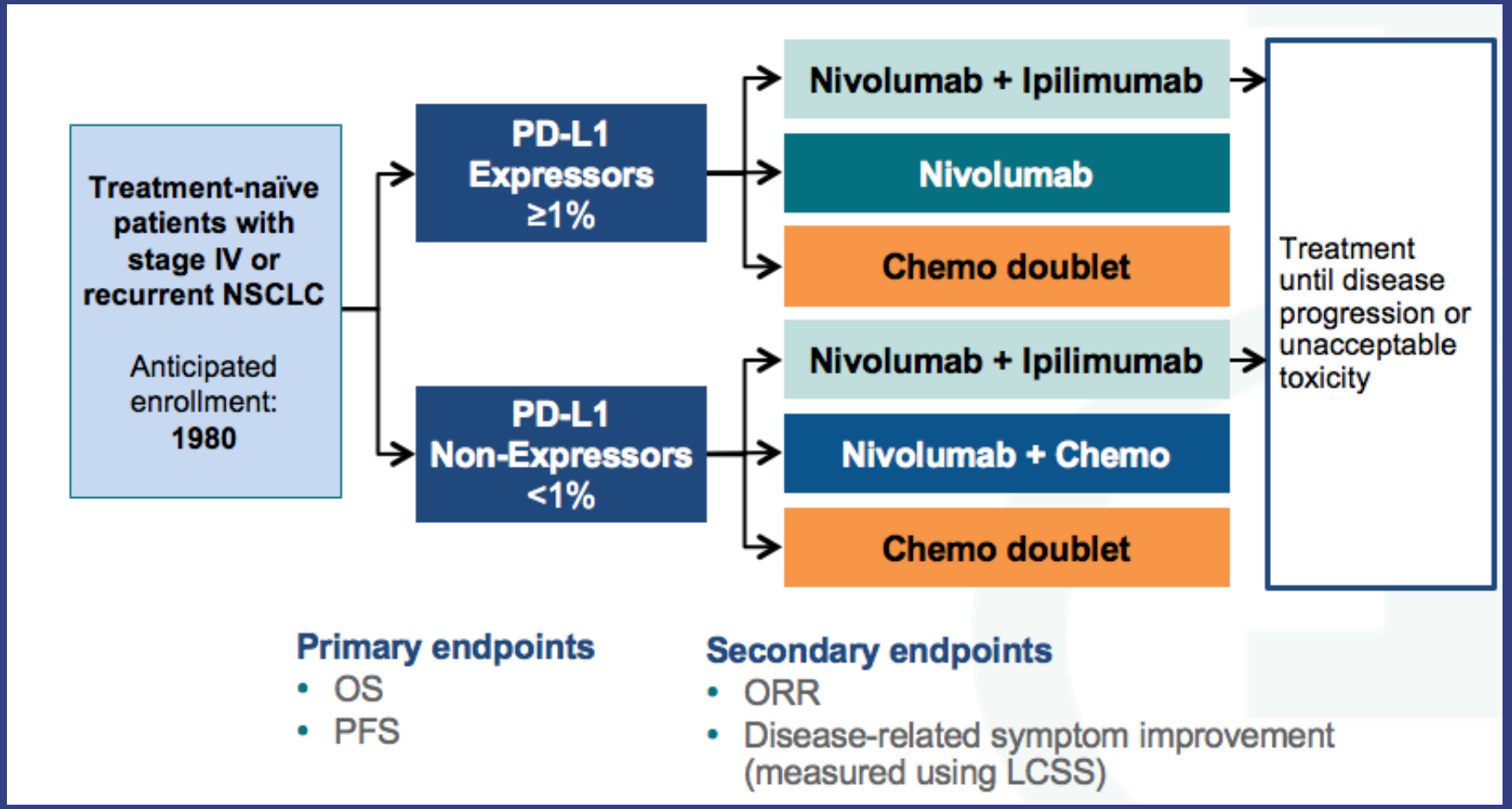
	≥1% PD-L1 expression				<1% PD-L1 expression			
	Nivo 1 + Ipi 1 Q3W (n = 12)	Nivo 1 Q2W + Ipi 1 Q6W (n = 21)	Nivo 3 Q2W + Ipi 1 Q12W (n = 21)	Nivo 3 Q2W + Ipi 1 Q6W (n = 23)	Nivo 1 + Ipi 1 Q3W (n = 13)	Nivo 1 Q2W + Ipi 1 Q6W (n = 7)	Nivo 3 Q2W + Ipi 1 Q12W (n = 9)	Nivo 3 Q2W + Ipi 1 Q6W (n = 7)
ORR, %	8	24	48	48	15	14	22	0
mPFS, wks (95% CI)	11.5 (7.1,)	21.1 (11.4,)	34.6 (15.9, 35.3)	NR (15.4,)	34.0 (8.9,)	NR (10.1,)	23.1 (4.0,)	10.3 (7.4, 12.7)
PFS rate at 24 wks, % (95% CI)	42 (15, 67)	40 (18, 61)	74 (48, 88)	65 (42, 81)	57 (25, 80)	NC	39 (9, 69)	0

- PD-L1 expression was measured using the Dako/BMS automated IHC assay[1,16]
  - Fully validated with analytical performance having met all predetermined acceptance criteria for sensitivity, specificity, precision, and robustness
- All patients had available pretreatment tumor samples; 76% (113/148) had samples evaluable for PD-L1 expression
- Median DOR was not reached in any arm, regardless of PD-L1 expression

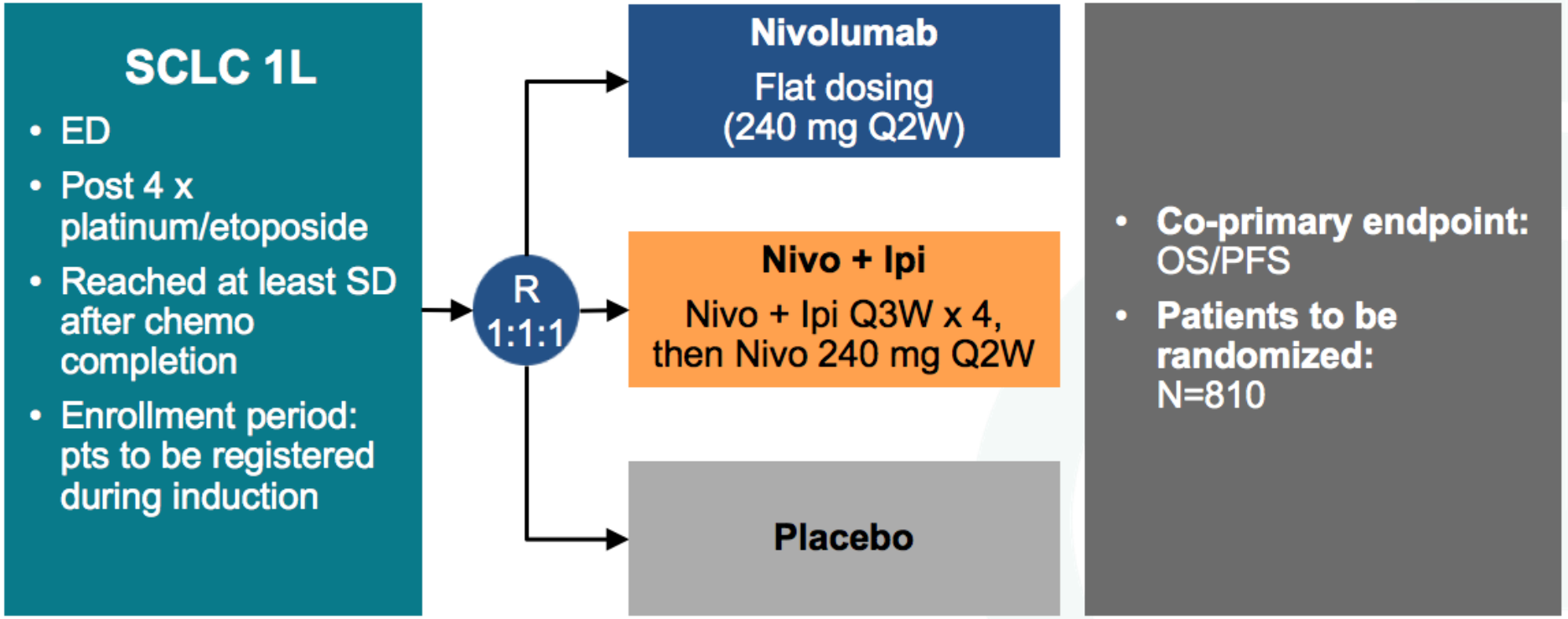
Safety

	Nivo 1 + Ipi 1 Q3W (n = 31)		Nivo 1 Q2W + Ipi 1 Q6W (n = 40)		Nivo 3 Q2W + Ipi 1 Q12W (n = 38)		Nivo 3 Q2W + Ipi 1 Q6W (n = 39)		Nivo 3 Q2W[a] (n = 52)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Endocrine, %	13	6	30	8	8	3	21	5	13	0
Gastrointestinal, %	19	0	28	8	18	5	26	5	12	2
Hepatic, %	10	6	23	10	3	0	5	5	2	2
Pulmonary, %	10	3	8	0	5	3	3	3	6	2
Renal, %	0	0	3	0	8	5	5	0	6	2
Skin, %	48	13	33	5	39	3	31	5	25	4
Hypersensitivity/infusion reaction, %	0	0	3	0	5	0	0	0	6	0

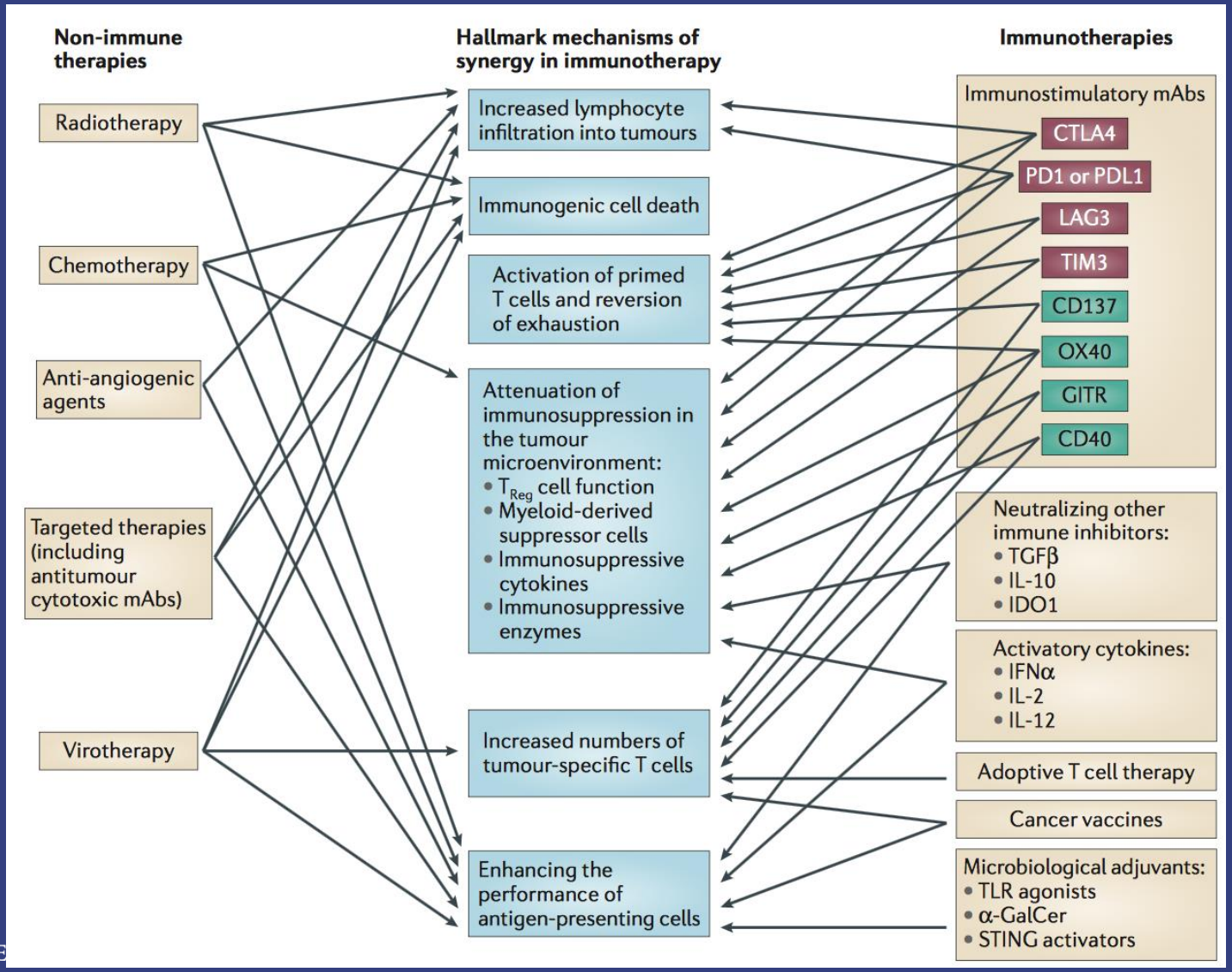
CheckMate 227



CheckMate 451

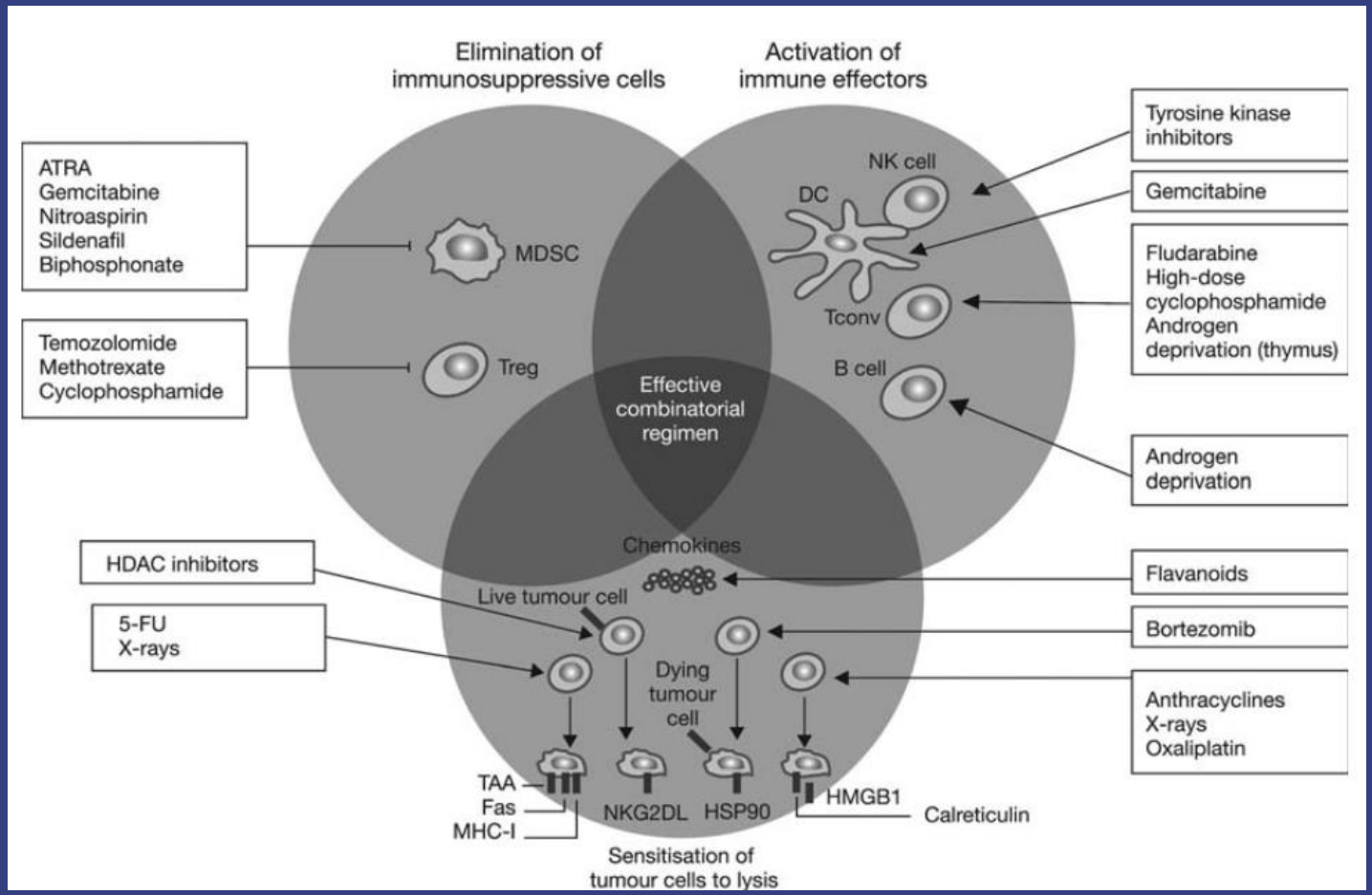


Interaction Between Treatment Modalities



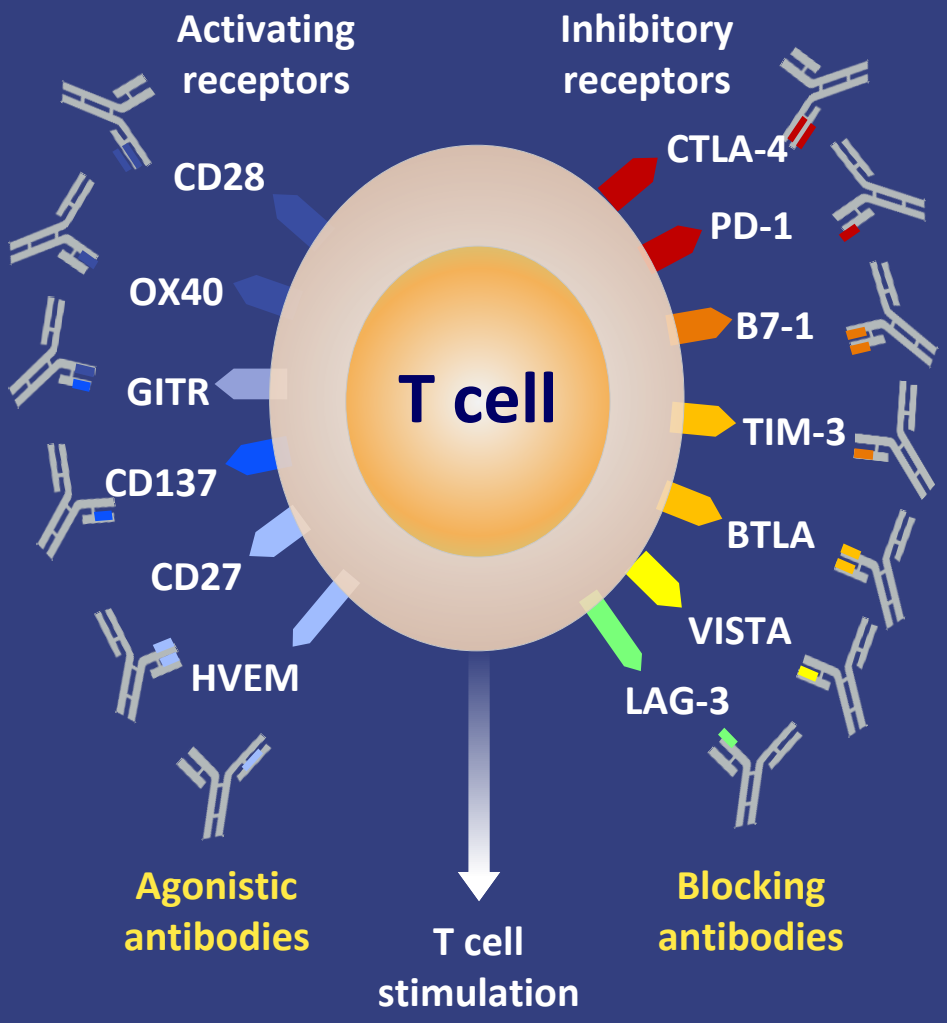
Melero et al, Nature Reviews, 2015

Interaction of Chemotherapy with Immunotherapy



Drake CG, Ann Oncol, 2012

T-Cell Immune Checkpoints as Targets for Immunotherapy



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Mellman I et al. *Nature*. 2011;480:481–489.

TOLERABILITY OF IMMUNOTHERAPY

Tolerability of Oncology Therapies

Chemotherapy

Target
Rapidly dividing tumour and normal cells

Adverse events
Diverse due to non-specific nature of therapy

I-O therapies

Target
Immune system

Adverse events
Unique events can occur as a result of immune-system activity

Targeted therapies

Target
Specific molecules involved in tumour growth and progression

Adverse events
Reflect targeted nature

Different spectrum of AEs with each modality

Some AEs with I-O may present like those with other therapies

BUT – AEs may have different etiologies
e.g. diarrhoea/colitis, fatigue, rash/pruritus, endocrinopathies

Require different management strategies

Nivolumab Vs. Docetaxel in NSCLC

	NIVO N = 287		DOC N = 268	
	Any Grade	Grade 3–4[a]	Any Grade	Grade 3–4[a]
Endocrine				
Hypothyroidism, %	6.6	0	0	0
Gastrointestinal, %				
Diarrhea	7.7	0.7	23	1.1
Hepatic, %				
ALT increased	3.1	0	1.5	0.4
AST increased	3.1	0.3	0.7	0
Pulmonary, %				
Pneumonitis	2.8	1.0	0.4	0.4
Skin, %				
Rash	9.4	0.3	3.0	0
Pruritus	8.4	0	1.5	0
Erythema	1.4	0	4.1	0
Hypersensitivity/Infusion reaction, %				
Infusion-related reaction	2.8	0	3.0	0.4

Includes events reported in ≥2.5% of pts.

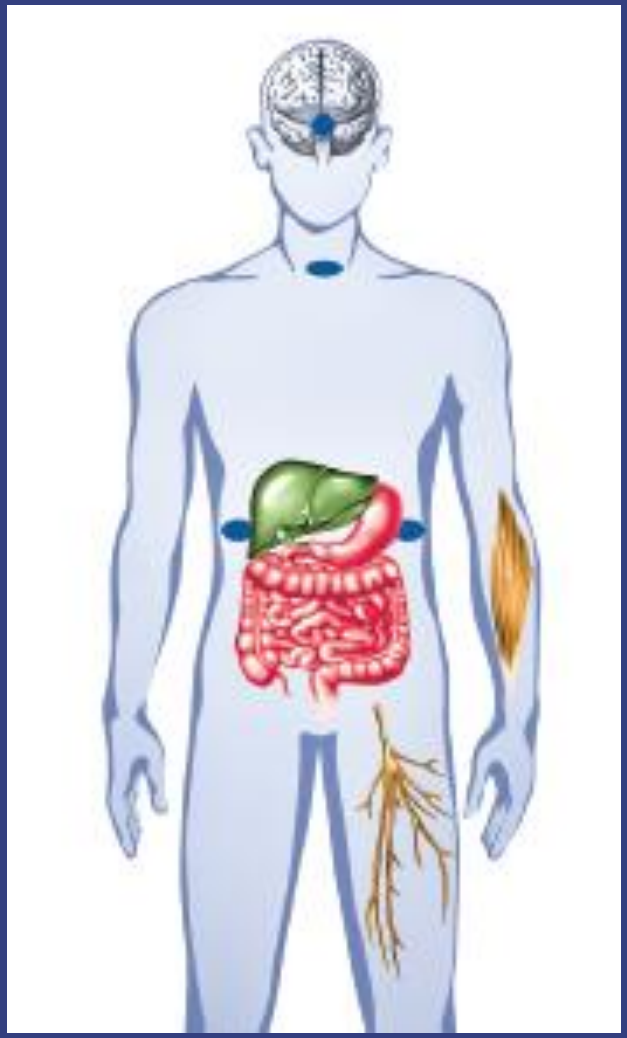
[a] No grade 5 events were reported at DBL.

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Borghaei et al, N Engl J Med, 2015

Select immune-related adverse reactions

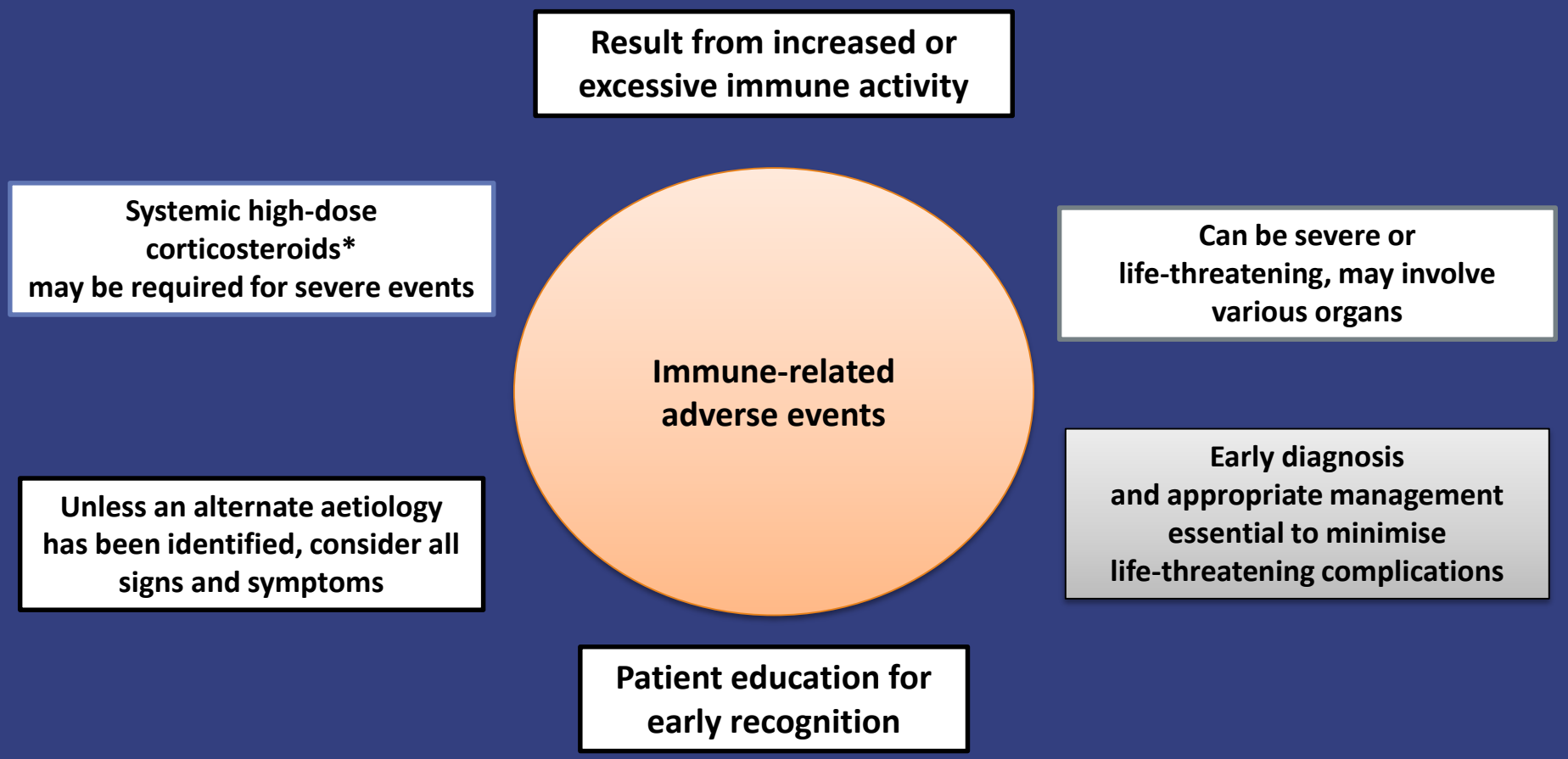
- Hypophysitis
- Thyroiditis
- Adrenal insufficiency
- Enterocolitis
- Dermatitis



- Pneumonitis
- Hepatitis
- Pancreatitis
- Motor & sensory neuropathies
- Arthritis

Lipson, ASCO 2014

General Approach to Manage Immune-related AE



*with or without additional immunosuppressive therapy

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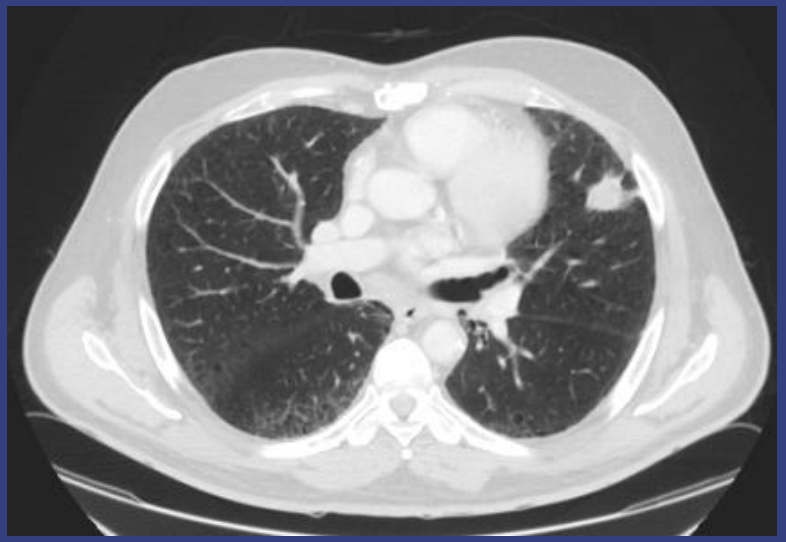
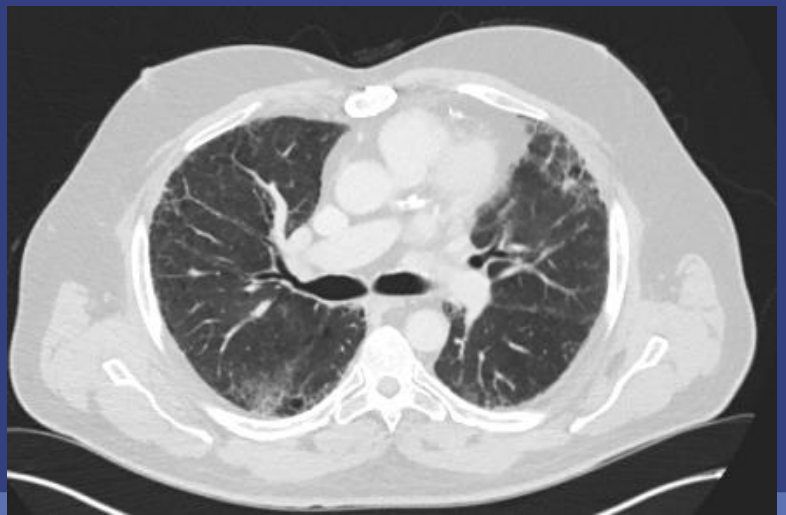
Case Study

Aug 6, 2013



Feb 19, 2015

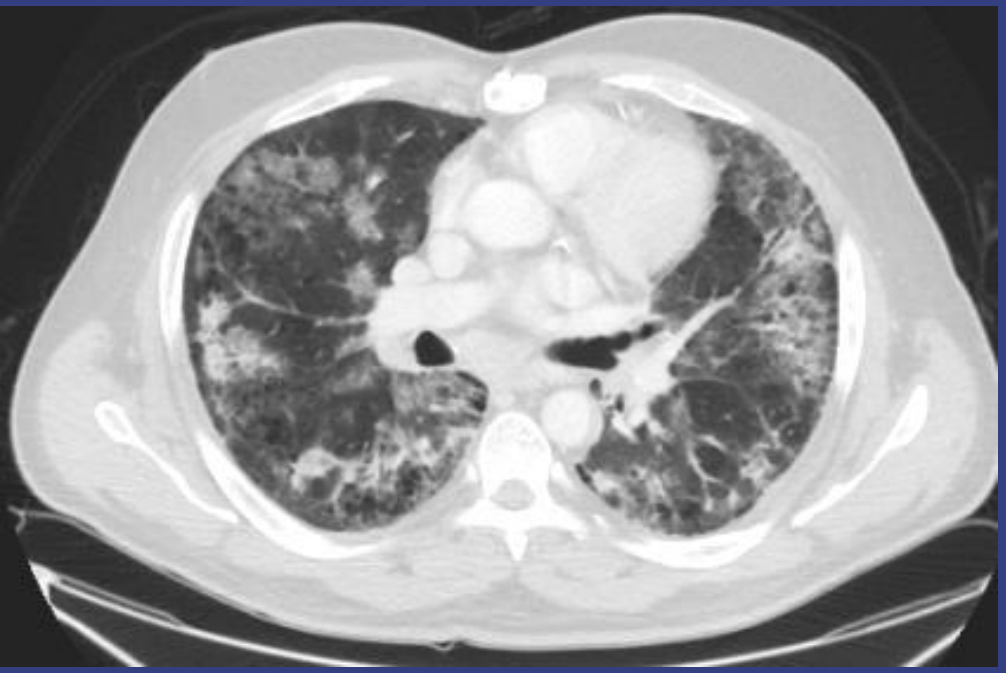


61/M
Newly Diagnosed stage IV
Squamous NSCLC
Bone metastasis
PS=1

Treatment:

1. **Palliative RT to rib lesion for pain control**
2. **Enrolled to a clinical trial with an immune check point inhibitor**

Case Study

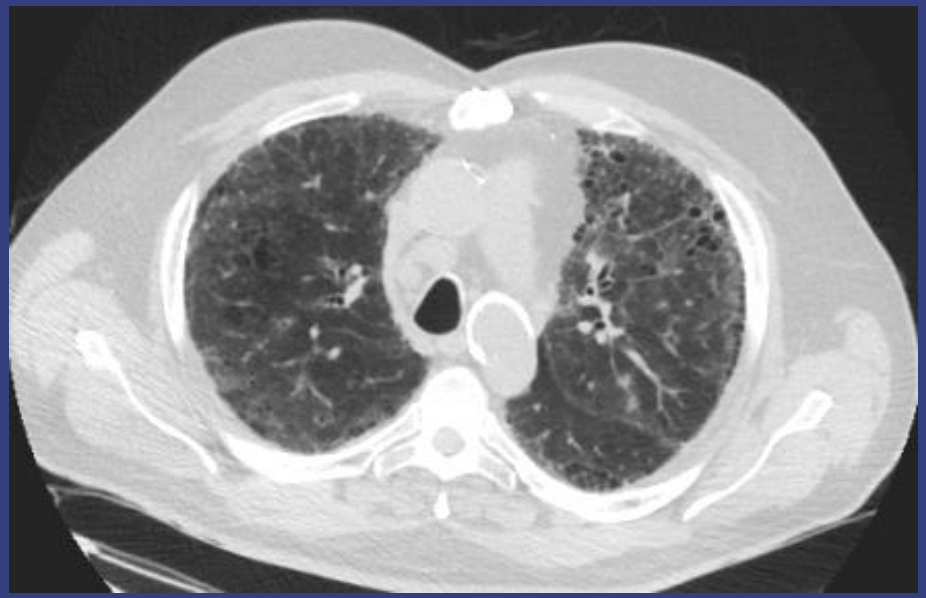


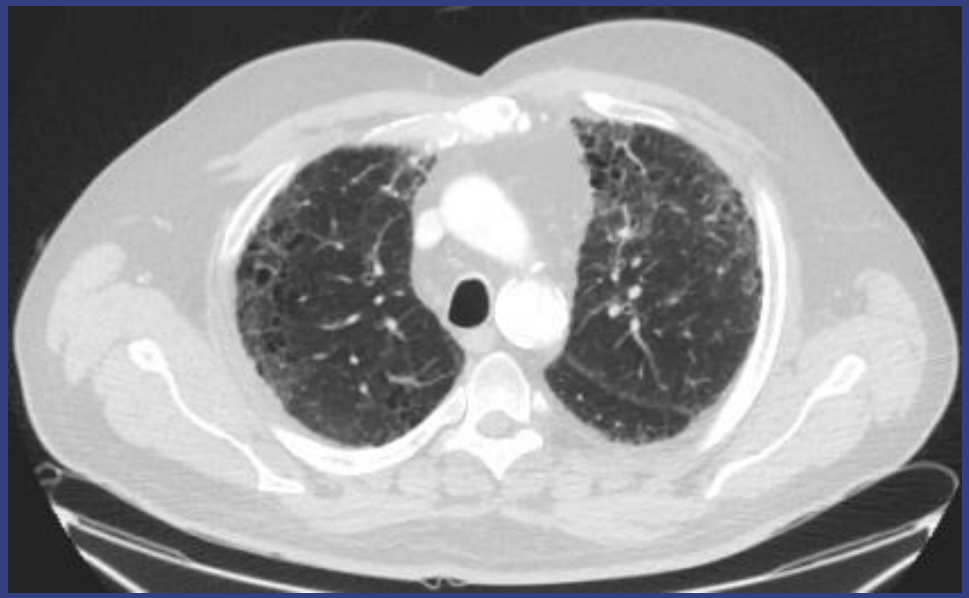
- Patient presents with:
- Dyspnea
- Non-productive cough
- Fever
- X 2 weeks

Feb 17, 2014

Case Study

- The patient was given high dose steroids and PD-1 inhibitor therapy was withheld





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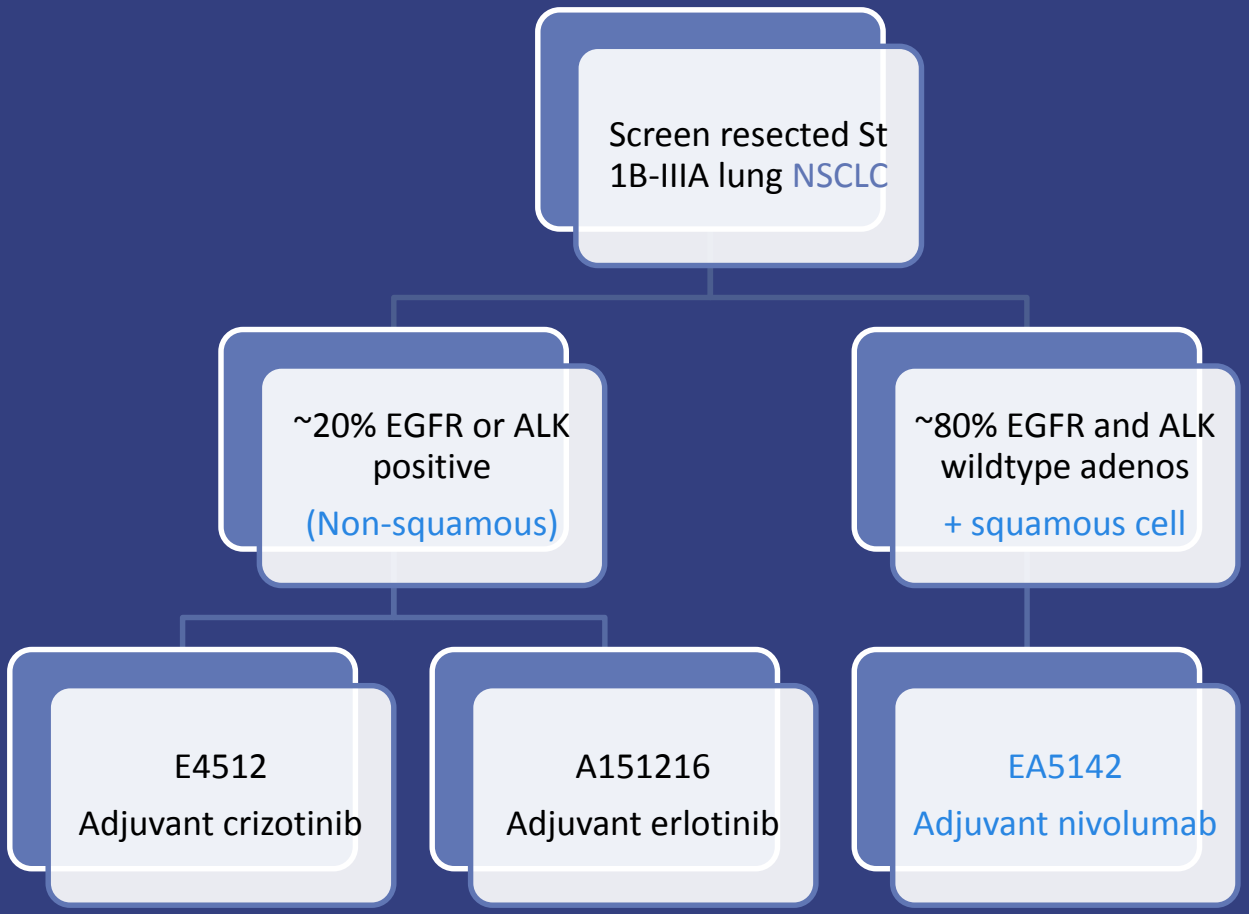
April 21, 2014

June 17, 2014

Ipilimumab: Immune-related AEs

- Mechanism-based adverse events (G 3/4)
  - Colitis (8-23%)
  - Hypophysitis (1-4%)
  - Hepatitis (3-7%)
  - Skin eruptions (0-4%)
  - Pneumonitis
- Cytokine release by activated T-cells are thought to be responsible

Immunotherapy in Curative Settings (NSCLC): ALCHEMIST



Important Clinical Issues

- Duration of therapy
- Fixed versus weight-based dosing
- Role of maintenance therapy
- Combination with chemotherapy
- Combination with targeted therapies

Conclusions

- Immune checkpoint inhibitors have improved outcomes for various solid organ malignancies
- Mutation burden appears to predict for benefit with immune checkpoint inhibitors
- Evaluation in curative settings is ongoing

The Drug Development Cycle