Cancer Immunotherapy Patient Forum

for the Treatment of Melanoma, Leukemia, Lymphoma, Lung and Genitourinary Cancers - November 7, 2015

sitc
Society for Immunotherapy of Cancer

Melanoma Research Alliance

Global Resource for Advancing Cancer Education

The Current Role of Immunotherapy in the Treatment of Patients with Cancer

Michael B. Atkins, M.D.
Deputy Director
Georgetown-Lombardi Comprehensive Cancer Center

November 7, 2015

Conflicts of Interest

Consultant:

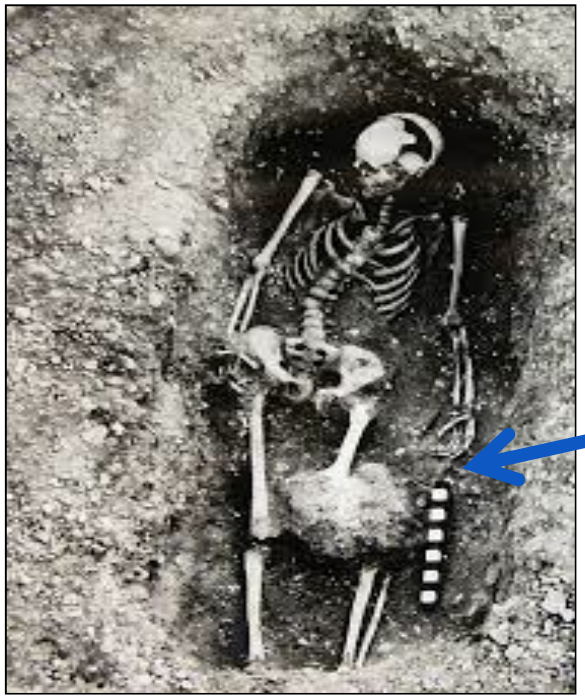
Genentech/Roche, BMS, Merck, Nectar, Novartis, Pfizer, Caladrius, Amgen, Alkermes

Advisory Board:

X4Pharma, Caladrius, Merck, Novartis

We Have Been at War Against Cancer Throughout Human History

President Nixon declares a "War on Cancer" in 1971



Medieval Saxon man with a large tumor of the left femur

The “War on Cancer”

is fought one person at a time…

- Primary Combatants:
  - Malignant cell population
  - Host immune system
- The host immune system is the dominant active enemy faced by a developing cancer
- All “successful” cancers must solve the challenges of overcoming defenses erected by host immune systems

Successful Cancers Escape (Solve the Challenge of Host Immunity) in Different Ways

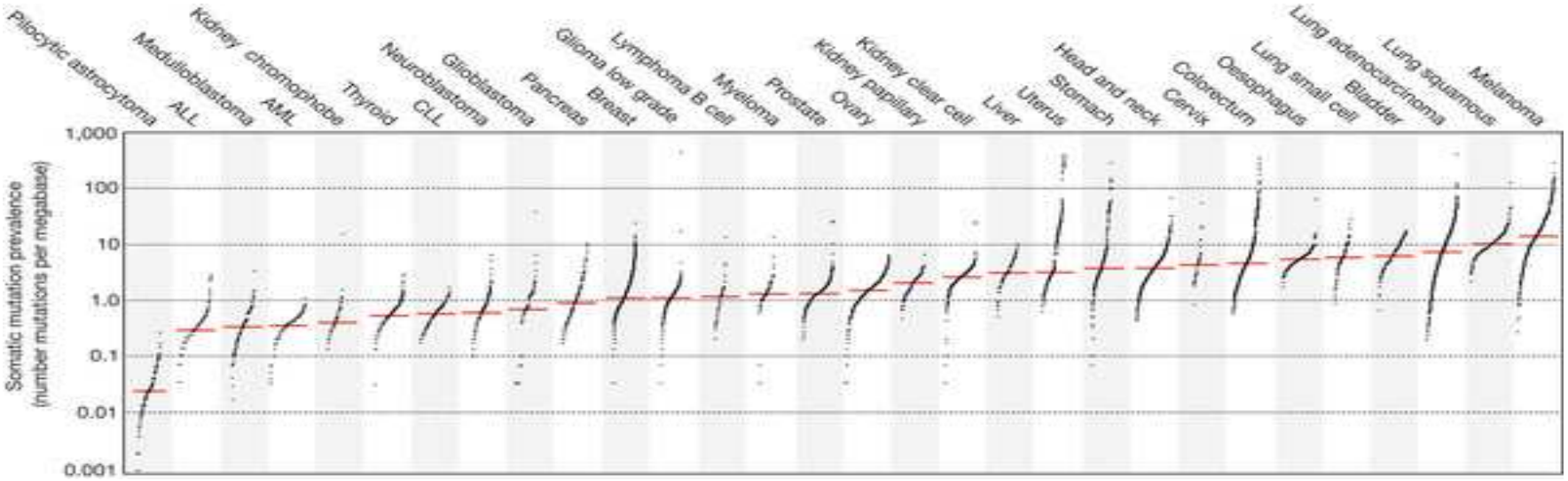
- *Overwhelm* – out-proliferate the immune response
- *Hide* – decreased antigen or MHC Class I or II expression
- *Subvert* – immunosuppressive chemokines, cytokines
- *Shield* – exclude infiltration by tumor antigen-reactive T cells
- *Defend* – deactivate tumor-targeting T cells that attack tumor cells

Weiner L, SITC Symposium 8/7/2015

Cancer Immunotherapy

- Treatment of disease by inducing, enhancing, or suppressing an immune response
- “Treating the immune system so it can treat the cancer” (J. Wolchok)
- Immunotherapy can cure cancers

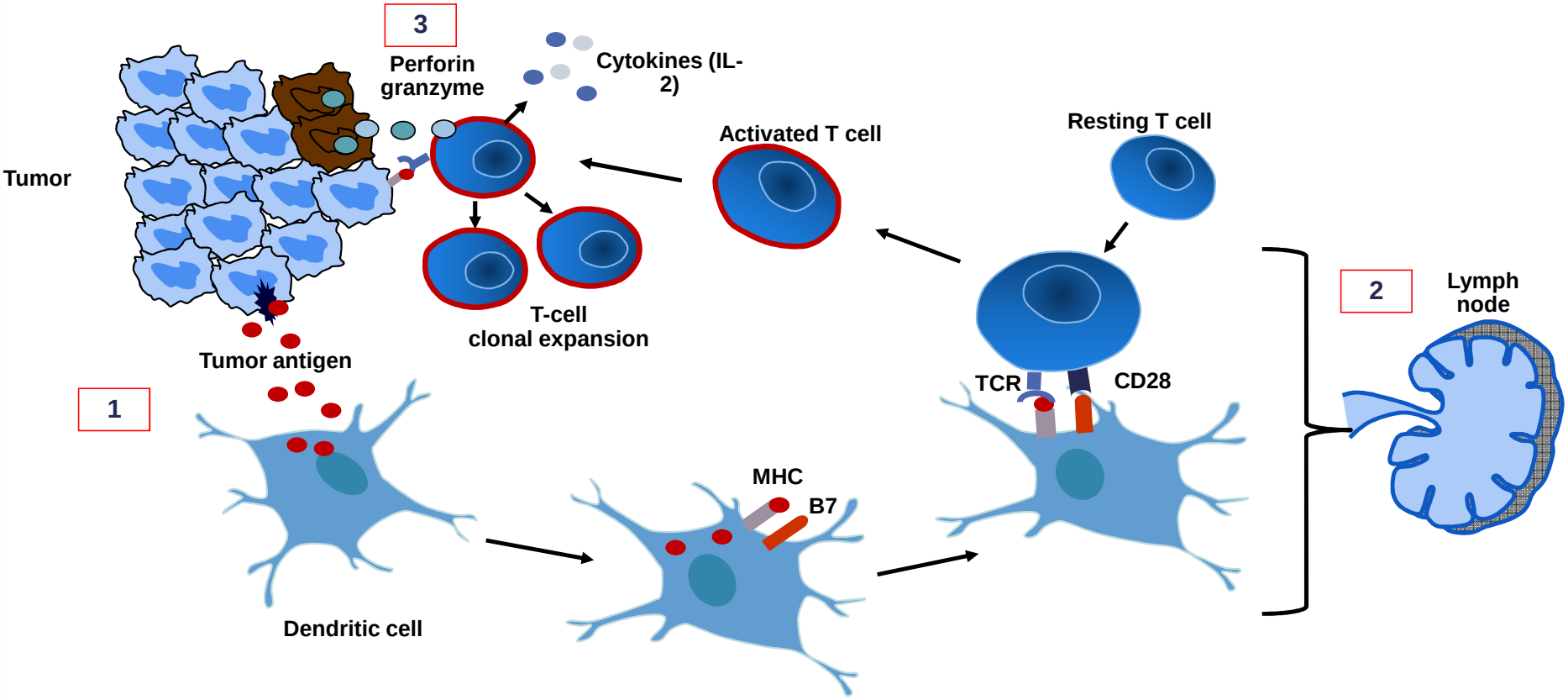
Most Cancers Have Mutations



Mutated proteins represent potential antigens – targets for immune recognition and destruction

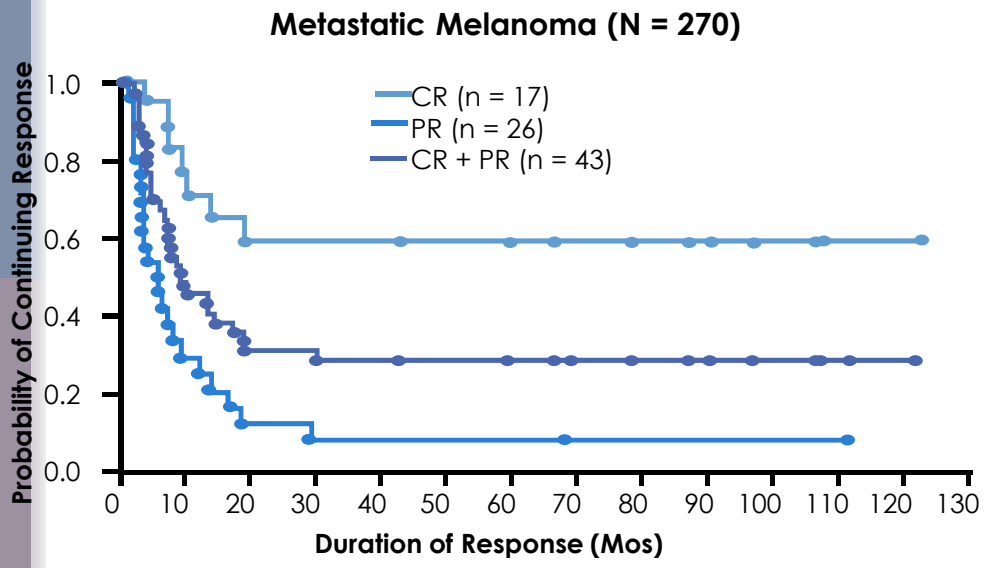
Lawrence, Nature 499:214 2013

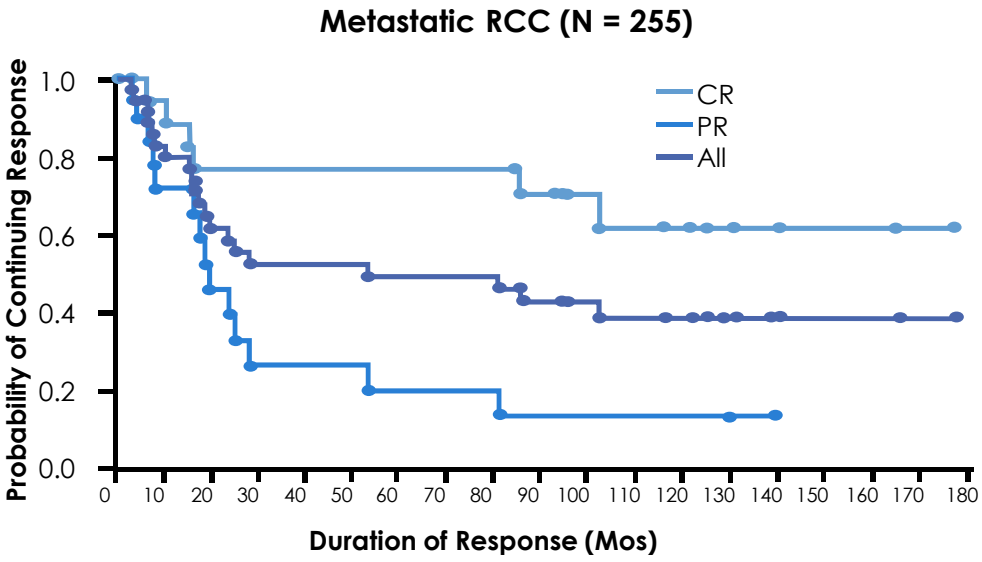
Tumor Immunology: Overview



HD IL-2 Therapy: Durable Responses

- HD IL-2 produces durable responses in ~10% of patients with advanced melanoma or RCC
- Few relapses in patients responding for over 2.5 years (likely cured)
- FDA approval in 1992 (RCC) and 1997 (melanoma)



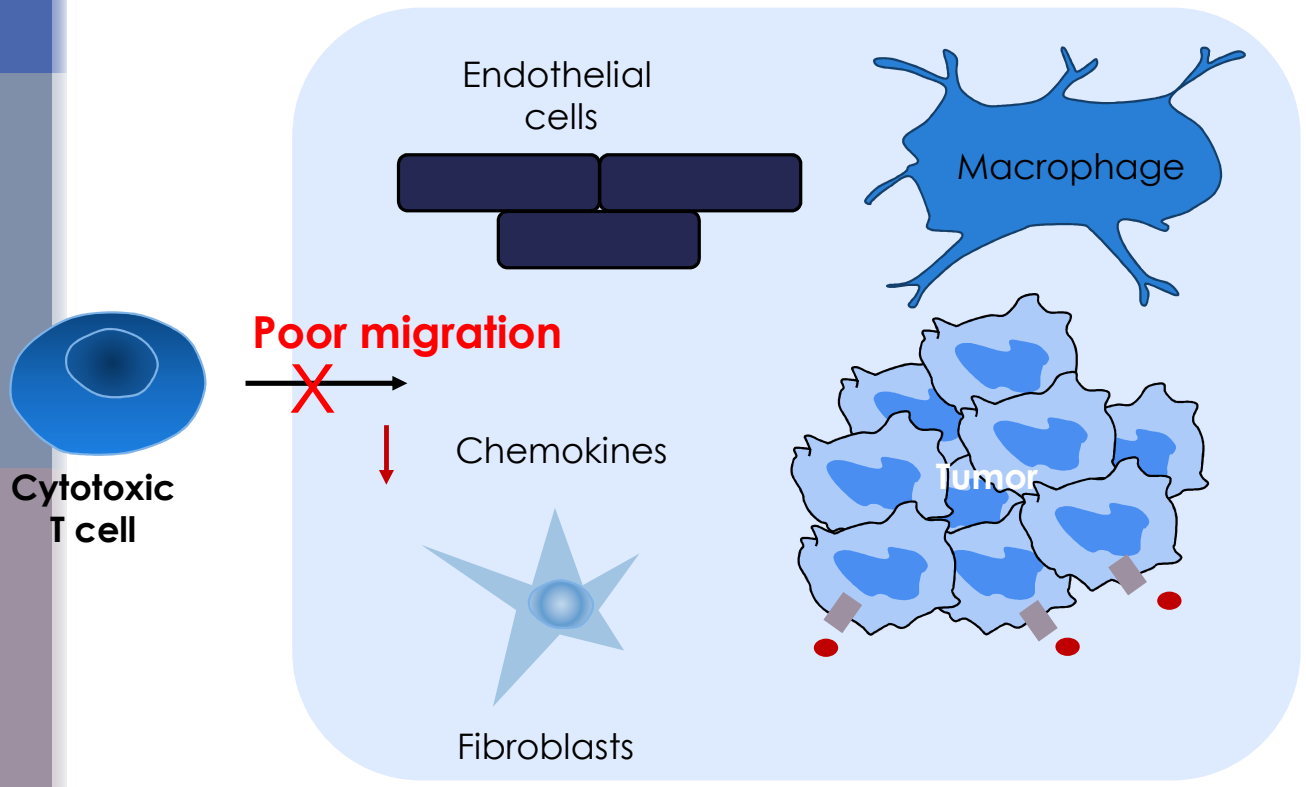


Atkins MB, et al. J Clin Oncol. 1999;17:2105-2116. McDermott DF, et al. Expert Opin Biol Ther. 2004;4:455-468.

High-Dose IL-2 Therapy: 30-year History

- High-dose IL-2 appears to benefit pts, but:
  - Toxic, complex; must be delivered as an inpatient regimen
- Use remained limited to selected pts treated at experienced centers
- Efforts to develop more tolerable regimens unsuccessful
- Efforts to better select pts who might benefit from high-dose IL-2 therapy produced modest advances
- Proof of principle that immunotherapy can produce durable benefit in pts with cancer, but newer immunotherapies are needed

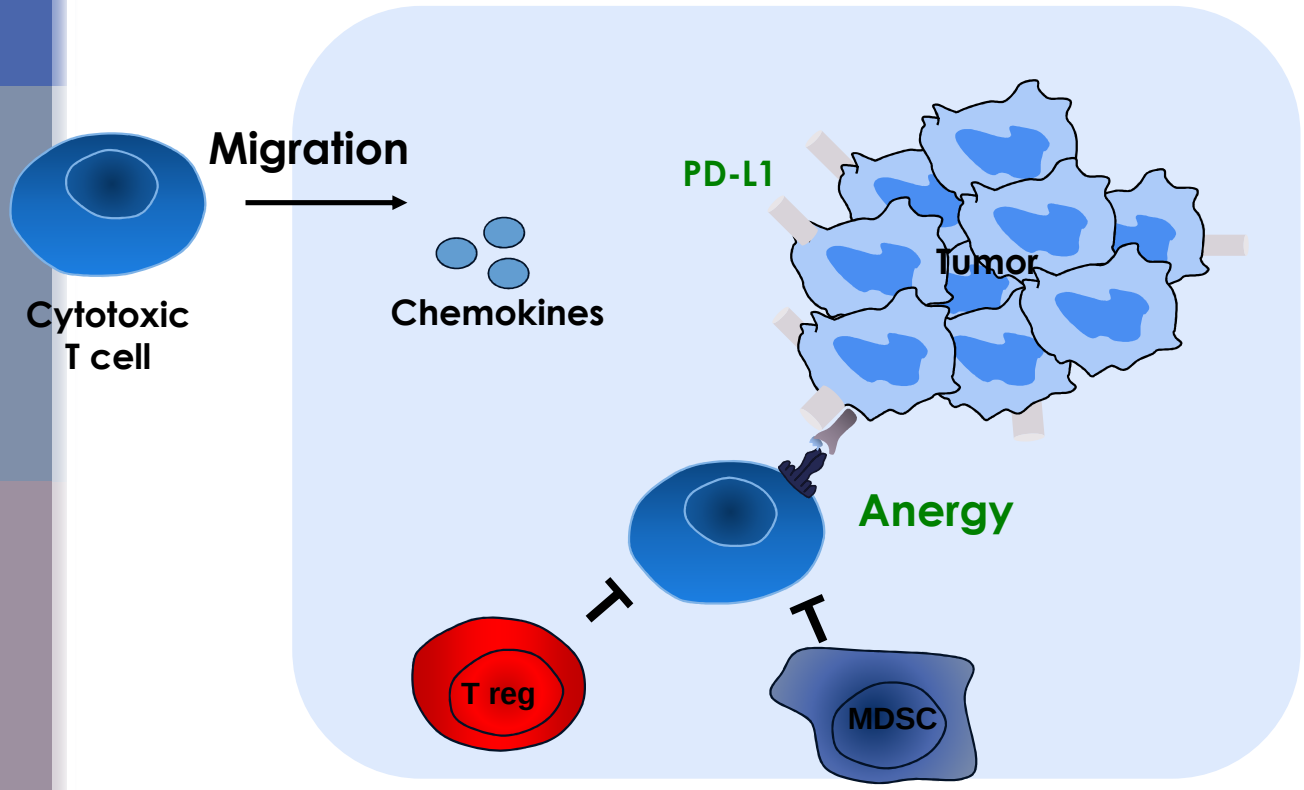
Non-inflamed Tumor Phenotype



- Poor effector cell trafficking due to:
  - Low inflammation and chemokine expression
- Poor effector cell function due to:
  - hypoxia and high expression of vascular markers, macrophages, fibroblasts

Gajewski TF, et al. Curr Opin Immunol. 2011;23:286-292.

Inflamed Tumor Phenotype

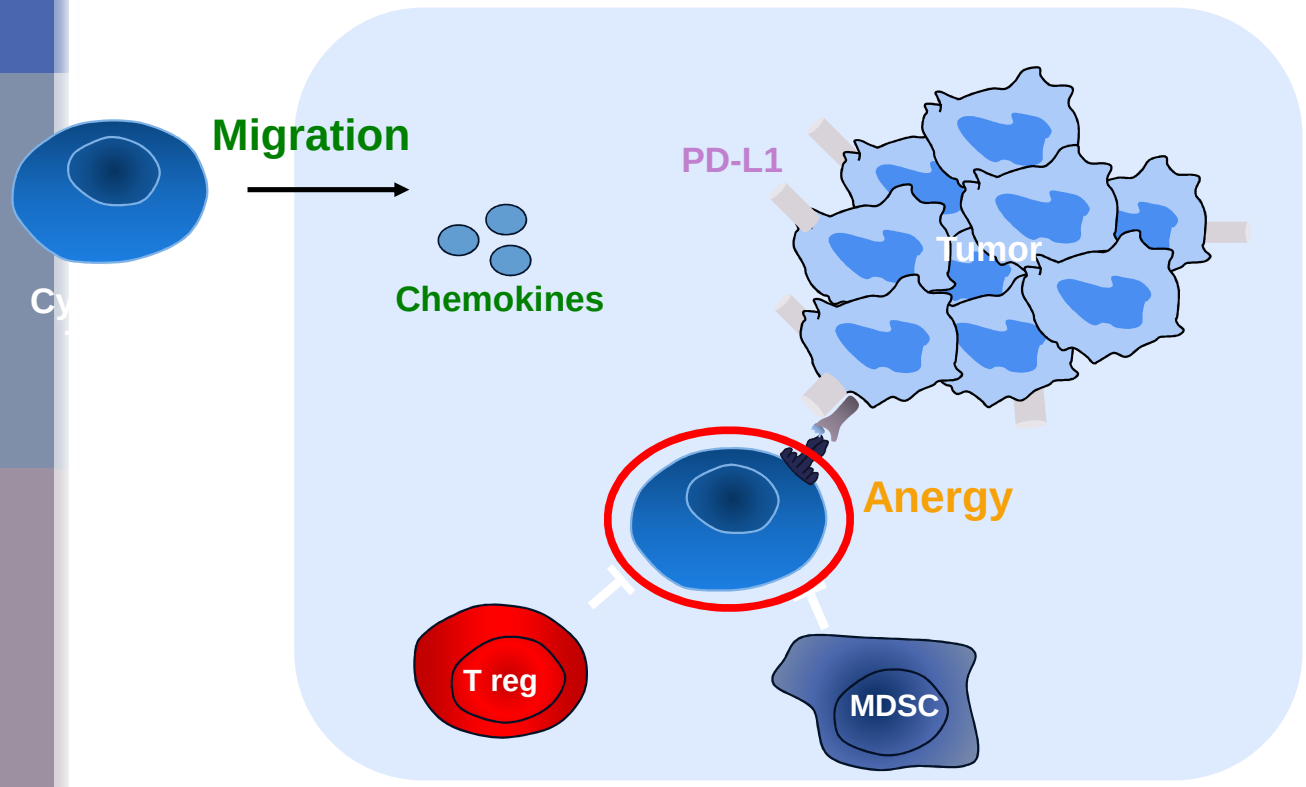


- T cell recruitment
  - High levels of innate immune signals
  - Chemokine expression
- Nevertheless, negative immune regulators dominate
  - Inhibitory receptors
  - Suppressive cells
  - Suppressive enzymes (IDO, arginase)

Studies suggest these are the tumors that can respond to Immunotherapy

Gajewski TF, et al. Curr Opin Immunol. 2011;23:286-292. Spranger S, Gajewski T. J Immunother Cancer. 2013;1:16.

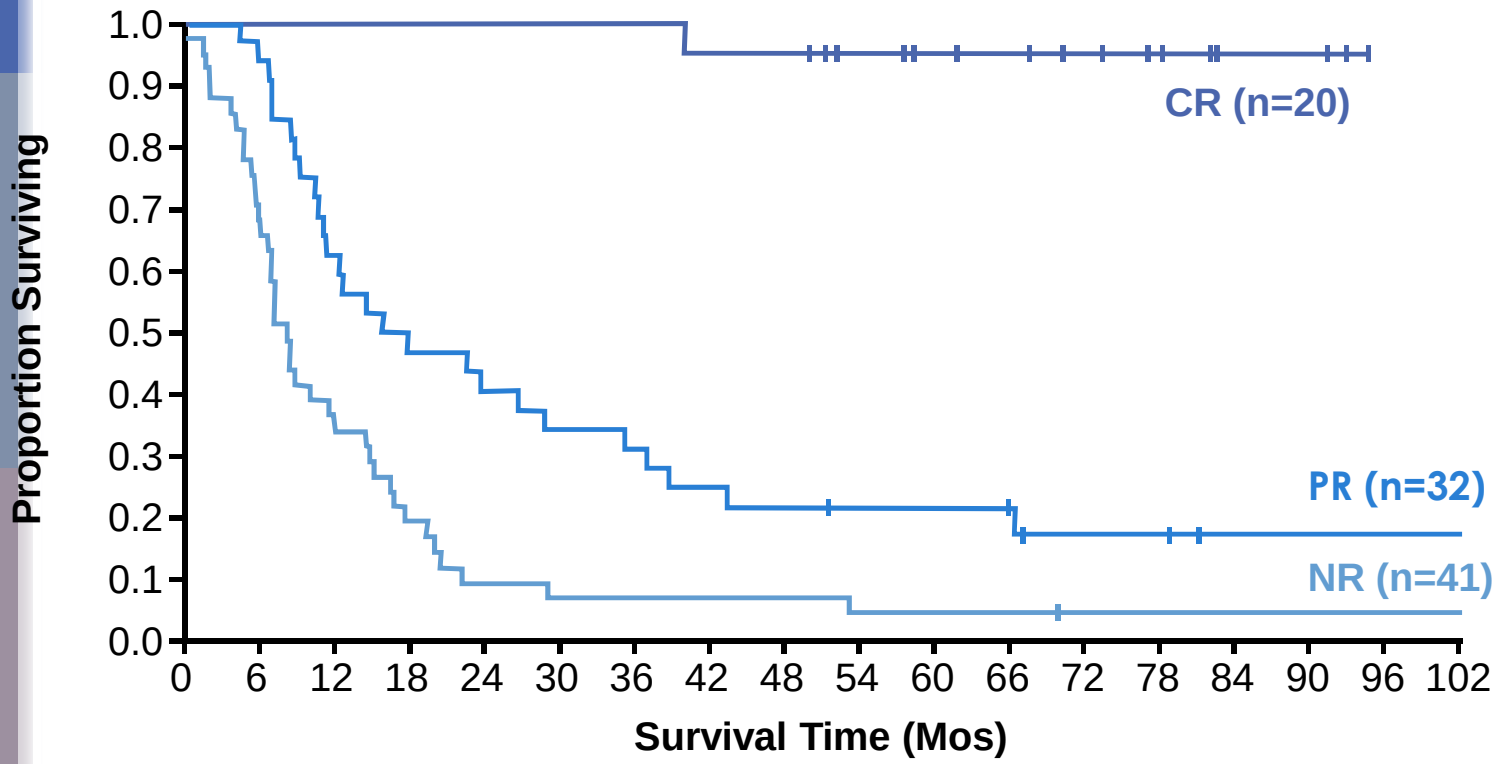
Inflamed Tumor Phenotype



- T cell recruitment
  - High levels of innate immune signals
  - Chemokine expression
- Nevertheless, negative immune regulators dominate
- TIL therapy: remove anti-tumor T cells from immunosuppressive environment, select/expand ex vivo then re-administer

Gajewski TF, et al. Curr Opin Immunol. 2011;23:286-292. Spranger S, Gajewski T. J Immunother cancer. 2013;1:16.

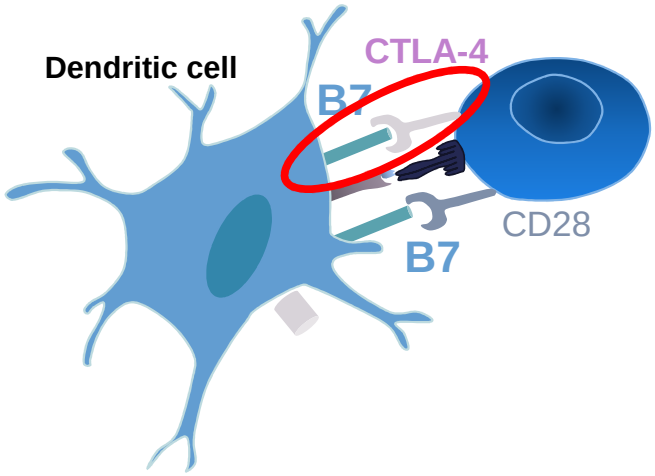
Tumor-Infiltrating Lymphocytes + IL-2 in Metastatic Melanoma: OS



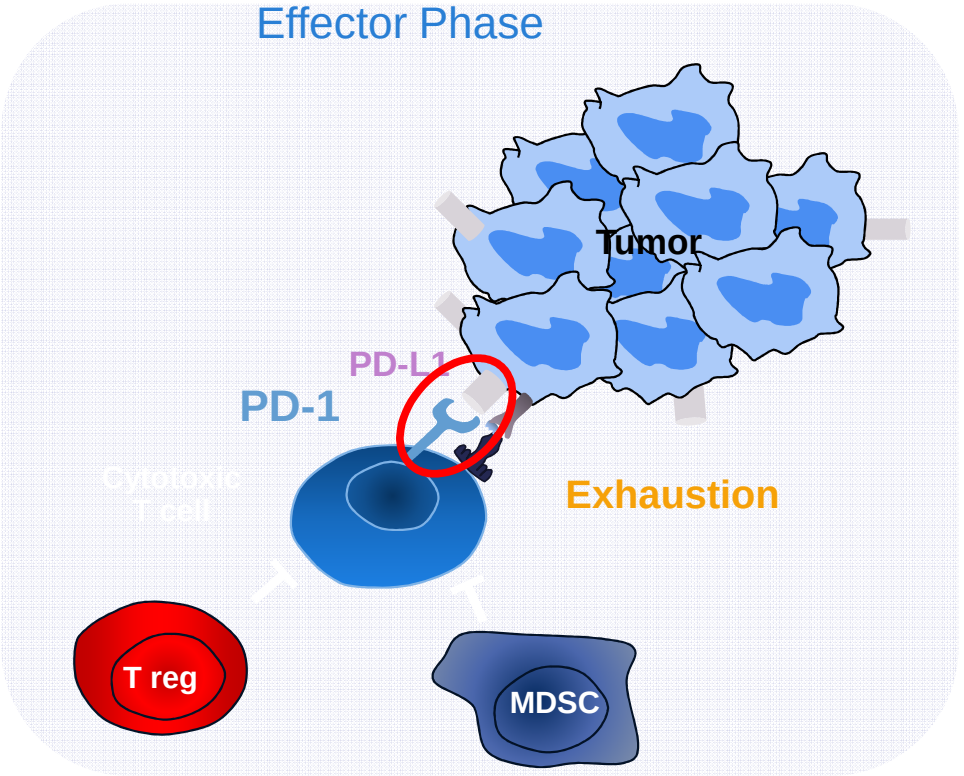
Robbins PF, et al. Nat Med. 2013;19:747-752.

Dampening the Immune System in Cancer

Priming Phase



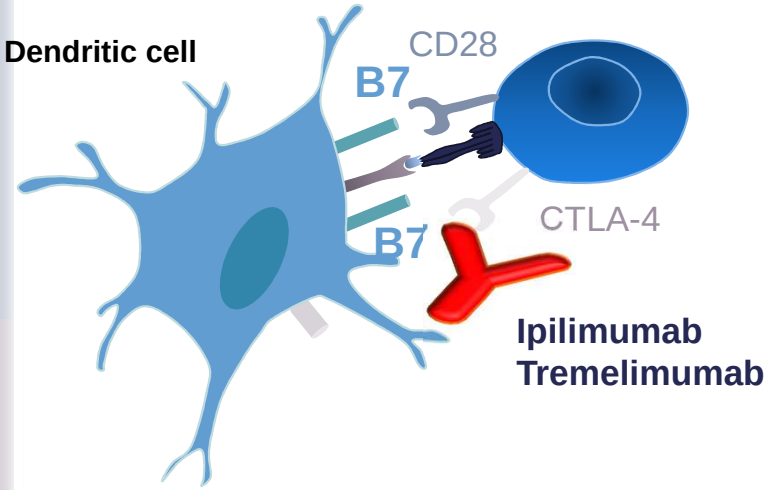
Effector Phase



Ribas A. N Engl J Med. 2012;366:2517-2519. Spranger S, et al. J Immunother Cancer. 2013;1:16.

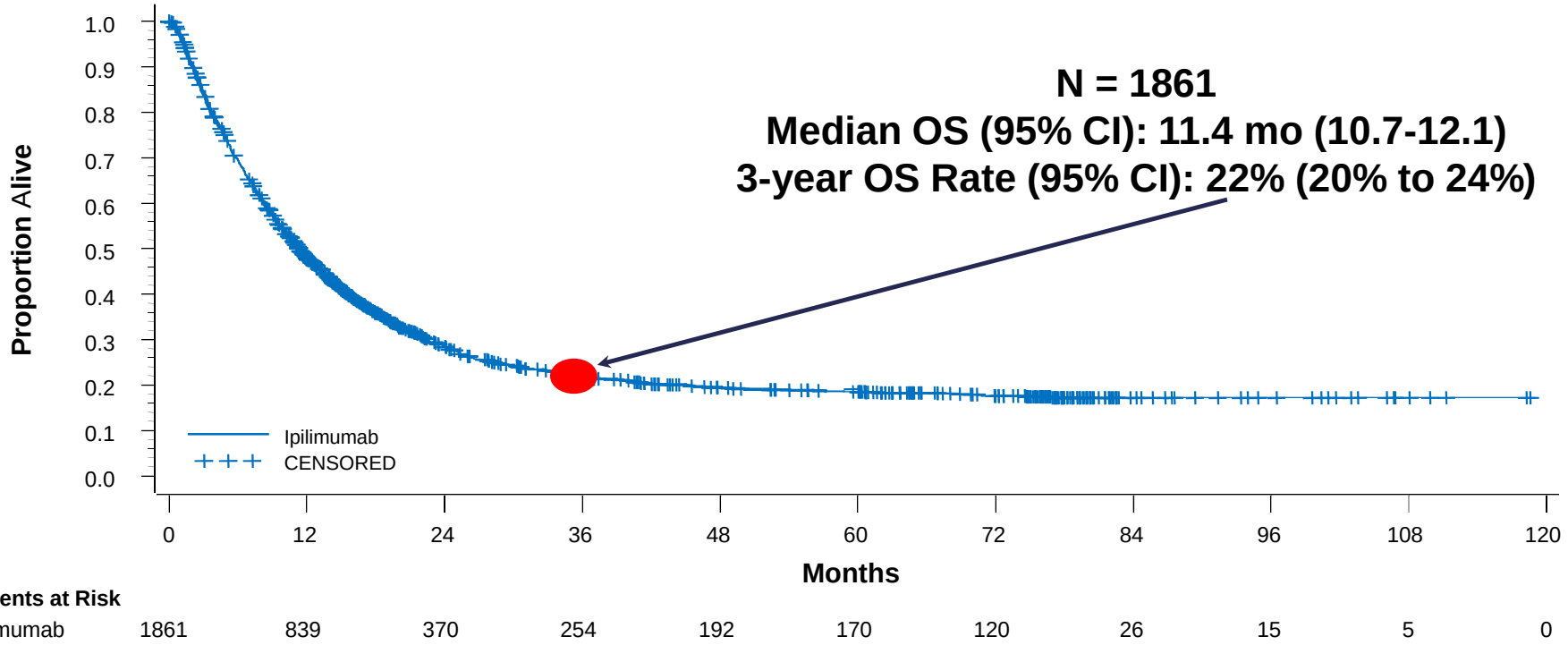
Blocking Immunologic Checkpoints

Priming:
T-Cell Activation in the Lymph Node



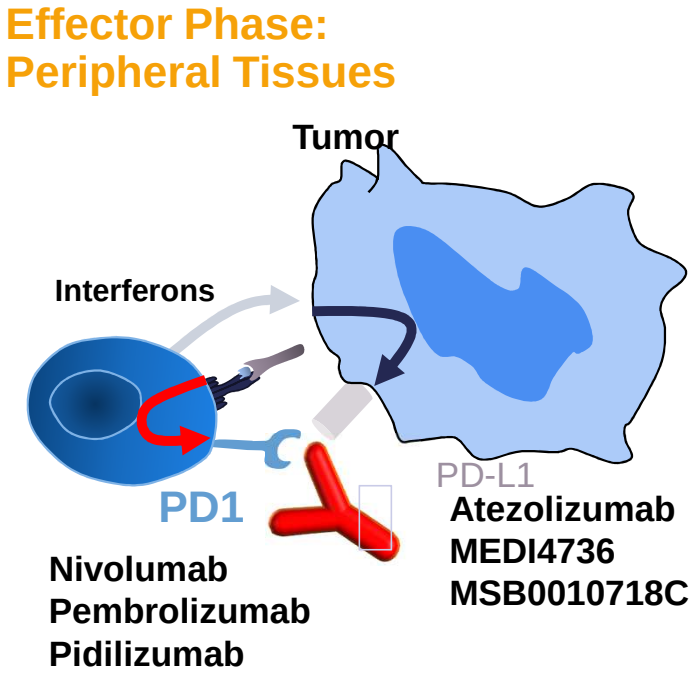
Ribas A. N Engl J Med. 2012;366:2517-2519. Spranger S, et al. J Immunother Cancer. 2013;1:16.

Ipilimumab: Pooled Survival Analysis from Phase II/III Trials in Advanced Melanoma



Schadendorf D, J Clin Oncol 2015.

Blocking Immunologic Checkpoints



Ribas A. N Engl J Med. 2012;366:2517-2519. Spranger S, et al. J Immunother Cancer. 2013;1:16.

Clinical Development of Inhibitors of PD-1 Immune Checkpoint

Target	Antibody	Molecule	Company	Development stage
PD-1	Nivolumab (Opdivo)	Fully human IgG4	Bristol-Myers Squibb	Approved in Melanoma, NSCLCa Phase III in RCC, HNSCC etc
	Pembrolizumab (Keytruda)	Humanized IgG4	Merck	Approved in Melanoma, NSCLCa Phase III in bladder etc
	Pidilizumab	Humanized IgG1	Curetech Medivation	Phase II Melanoma, Heme Malignancies
PD-L1	Durvalumab	Engineered human IgG1	MedImmune	Phase I-II multiple tumors
	Atezolizumab	Engineered human IgG1	Genentech	Phase III in bladder, RCC, NSCLC
	Avelumab	Fully human IgG1	EMD Serono (Pfizer)	Phase II in ovarian, Phase I in multiple solid tumors

A1

Nivolumab: Clinical Activity

Tumor Type	Dose, mg/kg	ORR (CR/PR), n (%)	SD ≥ 24 Wks, n (%)	Median PFS, Mos	MedianOS, Mos	1 yr, %	2 yr, %
MEL (n = 107)	0.1-10	32 (34)	7 (7)	3.7	17.3	68	48
NSCLC (n = 129)	1-10	22 (17)	13 (10)	2.3	9.9	42	24
RCC (n = 34)	1 or 10	10 (29)	9 (27)	7.3	> 22	70	50

Topalian SL, et al. N Engl J Med. 2012;366:2443-2454. Hodi FS, et al. ASCO 2014. Abstract 9002. Brahmer JR, et al. ASCO 2014. Abstract 8112.

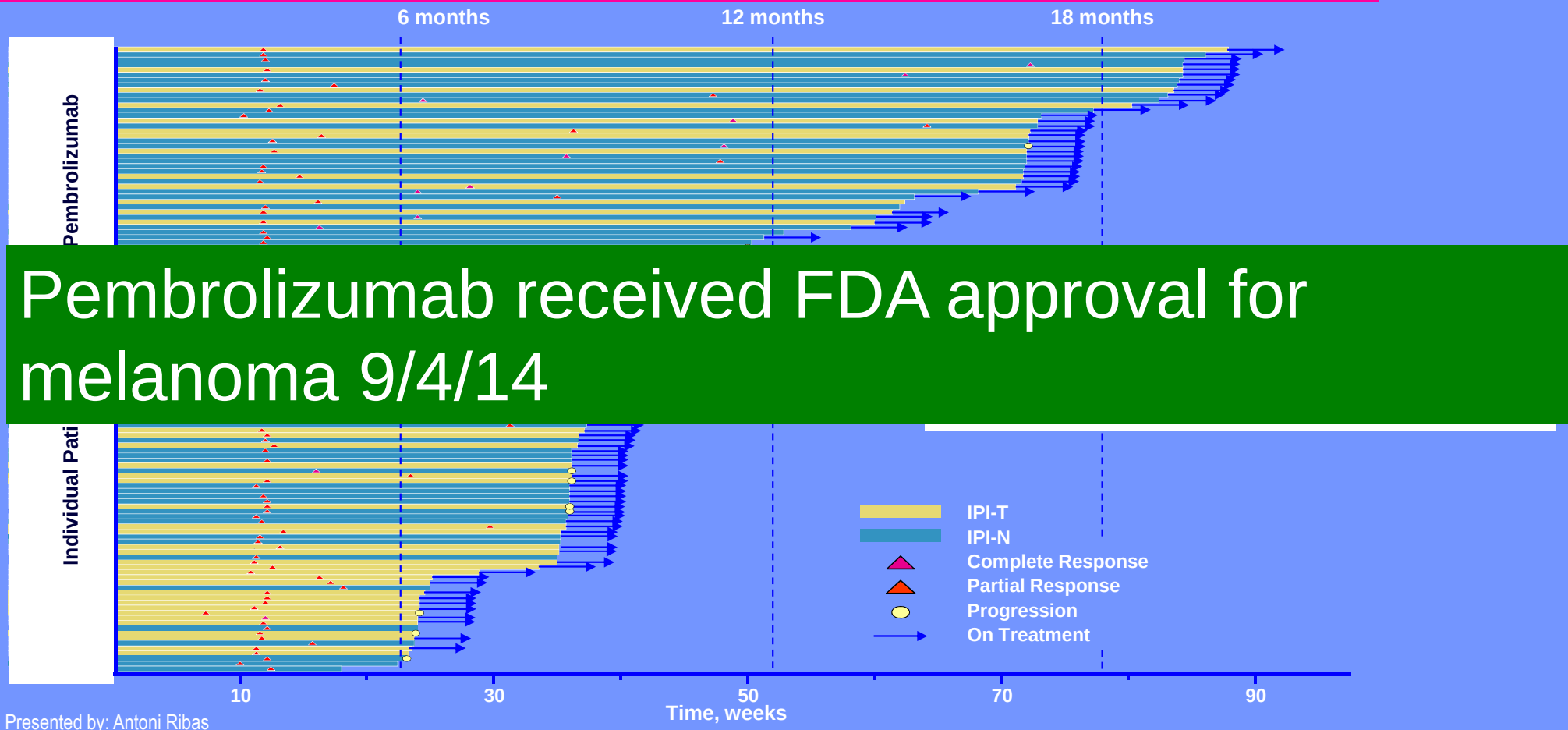
Slide 21

A1 Will need updating from ASCO 2014 reports.

Mel - Abst 9002
NSCLC - Abst 8112
Author, 7/14/2014

A6

Pembrolizumab: Time to Response and On-Study Duration



Pembrolizumab received FDA approval for melanoma 9/4/14

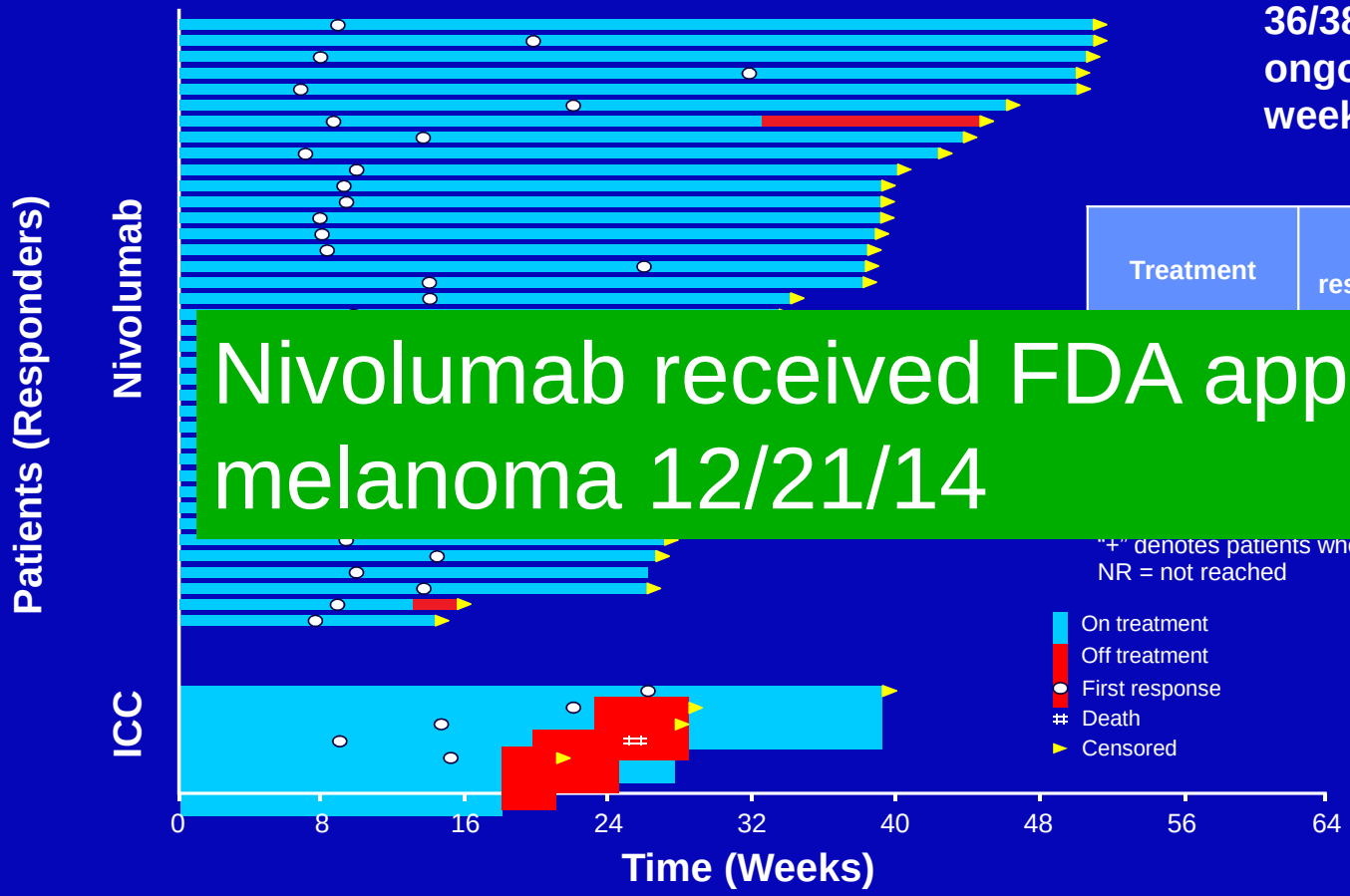
Presented by: Antoni Ribas

[a]Ongoing response defined as alive, progression free, and without new anticancer therapy.

A6 Design - please format with our style

Author, 6/24/2014

Nivo 037 Study: Time and Duration of Response



36/38 (95%) of nivolumab responses ongoing with minimum follow-up of 24 weeks in all patients

Treatment	Median time to response, (range), mo	Median duration of response(range), mo

Nivolumab received FDA approval for melanoma 12/21/14

"+" denotes patients who are censored (still in response);
NR = not reached

Spectrum of PD-1/PD-L1 Antagonist Activity

Active

- **Melanoma**
- **Renal cancer (clear cell and non-clear cell)**
- **NSCLC – adenocarcinoma and Squamous cell**
- Small cell lung cancer
- **Head and neck cancer**
- Gastric and GE junction
- **Mismatch repair deficient tumors (colon, cholangiocarcinoma)**
- **Bladder cancer**
- Triple negative breast cancer
- Ovarian cancer
- Glioblastoma
- Hepatocellular carcinoma
- Thymic carcinoma
- Mesothelioma
- Cervical cancer
- **Hodgkin Lymphoma**
- Diffuse large cell lymphoma
- Follicular lymphoma
- T-cell lymphoma (CTCL, PTCL)
- **Merkel Cell**

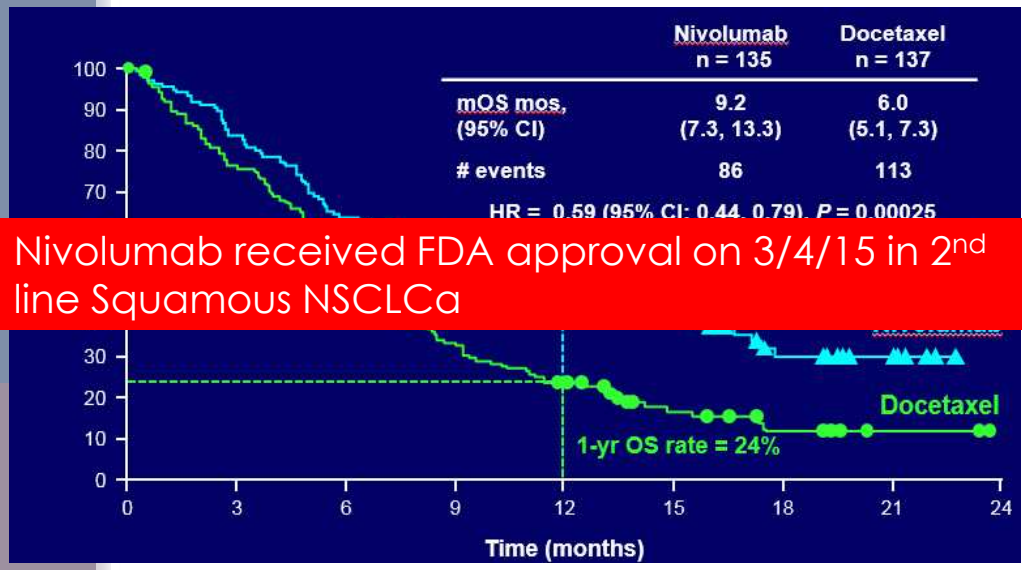
8 for 8 Phase III Trials

Minimal to no activity:

- Prostate cancer
- MMR+ Colon cancer
- Myeloma
- Pancreatic Cancer
- ER+ breast cancer

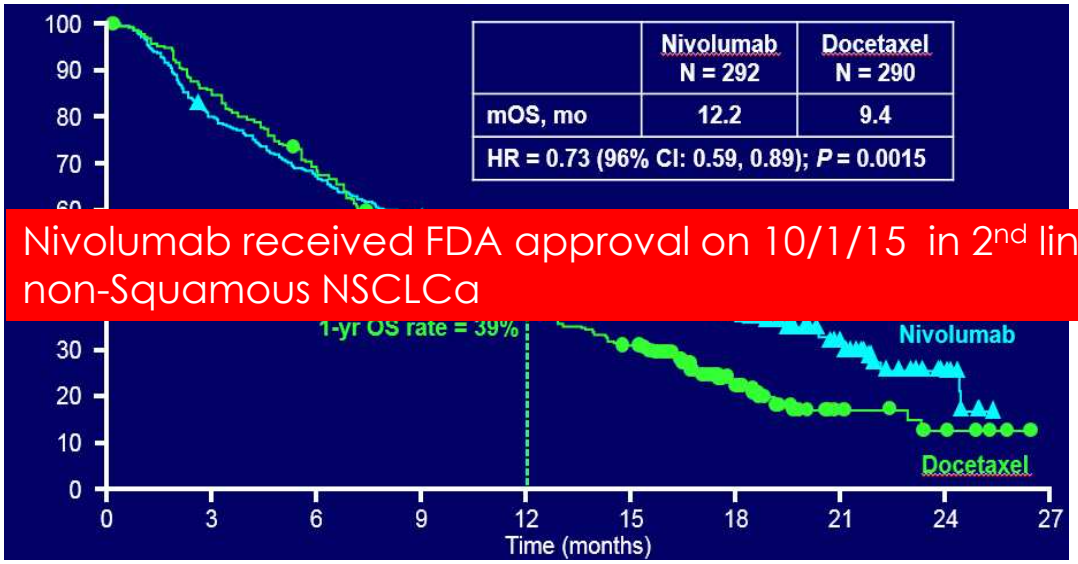
Randomized phase III trials of nivolumab vs. docetaxel in NSCLC

Trial 17: Squamous Cell Carcinoma



Nivolumab received FDA approval on 3/4/15 in 2nd line Squamous NSCLCa

Trial 57: Non-Squamous Cell Carcinoma



Nivolumab received FDA approval on 10/1/15 in 2nd lin non-Squamous NSCLCa

Pembrolizumab Monotherapy for NSCLC: Efficacy Data Supporting the Approved Indication

KEYTRUDA is indicated for the treatment of:

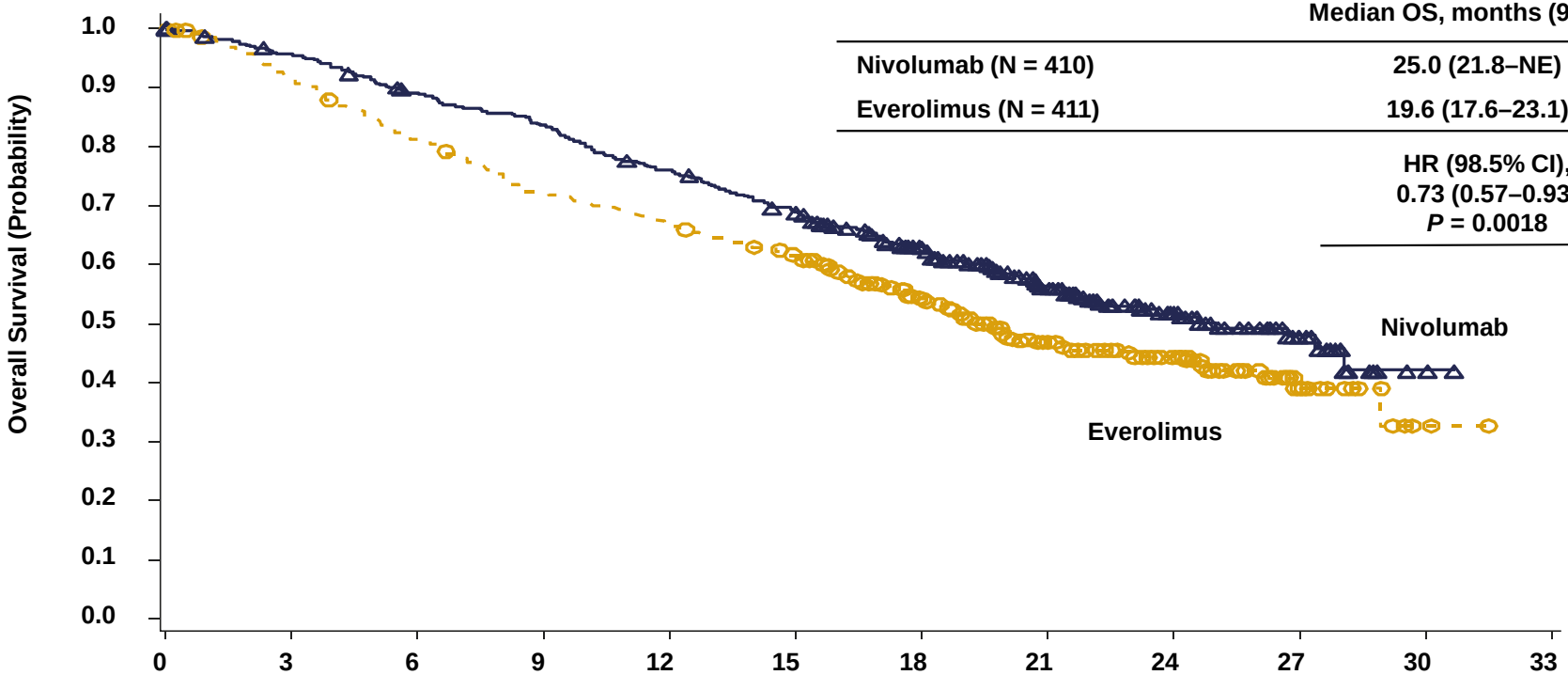
- Patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy
- Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA

FDA Approval with companion biomarker 10/2015

ORR%, (95% CI)	41% (29, 54)
Complete Response	0%
Partial Response	41%

Keytruda (pembrolizumab) Prescribing Information. Whitehouse Station, NJ: Merck & Co, Inc; October 2015.

Nivolumab RCC Ph3: Overall Survival



	Median OS, months (95% CI)
Nivolumab (N = 410)	25.0 (21.8–NE)
Everolimus (N = 411)	19.6 (17.6–23.1)

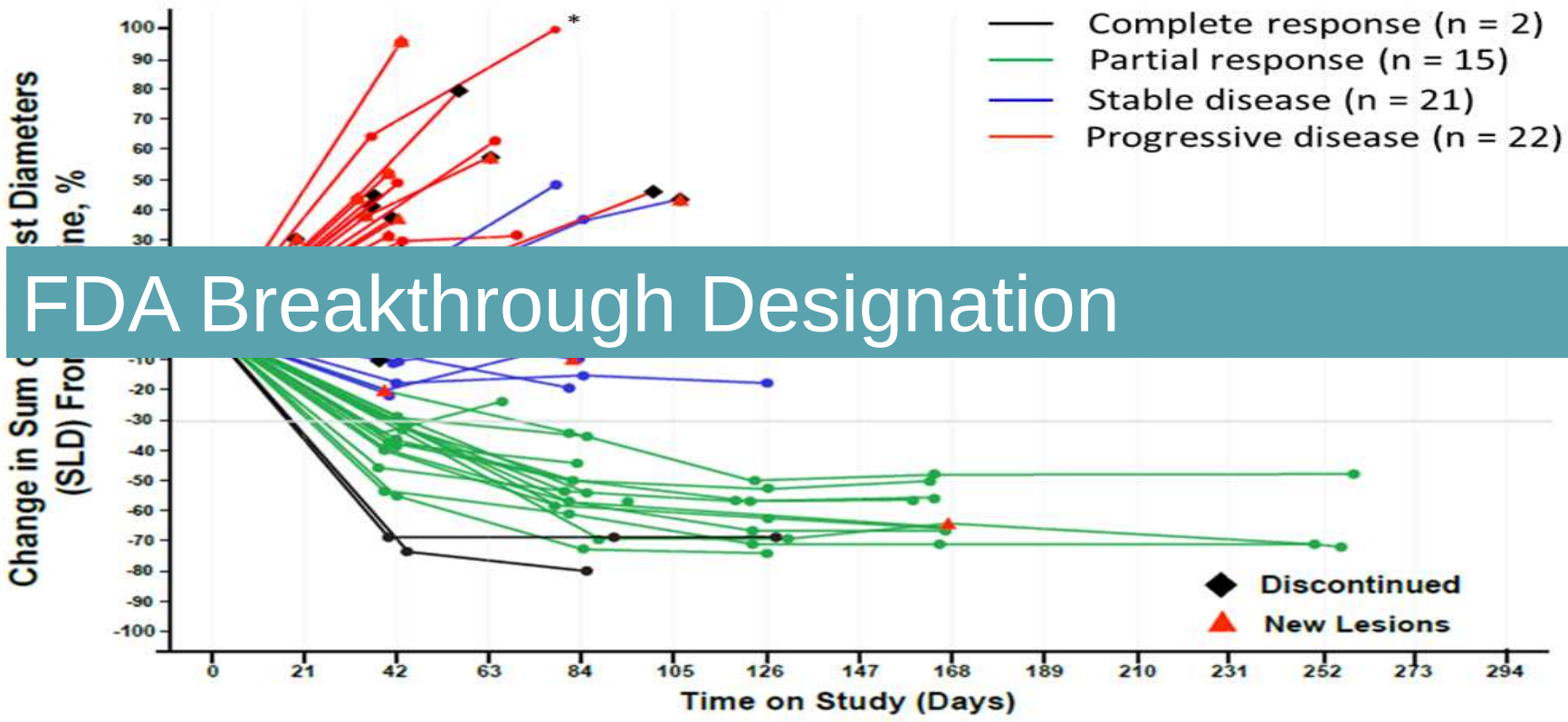
HR (98.5% CI), 0.73 (0.57–0.93)
P = 0.0018

No. of patients at risk												
Nivolumab	410	389	359	337	305	275	213	139	73	29	3	0
Everolimus	411	366	324	287	265	241	187	115	61	20	2	0

- Minimum follow-up was 14 months

CI, confidence interval; HR, hazard ratio; NE, not estimable.

Atezolizumab: Tumor Burden Over Time in Urothelial Bladder Cancer

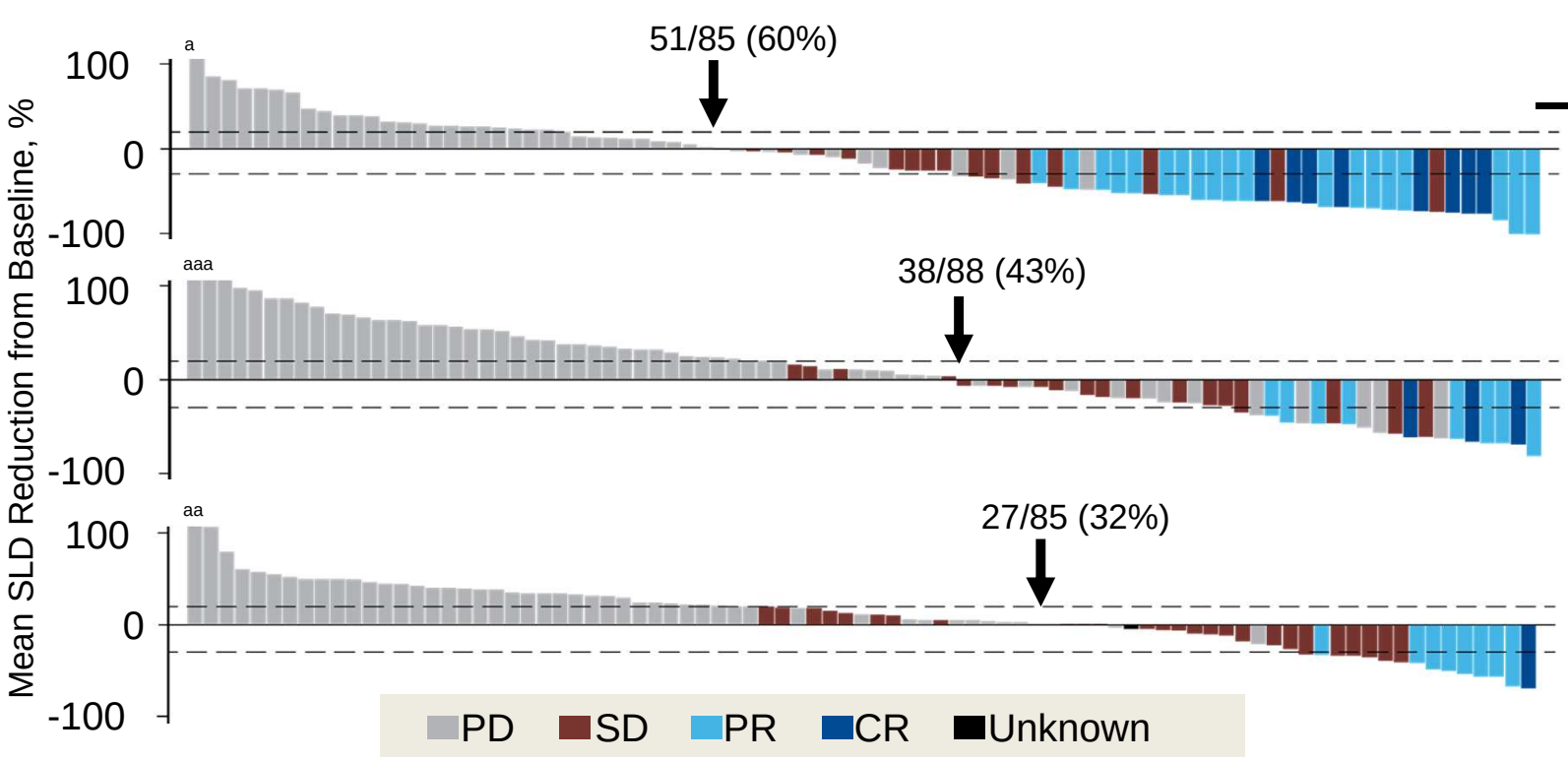


FDA Breakthrough Designation

Powles T, et al. ASCO 2014. Abstract 5011.

IMvigor 210: Efficacy

Changes in Target Lesions by PD-L1 Subgroup



PD-L1 status	ORR[b]
IC2/3	27%
IC1	10%
IC0	9%

111/258 (43%) patients with tumor assessments had SLD reduction

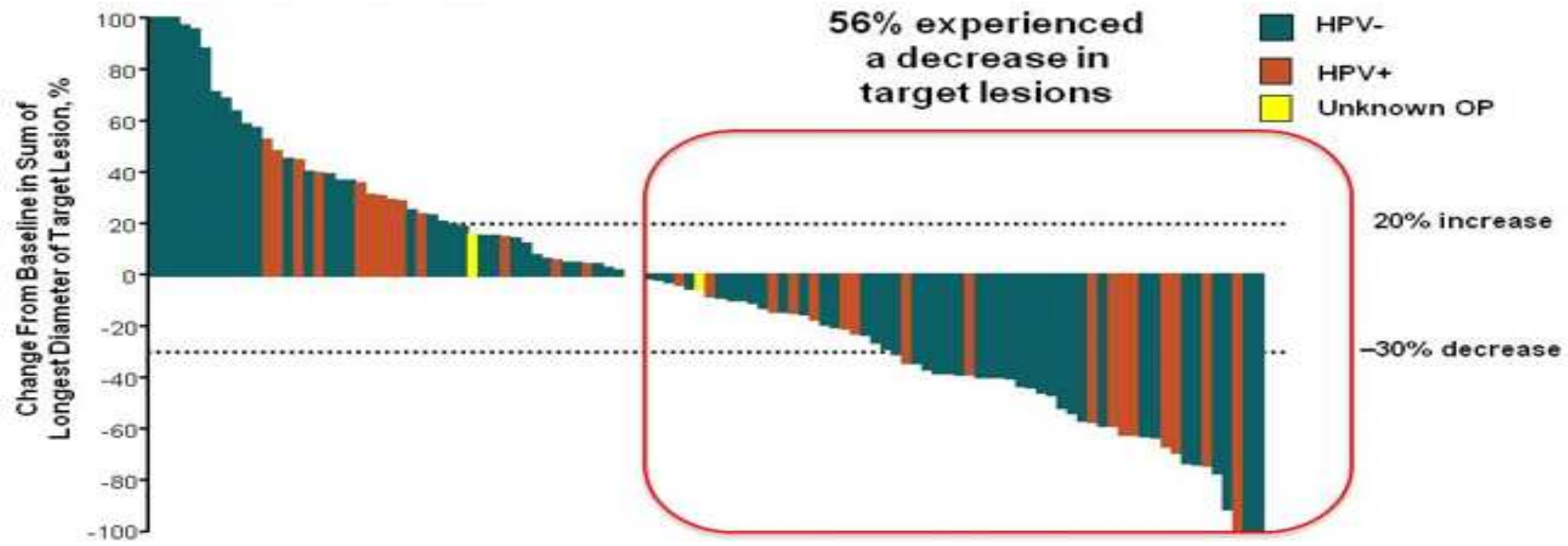
SLD, sum of longest diameters. [a]> 100% increase. [b]Per confirmed RECIST v1.1 (independent review).
Data cutoff May 5, 2015. Follow up ≥ 24 weeks. Patients without post-baseline tumor assessments not included.
Several patients with CR had < 100% reduction due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.

Rosenberg JE, et al.: IMvigor 210: Phase II Atezolizumab in mUC

A1

Phase Ib KEYNOTE-12 Pembrolizumab Study: SCCHN Cohort

- N = 132 patients with recurrent or metastatic SCCHN (HPV+ or HPV-)
- ORR: 25% with 1 CR and 28 PRs

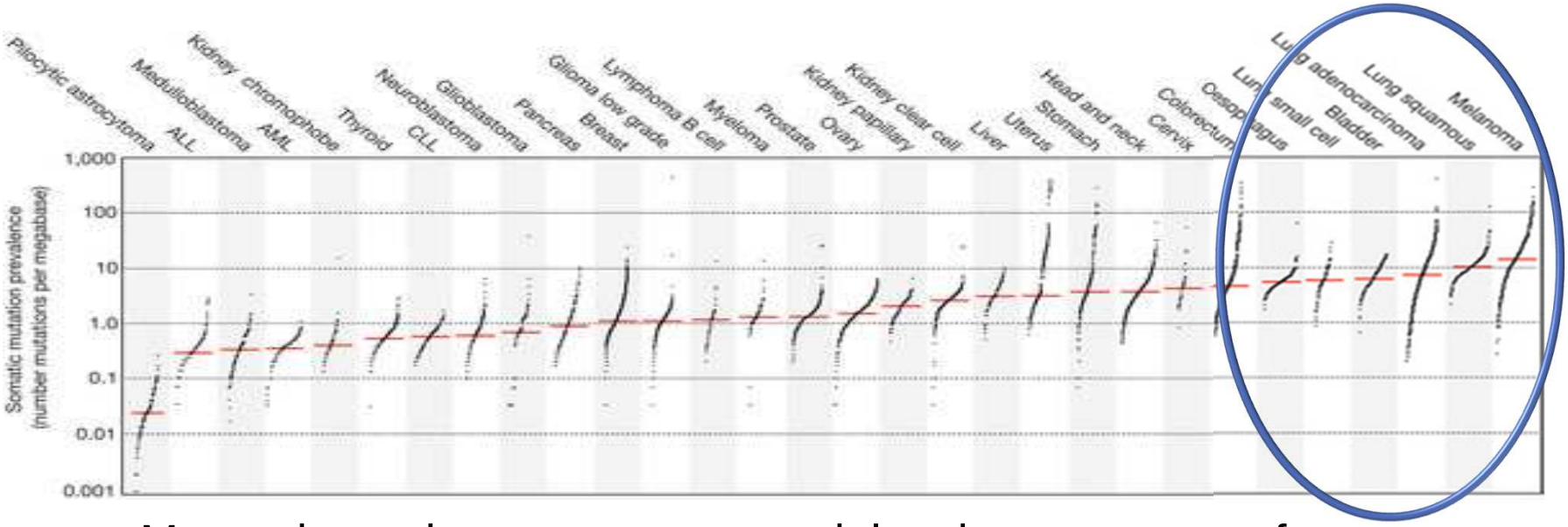


Siewert TY, et al. ASCO 2015. Abstract LBA6008.

Slide 30

A1 No permission yet.
Author, 6/11/2015

Most Cancers Have Mutations



Mutated proteins represent potential antigens – targets for immune recognition and destruction

Tumors with more mutations appear more likely to respond to PD1 blockade

Lawrence, Nature 499:214 2013

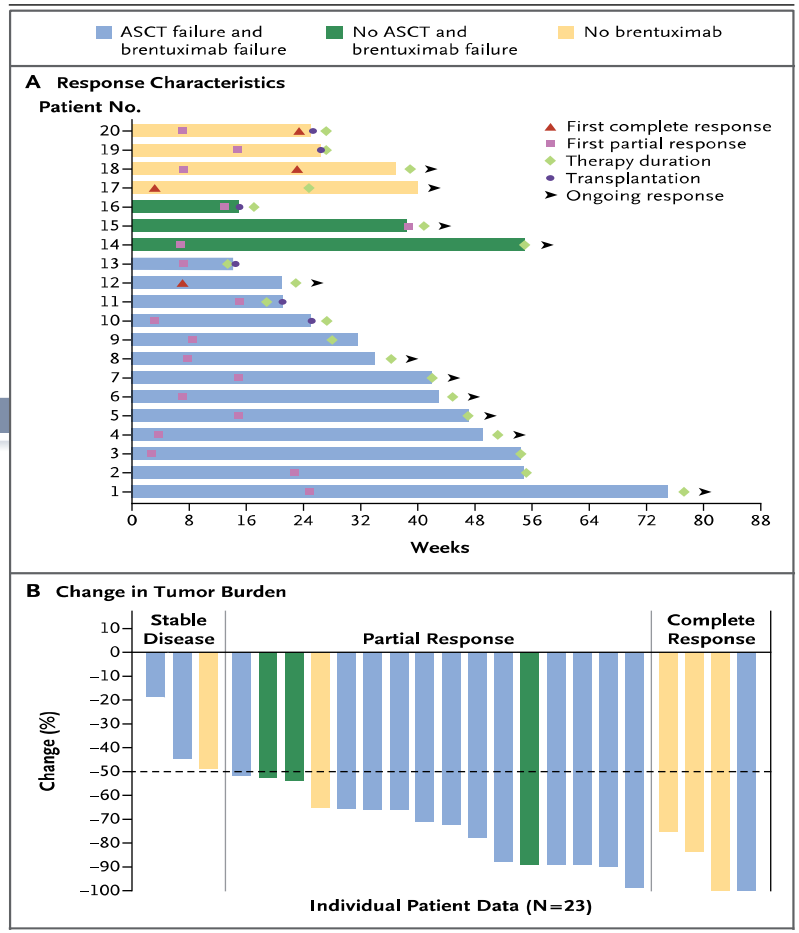
PD-1 Blockade in MMR-Deficient Tumors: Efficacy

Efficacy Outcome (RECIST), %	MMR-Deficient CRC (n = 13)	MMR-Proficient CRC (n = 25)	MMR-Deficient Other tumors (n = 10)
ORR	62	0	60
Disease control rate	92	16	70

Le DT, et al. ASCO 2015. Abstract LBA100.

Nivolumab in Relapsed/Refractory Hodgkin Lymphoma

- 23 pts / **double refractory** (ASCT and brentuximab)
- Nivolumab 3 mg/kg q2 wks until POD / toxicity up to 2y max
- 20/ 23 resp: **ORR 78% / 17% CR** (3 others had SD)
- 2y PFS 86% ++
- Well tolerated

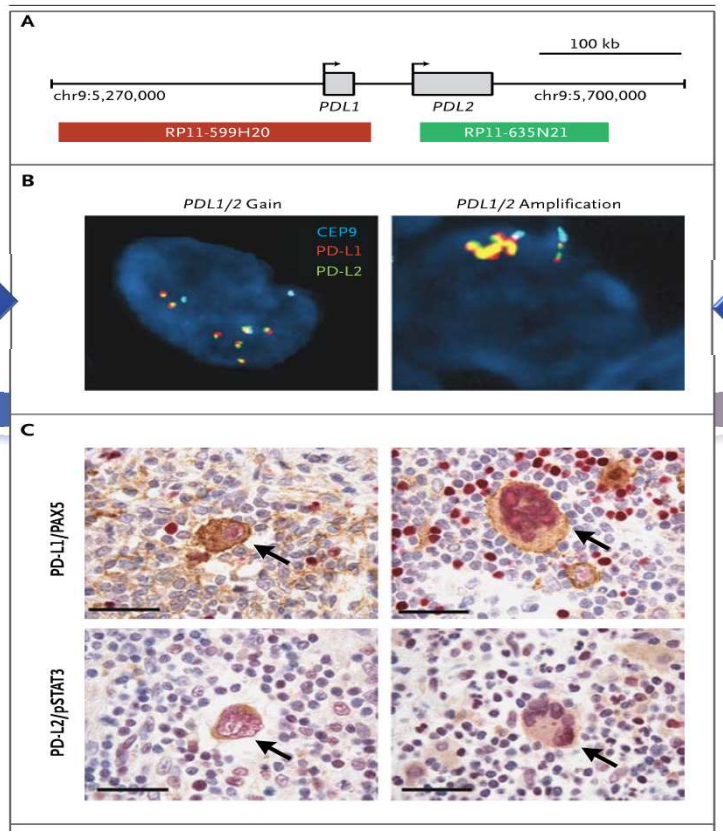


Ansell, NEJM;Jan 2015

Nivolumab in Hodgkin Lymphoma - Biology

Amplification PDL1 and / or PDL2 (ligands for PD1) at 9p24.1

Overexpression PDL1 or PDL2 in RS cells



Evidence of fusion PDL1 / PDL2

Highlight the importance of the PD-1 immune evasion pathway w/ structural basis

Ansell, NEJM; Jan 2015

Summary of PD-1/PD-L1 Blockade Immune-Mediated Toxicities

- Fatigue
- Rash: maculopapular and pruritus
  - Topical treatments
- Diarrhea/colitis
- Hepatitis/liver enzyme abnormalities
- Infusion reactions
- Endocrinopathies: thyroid, adrenal, hypophysitis
- Pneumonitis
- Grade 3/4 toxicities uncommon

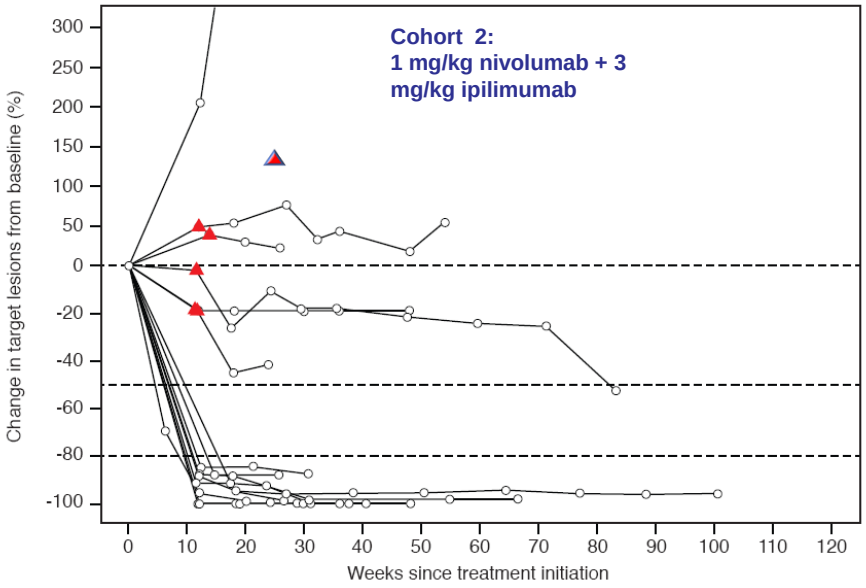
1. Topalian SL, et al. N Engl J Med. 2012;366:2443-2454. 2. Patnaik A, et al. ASCO 2012. Abstract 2512.
3. Brahmer JR, et al. N Engl J Med. 2012;366:2455-2465. 4. Herbst RS, et al. ASCO 2013. Abstract 3000.

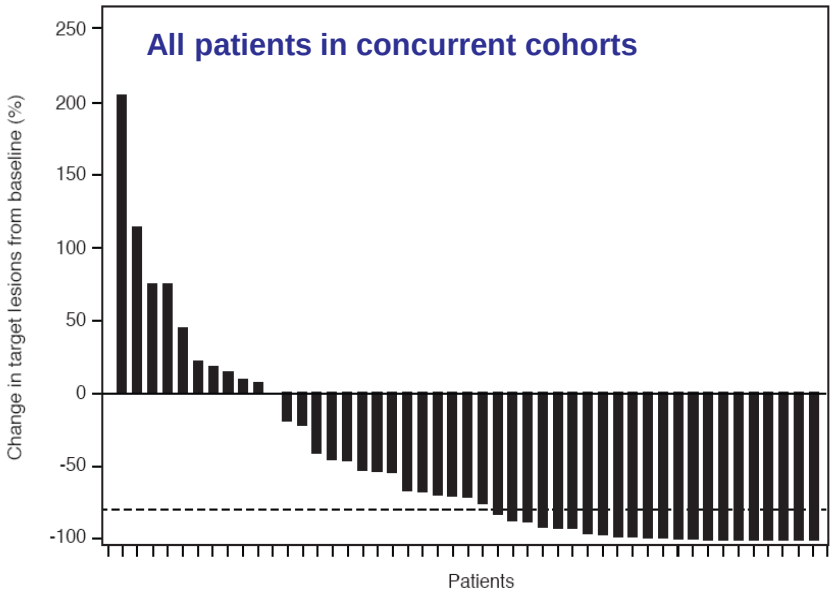
Single Agent Anti-PD1/PDL1 Blockade: Current and Future Directions

- Determine treatment length
- Adjuvant protocols (melanoma, others?)
- Combinations:
  - Immunotherapy, targeted therapy, RT, Vaccines
- Biomarker refinement

A3

Ipilimumab + Nivolumab: Change in Target Lesions





Therapy, %	ORR	≥ 80% Tumor Reduction
Ipilimumab A1	10	< 3
Nivolumab A2	28	< 2
Combination (cohort 2) A7	53	41

Wolchok JD, et al. N Engl J Med. 2013;356:122-133..

Slide 37

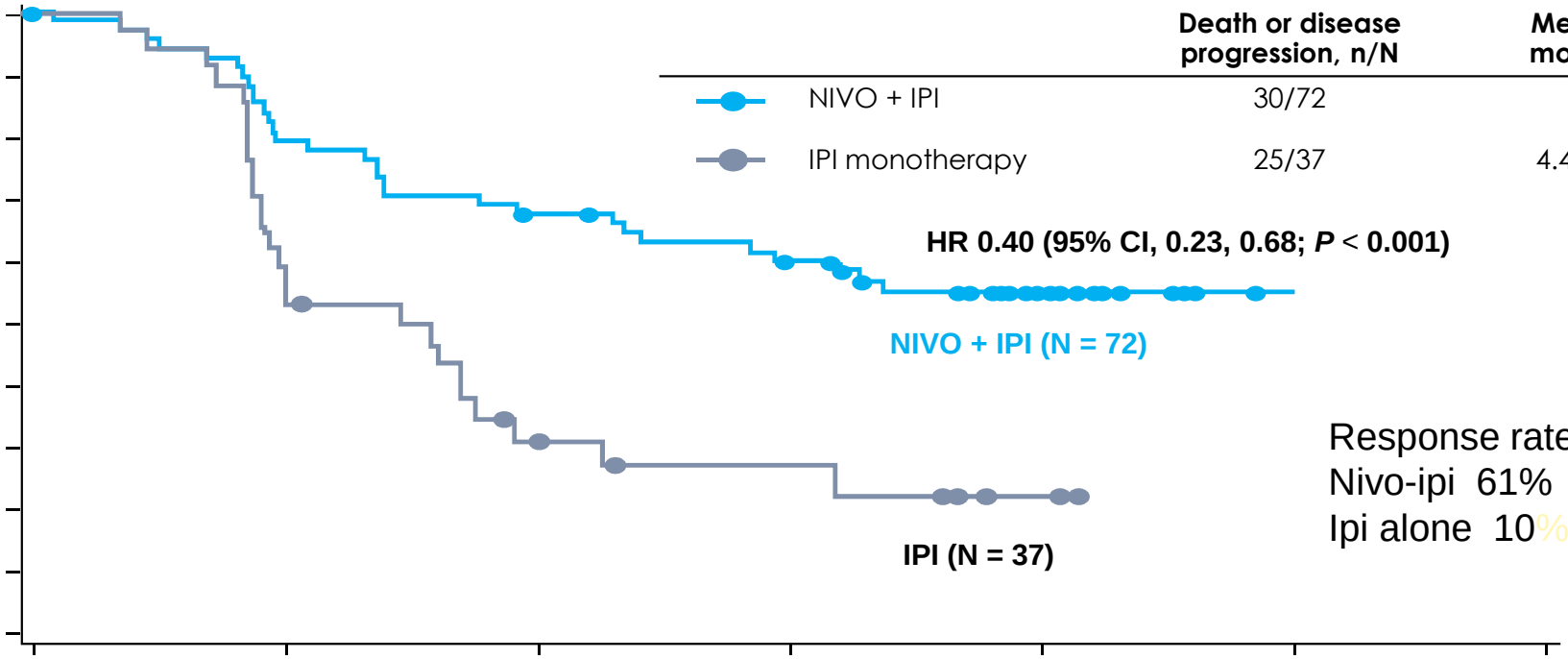
A1 Please verify. I could not confirm these numbers. ORR from ipilimumab was 11% per ASCO presentation slide and >80% tumor reduction was "<10%"
Author, 5/12/2014

A2 Please verify. I could not confirm these numbers. ORR from nivolumab was 41% per ASCO presentation slide and >80% tumor reduction was "<10%"
Author, 5/12/2014

A7 Perhaps the data from the ipilimumab and nivolumab monotherapy rows are from another source?
Author, 5/13/2014

A3 Data to be updated at ASCO 2014
Author, 5/21/2014

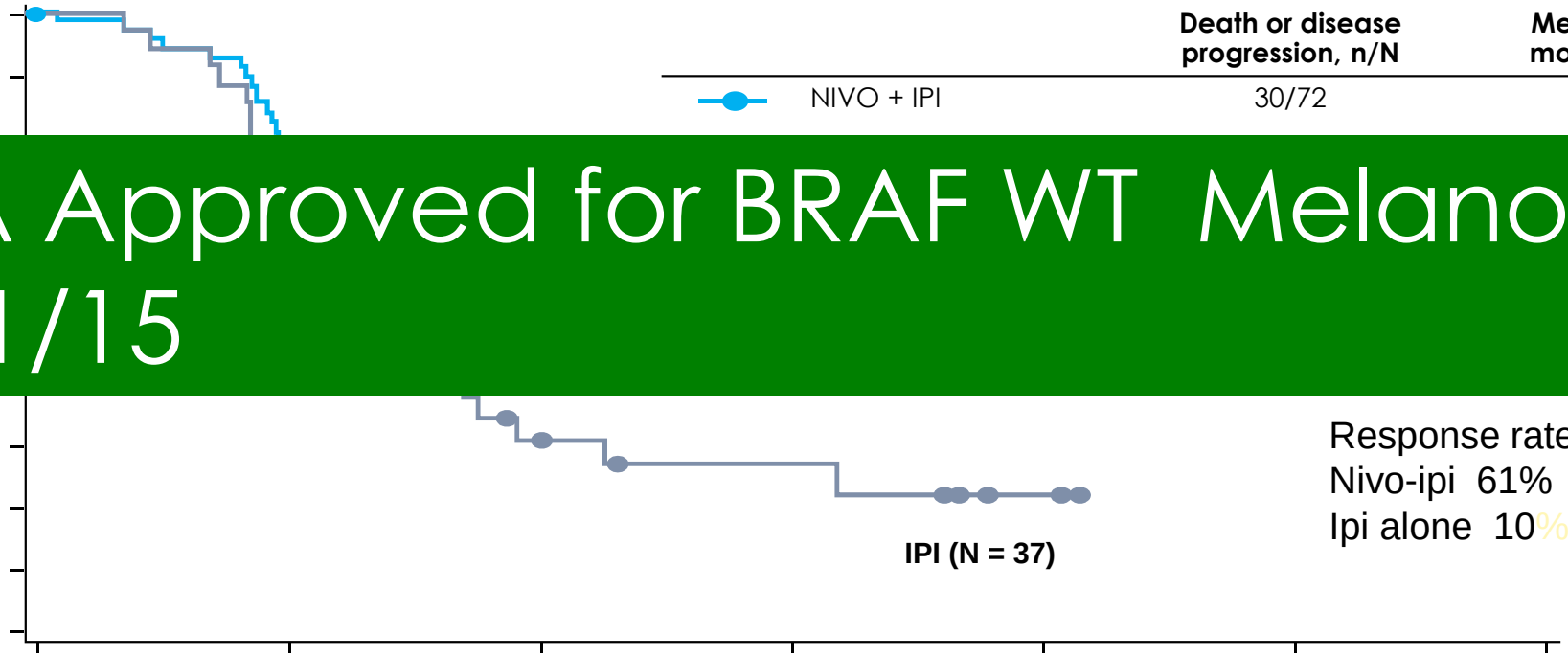
Nivo-Ipi vs Ipi alone



Response rates
Nivo-ipi 61%
Ipi alone 10%

Postow et al NEJM, 2015

Nivo-Ipi vs Ipi alone



FDA Approved for BRAF WT Melanoma 10/1/15

Response rates
Nivo-ipi 61%
Ipi alone 10%

Postow et al NEJM, 2015

Nivo vs Nivo + Ipi: Topline Melanoma Data

	Nivo	Nivo + Ipi
Med PFS (months)	**6.9** (4.3-9.5)	**11.5** (8.9-16.7)
ORR, % (95% CI)	**43.7** (38.1-49.3)	**57.6** (52.0-63.2)
CR %	8.9	11.5
Tumor Burden change	- 34.5%	- 51.9%
Response Duration	NR	NR
Med OS	NR	NR
Grade 3-4 SAEs	16%	55%

Proof of principle that combination immunotherapy can produce greater activity than anti-PD1 alone

Additional Issues/opportunities for Nivo + Ipi

- Transition into the community
- Less toxic regimen
  - Less ipi (2 cycles; lower dose, less frequent)
  - Better toxicity management (more liberal immune suppression)
  - Substitute for ipi (many options)
- **Explore activity of nivo + ipi rescue, if no response to nivo/pembro**
- Sequencing with standard therapies
  - BRAF inhibitors, RT etc
- Role in other cancers
  - RCC, Lung etc

CheckMate 012: Nivolumab Plus Ipilimumab in First-line NSCLC: Efficacy

	Nivo 1 + Ipi 1 Q3W	Nivo 1 Q2W + Ipi 1 Q6W	Nivo 3 Q2W + Ipi 1 Q12W	Nivo 3 Q2W + Ipi 1 Q6W
Confirmed ORR, %	13	25	39	31
Unconfirmed PR, %	3	3	5	8
Confirmed DCR, %	55	58	74	51
ORR in PD-L1 ≥1% (+)	8	24	48	48
ORR in PD-L1 negative	15	14	22	0

Rizvi, et al WCLC 2015

Anti-tumour efficacy of nivolumab-ipilimumab combination therapy (CheckMate-016)

		Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (n=47)	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (n=47)	Nivolumab 3 mg/kg + ipilimumab 3 mg/kg (n=6)
Confirmed ORR, n (%) 95% CI		18 (38.3) 24.5–53.6	19 (40.4) 26.4–55.7	0
Best overall response, n (%)	**CR**	4 (8.5)	1 (2.1)	0
	PR	14 (29.8)	18 (38.3)	0
	SD	17 (36.2)	17 (36.2)	5 (83.3)
	PD	10 (21.3)	7 (14.9)	1 (16.7)

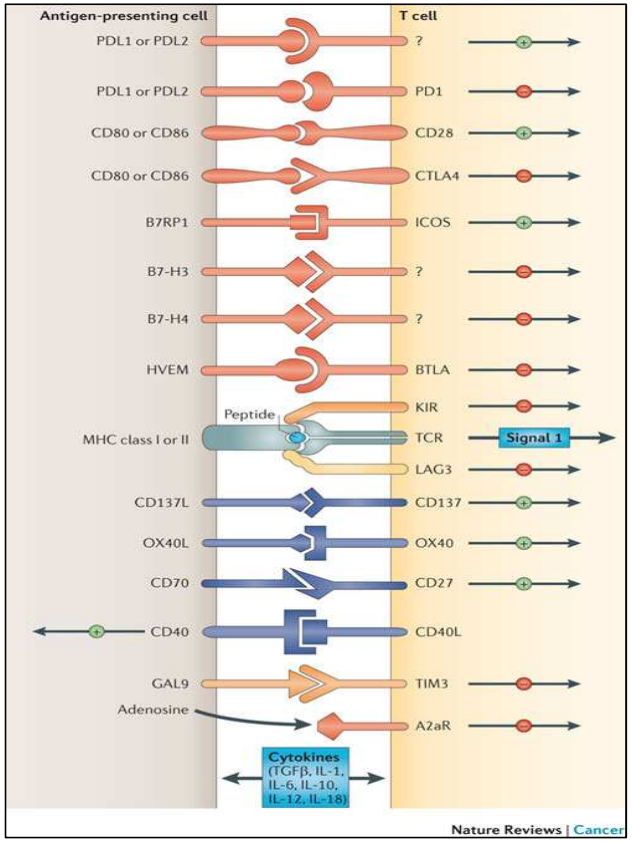
Ipilimumab ORR = 9%

Nivolumab ORR = 13-25%

Nivo/Ipi RR > Nivo RR + Ipi RR

Hammers H, et al. ASCO 2015. Abstract 4516.

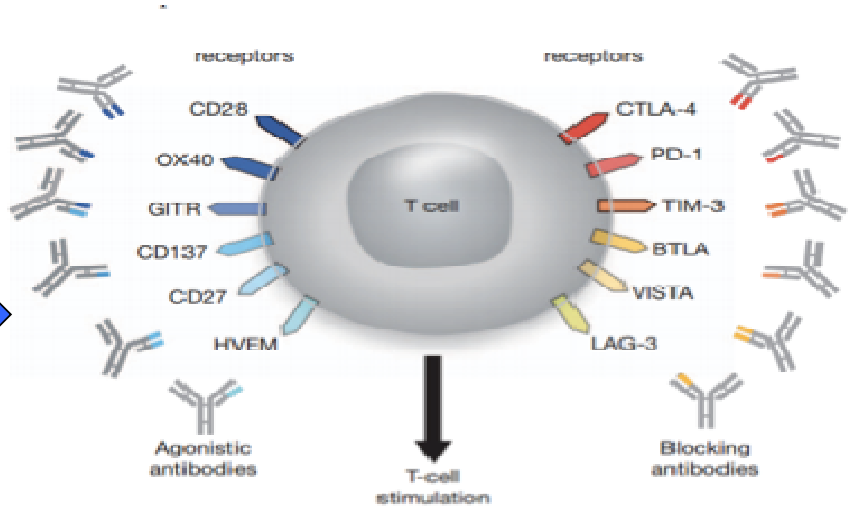
Immune Checkpoints Regulate Strength and Type of Anti-Tumor Immune Response



Pardoll, Nat Rev Cancer 2012

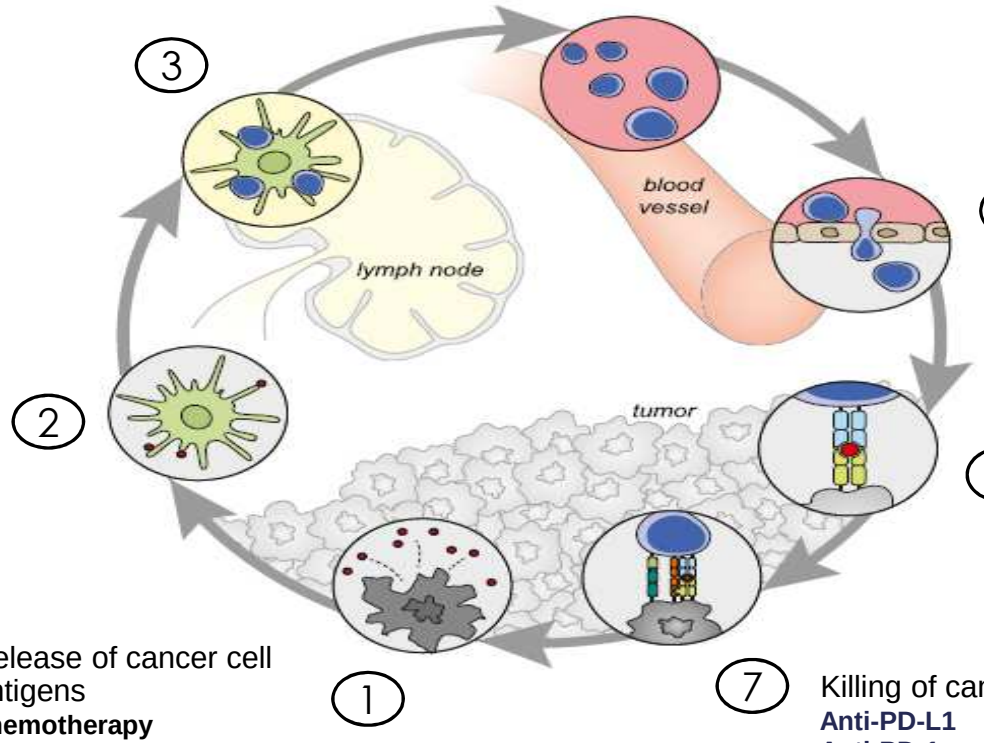
Science

Business



Fink Z, Prop Think, Dec 2014

A Roadmap of Immunotherapy- Tumor Interactions



4 Trafficking of T cells to tumors

Priming and activation
Anti-CTLA4
Anti-CD137 (agonist)
Anti-OX40 (agonist)
Anti-CD27 (agonist)
IL-2
IL-12

5 Infiltration of T cells into tumors
Anti-VEGF

Cancer antigen presentation
Vaccines
IFN-α
GM-CSF
Anti-CD40 (agonist)
TLR agonists

6 Recognition of cancer cells by T cells
CAR Ts

Release of cancer cell antigens
Chemotherapy
Radiation therapy
Targeted therapy

7 Killing of cancer cells
Anti-PD-L1
Anti-PD-1
IDO inhibitors

Chen DS, et al. Immunity. 2013;39:1-10.

A4

Considerable research is still required to optimally apply novel immunotherapies

- Optimal treatment setting for a particular tumor
- Optimal combinations for particular tumors
- Integration with standard therapies
- Approach to patients with innately resistant (non-inflamed) tumors
- Treatment of anti-PD1 failures
- Role of the gut microbiome (toxicity and activity) and host immune polymorphisms
- Cost

Slide 46

A4 updated as previous focus on PD-1 pathway was not balanced

Author, 7/20/2014