UNIVERSITY OF IOWA
HOLDEN
COMPREHENSIVE
CANCER CENTER
University of Iowa Health Care

Immunotherapy, an exciting era!!

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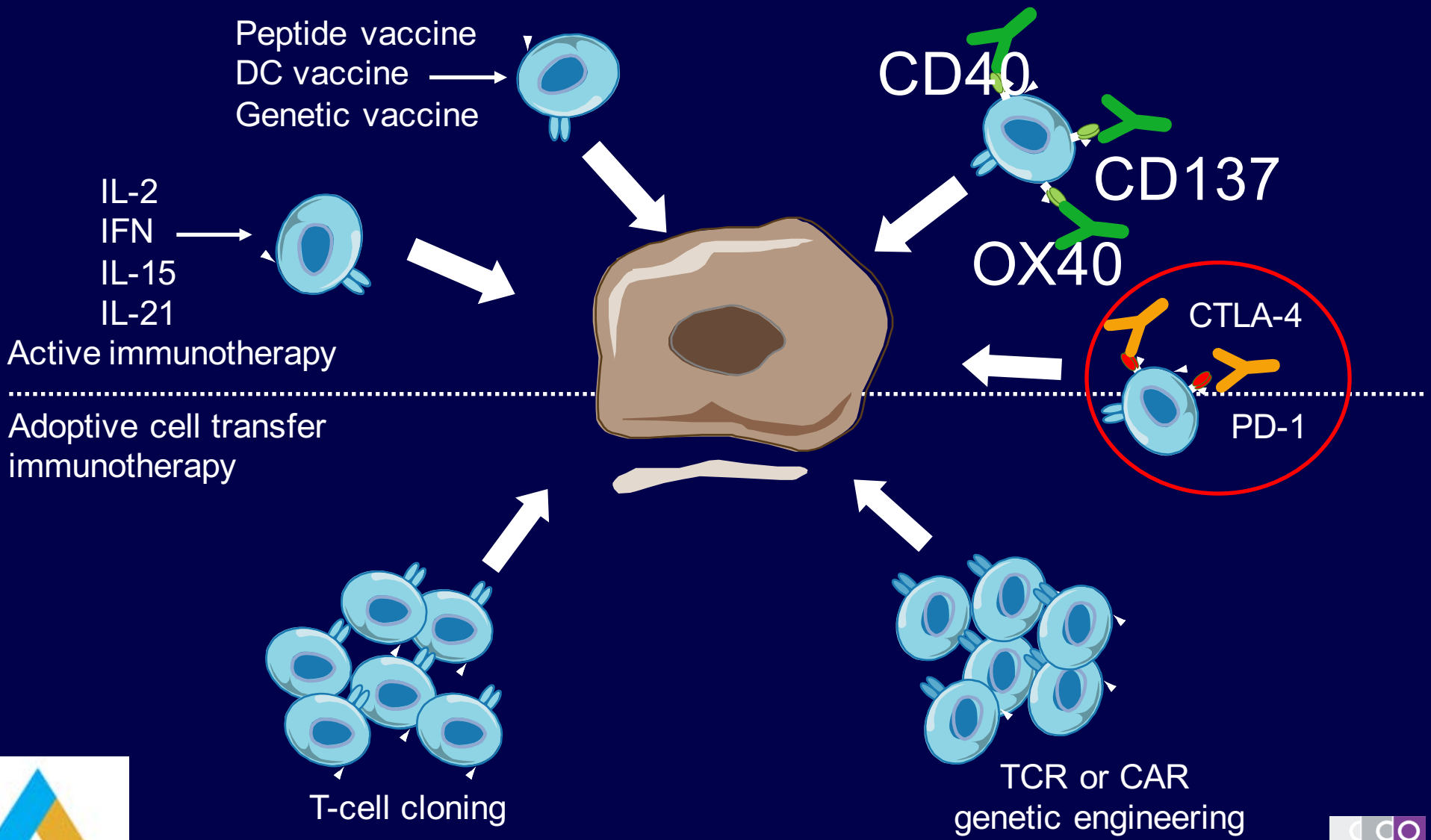
University of Iowa and Holden Comprehensive Cancer Center

Alliance Meeting, Chicago November 2016

Presentation Objectives

- General approach to immunotherapy
- Learn pathophysiology of checkpoint inhibitors.
- Review the landmark trials that lead to FDA approvals.

General Approaches for Cancer Immunotherapy

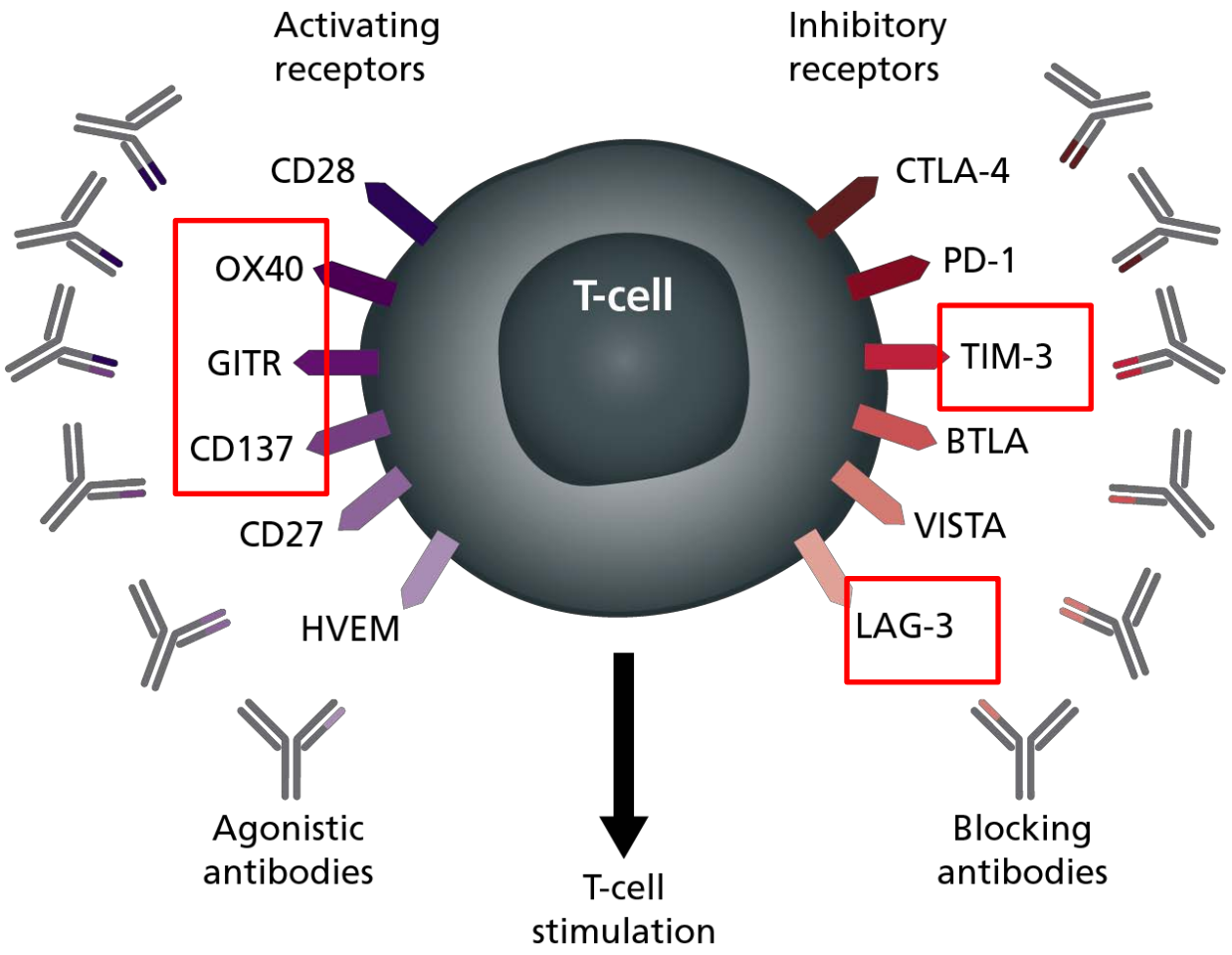


Slide credit: clinicaloptions.com

Immune Modulatory Receptors

Turning Up The Activating

Blocking the Inhibiting



Activating

Inhibiting

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

Mechanisms of Immune System Evasion/Suppression by Tumors

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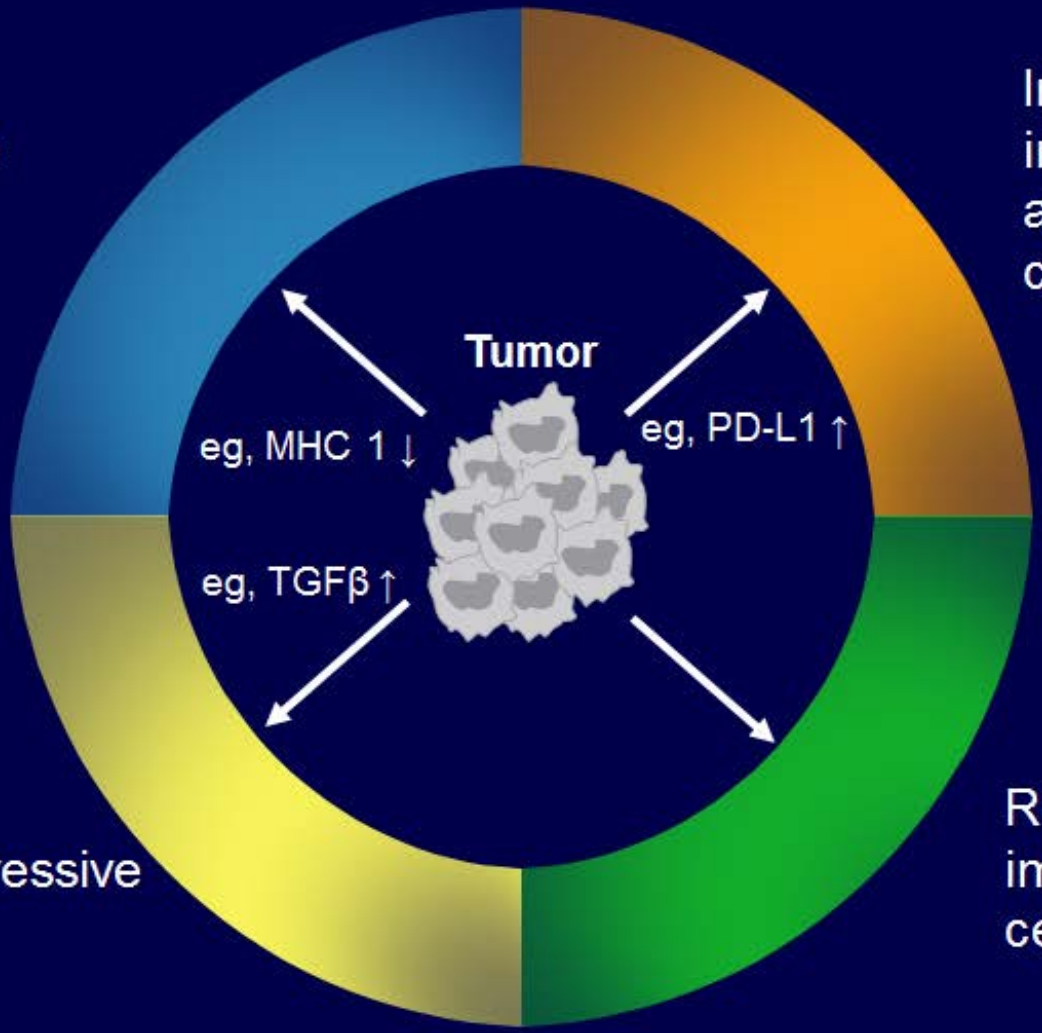
Inhibition of tumor antigen presentation

Inhibition of immune cell attack through checkpoint proteins



Secretion of immunosuppressive factors

Recruiting of immunosuppressive cells (Treg, MDSC)

Drake CG, et al. Adv Immunol. 2006;90:51-81.
Vesely MD, et al. Annu Rev Immunol. 2011;29:235-271.

Historical Overview of Development of Immunotherapy Approaches in Melanoma

1970

- Autologous and allogeneic tumor cell cancer vaccines
- Intratumoral Bacillus Calmette-Guérin

1980

- IFN-α
- IL-2
- IL-2 and LAK cells
- Other cytokines (TNF, IFNγ)
- IL-2 and TILs

1990

- Gene-transfected tumor cell vaccines
- Defined antigen vaccines, viral vectors, and DCs

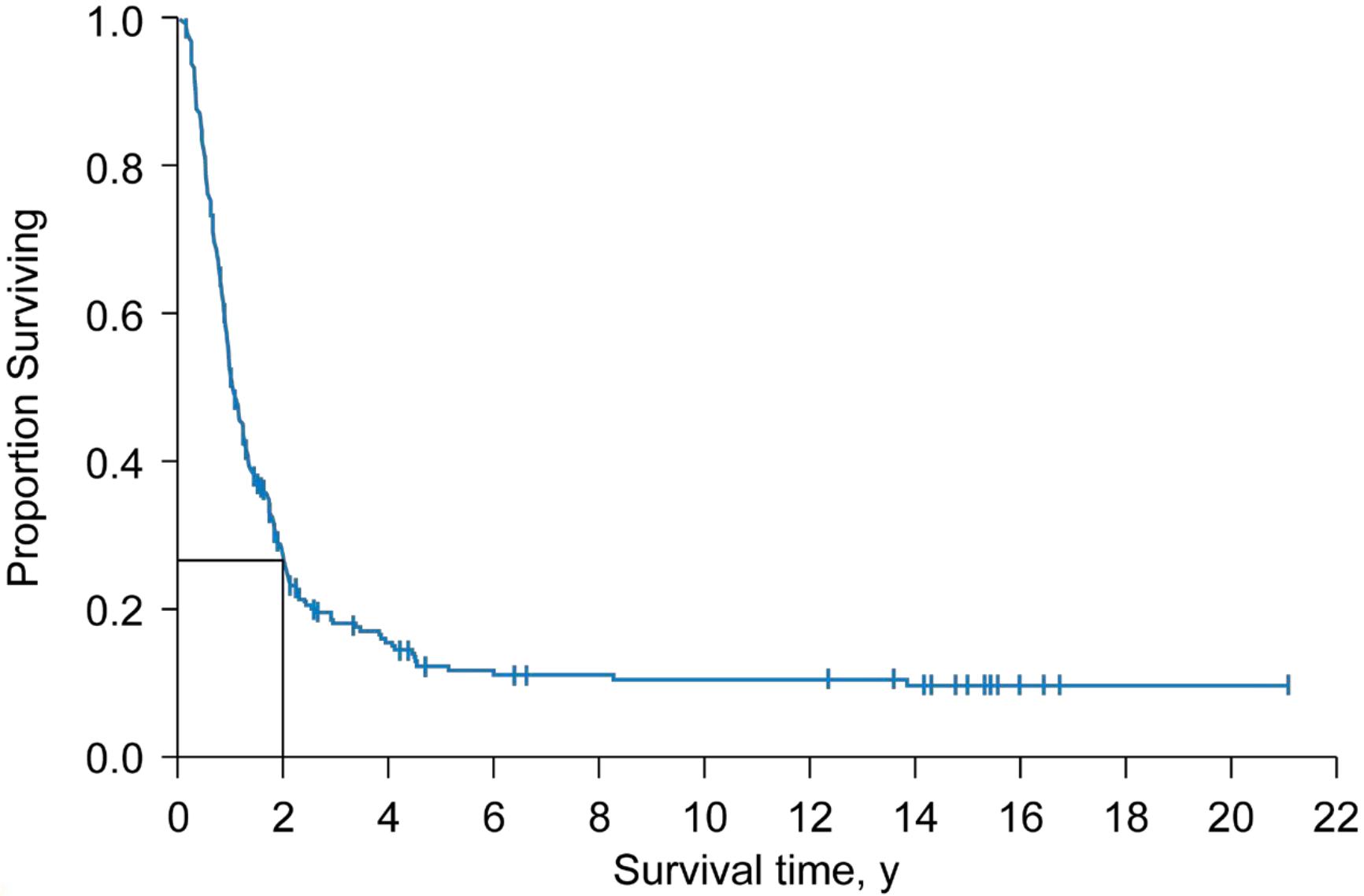
2000

- Blockade of T-cell activation checkpoints (CTLA-4)
- Lymphocyte ablation + TIL
- T-cell and DC co-stimulatory antibodies
- Blockade of tumor immune suppressive mechanisms (PD-1)
- Gene (CAR, TCR, cytokine) modified lymphocytes for adoptive cell transfer

2011

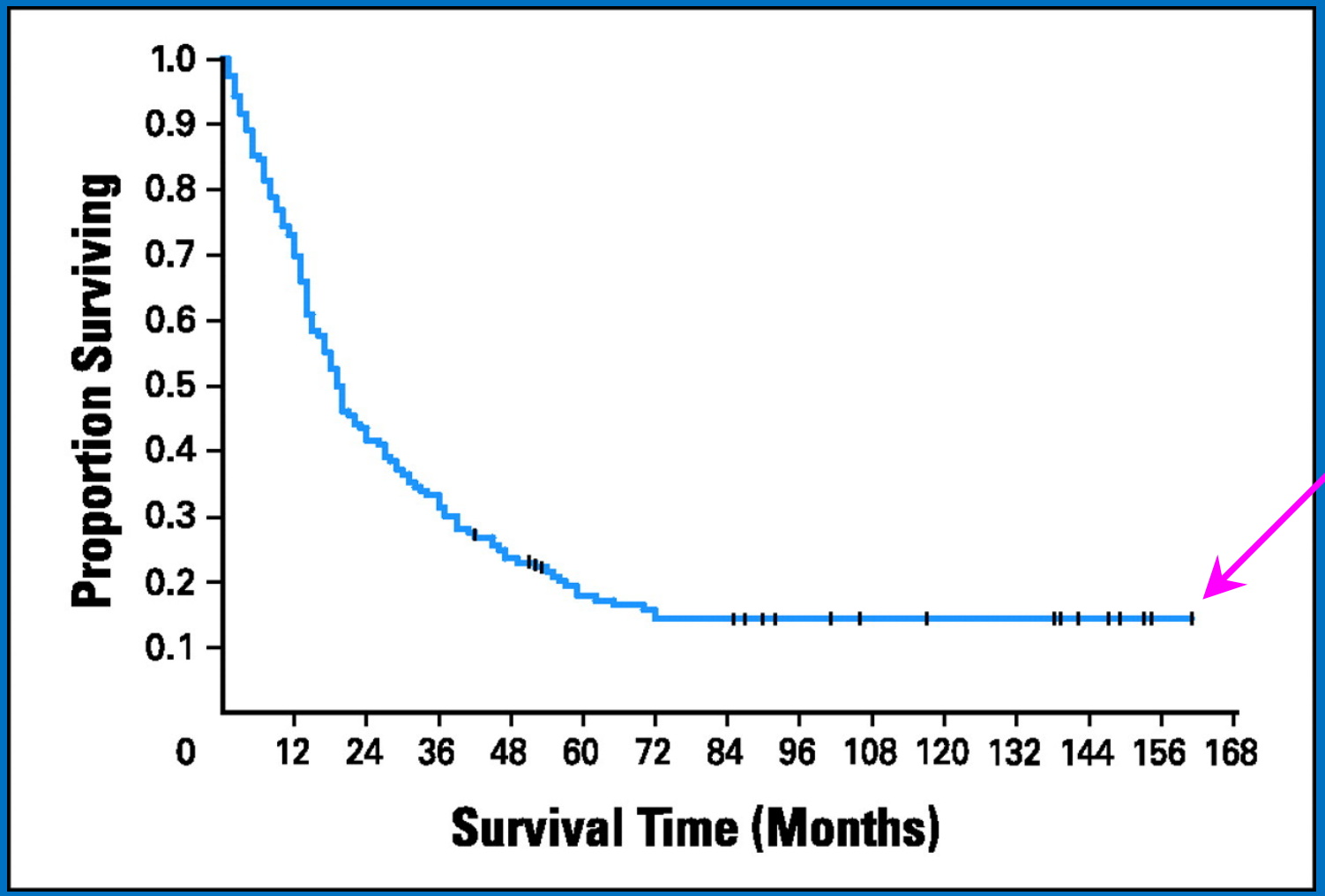
- Combination of immune checkpoint inhibitors (CTLA-4, PD-1)

Surgery Branch, NCI: Overall Survival With High Dose IL-2



1. Smith FO et al. *Clin Cancer Res*. 2008;14(17):5610-5618.

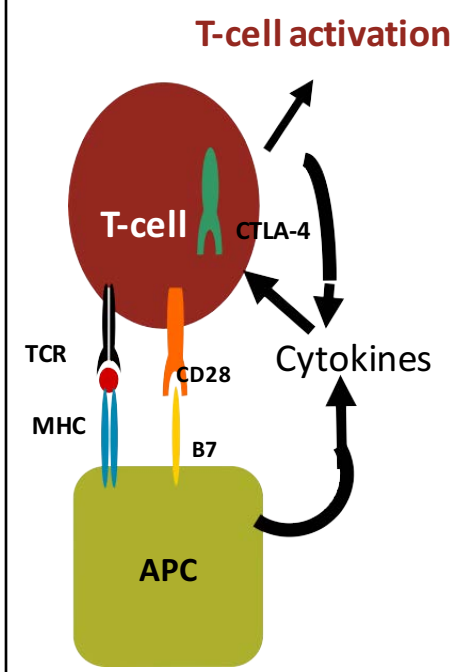
Survival of 156 patients with metastatic renal cell cancer randomly assigned to receive high-dose bolus interleukin-2



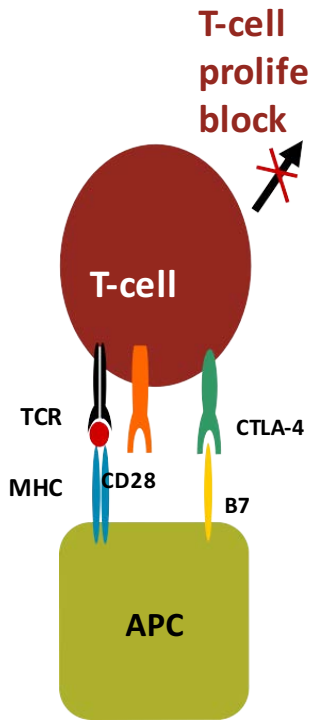
Yang, J. C. et al. J Clin Oncol; 24:5576-5583 2006

T-Cell Activation, Proliferation, and Function Is Controlled by Multiple Agonist and Antagonist Signals

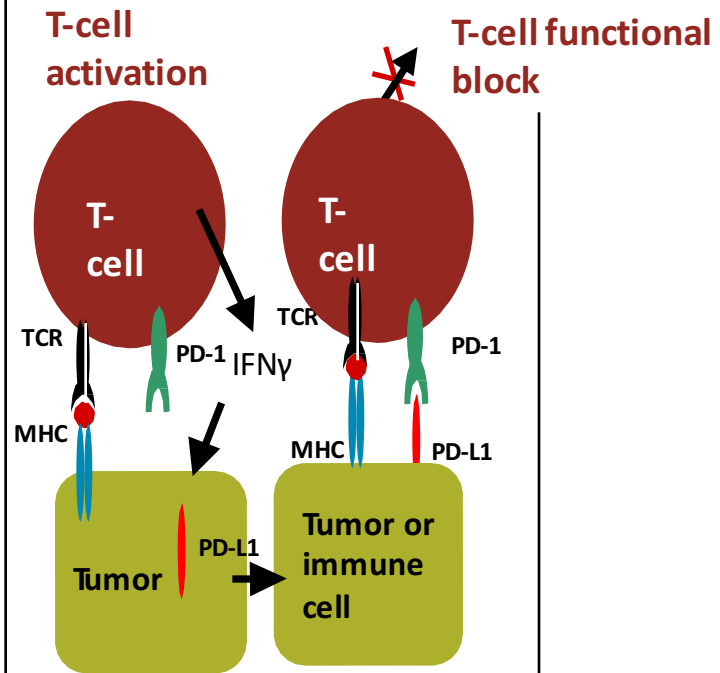
1. Co-stimulation via CD28 ligation transduces T-cell activating signals



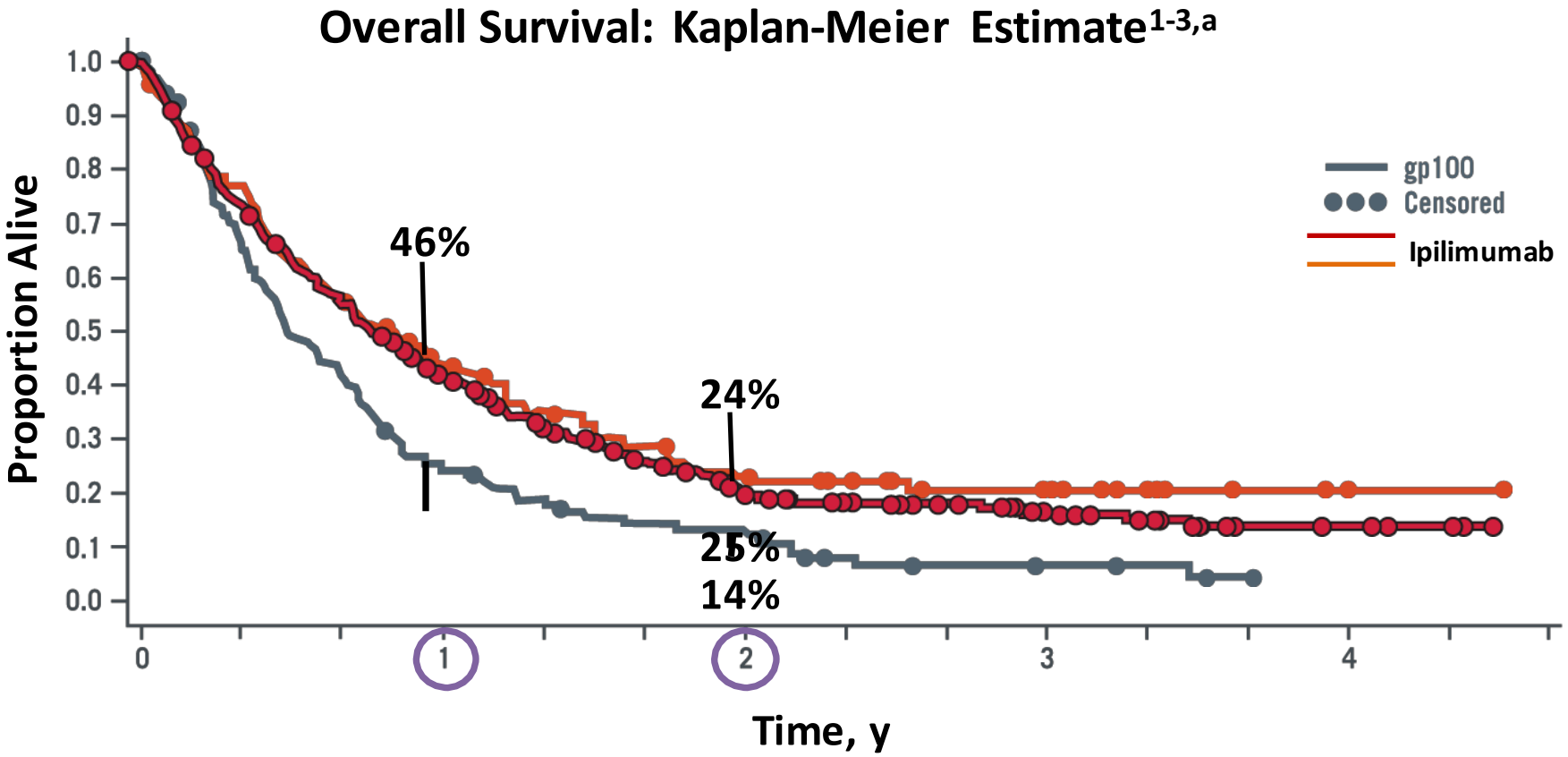
2. CTLA-4 ligation on activated T-cells down-regulates T-cell responses



3. T-cell function in tissue is subject to feedback inhibition



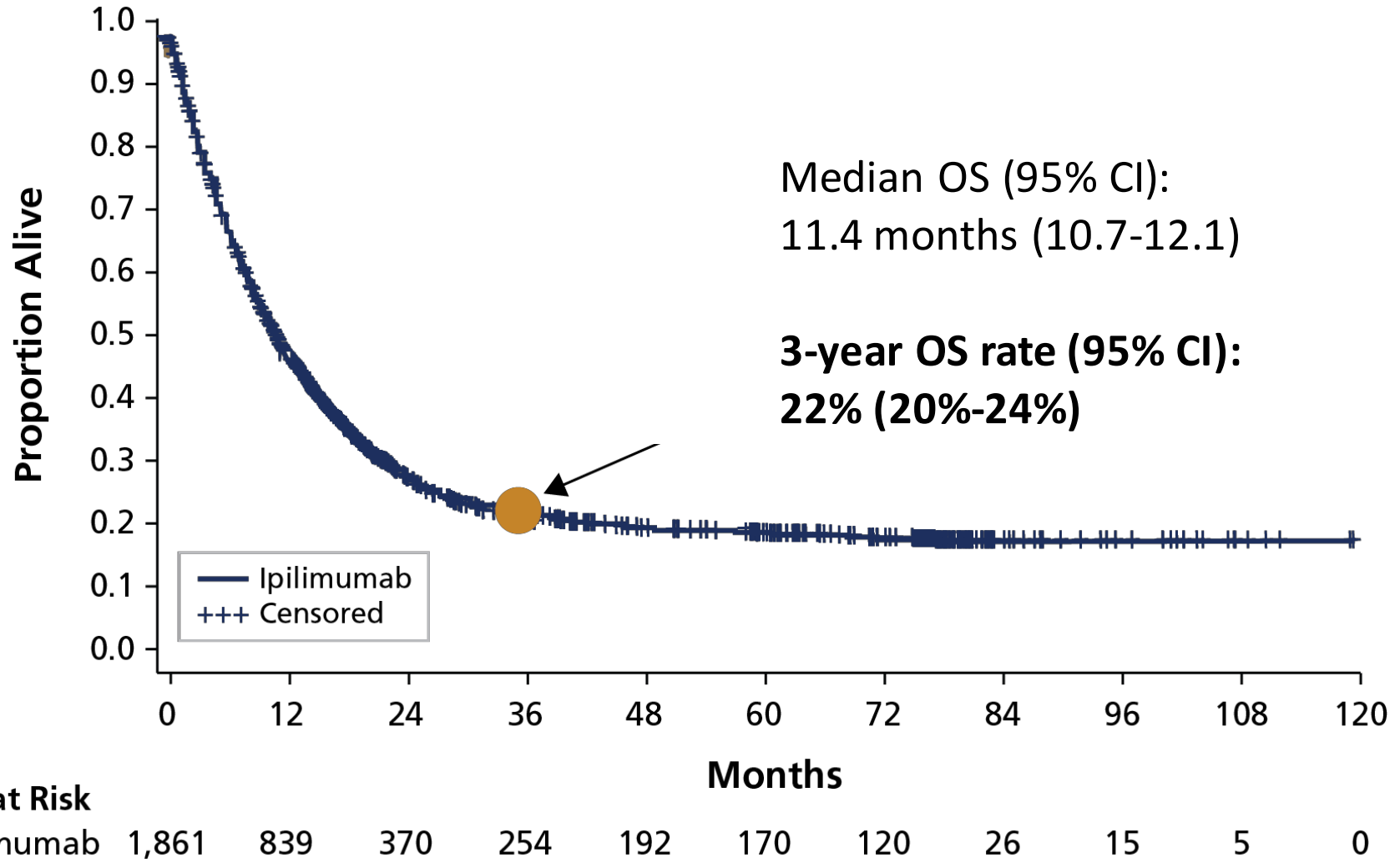
The CTLA-4 Experience: Ipilimumab in Melanoma[1]



[a] Estimated overall survival rates as in the pivotal phase 3 study publication.[2]

1. Yervoy (ipilimumab) [package insert]. http://packageinserts.bms.com/pi/pi_yervoy.pdf.
2. Hodi FS et al. *N Engl J Med*. 2010;363:711-723.
3. Wolchok JD et al. *Cancer Immun*. 2010;10:9.

The CTLA-4 Experience: Primary Analysis of Pooled OS Data on Ipilimumab in 1,861 Patients[1]



Median OS (95% CI):
11.4 months (10.7-12.1)

3-year OS rate (95% CI):
22% (20%-24%)

1. Schadendorf D et al. European Cancer Congress 2013 (ESMO 2013). Abstract 24.

Targeting PD-1 in Melanoma: KEYNOTE-006 International, Randomized, Phase 3 Study[1]

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Patients

- Unresectable, stage 3 or 4 melanoma
- ≤1 prior therapy, excluding anti–CTLA-4, PD-1, or PD-L1 agents
- Known *BRAF* status[a]
- ECOG PS 0-1
- No active brain metastases
- No serious autoimmune disease

R
1:1:1

- **Pembrolizumab** 10 mg/kg IV Q2W
- **Pembrolizumab** 10 mg/kg IV Q3W
- **Ipilimumab** 3 mg/kg IV Q3W x 4 doses

Stratification factors:

- ECOG PS (0 vs 1)
- Line of therapy (first vs second)
- PD-L1 status (positive[b] vs negative)

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

[a] Prior anti-*BRAF* targeted therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.

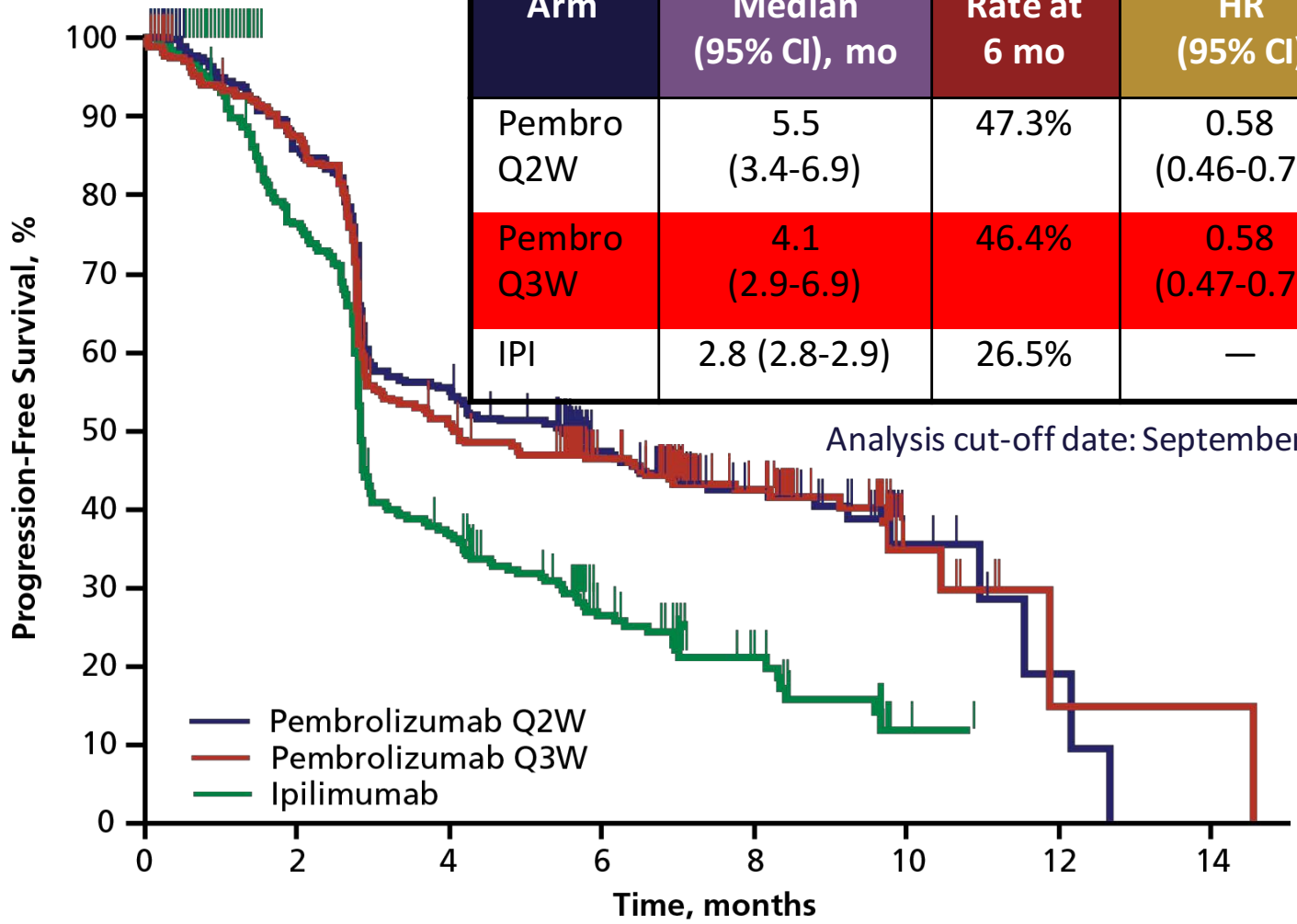
[b] Defined as membranous PD-L1 expression in ≥1% of tumor cells as assessed by IHC using the 22C3 antibody.

1. Robert C et al. *N Engl J Med*. 2015;372:2521-2532.

First Interim Analysis: PFS[1]

Arm	Median (95% CI), mo	Rate at 6 mo	HR (95% CI)	*P*
Pembro Q2W	5.5 (3.4-6.9)	47.3%	0.58 (0.46-0.72)	< .0001
Pembro Q3W	4.1 (2.9-6.9)	46.4%	0.58 (0.47-0.72)	< .0001
IPI	2.8 (2.8-2.9)	26.5%	—	—

Analysis cut-off date: September 3, 2014.



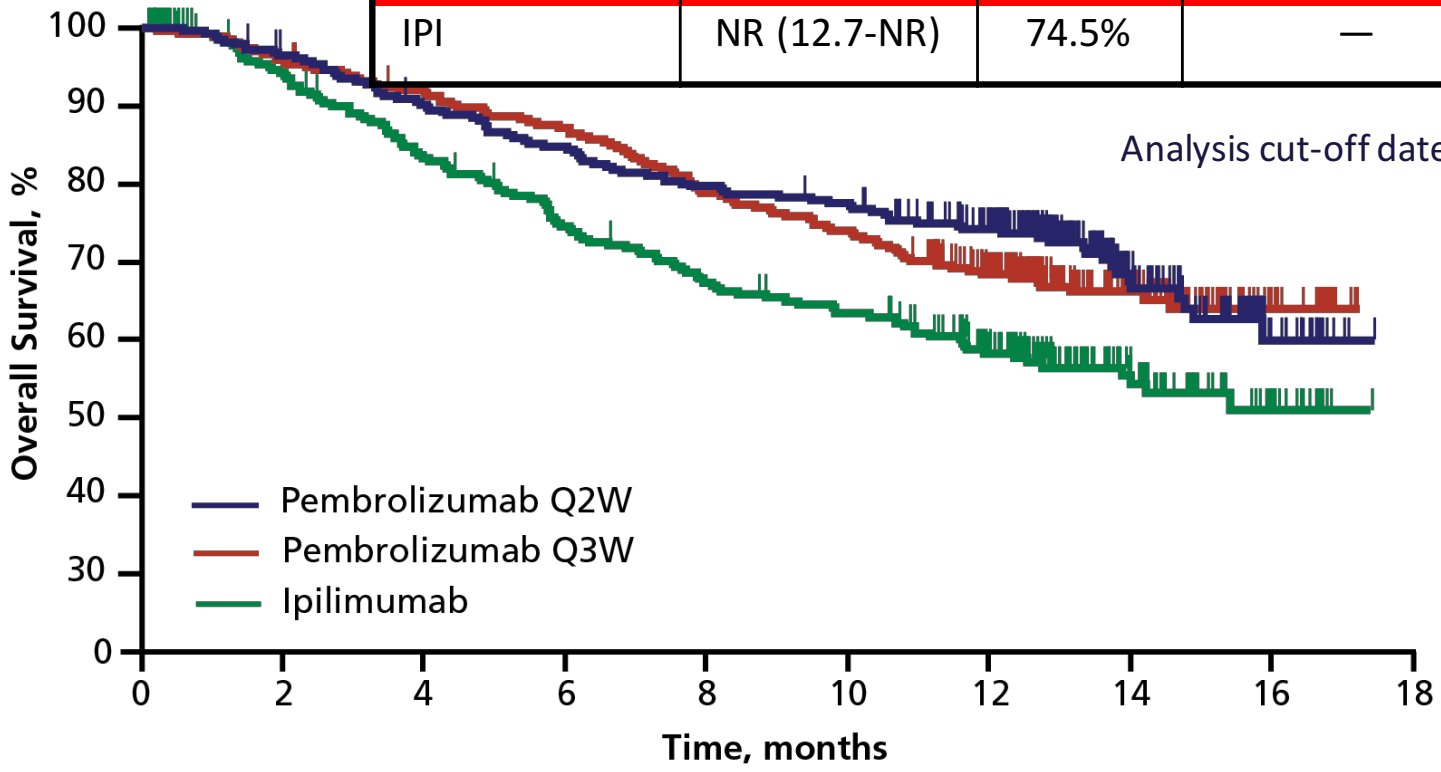
No. at risk								
Pembrolizumab Q2W	279	231	147	98	49	7	2	0
Pembrolizumab Q3W	277	235	133	95	53	7	1	1
Ipilimumab	278	186	88	42	18	2	0	0

1. Robert C et al. *N Engl J Med*. 2015;372:2521-2532.

Second Interim Analysis: OS[1]

Arm	Median (95% CI), mo	Rate at 6 mo	HR (95% CI)	*P*
Pembro Q2W	NR (NR-NR)	84.8%	0.63 (0.47-0.83)	.00052
Pembro Q3W	NR (NR-NR)	87.8%	0.69 (0.52-0.90)	.00358
IPI	NR (12.7-NR)	74.5%	—	—

Analysis cut-off date: March 3, 2015.



No. at risk										
Pembrolizumab Q2W	279	266	248	233	219	212	177	67	19	0
Pembrolizumab Q3W	277	266	251	238	215	202	158	71	18	0
Ipilimumab	278	242	212	188	169	157	117	51	17	0

1. Robert C et al. *N Engl J Med*. 2015;372:2521-2532.

Response Rate Was Superior With Pembrolizumab Over Ipilimumab In the Total Population (RECIST v1.1, Central Review)

	Pembrolizumab n = 556	Ipilimumab n = 278
ORR (95% CI)	36% (32-40)	13% (9-18)
Best overall response		
Complete response (CR)	9%	3%
Partial response	27%	10%
Stable disease	11%	15%
NonCR/nonPD[a]	5%	4%
Progressive disease (PD)	40%	49%
Not evaluable[b]	6%	18%
No assessment[c]	2%	<1%
Ongoing responses[d]	81%	81%
Median duration of response (range), days	NR (41 – 429+)	NR (33+ – 418+)

[a]Patients without measurable disease per central review at baseline who did not experience complete response or disease progression.
[b]Patients for which target lesion was not captured by postbaseline scans or for whom a target lesion was surgically removed.
[c]Patients for which no postbaseline scan was performed or those who were not able to be evaluated.
[d]In patients with objective response.
Schachter J, et al. Presented at: SMR Annual Meeting 2015; November 18-21, 2015; San Francisco, CA.
Analysis cut-off date: March 3, 2015.

Response Rate Was Superior With Pembrolizumab Over Ipilimumab In the Total Population (RECIST v1.1, Central Review)

	Pembrolizumab n = 556	Ipilimumab n = 278
ORR (95% CI)	36% (32-40)	13% (9-18)

P = 0.00003 for combined pembrolizumab arms vs ipilimumab

Partial response	27%	10%
Stable disease	11%	15%
NonCR/nonPD[a]	5%	4%
Progressive disease (PD)	40%	49%
Not evaluable[b]	6%	18%
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[a]Patients without measurable disease per central review at baseline who did not experience complete response or disease progression.
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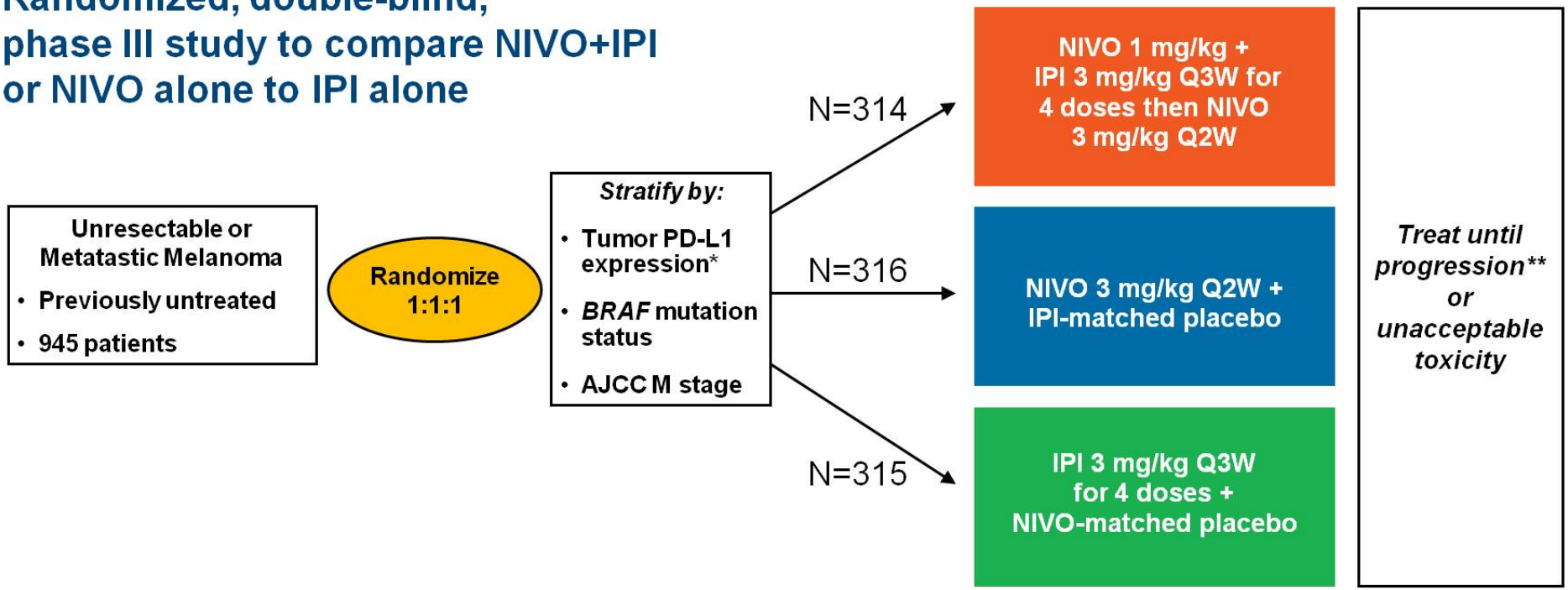
[d]In patients with objective response.
Schachter J, et al. Presented at: SMR Annual Meeting 2015; November 18-21, 2015; San Francisco, CA.
Analysis cut-off date: March 3, 2015.

CA209-067: Study Design

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone



*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

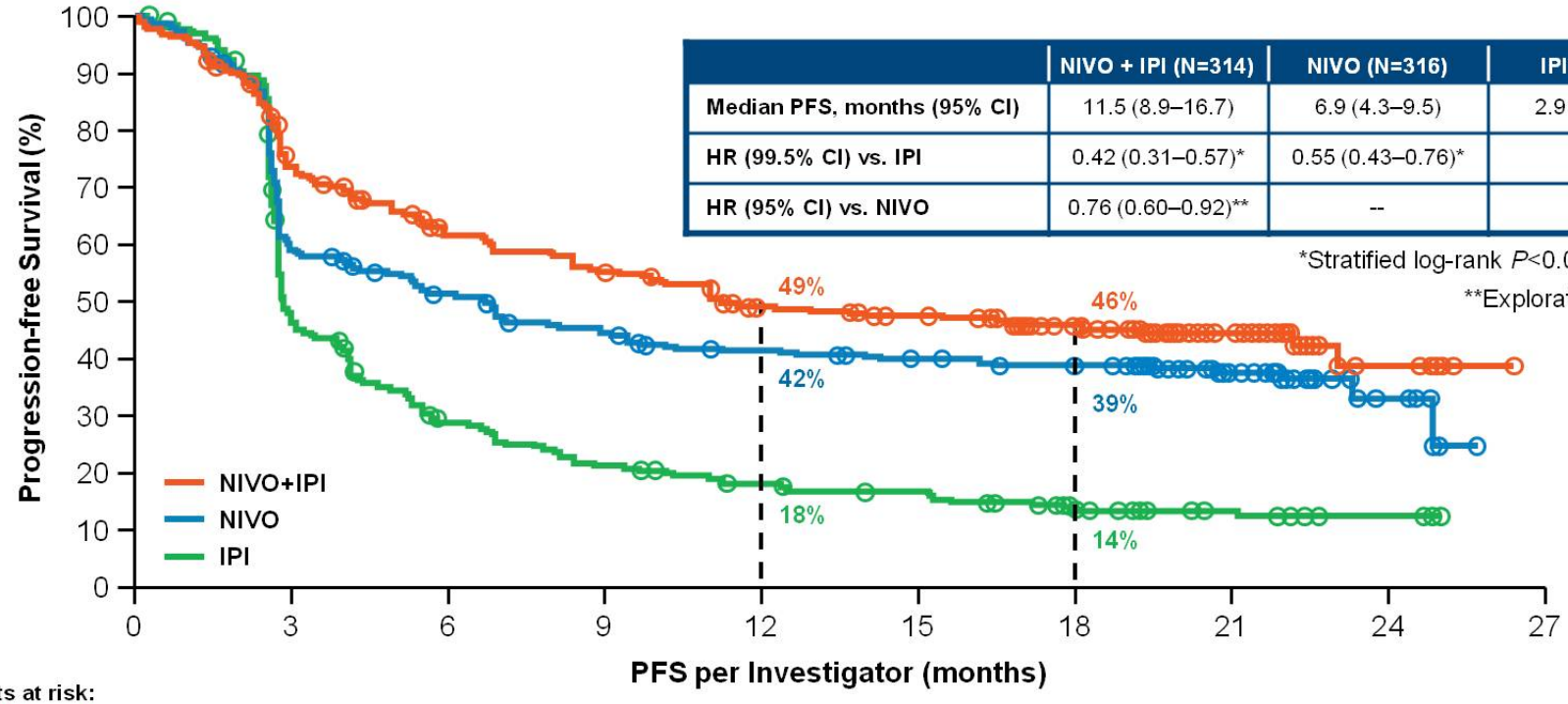
**Patients could have been treated beyond progression under protocol-defined circumstances.

Progression-Free Survival (Intent-to-Treat Population)

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.55 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.76 (0.60–0.92)**	--	--

*Stratified log-rank $P<0.00001$ vs. IPI

**Exploratory endpoint



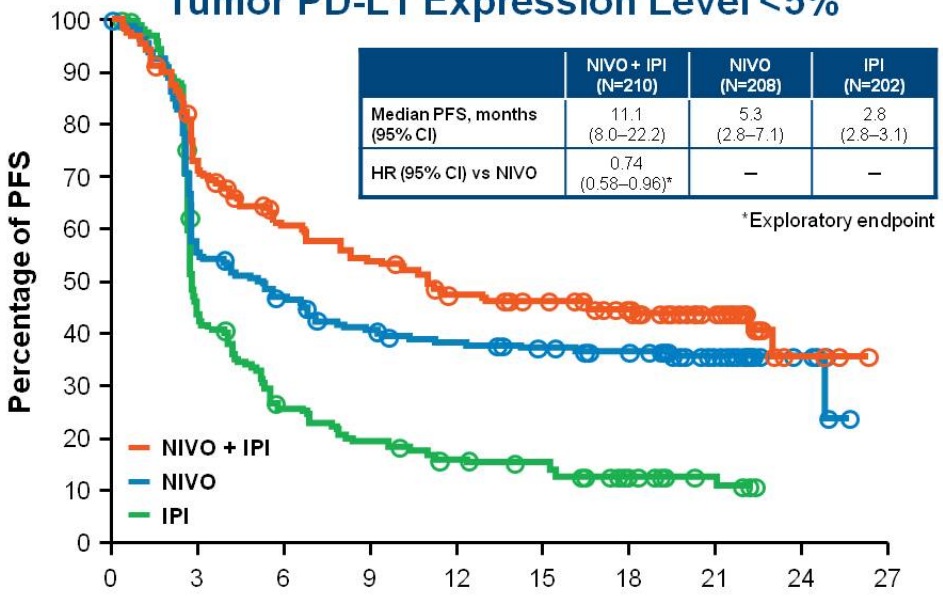
Number of patients at risk:

Nivolumab + Ipilimumab	314	219	174	156	133	126	103	48	8	0
Nivolumab	316	177	148	127	114	104	94	46	8	0
Ipilimumab	315	137	78	58	46	40	25	15	3	0

Database lock Nov 2015

Progression-free Survival by Tumor PD-L1 Expression

Tumor PD-L1 Expression Level <5%

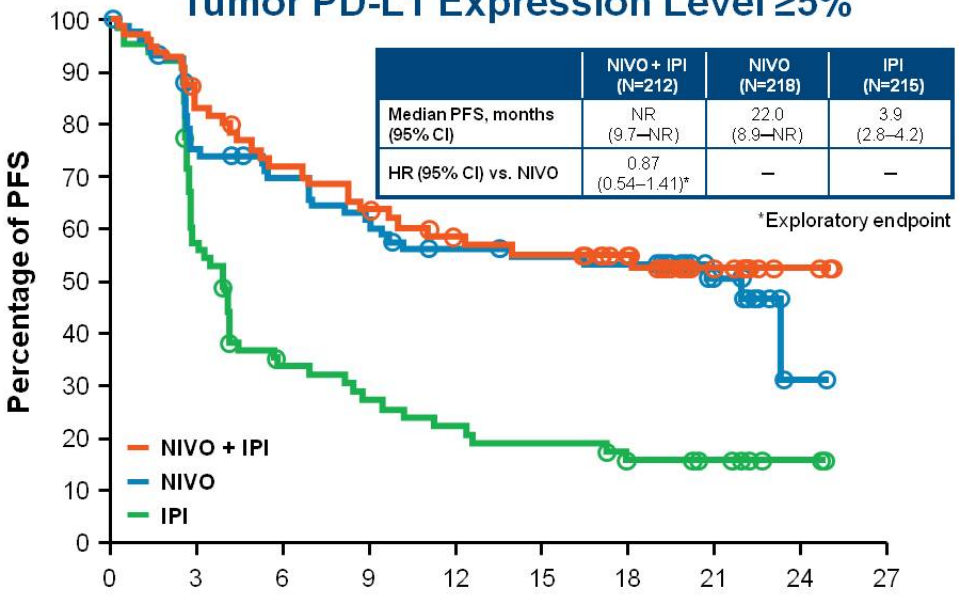


	NIVO + IPI (N=210)	NIVO (N=208)	IPI (N=202)
Median PFS, months (95% CI)	11.1 (8.0–22.2)	5.3 (2.8–7.1)	2.8 (2.8–3.1)
HR (95% CI) vs NIVO	0.74 (0.58–0.96)*	–	–

*Exploratory endpoint

Number of patients at risk:										
NIVO + IPI	210	142	113	101	86	81	69	31	5	0
NIVO	208	108	89	75	69	62	55	29	7	0
IPI	202	82	45	34	26	22	12	7	0	0

Tumor PD-L1 Expression Level ≥5%



	NIVO + IPI (N=212)	NIVO (N=218)	IPI (N=215)
Median PFS, months (95% CI)	NR (9.7–NR)	22.0 (8.9–NR)	3.9 (2.8–4.2)
HR (95% CI) vs. NIVO	0.87 (0.54–1.41)*	–	–

*Exploratory endpoint

Number of patients at risk:										
NIVO + IPI	68	53	44	39	33	31	22	13	3	0
NIVO	80	57	51	45	39	37	36	16	1	0
IPI	75	40	21	17	14	12	8	6	2	0

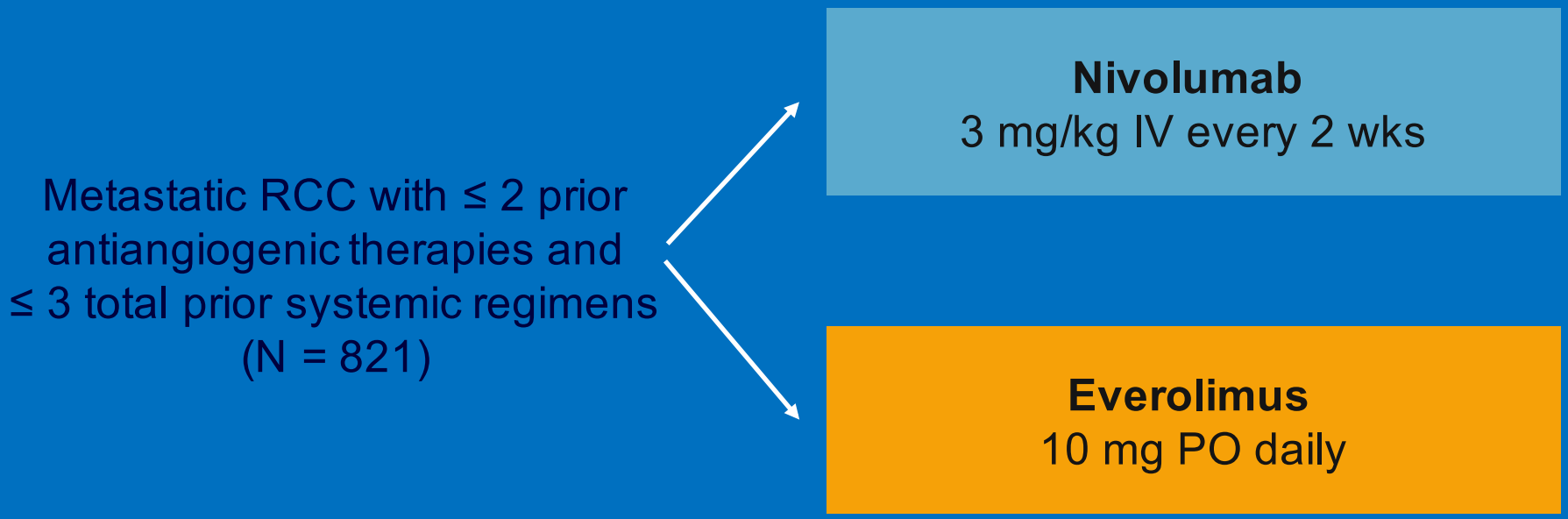
- For the original PD-L1 PFS analysis, the descriptive hazard ratio comparing NIVO+IPI vs NIVO was 0.96, with a similar median PFS in both groups (14 months)

Database lock Nov 2015

Current FDA approved SOC in melanoma

- Ipilimumab + Nivolumab
- Pembrolizumab
- Nivolumab

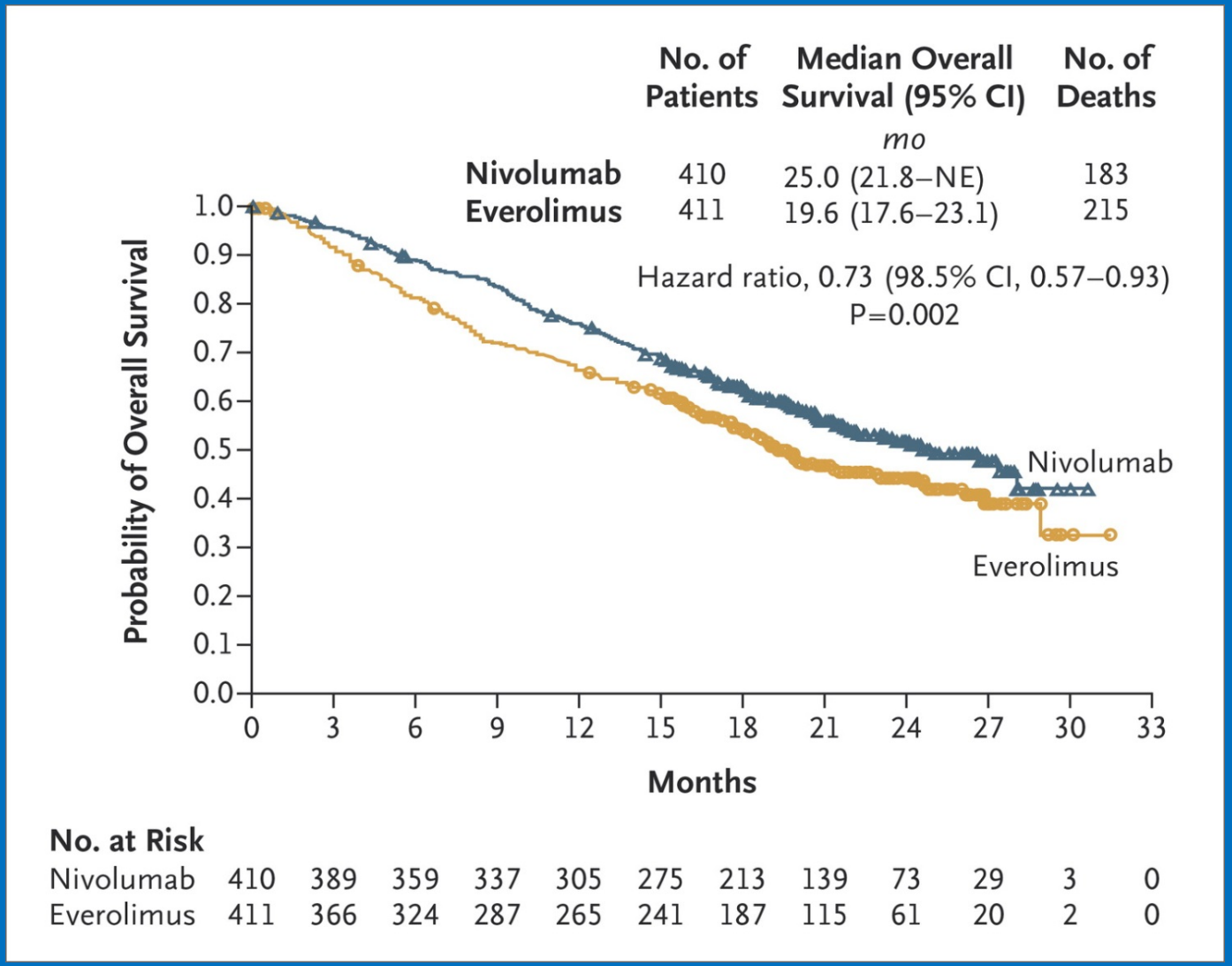
CheckMate-025: Nivolumab in Previously Treated Metastatic RCC



- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, OR duration, Safety

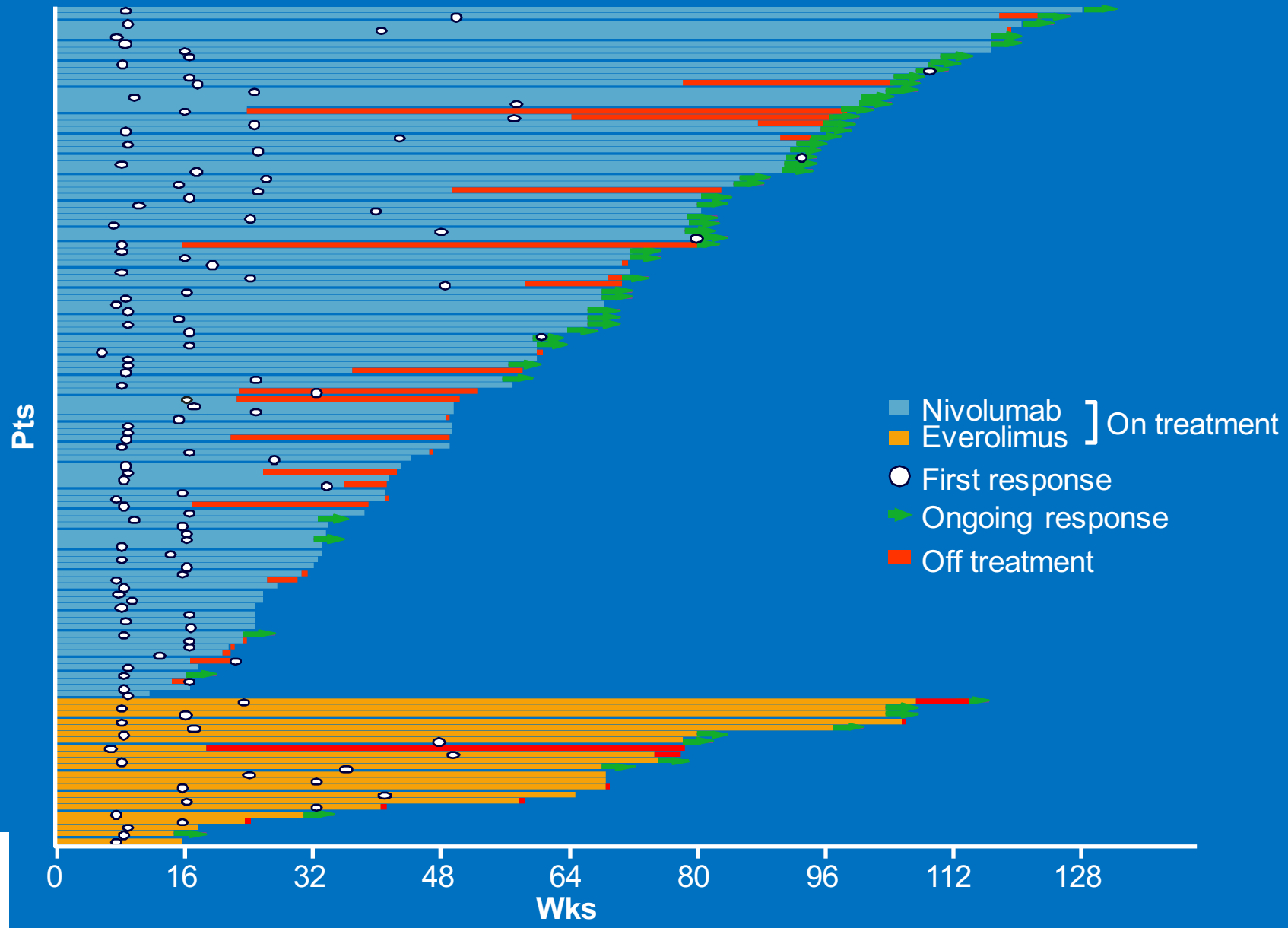
Motzer R, et al. N Engl J Med. 2015;373:1803-1813.

Kaplan–Meier Curve for Overall Survival.



Motzer RJ et al. N Engl J Med 2015;373:1803-1813.

CheckMate-025: Response Characteristics

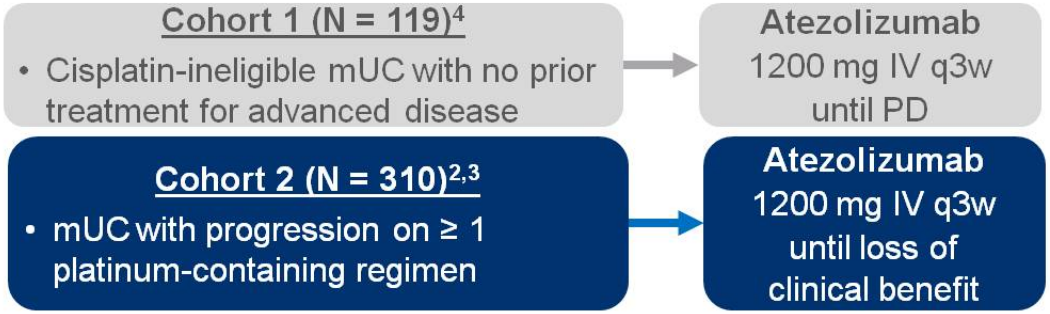


Motzer R, et al. N Engl J Med. 2015;373:1803-1813.

Nivolumab is FDA approved for second line metastatic RCC

IMvigor210 and biomarkers of Atezolizumab in mUC

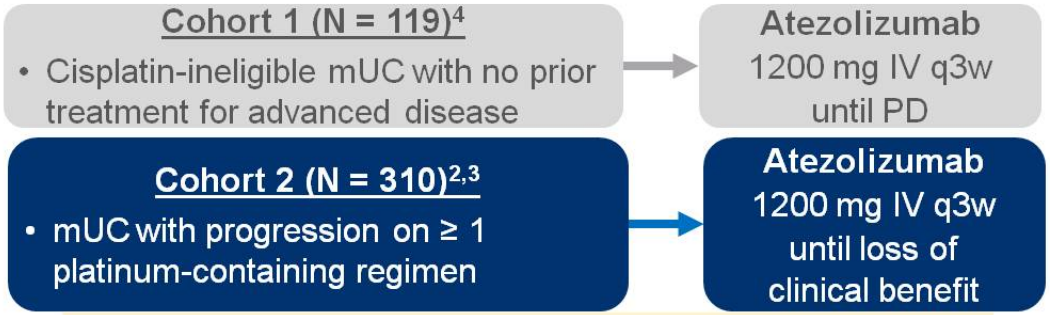
- Atezolizumab (anti-PDL1), the first FDA-approved PD-L1 inhibitor,[1] has demonstrated efficacy in mUC,[2,3] a disease with high unmet need



Effector T cell, T_{eff}; PD-L1, programmed death-ligand 1. 1. Press release: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm501762.htm. Trial ID: NCT02108652. 2. Rosenberg *Lancet* 2016. 3. Dreicer ASCO [abstract 4515]. 4. Balar ASCO [abstract LBA4500].

IMvigor210 and biomarkers of Atezolizumab in mUC

- Atezolizumab (anti-PDL1), the first FDA-approved PD-L1 inhibitor,[1] has demonstrated efficacy in mUC,[2,3] a disease with high unmet need
- Clinical benefit with cancer immunotherapy may be associated with biomarkers such as T_{eff} genes and mutation load[5-7]



Co-primary endpoints (cohort 2):
ORR per confirmed RECIST v1.1 by central review and per immune-modified RECIST by investigator

Key secondary endpoints: DOR, PFS, OS, safety

Effector T cell, T_{eff}; PD-L1, programmed death-ligand 1. 1. Press release: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm501762.htm. Trial ID: NCT02108652. 2. Rosenberg *Lancet* 2016. 3. Dreicer ASCO [abstract 4515]. 4. Balar ASCO [abstract LBA4500]. 5. Rizvi *Science* 2015. 6. Van Allen *Science* 2015. 7. Peng *Nature* 2015.

IMvigor210: Baseline Characteristics

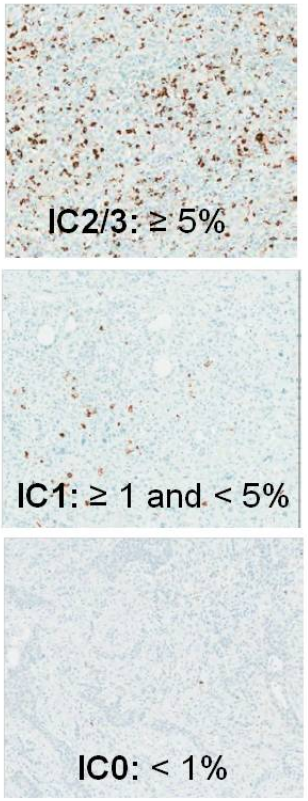
Characteristic	All Pts (N = 310)
Age, yrs (range)	66 (32-91)
Male, %	78
White race, %	91
No previous tobacco use, %	35
ECOG PS 0/1, %	38/62
CrCl < 60 mL/min, %	36
Hg < 100 g/L, %	22
Site of primary tumor, % ▪Bladder or urethra/upper tract	82/16
No. of previous systemic regimens in the metastatic setting, % ▪0/1/2/3/≥ 4	19/40/21/13/8
Previous platinum-based regimen, % ▪Cisplatin/carboplatin/other	73/26/1

Rosenberg JE, et al. Lancet. 2016;387:1909-1920.

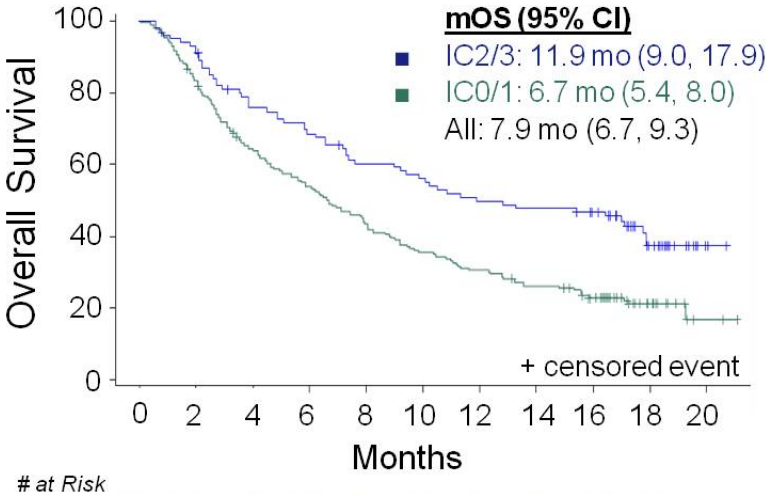
PD-L1 Expression on Immune Cells and Efficacy

- IMvigor210 samples were evenly distributed in PD-L1 IC expression (VENTANA SP142 IHC assay)
- Atezolizumab efficacy in cohort 2 was associated with PD-L1 on IC[2]
  - Responses occurred in all IC subgroups, but ORR increased with higher PD-L1 expression
  - Longer OS was observed with higher PD-L1 status

PD-L1 IHC[1]



PD-L1 Status	ORR (95% CI)
IC2/3 (n = 100)	28% (19, 38)
IC0/1 (n = 210)	10% (6, 15)
All (N = 310)	16% (12, 20)

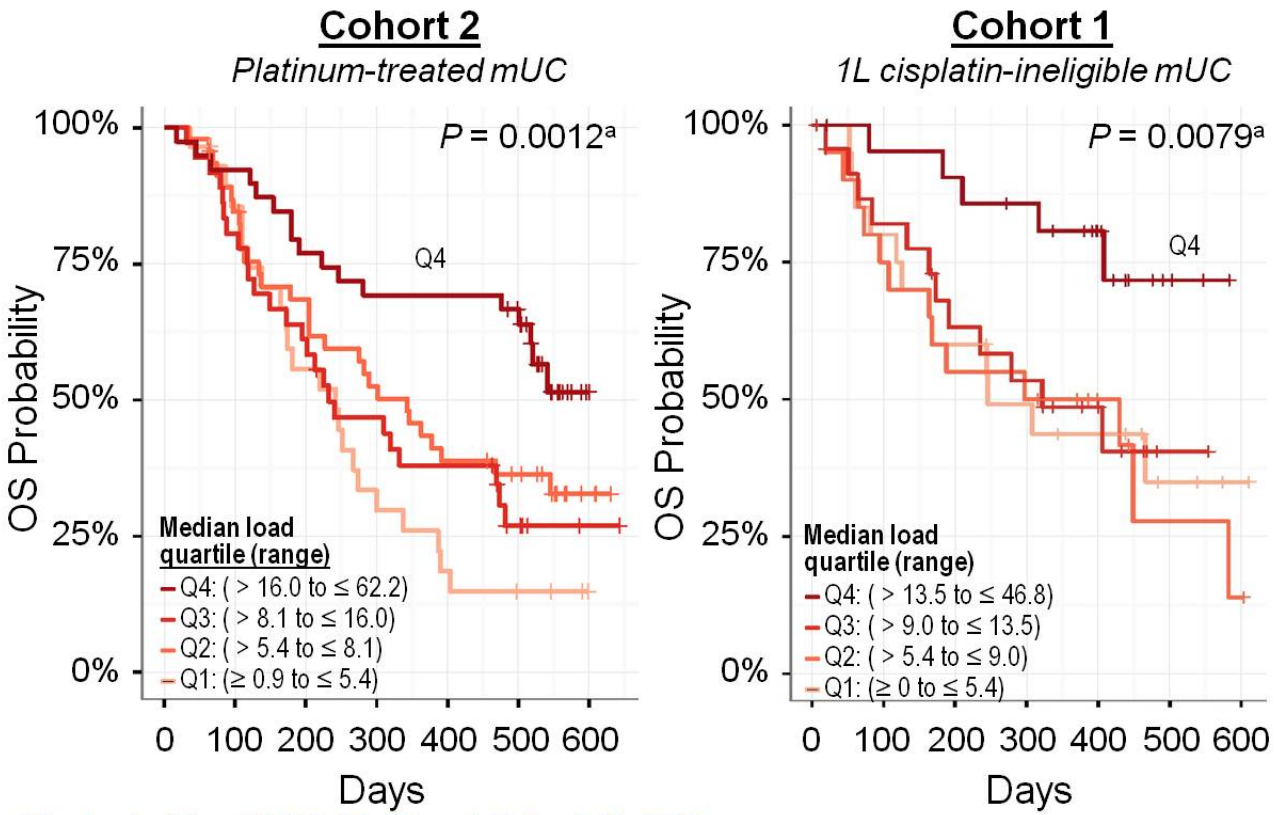


 # at Risk

IC2/3:	100	92	74	67	58	54	48	46	43	20	3
IC0/1:	210	173	129	109	88	72	62	51	39	15	2

IC, tumor-infiltrating immune cell. NE, not estimable. Data cutoff: March 14, 2016. Median follow up: 17.5 mo. 1. Rosenberg ECC 2015 [abstract 21LBA]. 2. Dreicer ASCO 2016 [abstract 4515].

Mutation Load by FoundationOne and Survival

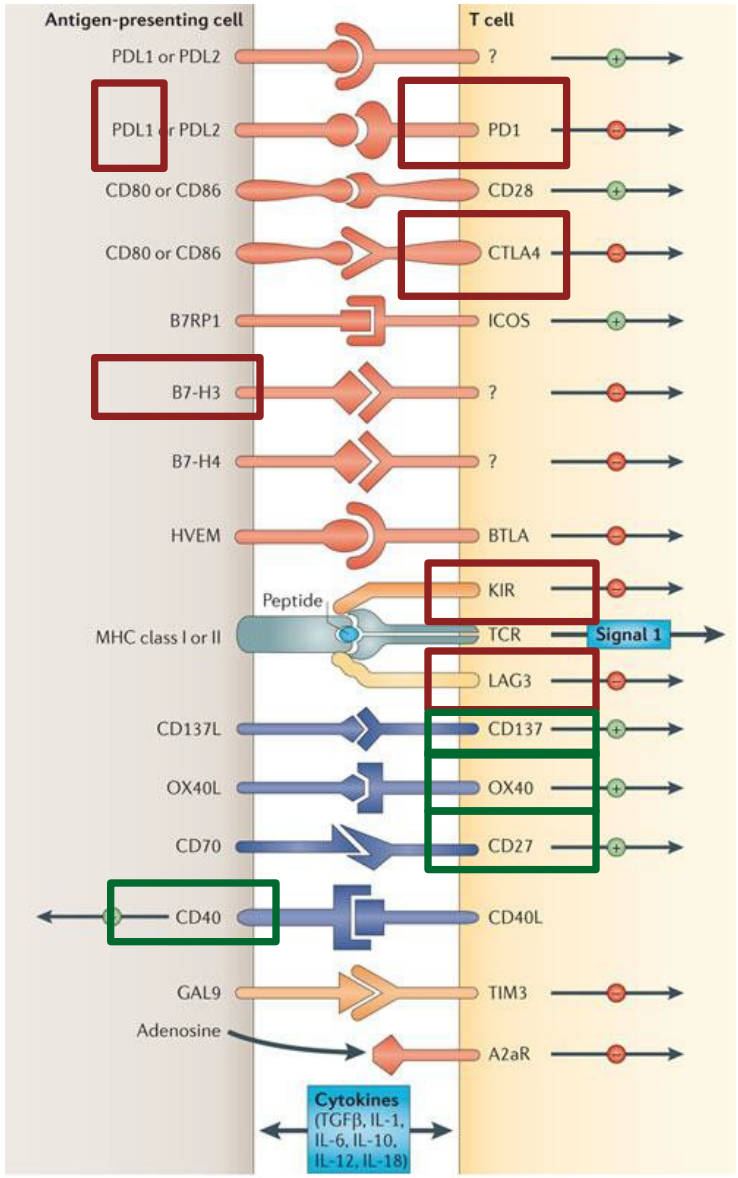


[a] *P* value for Q4 vs Q1, Q2, Q3. Data cutoff: March 14, 2016.

- Quartile-split mutation load was associated with OS in platinum-treated patients (cohort 2)
- Similar results were seen for 1L cisplatin-ineligible patients (cohort 1)
  - In both cohorts, patients with the highest median mutation load (Q4) had significantly longer OS vs those in Q1-Q3[a]

- Atezolizumab produced durable responses in mUC pts progressing during/after treatment with ≥ 1 platinum-based regimen across all evaluated biomarker subgroups.
- Better ORR and/or longer OS associated with elevated PD-L1 expression on tumor infiltrating cells, higher median mutation load.
- The first agent in its class approved to treat locally advanced or metastatic urothelial carcinoma during or following platinum-based chemotherapy.

The Future Is in Combinations



Other Interesting Immune Approaches

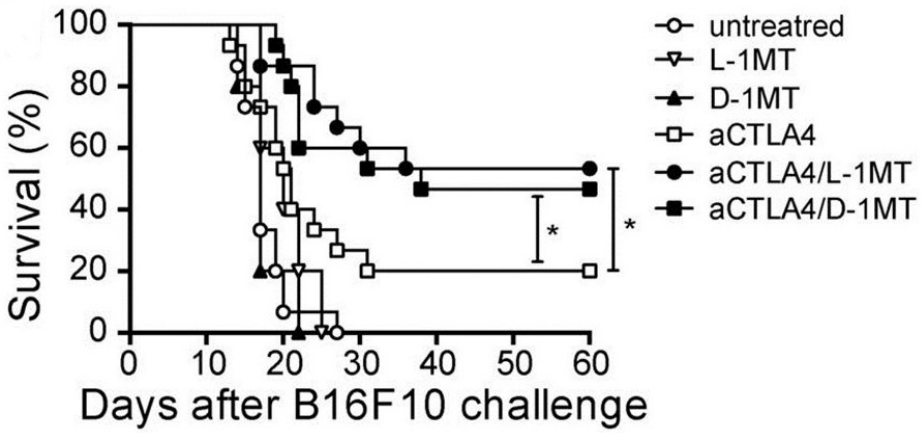
- Metabolic
  - IDO inhibitor
- Cytokines
  - IL-2, IL-12, etc.
- Oncolytic viruses
  - TVEC
- Targeted therapy
  - *BRAF*, VEGF, etc.
- Chemotherapy
  - Gemcitabine, cisplatin
- Radiation

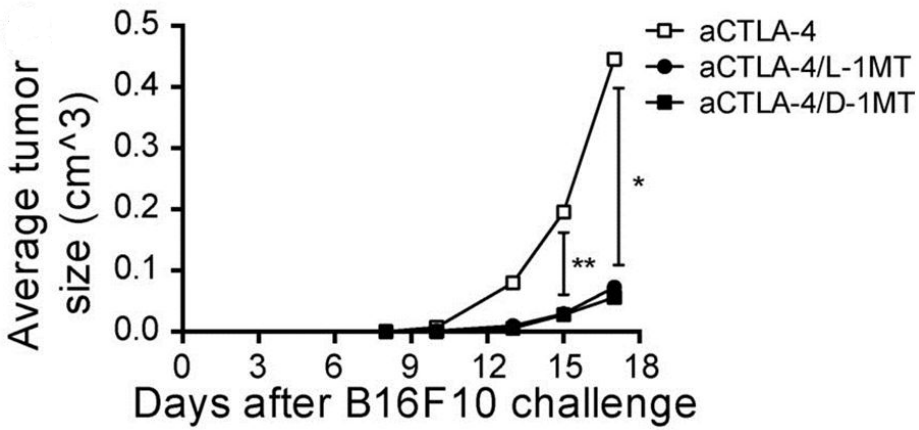
1. Pardoll DM. *Nat Rev Can.* 2012;12:252-264.

IDO Background

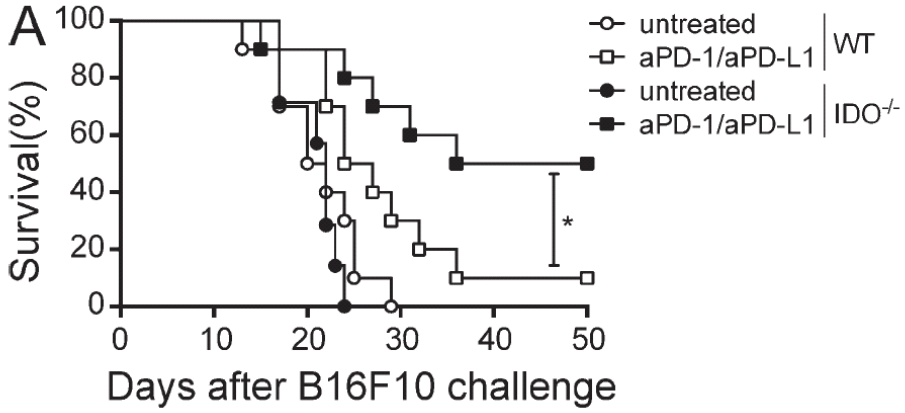
- Indoleamine 2,3-dioxygenase (IDO) catalyzes conversion of tryptophan to kynurenine. (Munn et al., 1998)
  - Inhibits the effector T cells.
  - Enhances the suppressive Treg.
- IDO can be expressed by tumor cells or by host antigen-presenting cells. (Uyttenhove et al., 2003)
- IDO is commonly found in melanoma and correlates with tumor progression and invasiveness. (Munn et al., 2004).

Anti–CTLA-4 and indoximod synergize to mediate tumor rejection





Synergy of IDO deficiency and PD-1/PDL-1



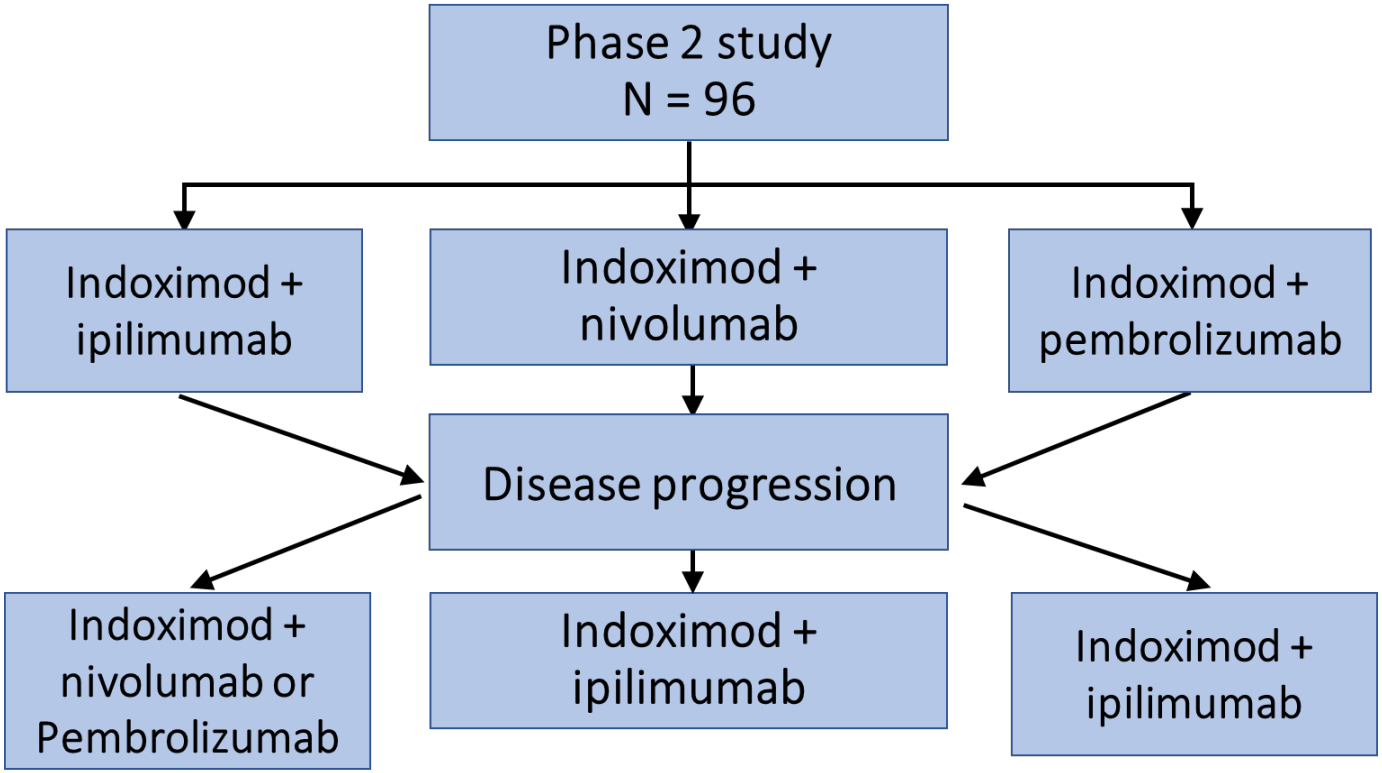
m Holmgaard et al. J Exp Med 2013;210:1389-1402

Methods

- Study Design:
  - Phase 1b: Dose-escalation

Dose Level	Indoximod (oral)	Ipilimumab (IV)
1	600 mg BID × 28 days	3 mg/kg q3 weeks × 4 doses
2	1200 mg BID × 28 days	3 mg/kg q3 weeks × 4 doses

  - Phase 2: RP2D indoximod with provider choice of anti-PD-1/ CTLA-4.
  - Progression: Change therapy from one checkpoint inhibitor (anti-CTLA-4 or anti-PD-1) to another while continuing indoximod.


Phase 2 study
N = 96
Indoximod + ipilimumab
Indoximod + nivolumab
Indoximod + pembrolizumab
Disease progression
Indoximod + nivolumab or Pembrolizumab
Indoximod + ipilimumab
Indoximod + ipilimumab

Patient Eligibility

- Inclusion criteria
  - Unresectable stage 3 or 4 melanoma, treatment naïve.

- Exclusion criteria
  - Patients with known active, uncontrolled brain metastases.
  - Patients with autoimmune diseases.
  - Concurrent use of any systemic immunosuppressants or steroids.

Results:

- 9 patients enrolled in phase 1 (3 female)
- No dose-limiting toxicities were observed
- Indoximod RP2D: 1200 mg PO BID

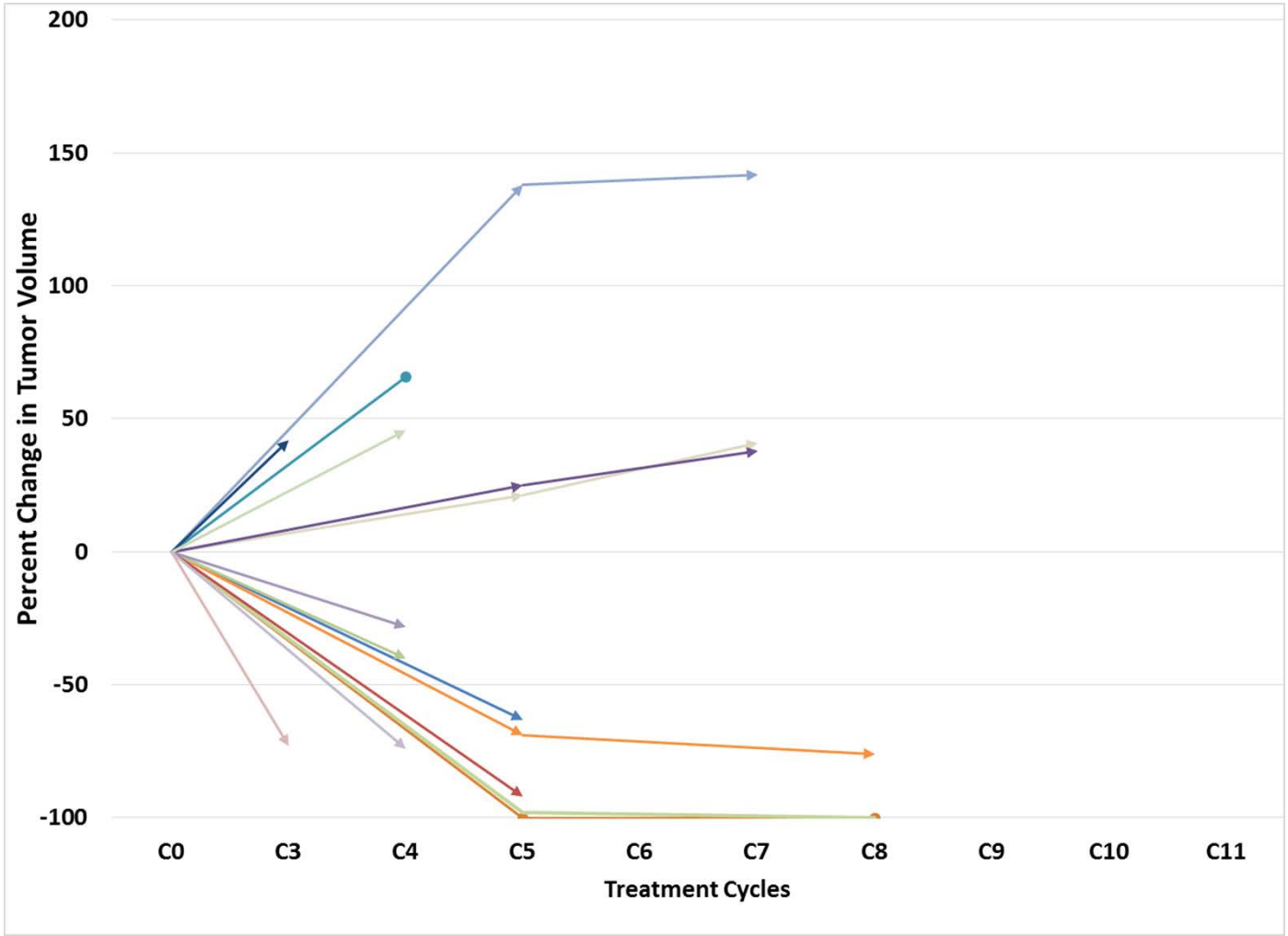
- CR at 14 months

- 6/9 patients are still alive (10-15 months from enrollment) and receiving additional treatment after coming off study.

- Phase 2 is ongoing, 92 Of a planned 96 patients are enrolled.

Zakharia, Y et al, Abstract #514, ESMO/ECC Vienna, September 2015

Responses with Indoximod and Pembrolizumab



Response rate is 53% (8/15) with two CRs

Zakharia, Y et al, Abstract #3075, ASCO Chicago, May 2016.

How about vaccines??

GOING VIRAL AGAINST CANCER

The virus-based cancer therapy T-VEC infects tumour cells and destroys them by stimulating the immune system to direct an attack against malignant cells in the body.

T-VEC enters but cannot replicate in normal cells.

T-VEC destroys malignant cells directly, releasing the protein GM-CSF and antigens that enable the immune system to target cancerous cells nearby and throughout the body.

GM-CSF attracts dendritic cells, which present tumour antigens to the immune system's T-cells, programming them to destroy cancer cells throughout the body.

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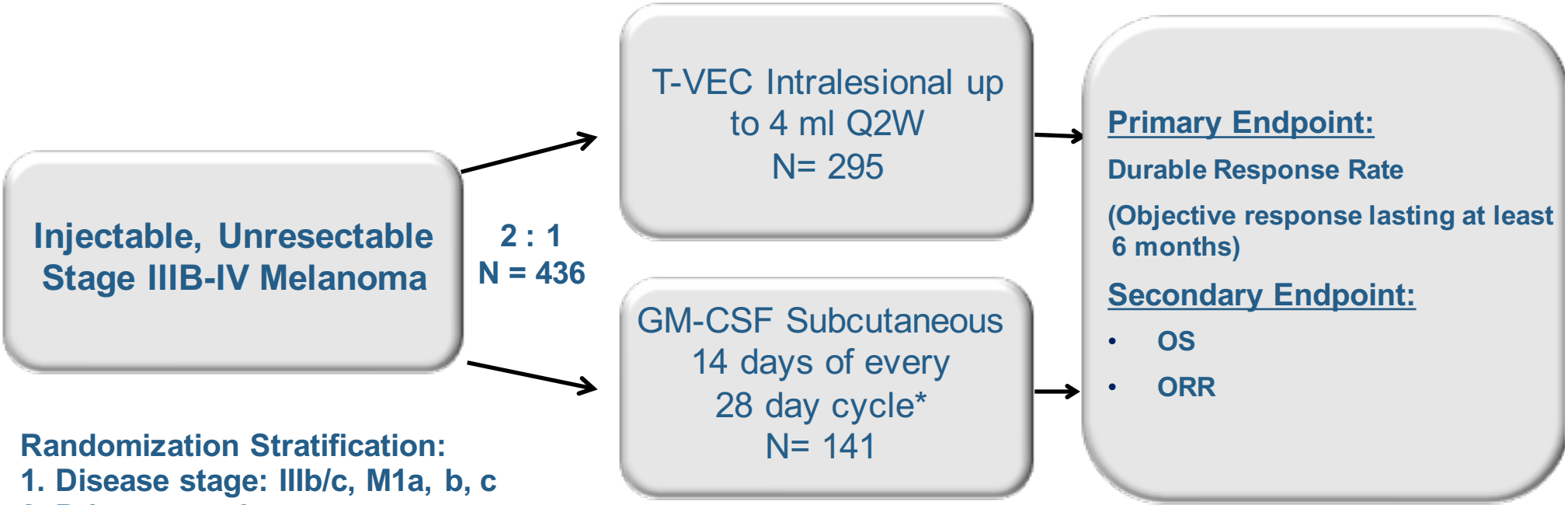
Ledford: 622, Nature,Vol 526, 29 October 2015

OPTiM Phase III Study Design



Randomization Stratification:
1. Disease stage: IIIb/c, M1a, b, c
2. Prior systemic treatment
3. Site of disease at first recurrence: local/distant
4. Presence of liver metastases

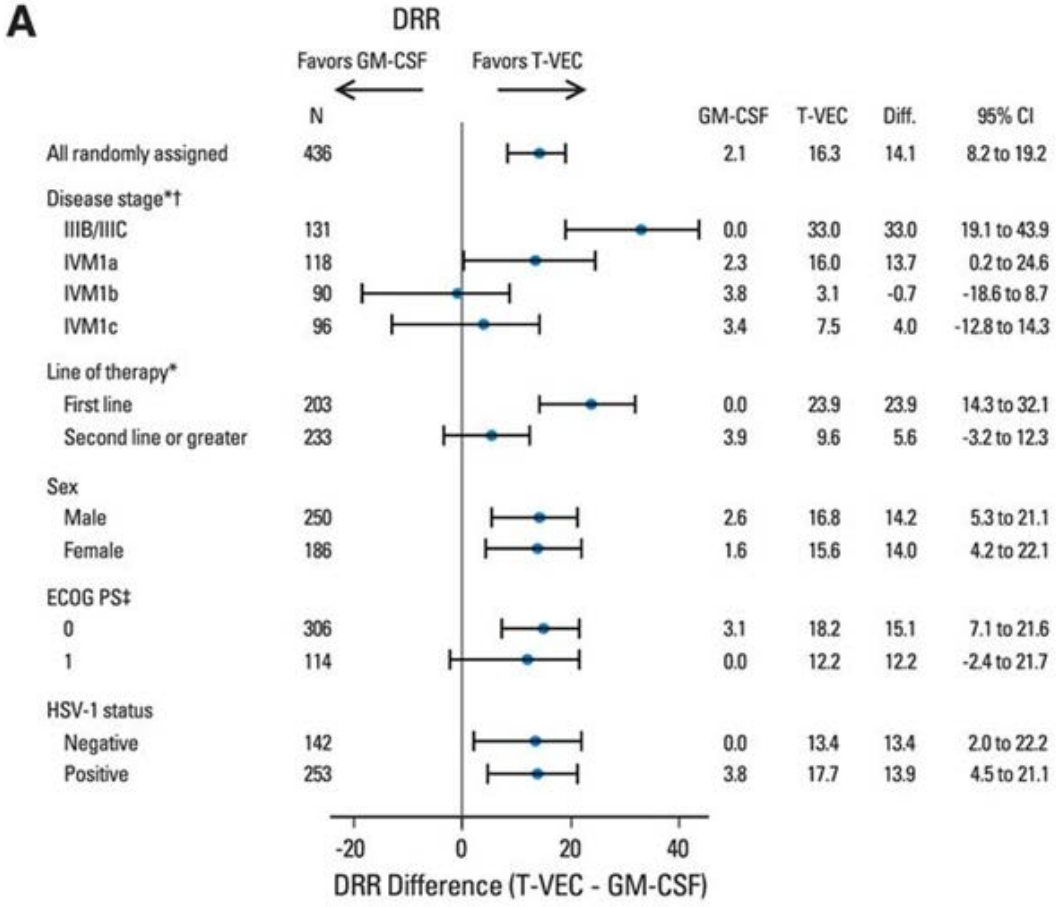
Patients were to remain on treatment beyond progression unless clinically significant (ie, associated with reduced performance status) after 24 weeks. Progression allowed before response.

- Dosing of intralesional T-VEC was ≤ 4 mL x10^6 pfu/mL once, then after 3 weeks, ≤ 4 mL x10^8 pfu/mL Q2W.
- Dosing of GM-CSF was 125 µg/m^2 subcutaneous daily x14 days of every 28 day cycle.

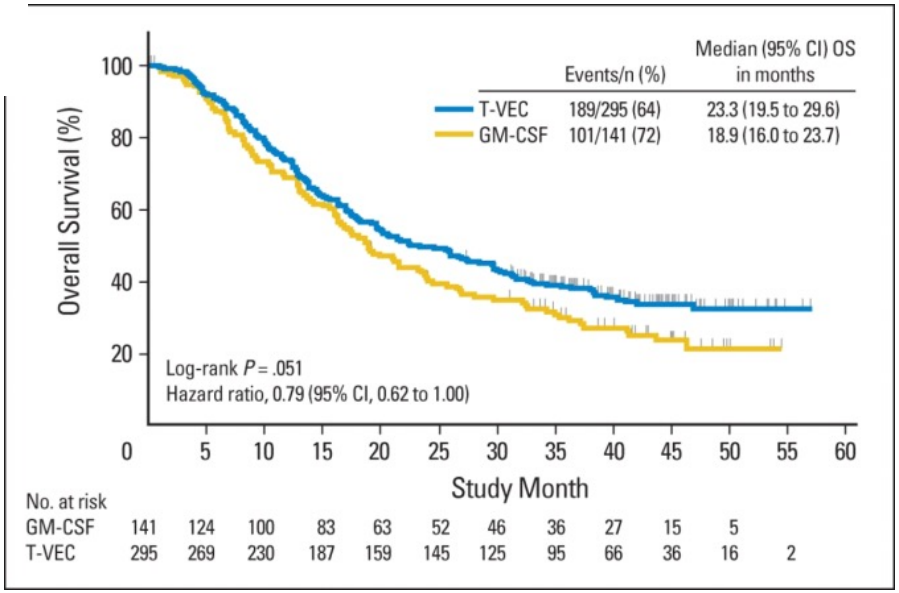
Andtbacka *et al*: J Clin Oncol. 2015 Sep 1;33(25):2780-8.

Response	T-VEC (n = 295)	GM-CSF (n = 141)	*P*	Difference	
				%	95% CI
DRR			< .001		
Patients with durable response, No.	48	3			
DRR, %*	16.3	2.1			
95% CI	12.1 to 20.5	0 to 4.5			
Unadjusted odds ratio	8.9				
95% CI	2.7 to 29.2				
ORR			< .001†		
CR					
No.	32	1			
%	10.8	< 1			
PR					
No.	46	7			
%	15.6	5.0			
ORR, %*	26.4	5.7			
95% CI	21.4 to 31.5	1.9 to 9.5			
Duration of response					
Patients with response, No.	78	8			
Median	NE	2.8			
95% CI		1.2 to NE			
Probability of being in response for all responders‡					
For ≥ 9 months, %	68	47			
95% CI	55 to 78	12 to 76			
For ≥ 12 months, %	65	47			
95% CI	51 to 76	12 to 76			

Andtbacka *et al*: J Clin Oncol. 2015 Sep 1;33(25):2780-8.



Primary analysis of overall survival (OS) in intent-to-treat population.



Robert H.I. Andtbacka et al. JCO 2015;33:2780-2788

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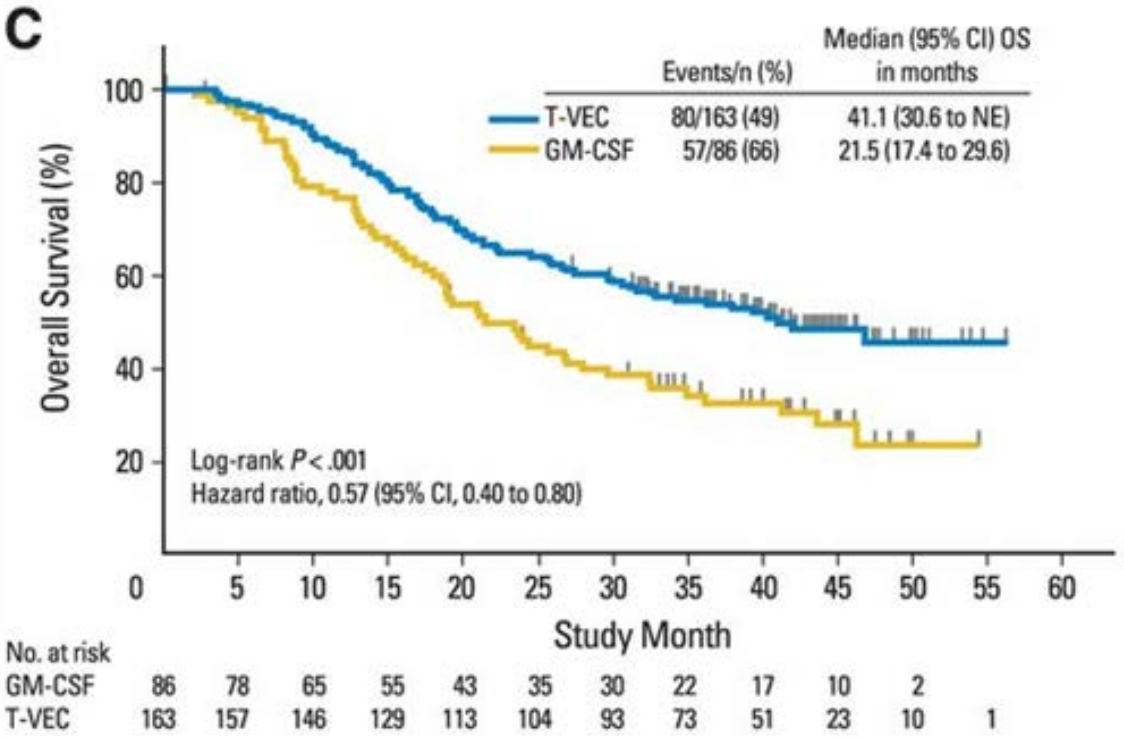
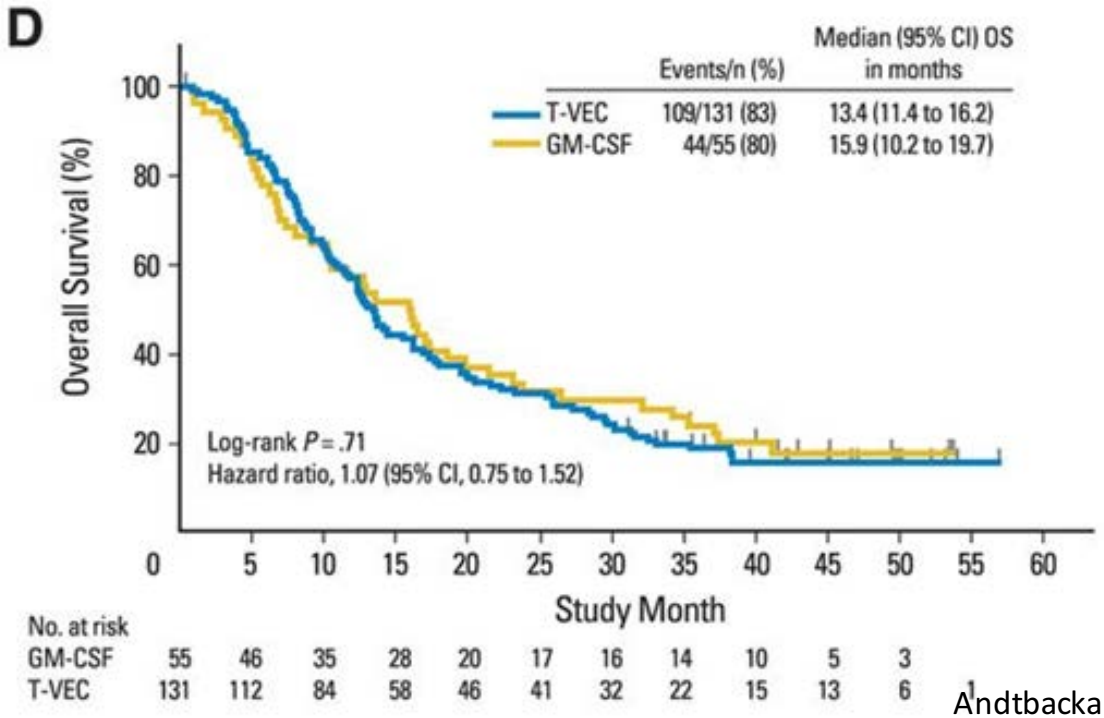
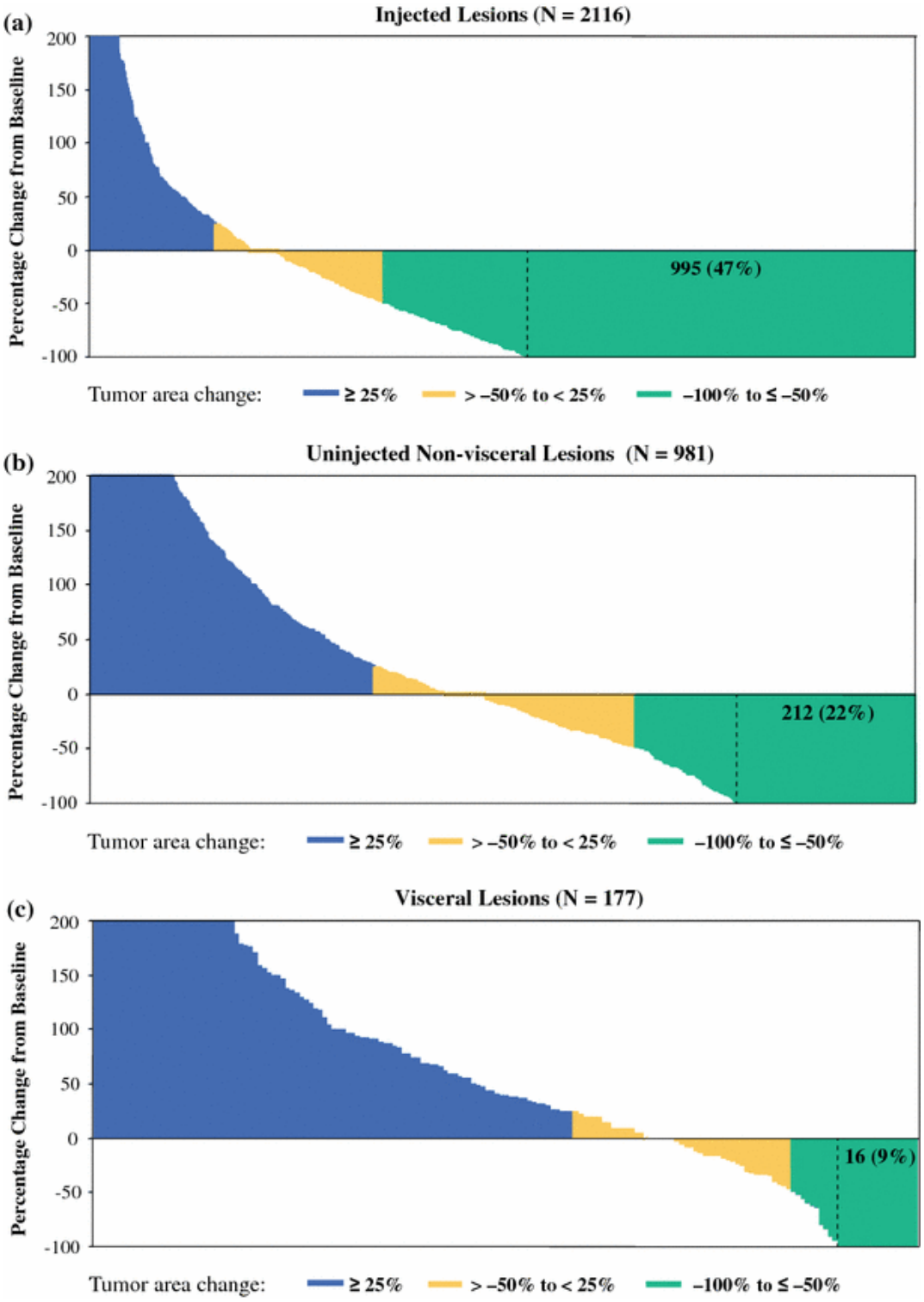
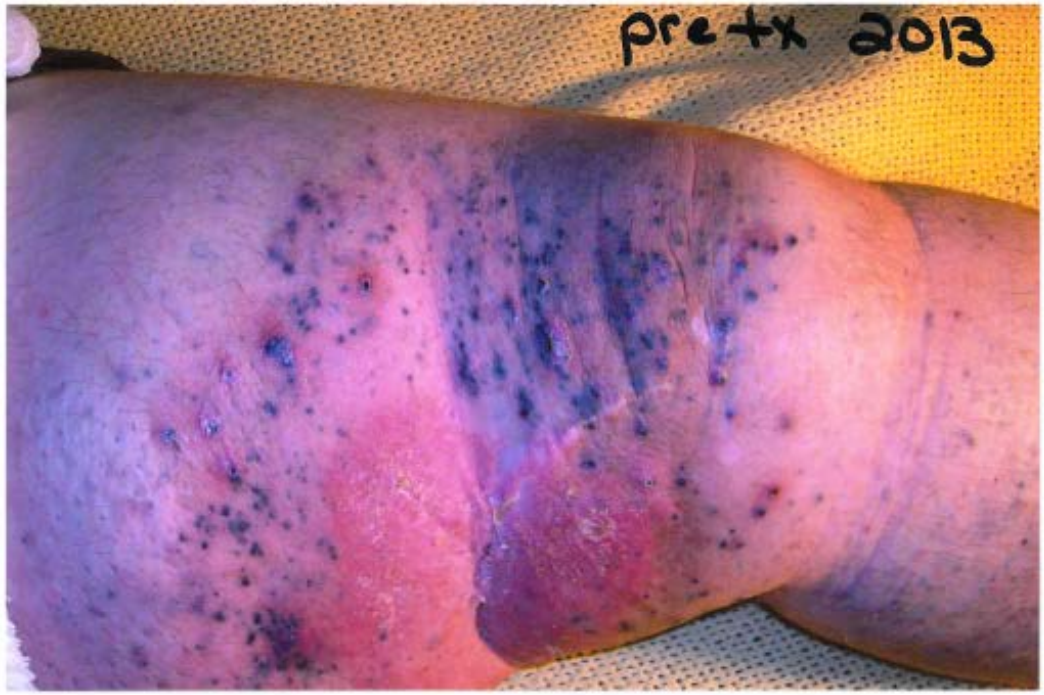


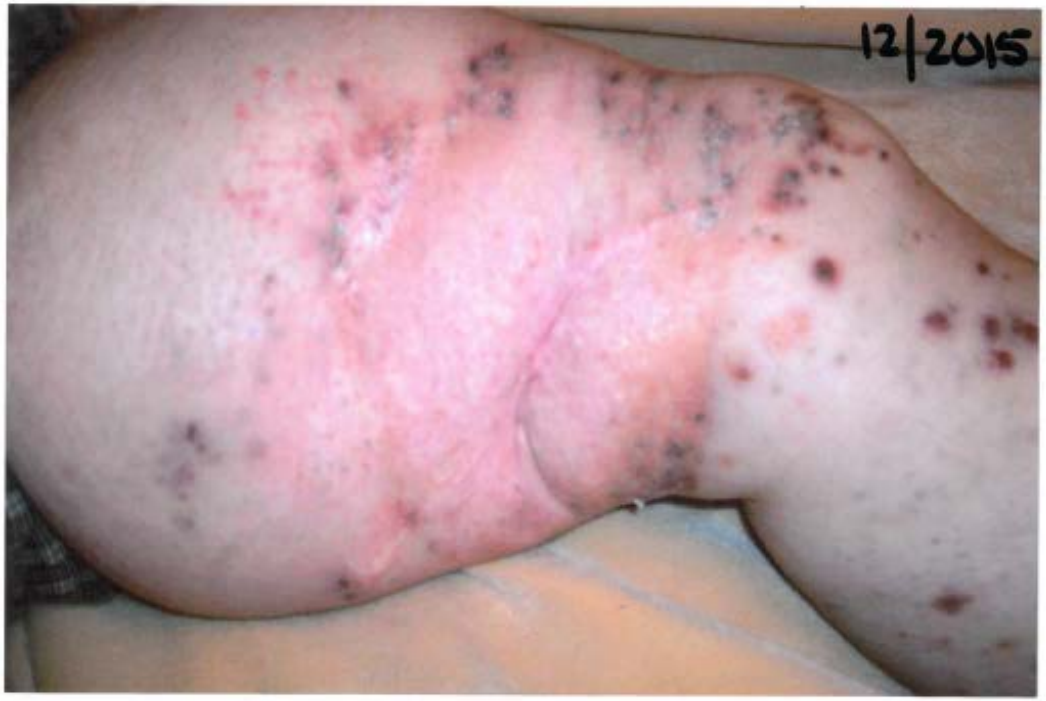


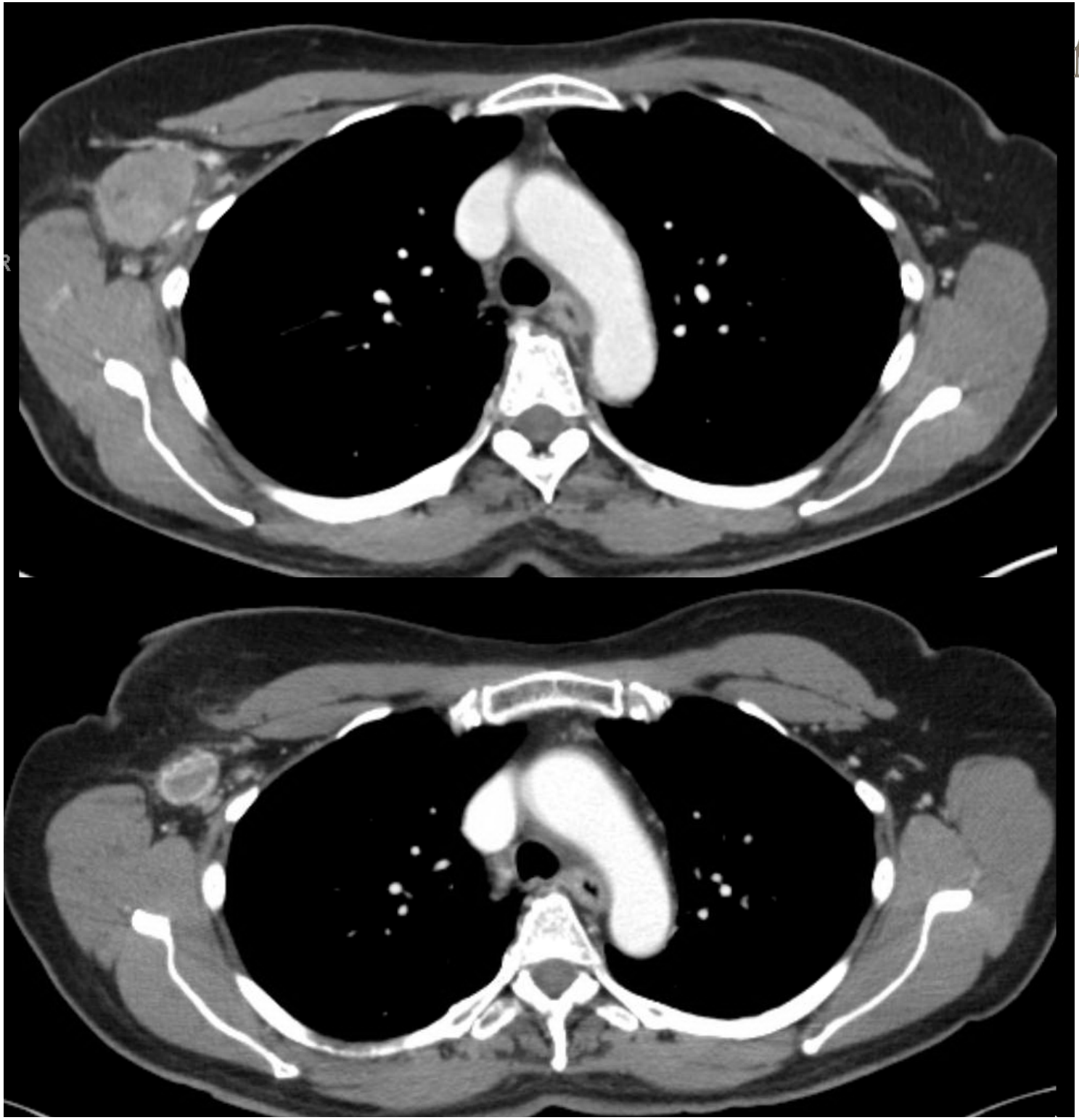
Andtbacka *et al*: J Clin Oncol. 2015 Sep 1;33(25):2780-8



Andtbacka et al: Ann Surg Oncol. 2016 Jun 24







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COMPREHENSIVE
CANCER CENTER
University of Iowa Health Care

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Take Home Message

- Exciting time for oncology in general
- Durable responses and improve survival can be achieved with immunotherapy.
- The field does not stop at PD-1/ PD-L1 inhibitors
- The future is for combination therapy.


THANK YOU