Immunotherapy for Metastatic Malignant Melanoma

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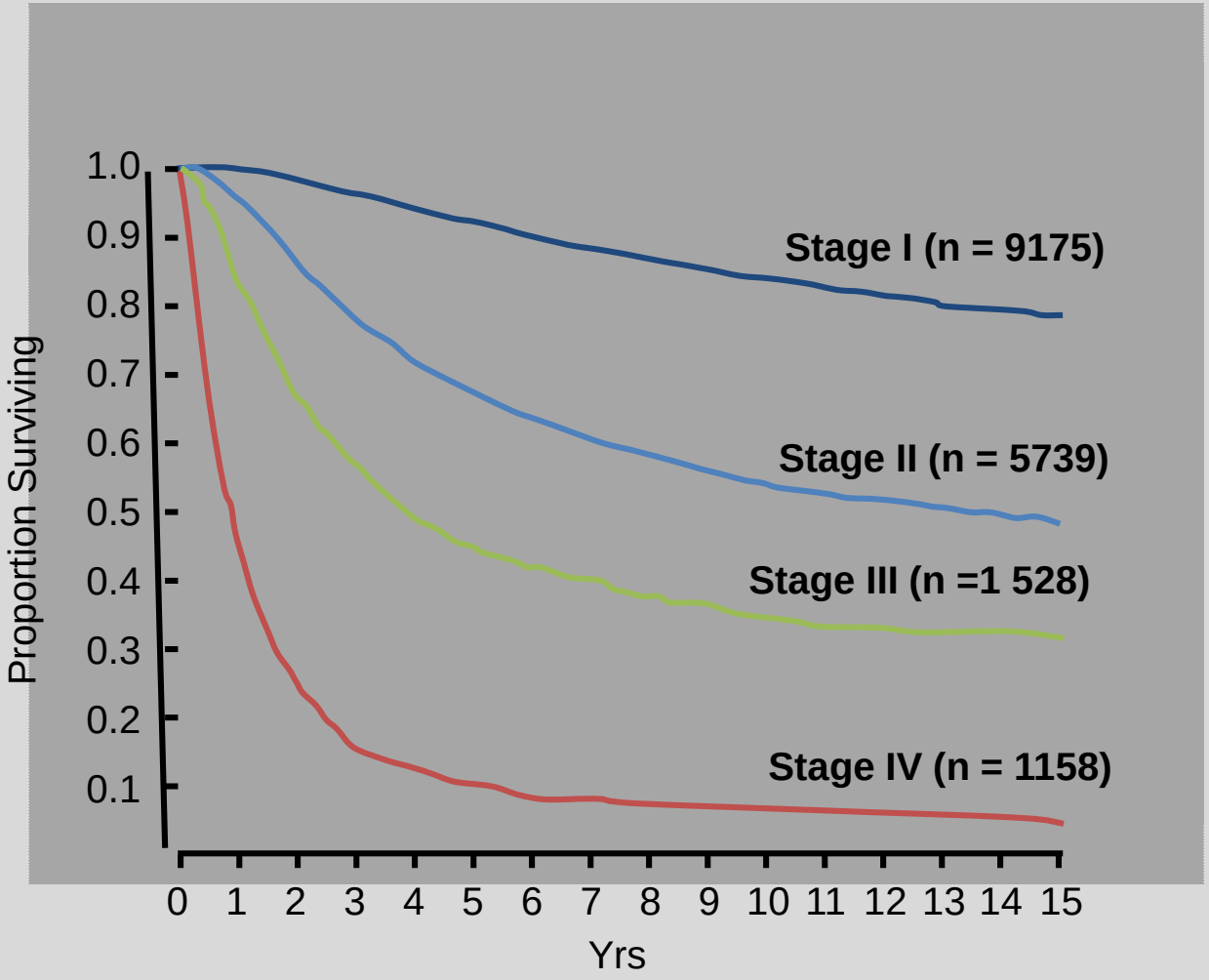
Survival in Melanoma by Stage



JOURNAL of CLINICAL ONCOLOGY ASCO

Balch CM, et al. J Clin Oncol. 2001;19:3635-3648

THE CASE FOR CANCER IMMUNOTHERAPY

No new truly curative anticancer cytotoxic drug developed in the last 20 years (until recently)

The immune response is designed to identify and disable "**escape routes**" that cancers employ.

Too many escape routes?

Melanoma is among the most immunogenic of all solid cancers

TUMORS CREATE CHAOS

Disordered

Blood flow and vascular distribution

Stroma and immune milieu

Immune shaping

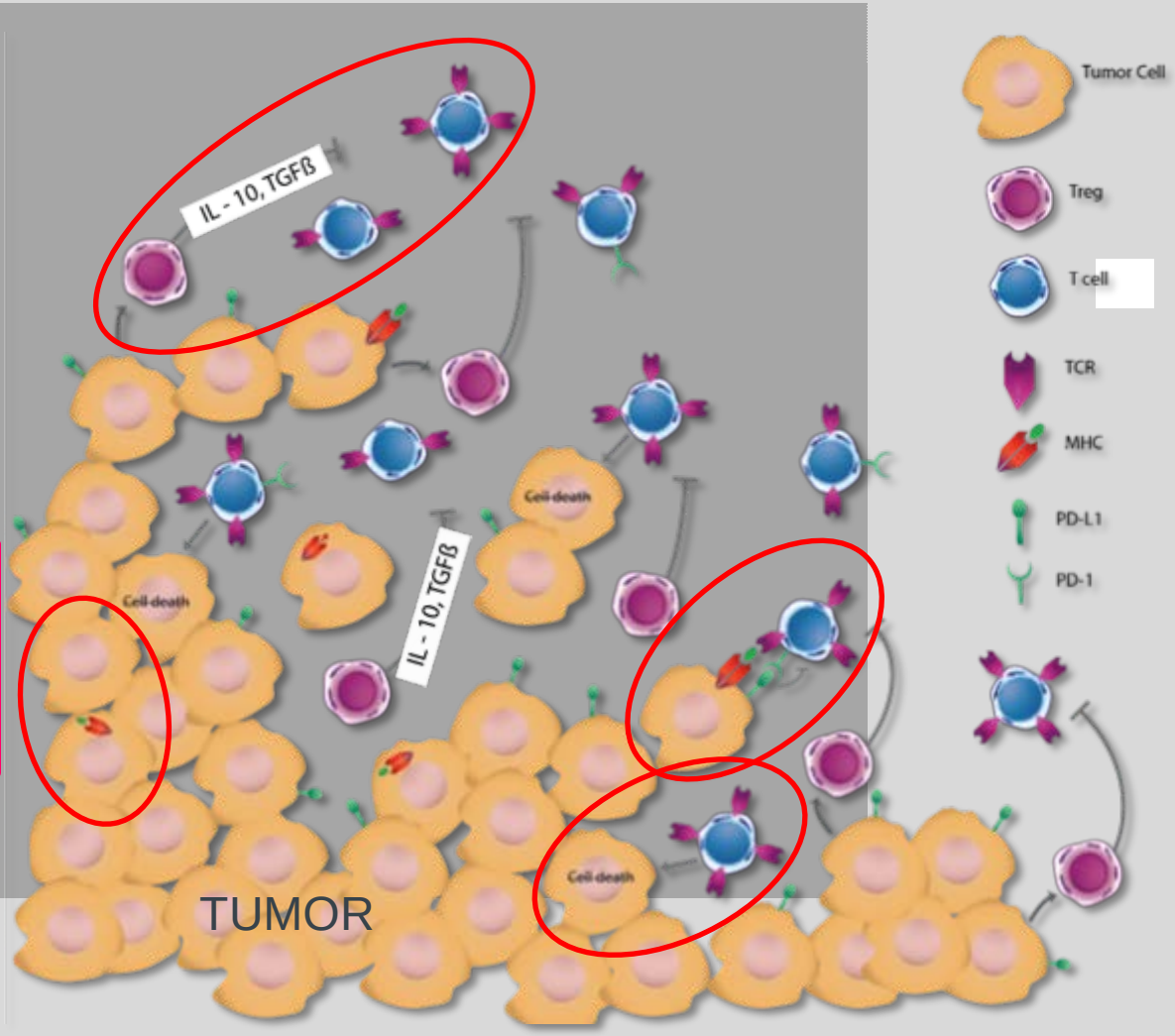
Create selection pressure so that cancers can evade immune destruction

Malignant “evolution”

Tumors go to great lengths to evade or subvert the immune response

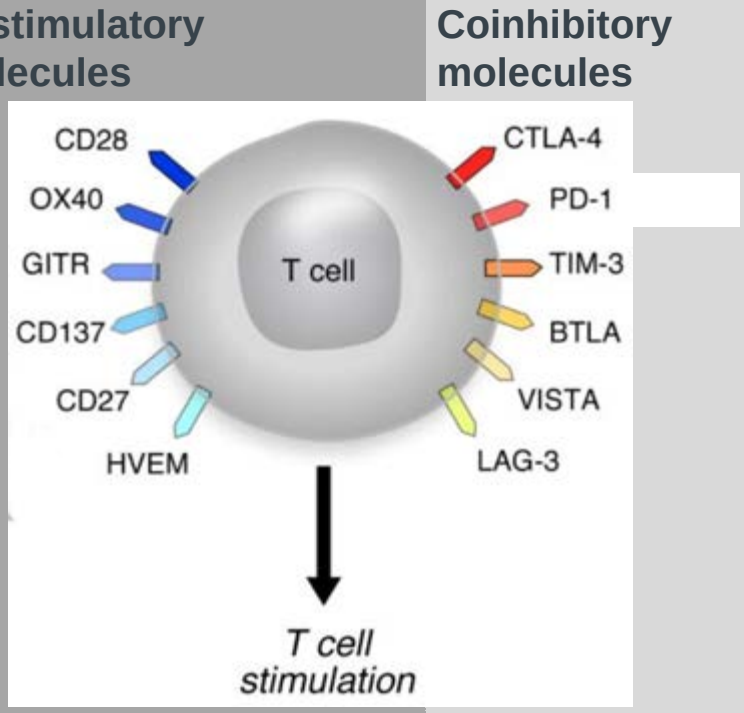
Tumors Evade Immune Detection and Destruction[1]

- The immune response to tumor cells can be evaded by a number of mechanisms:
  - Reduced antigen presentation[1]
  - Resistance to T-cell–mediated killing[1]
  - T-cell inhibition and anergy (eg, by upregulation of coinhibitory molecules, including PD-L1)[2]
  - Treg-mediated immunosuppression[1]



Cosignaling Molecules Contribute to Immune Regulation[1]

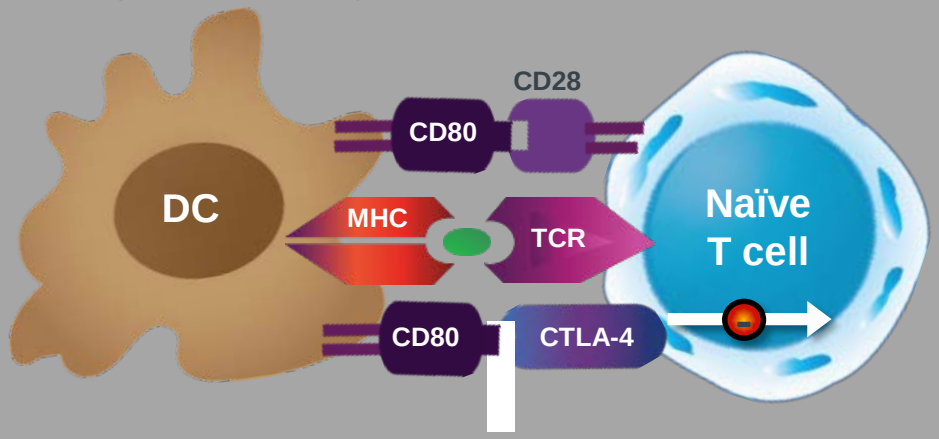
- Cosignaling regulates T-cell activation[2]
  - Signaling via costimulatory molecules (eg, CD28, GITR) promotes T-cell activation[3]
  - Signaling via coinhibitory molecules (eg, PD-1, LAG-3), also termed "immune checkpoints," suppresses T-cell activation[1,3]
- APCs can express the signaling partners of these costimulatory and coinhibitory molecules and direct T-cell function accordingly[2]



Physiological Roles of Immune Checkpoint Pathways *(cont)*

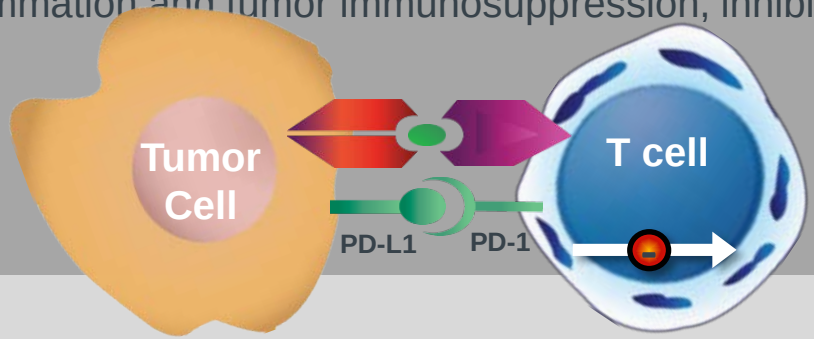
CTLA-4 pathway[1,2]

- Inhibits the activation of naïve and memory T cells at the lymph nodes, suppressing broad immune responses throughout the body

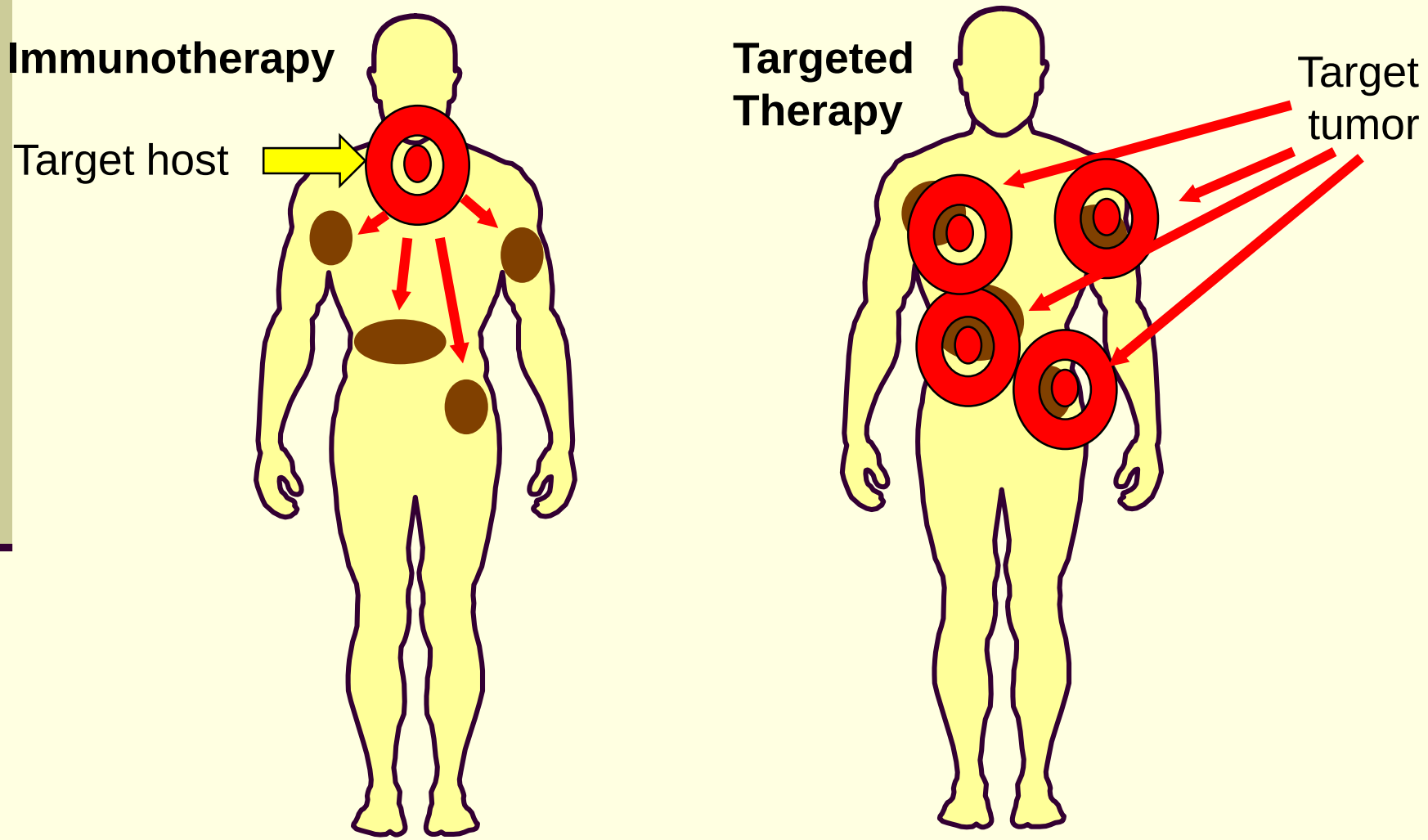


PD-1 pathway[1,2]

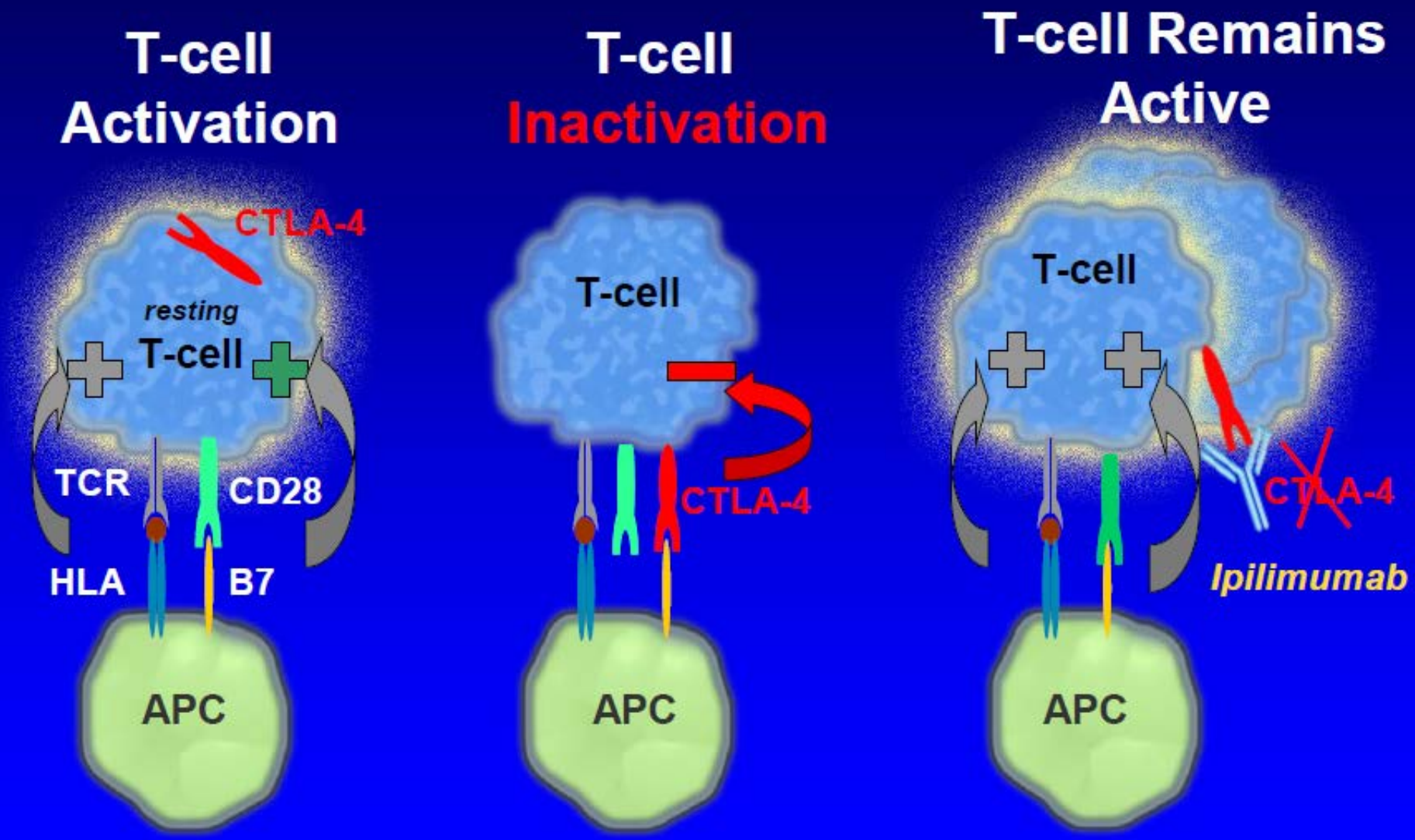
- Acts at sites of inflammation and tumor immunosuppression, inhibiting tumor-specific immune responses



Metastatic Melanoma: Treatment Advances



Ipilimumab, a CTLA-4 Blocking Monoclonal Antibody, Augments T-Cell Activation



Korman, Peggs and Allison: Adv. In Immunol. 2006;90:297-339

Ipilimumab

- CTLA-4 (cytotoxic T-lymphocyte associated antigen 4)
  - a negative regulator of T cells
- Ipilimumab:
  - IgG1 monoclonal Ab
  - Block CTLA-4

  ⇒Augments T cell activation and proliferation.
- Allowing the immune system to maintain responsiveness against an antigen
- Overcoming various mechanisms of immune evasion

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

NEJM 2011 June 30;364(26):2517-26.

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Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

Caroline Robert, M.D., Ph.D., Luc Thomas, M.D., Ph.D., Igor Bondarenko, M.D., Ph.D., Steven O'Day, M.D., Jeffrey Weber M.D., Ph.D., Claus Garbe, M.D., Celeste Lebbe, M.D., Ph.D., Jean-François Baurain, M.D., Ph.D., Alessandro Testori, M.D., Jean-Jacques Grob, M.D., Neville Davidson, M.D., Jon Richards, M.D., Ph.D., Michele Maio, M.D., Ph.D., Axel Hauschild, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Pere Gascon, M.D., Ph.D., Michal Lotem, M.D., Kaan Harmankaya, M.D., Ramy Ibrahim, M.D., Stephen Francis, M.Sc., Tai-Tsang Chen, Ph.D., Rachel Humphrey, M.D., Axel Hoos, M.D., Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

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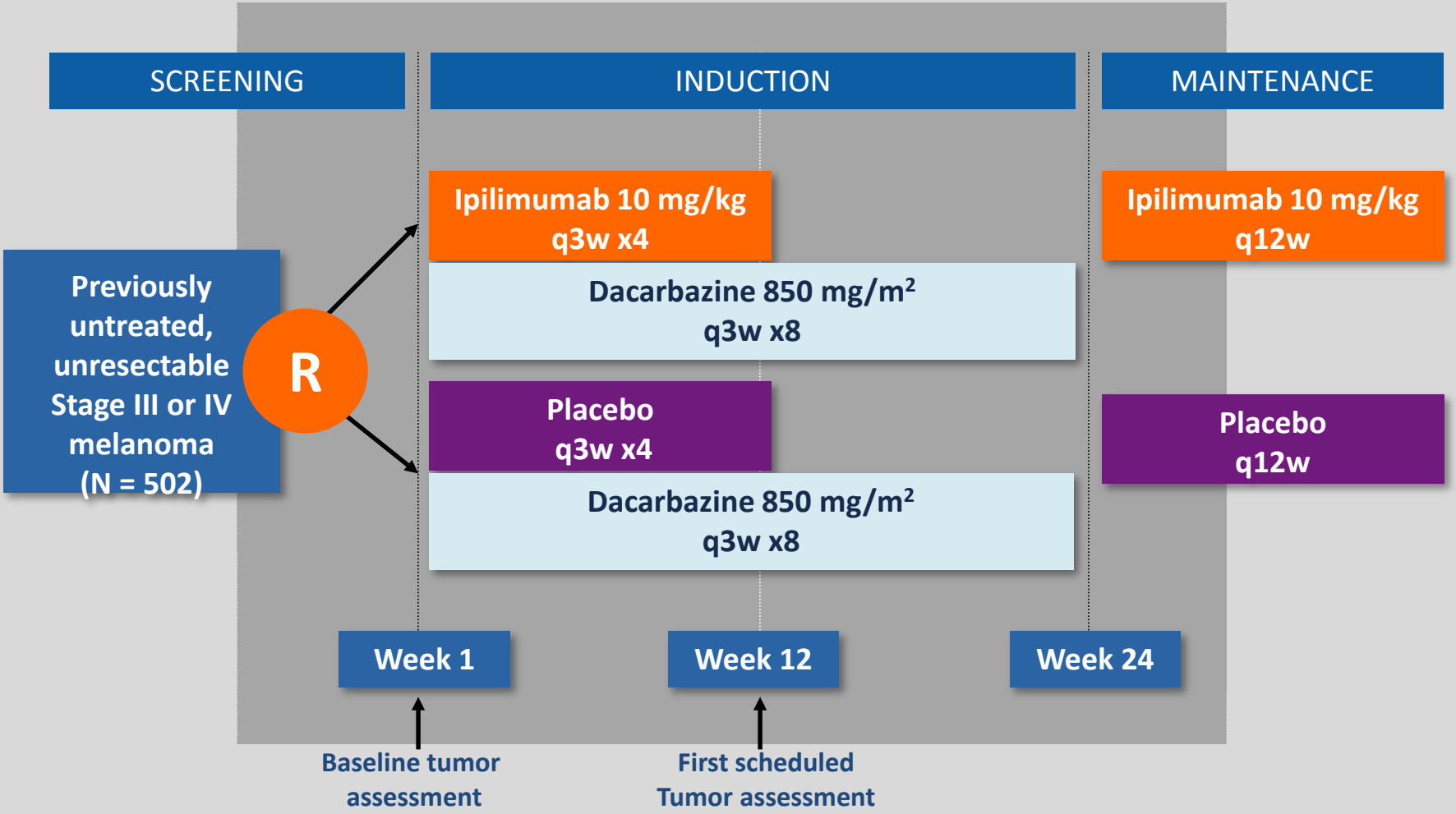
NEJM 2010 August 19;363(8):711-23.

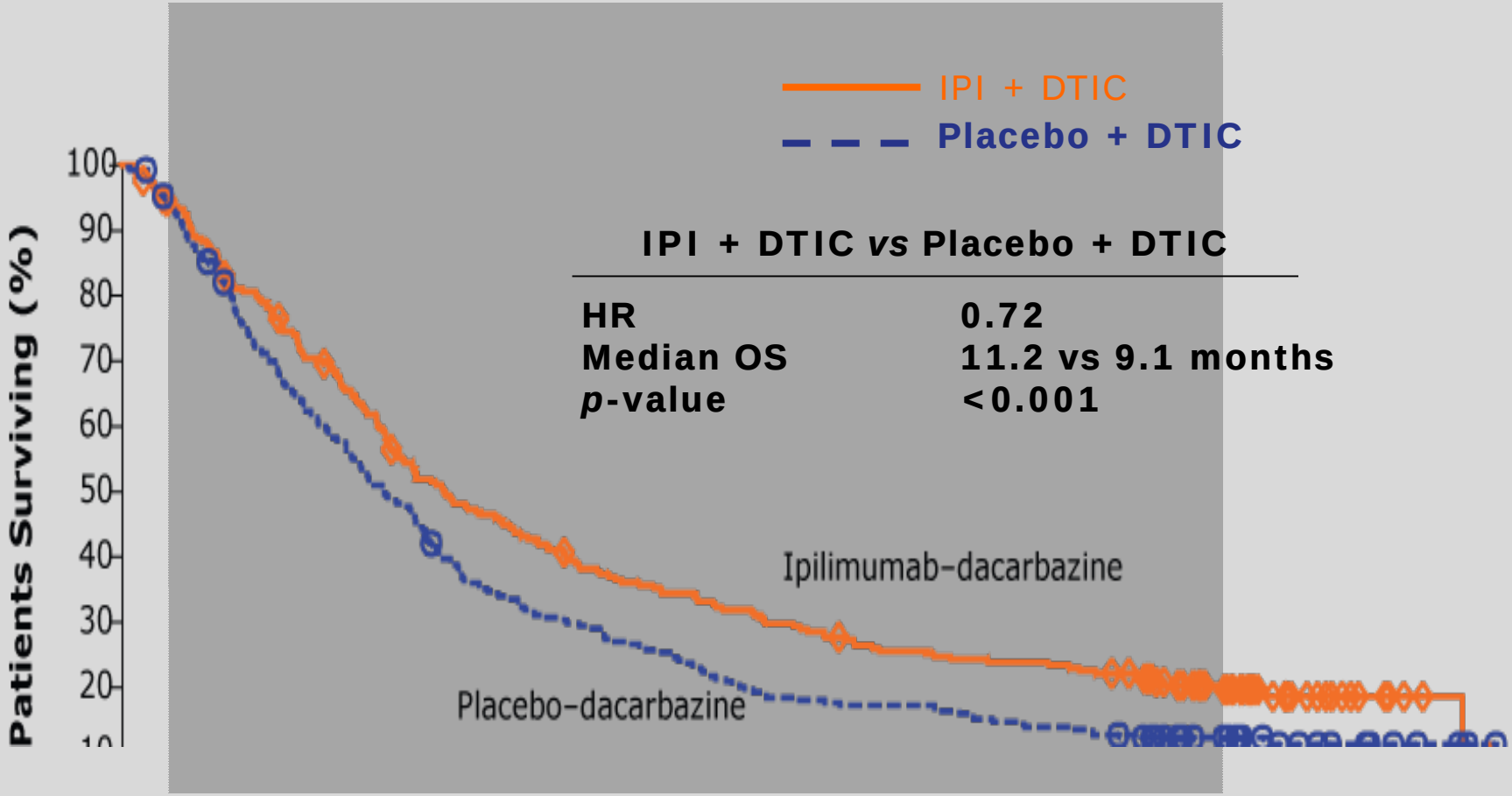
Study 024: Phase III Placebo-Controlled Trial of First-line DTIC ± IPI



The NEW ENGLAND JOURNAL of MEDICINE

Robert C et al. *N Engl J Med* 2011

Study 024: Overall Survival

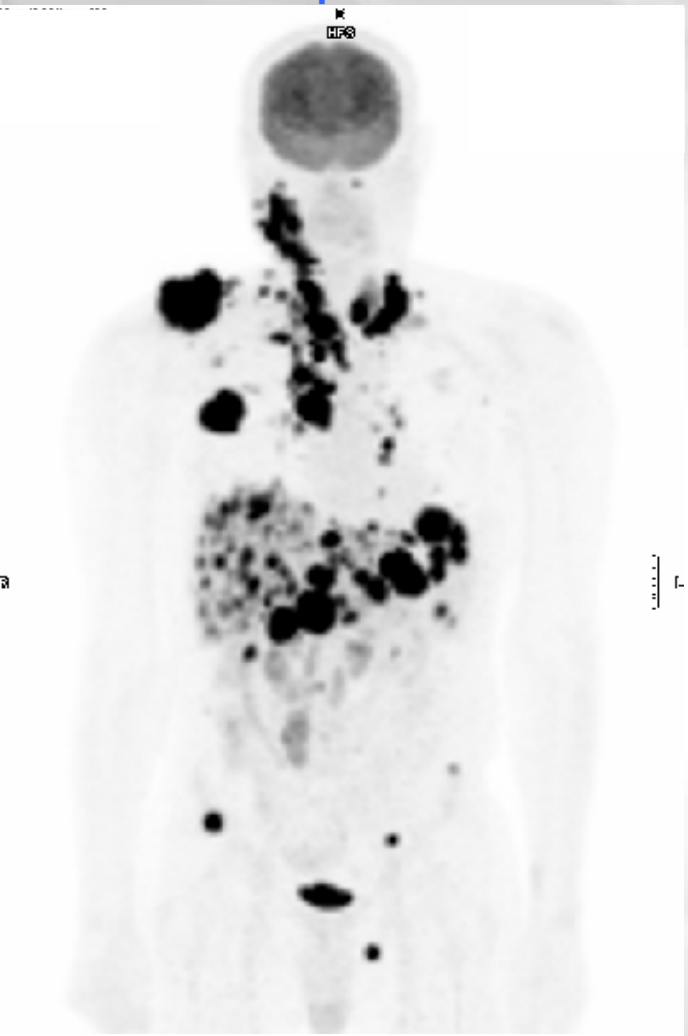


The NEW ENGLAND JOURNAL of MEDICINE

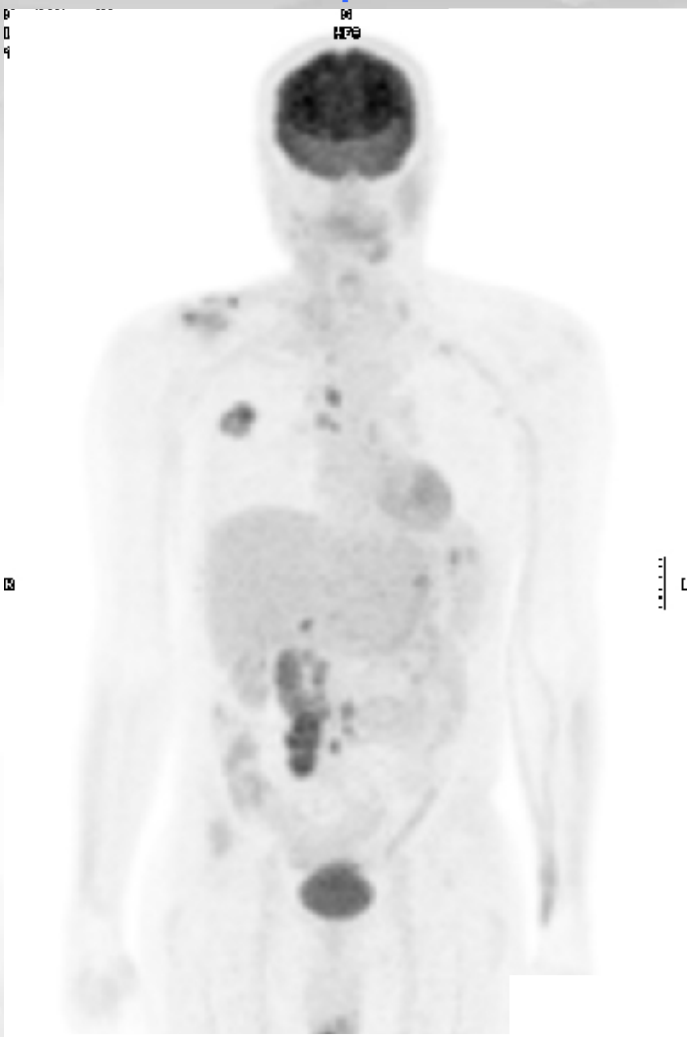
Robert C et al. *N Engl J Med* 2011;

Metastatic Melanoma Response to Ipilimumab

Before Ipilimumab



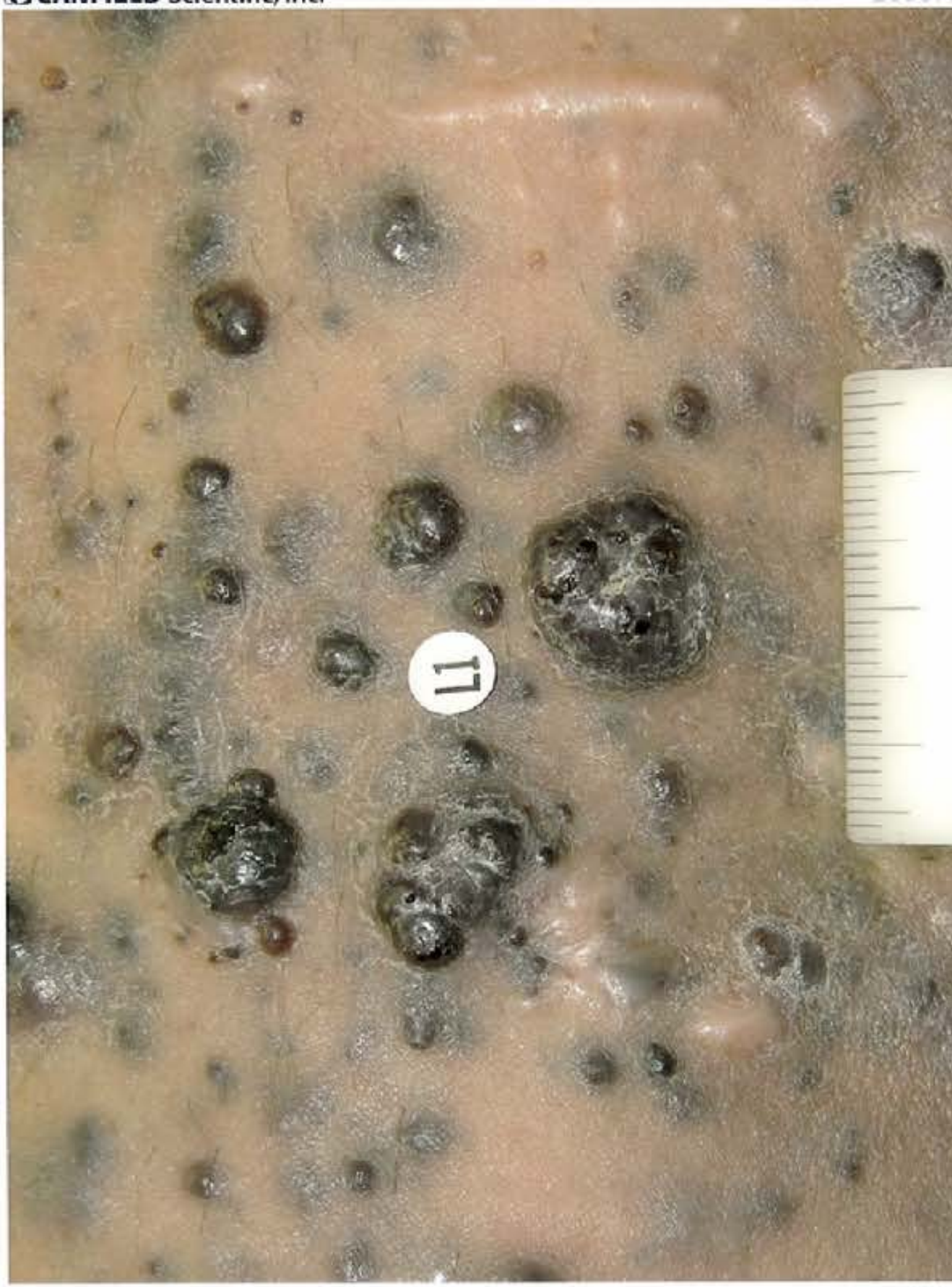
After Ipilimumab



Ipilimumab in Melanoma: Phase I / II Trials

- Durable responses (CR, PR, SD)
- Durable late responses (~ 10%)
- Learning curve toxicity management
- Immune-related toxicity correlates with clinical benefit
- Immunosuppressive treatment does not interfere with anti-tumor response

CANFIELD Scientific, Inc.
206285
BMS CA184-022 Ctr: 0070 ID#: 22118 Initials: M-T Visit: SCR Date: 02-Nov-2006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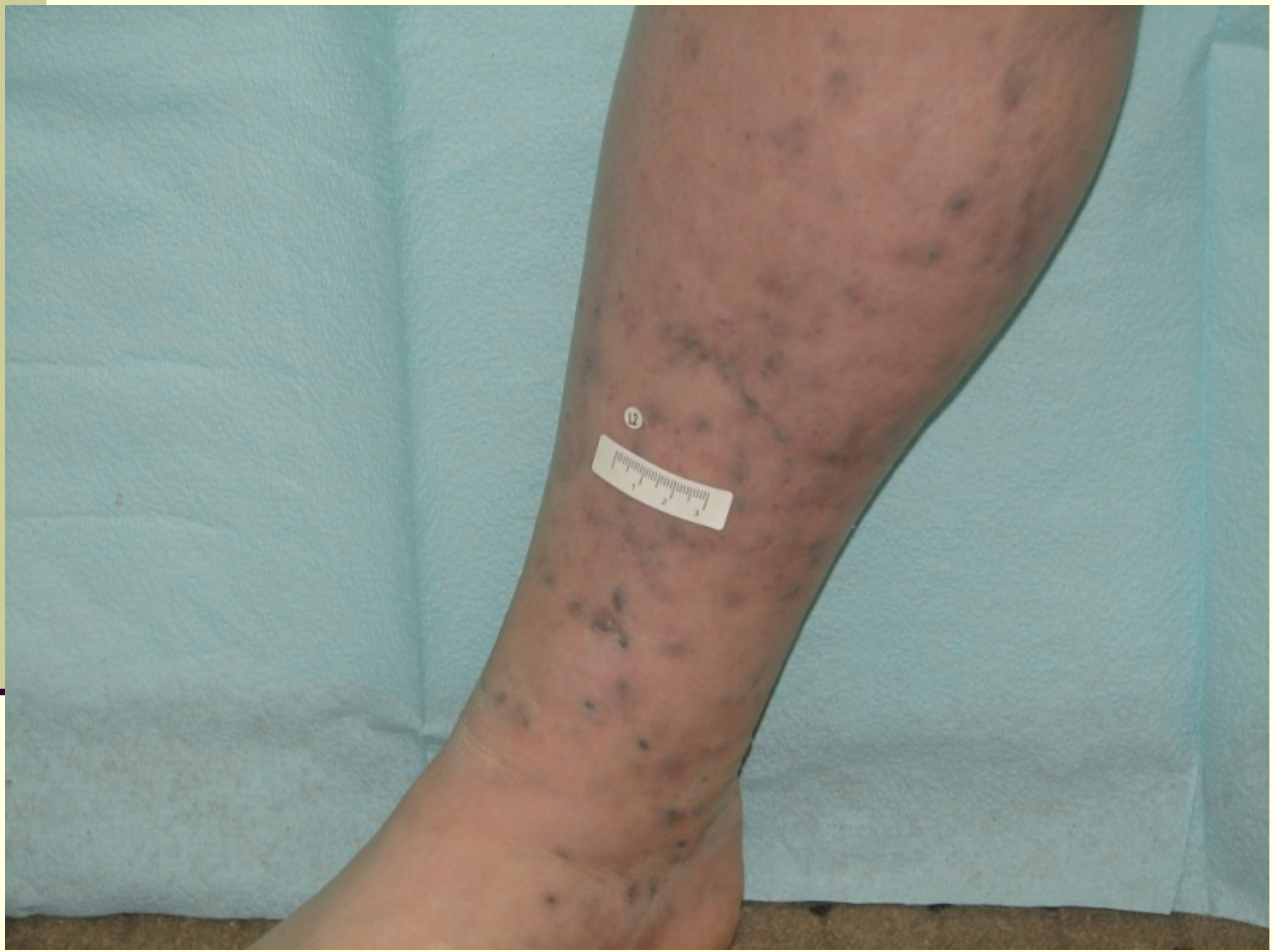

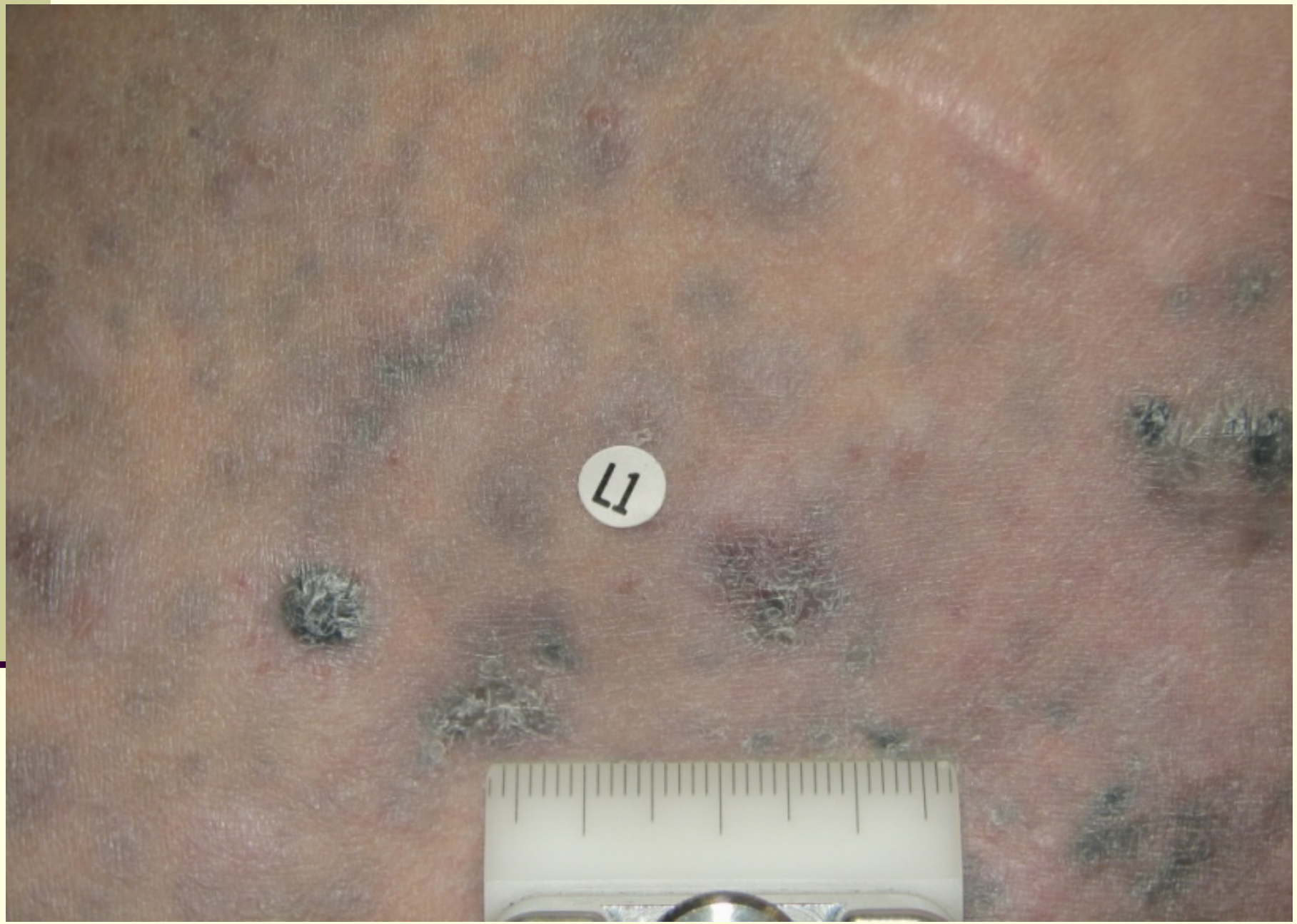
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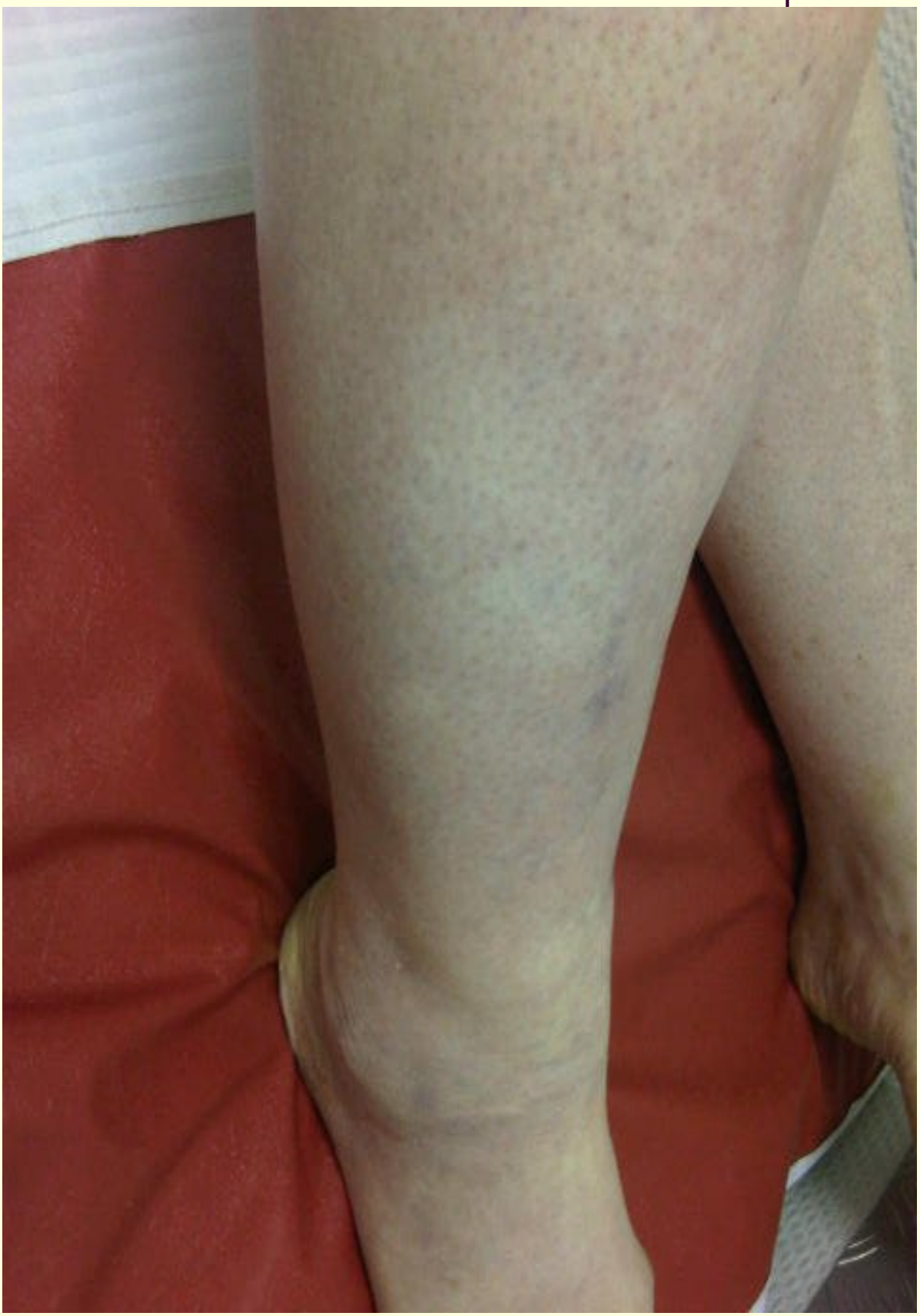


IPILIMUMAB South African EAP

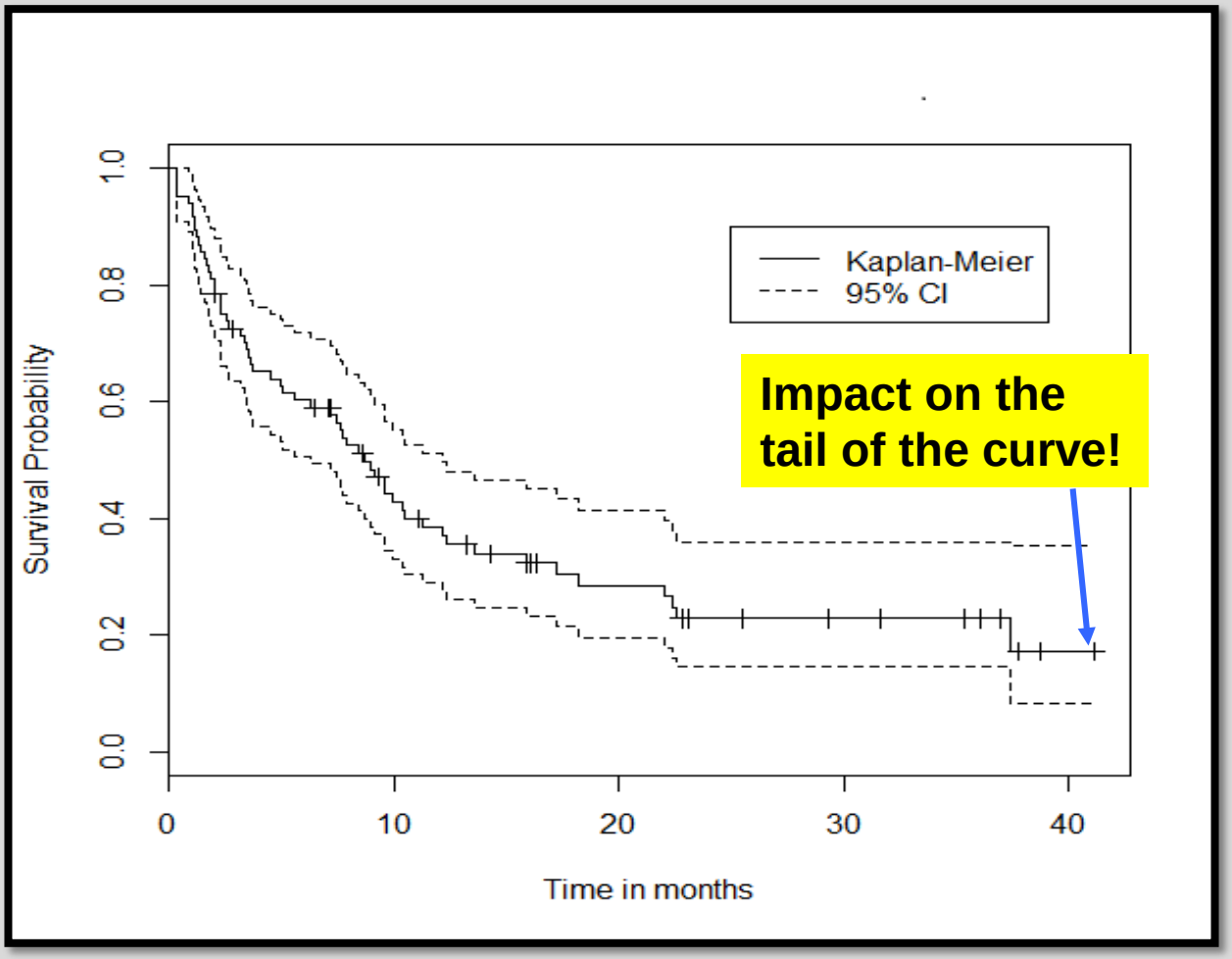
Baseline Characteristics of Treated Patients

Total	108pts
Age	
Median	59
Range	27-86
Gender	
Male	73 (68%)
Female	35 (32%)
ECOG performance status	
0	36 (33%)
1	63 (58%)
2	7 (6%)
Unknown	2 (3%)

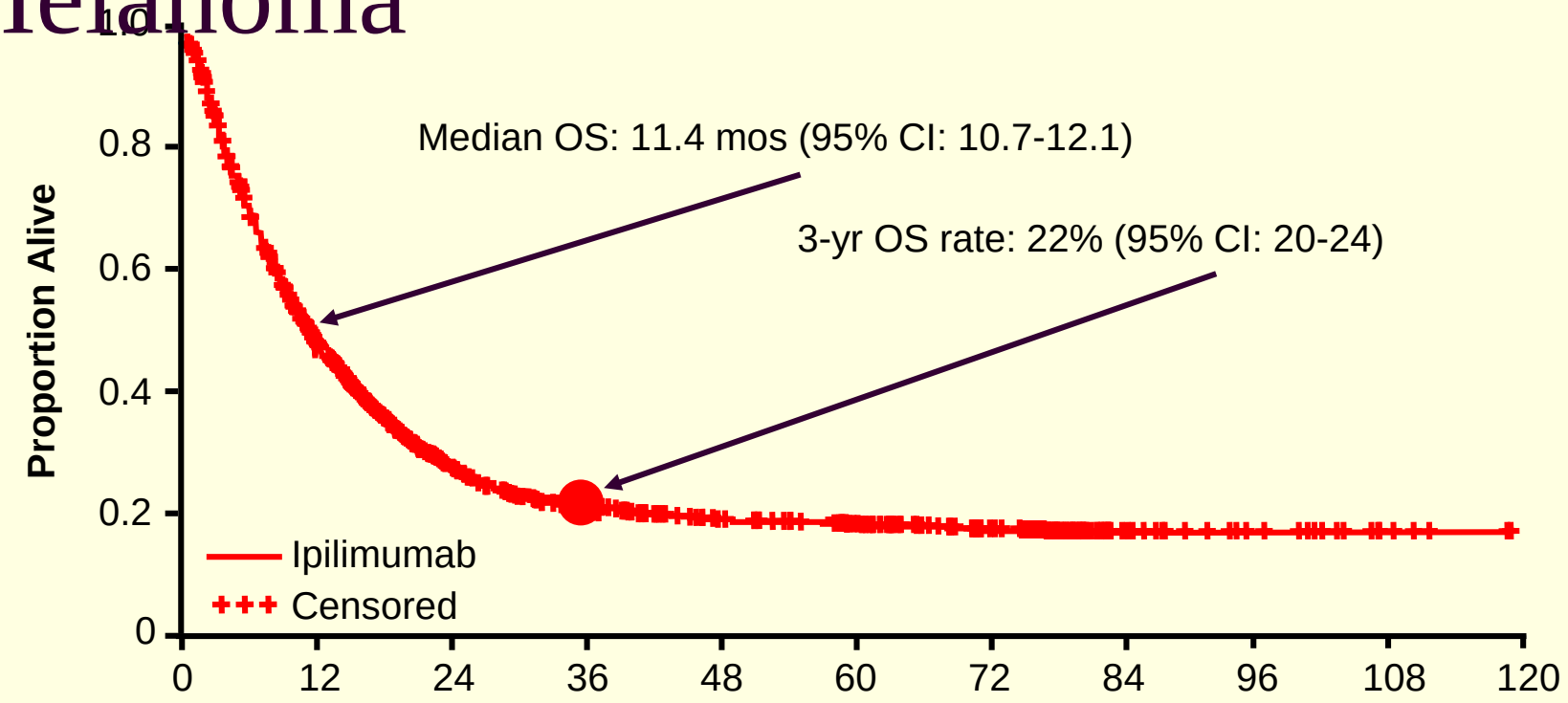
Overall Survival

		Median OS			1 year survival			2 year survival			3 year survival		
	N	Median	Lower	Upper	%	Lower	Upper	%	Lower	Upper	%	Lower	Upper
All	108	**8,98**	7,47	10,79	**36%**	26%	45%	**20%**	12%	27%	**20%**	12%	27%
Mucosal & uveal	15	**5,18**	3,74	NA	**8%**	2%	13%	**0%**	0%	0%	**0%**	0%	0%
Cutaneous & unknown	93	**9,54**	7,61	12,33	**40%**	30%	50%	**23%**	15%	32%	**23%**	15%	32%

Overall Survival of Cutaneous Met Melanoma



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



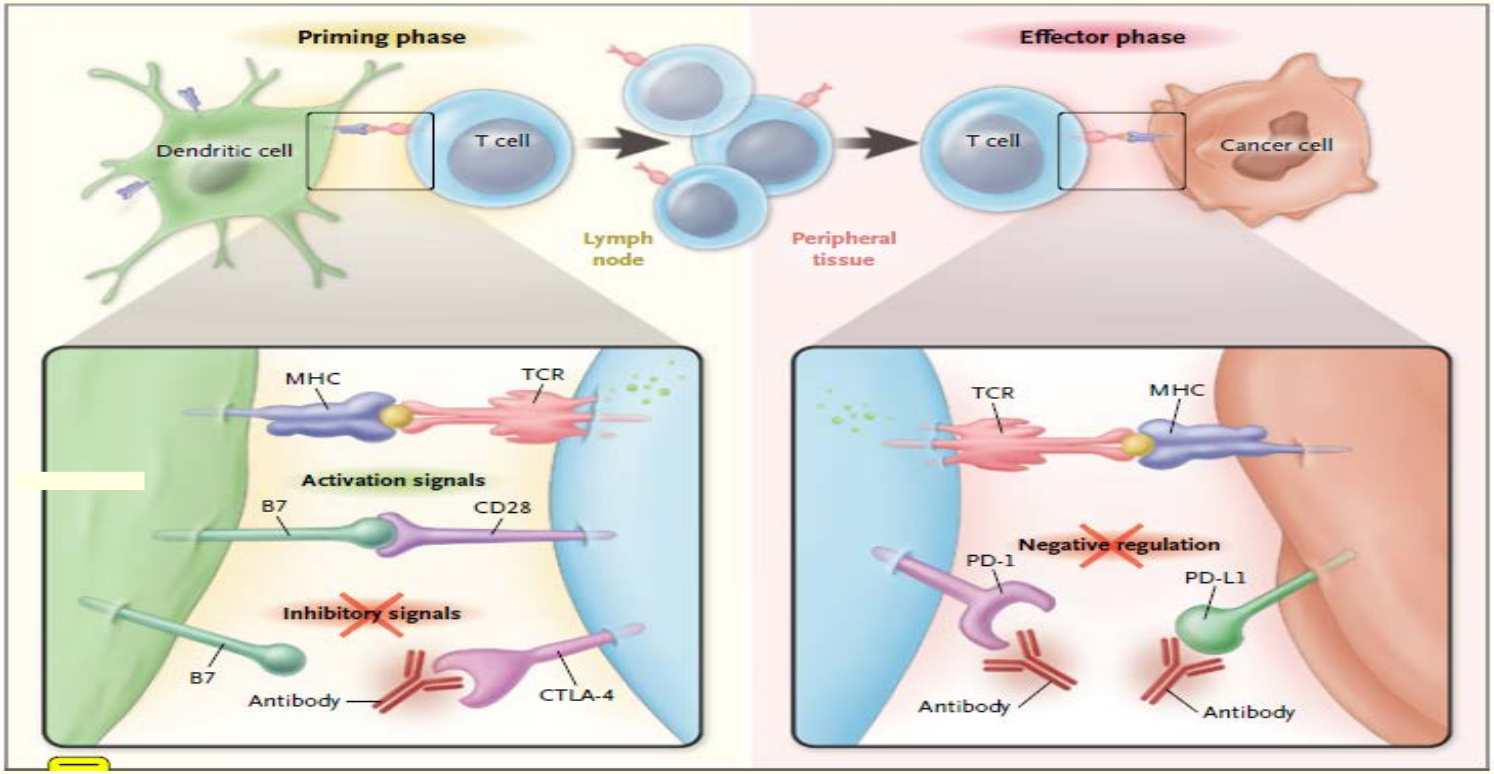
Pts at Risk, n

Ipilimumab	1861	839	370	254	192	170	120	26	15	5	0

Hodi S, et al. 2013 European Cancer Congress. Abstract LBA 24.
Schadendorf D, et al. J Clin Oncol. 2015;[Epub ahead of print].

Anti-PD1

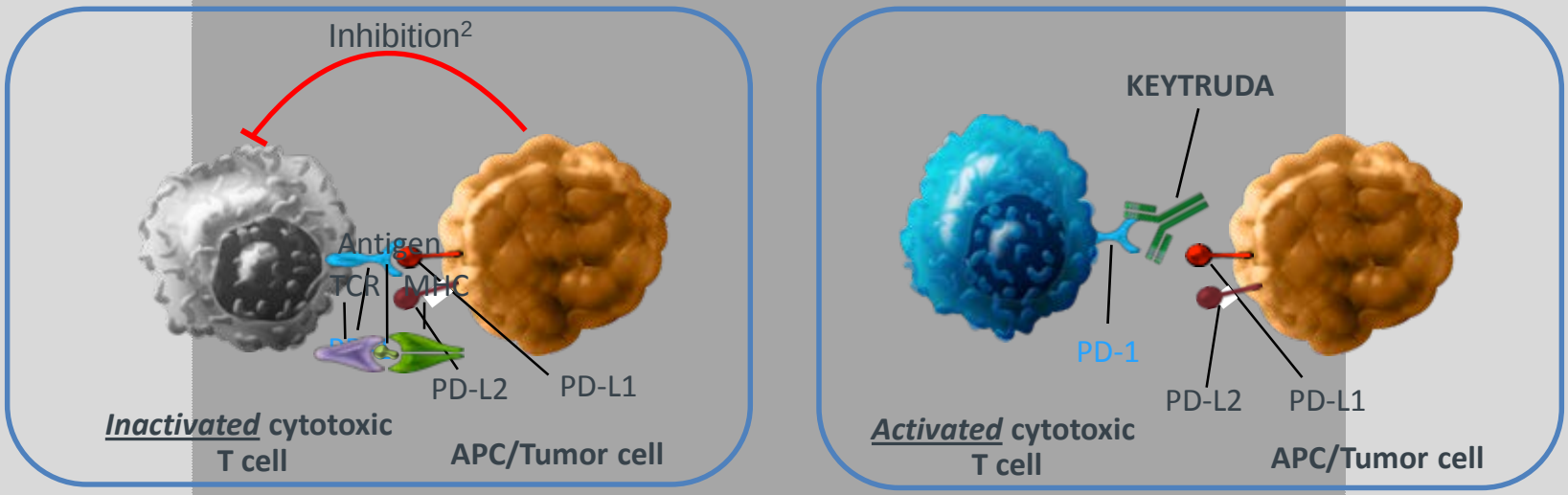
The interaction between the immune checkpoint receptor PD-1 and its ligands represents a potentially important tumor-specific immunomodulatory mechanism. By utilizing the PD-1 pathway, a tumor cell can prevent the activation of T-cells and therefore may block a key step that triggers the immune system.



Ribas, NEJM June 2, epub ahead of print

PD-1 Receptor Blockade With Pembrolizumab

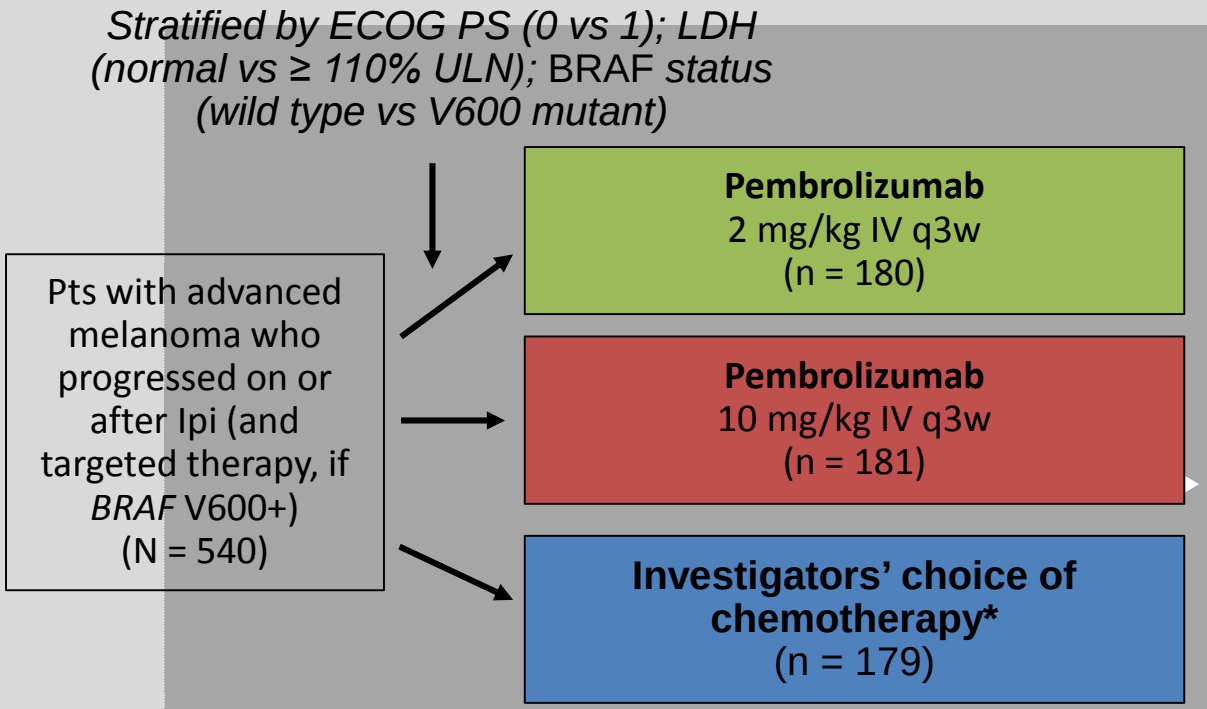
- Pembrolizumab is an antineoplastic agent, monoclonal antibody[1]
- Pembrolizumab is a high affinity antibody against PD-1, which exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen-presenting or tumor cells.
  - By inhibiting the PD-1 receptor from binding to its ligands, KEYTRUDA reactivates tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and reactivates antitumor immunity[1]



APC = antigen-presenting cell; MHC = major histocompatibility complex; PD-1 = programmed death receptor 1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2; TCR = T-cell receptor.

1. [Insert local label.]
2. Pardoll DM. *Nat Rev Cancer.* 2012;12(4):252–264.

KEYNOTE-002: Pembrolizumab vs Chemotherapy in Ipi-Refractory Melanoma



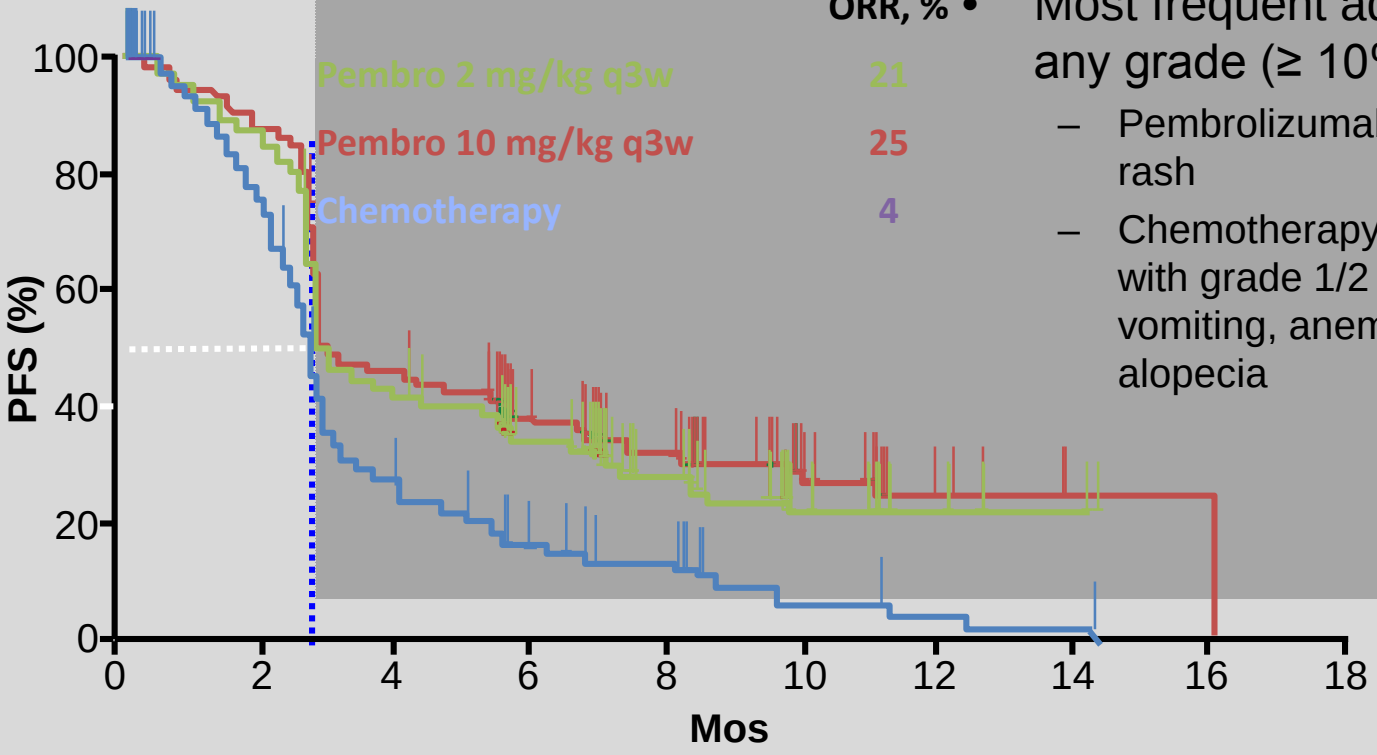
*Carboplatin + paclitaxel, paclitaxel alone, carboplatin alone, dacarbazine, or temozolomide. Pts with PD confirmed by independent central review could cross over to pembrolizumab treatment after the first 3-mo assessment.

- Primary endpoint: PFS, OS
- Secondary endpoints: ORR, DoR

Ribas A, et al. Lancet Oncol. 2015;16:908-918.

KEYNOTE-002: Efficacy and Safety

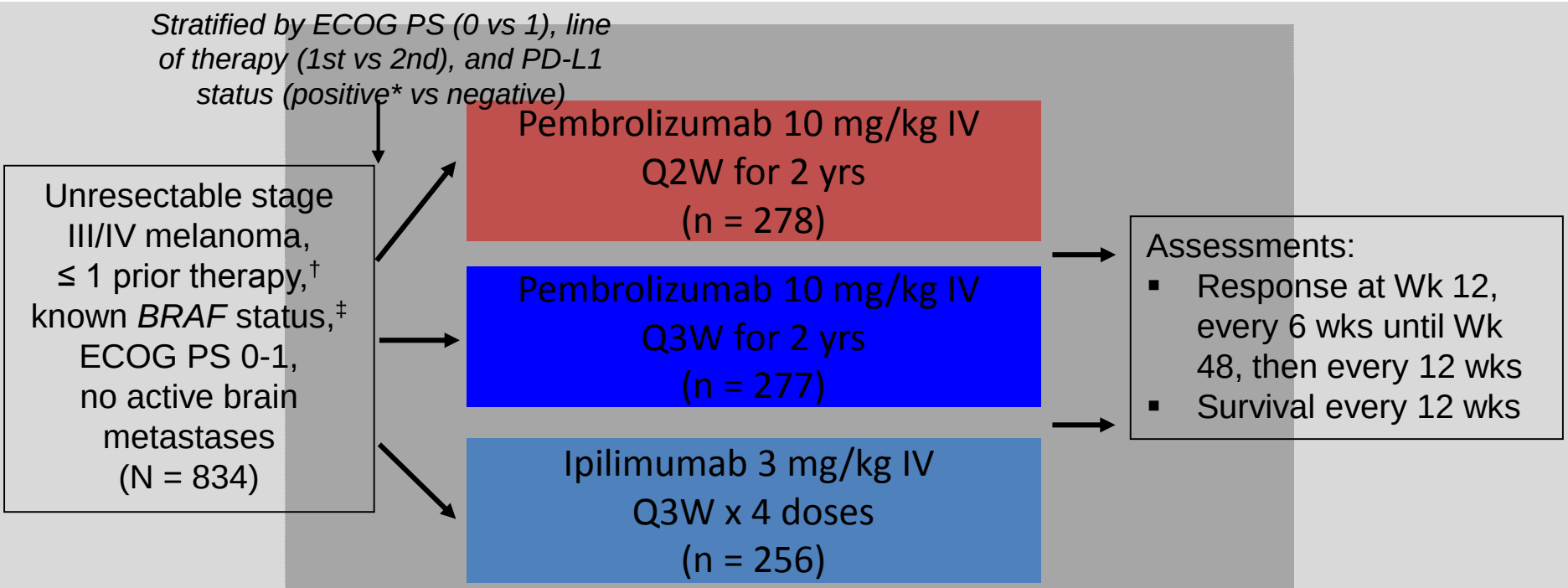
- An international, randomized phase II study in pts with advanced melanoma with PD within 24 wks after ≥ 2 Ipi doses



- Grade 3/4 toxicity incidence higher with chemotherapy (26%) vs pembrolizumab (11% at 2 mg/kg and 14% at 10 mg/kg)
- Most frequent adverse events of any grade (≥ 10%)
  - Pembrolizumab: fatigue, pruritus, and rash
  - Chemotherapy associated primarily with grade 1/2 fatigue, nausea, vomiting, anemia, reduced appetite, alopecia

Ribas A, et al. Lancet Oncol. 2015;16:908-918.

KEYNOTE-006: Study Design



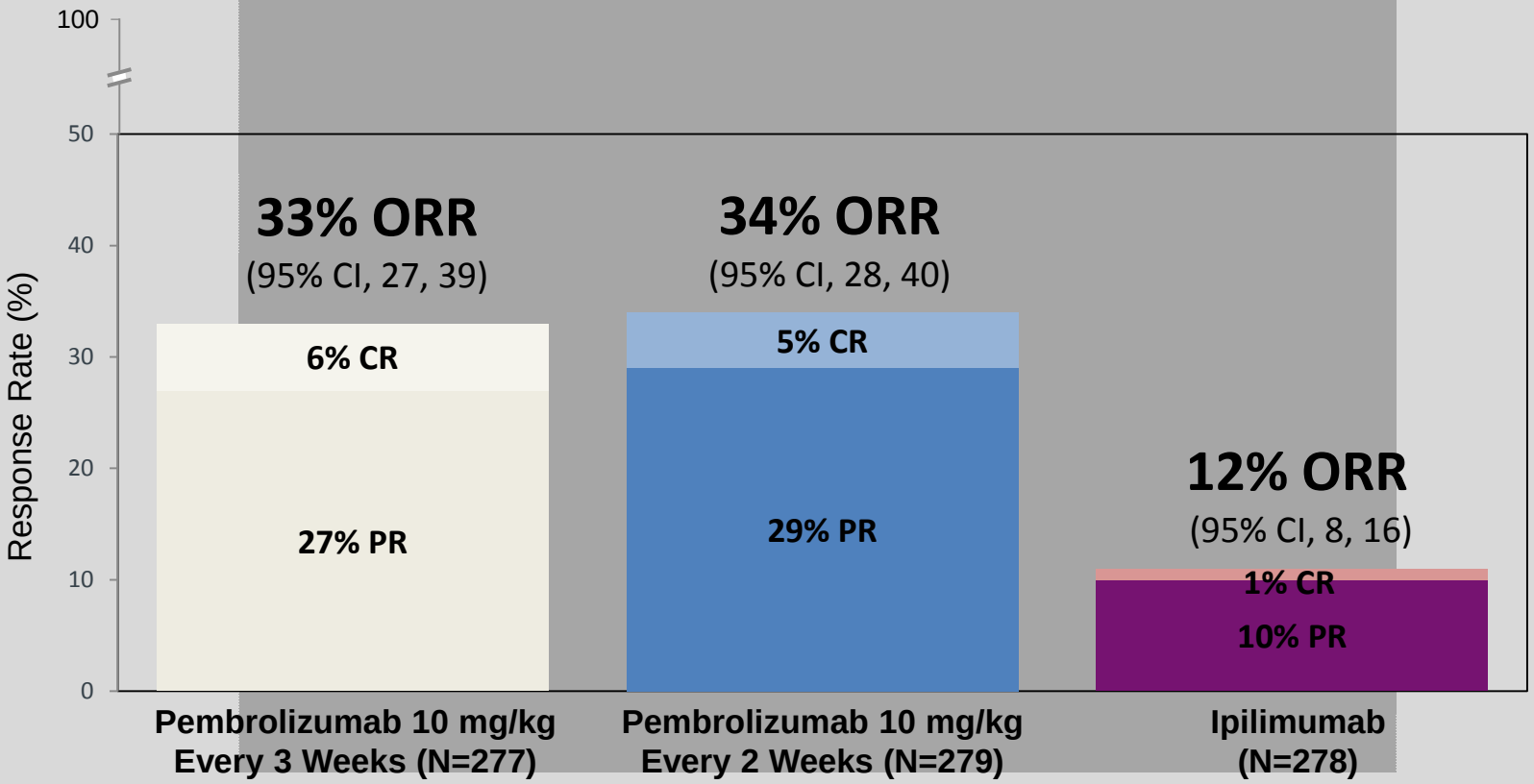
- Primary endpoints: PFS, OS
- Secondary endpoints: ORR, response duration, safety

*≥ 1% staining in tumor, adjacent immune cells by IHC (22C3 antibody).
†Excluding anti–CTLA-4, anti–PD-1, or anti–PD-L1 agents.
‡Prior anti-BRAF therapy not required if normal LDH levels, no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.

Schachter J, et al. ASCO 2016. Abstract 9504.

KEYNOTE-006: Overall Response Rate With Pembrolizumab

- Greater ORR with KEYTRUDA 10 mg/kg every 3 weeks vs ipilimumab[1,a,b]

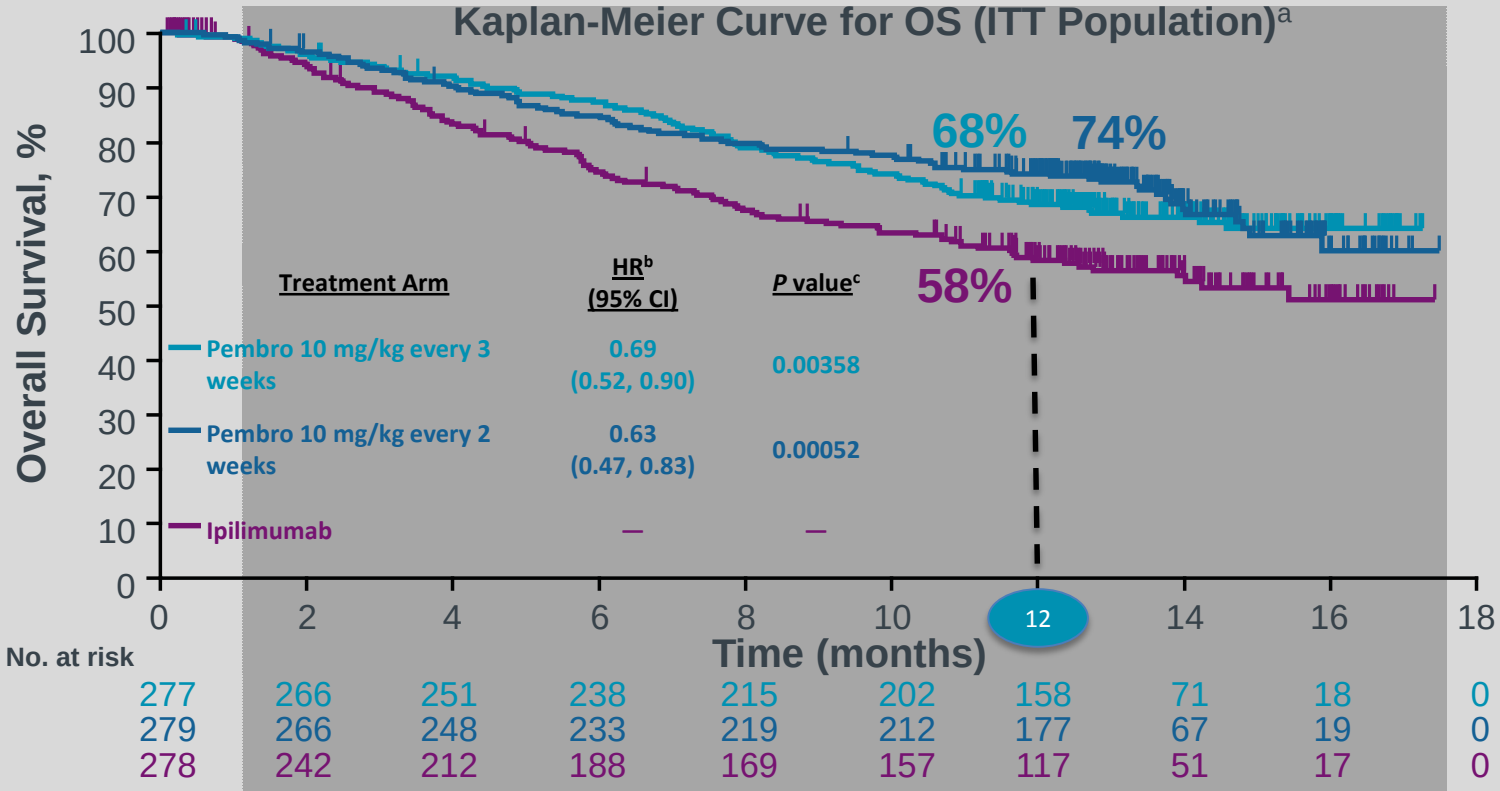


Analysis cutoff date: 3 September 2014.

Independent radiology plus oncologist review using RECIST 1.1.
CR = complete response; ORR = overall response rate; PR = partial response.

1. **[Insert local label.]**

KEYNOTE-006: Estimated OS With pembrolizumab[1,2]



- 31% reduction in the risk of death with KEYTRUDA 10 mg/kg every 3 weeks vs ipilimumab
- 37% reduction in the risk of death with KEYTRUDA 10 mg/kg every 2 weeks vs ipilimumab
- The recommended dose of KEYTRUDA is 2 mg/kg every 3 weeks[1]

Analysis cutoff date: 3 March 2015.

1. **[Insert local label.]**
2. Robert C et al, for the KEYNOTE-006 investigators. *N Engl J Med*. 2015;372(26):2521-2532.

KEYNOTE-006: Immune-Mediated AEs*

- Pembrolizumab
  - Thyroid abnormalities (hyperthyroidism, hypothyroidism, thyroiditis), pneumonitis, nephritis more common
  - Type 1 diabetes and uveitis only observed in pembrolizumab-treated pts
  - Hepatitis, myositis similar to rates with ipilimumab
- Ipilimumab
  - Colitis, hypophysitis more common
- Discontinuations ~ 5% in all arms
- ~ 10% of pts experienced grade 3/4 immune-mediated AEs
- No significant increase in incidence of immune-related AEs over time

*Not adjusted for exposure.

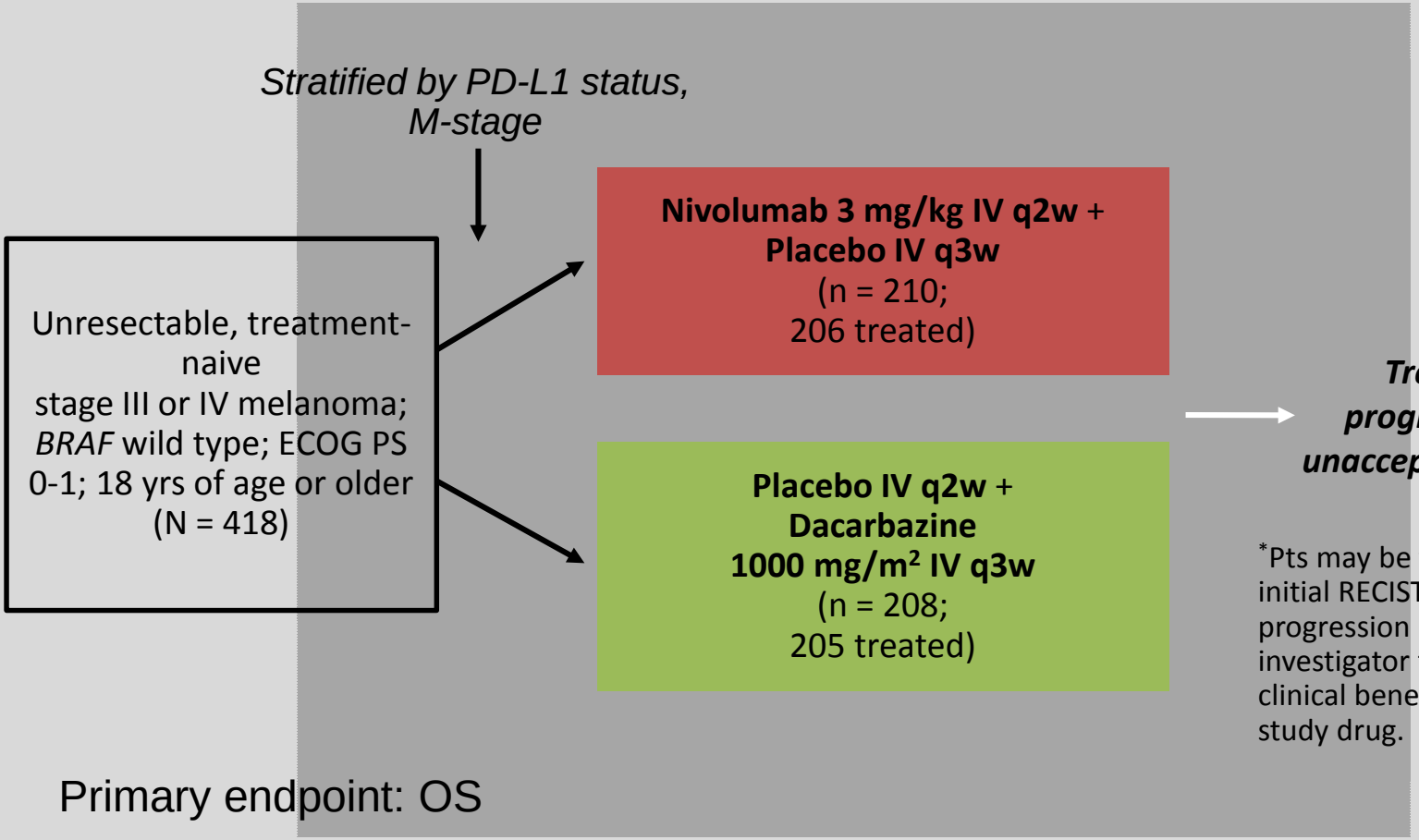
Schachter J, et al. ASCO 2016. Abstract 9504.

KEYNOTE-006
Conclusions

- Pembrolizumab associated with superior OS vs ipilimumab in pts with unresectable, stage III/IV melanoma with ≤ 1 previous line of therapy
  - Median OS for pembrolizumab not reached at median follow-up of 23 mos
- At 24 mos, ~ 30% of pembrolizumab-treated pts still **alive and free of disease progression**
- Pembrolizumab responses as durable as those with ipilimumab and continue to accrue, including CRs
- Long term safety profile for pembrolizumab remains favorable
- Investigators suggest that results confirm pembrolizumab as a standard of care for advanced melanoma

Schachter J, et al. ASCO 2016. Abstract 9504.

Phase III CheckMate 066: First-line Nivolumab vs Chemotherapy



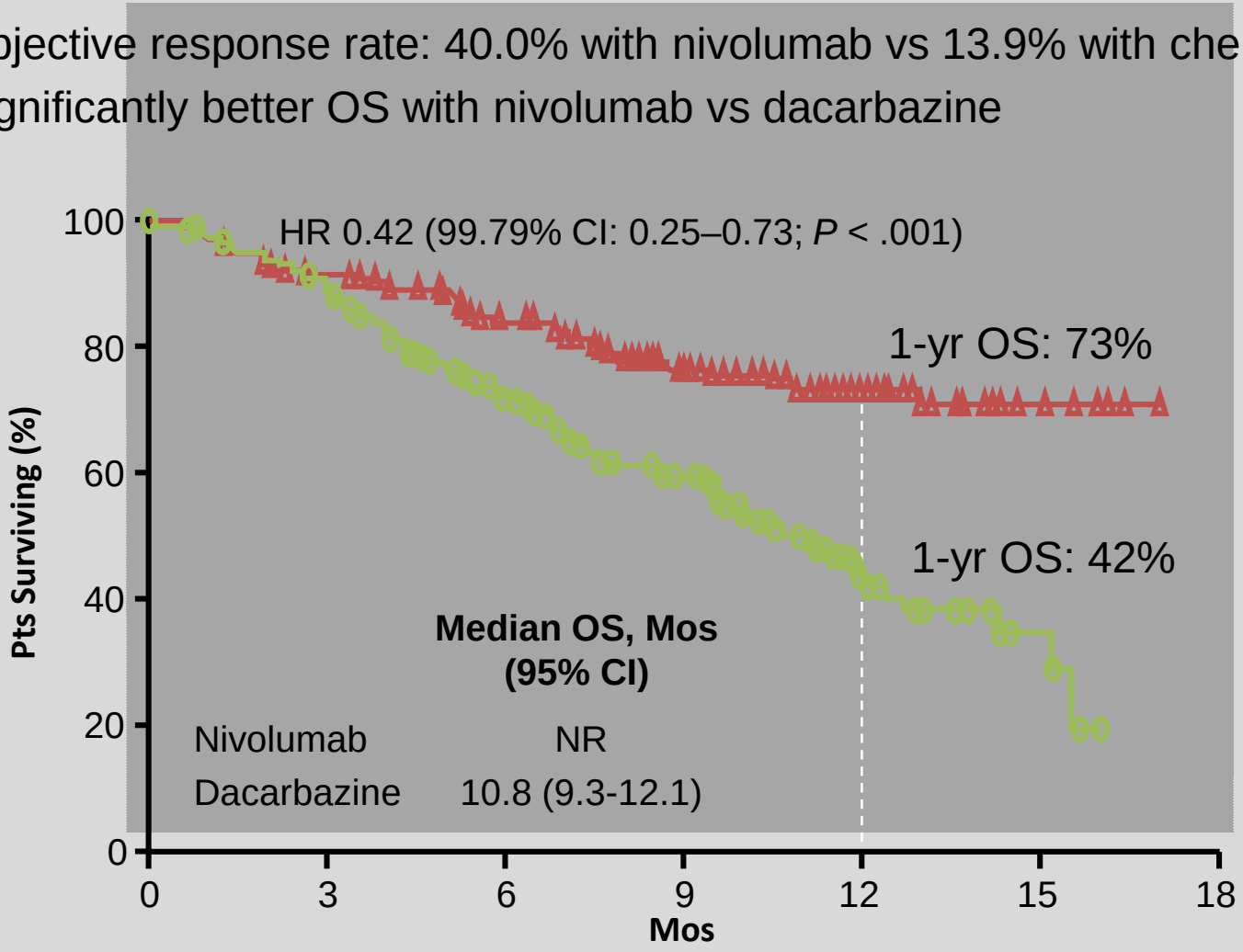
Primary endpoint: OS

Secondary endpoints: PFS, ORR, PD-L1 correlates

Robert C, et al. N Engl J Med. 2015;372:320-330.

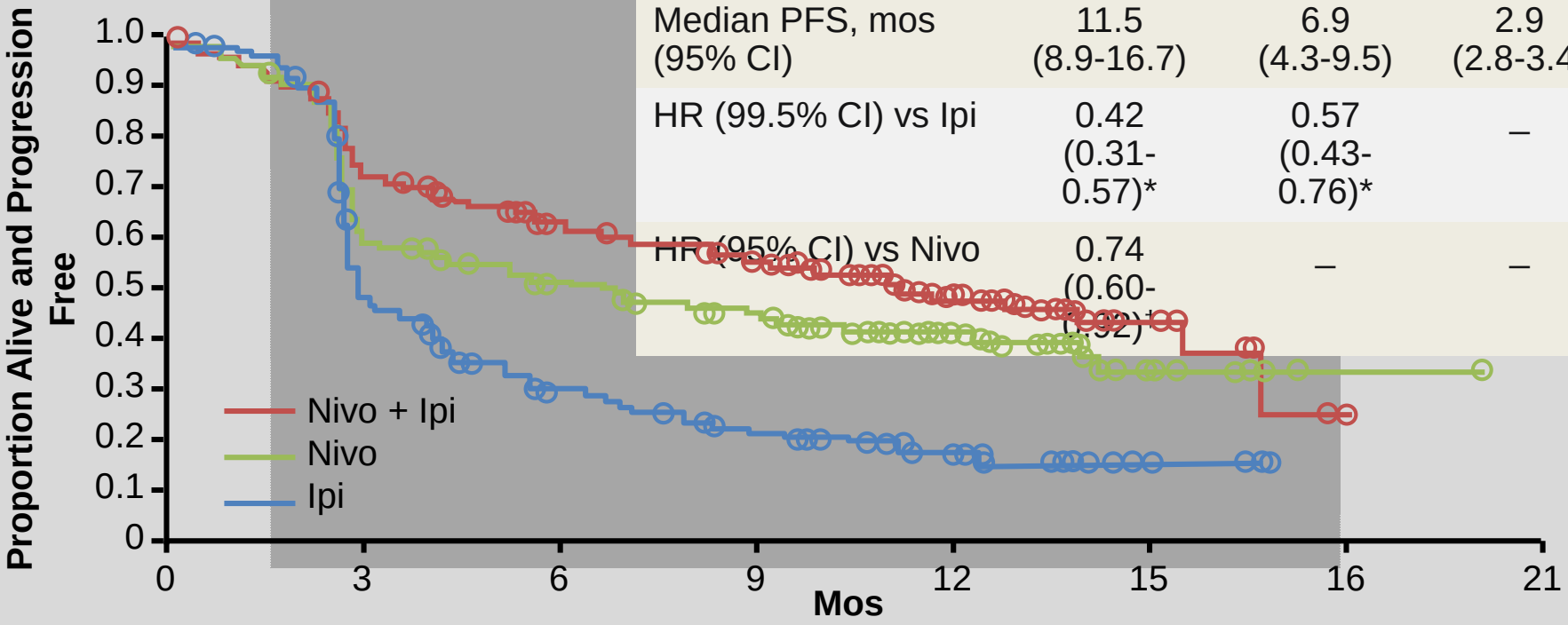
OS: First-line Nivolumab vs Chemotherapy

- Objective response rate: 40.0% with nivolumab vs 13.9% with chemo (*P* < .001)
- Significantly better OS with nivolumab vs dacarbazine



Robert C, et al. N Engl J Med. 2015;372:320-330.

CheckMate 067: Improved PFS with Nivo + Ipi or Nivo Alone vs Ipi Alone



	Nivo + Ipi (n = 314)	Nivo (n = 316)	Ipi (n = 315)
Median PFS, mos (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)*	0.57 (0.43-0.76)*	–
HR (95% CI) vs Nivo	0.74 (0.60-[illegible])	–	–

*Stratified log-rank $P < .00001$ vs Ipi.
†Exploratory endpoint.

Wolchok JD, et al. ASCO 2015. Abstract LBA1. *Reprinted with permission*.

Combination Immunotherapy

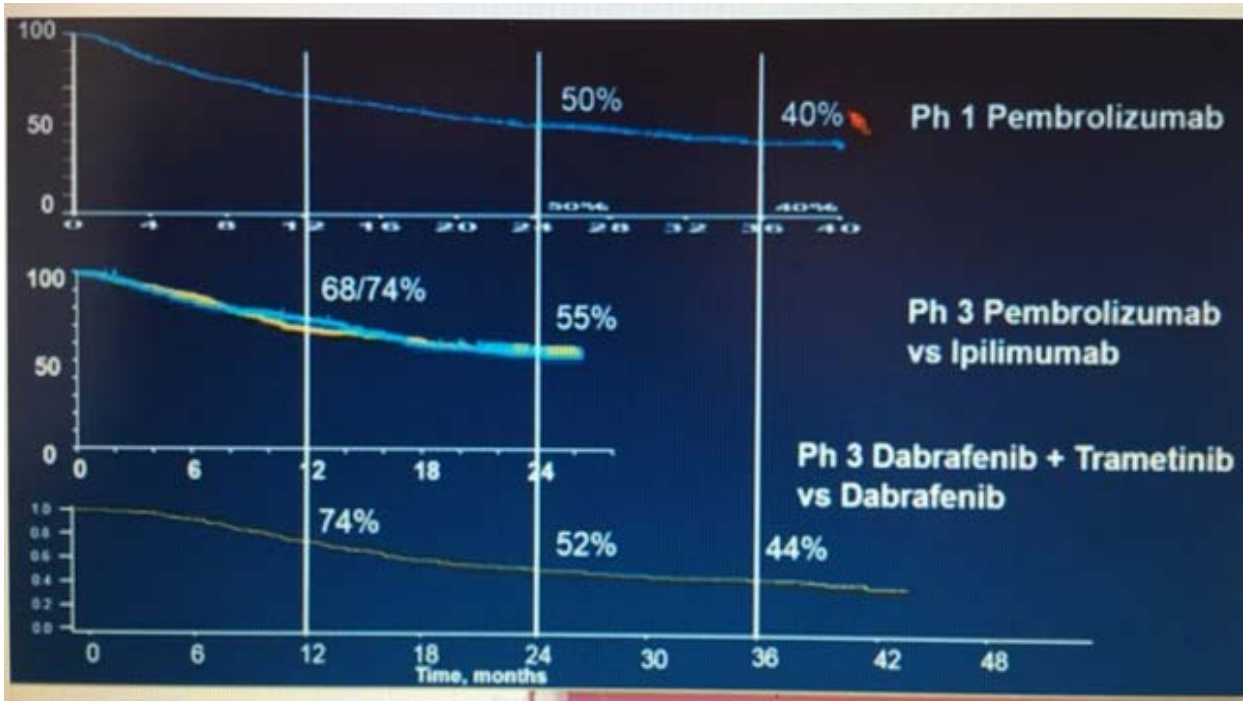
- ipilimumab + nivolumab
  - melanoma 60% response versus single agent responses 44% (nivo), 19% (ipi)
  - 12% CR
  - 80% two year survival

Combination Immunotherapies

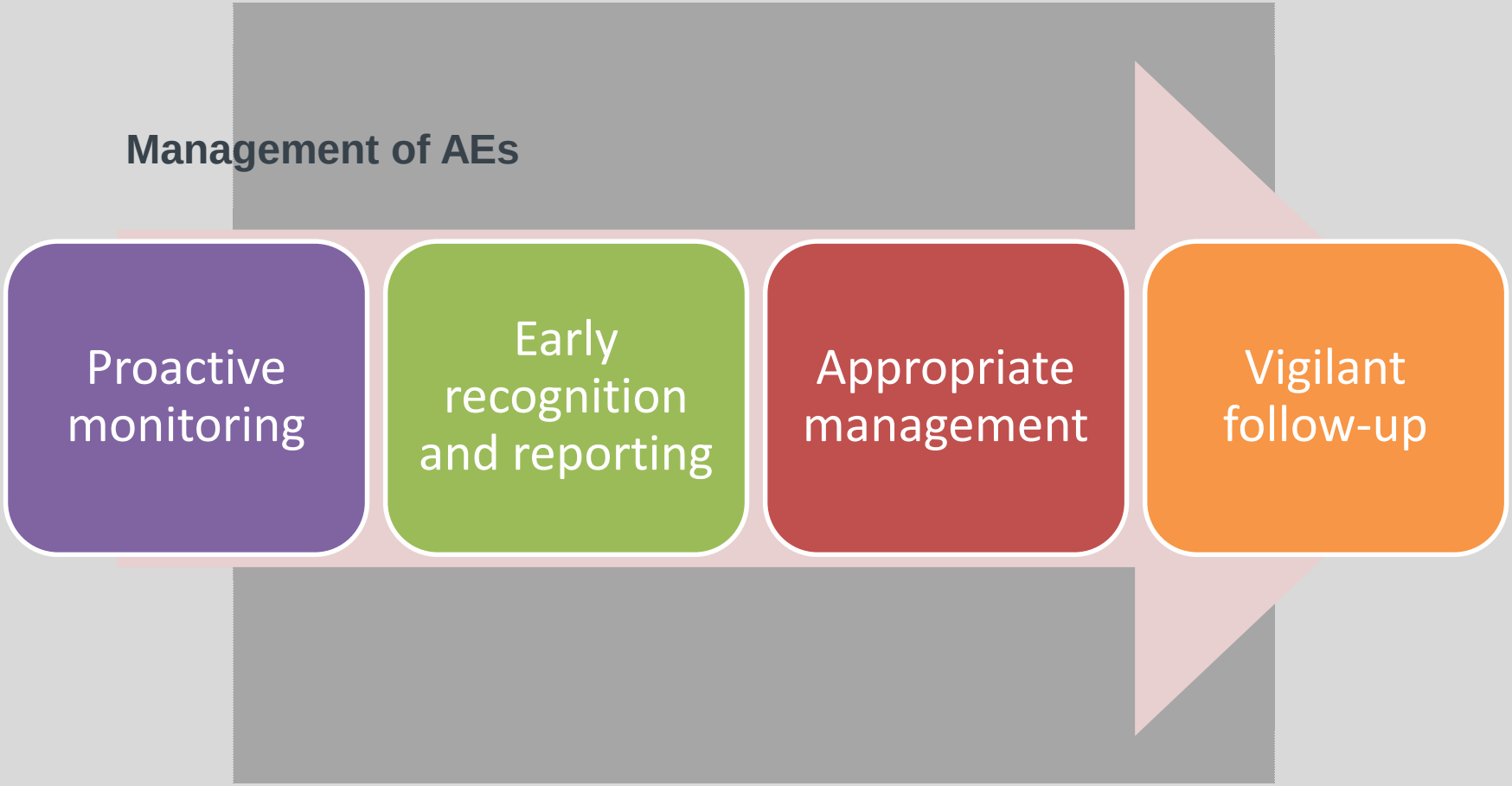
Combination Therapy	Mechanisms of Action	Phase	Indication
Nivolumab + ipilimumab	Anti-PD1 + anti-CTLA-4	I/II	Gastric, TNBC, PA, SCLC, Bladder, Ovarian
		II/III	Melanoma, RCC
		II	SCLC, GBM, NSCLC
Nivolumab + BMS-986016	Anti-PD1 + anti-LAG3	I	Solid tumors
Nivolumab + Viagenpumatucel-L	Anti-PD1 + vaccine	I	NSCLC
Nivolumab + urelumab	Anti-PD1 + anti-4-1ββ	I/II	Solid Tumors, B-Cell NHL
Atezolizumab + MOXR0916	Anti-PDL1 + anti-OX40	I	Solid Tumors
Atezolizumab + varlilumab	Anti-PDL1 + anti-CD27	II	RCC
Atezolizumab + GDC-0919	Anti-PDL1 + IDO inhibitor	I	Solid Tumors
Epacadostat + atezolizumab, durvalumab, or pembrolizumab	IDO inhibitor + anti-PDL1 or anti-PD1	I/II	Solid Tumors
Pembrolizumab + T-Vec	Anti-PD1 + vaccine	III	Melanoma
Durvalumab + tremelimumab	Anti-PDL1 + anti-CTLA-4	I/II	Melanoma
		I/II/III	SCCHN
		II	Mesothelioma, UBC, TNBC, PA
		III	NSCLC, Bladder

Combination of PD-1, PDL-1 and CTLA-4 Blockade

- higher clinical response rates than single agent
  - melanoma, NSCLC, head and neck
- lower tolerability and higher discontinuation rates
- management of toxicity in broad patient populations in community settings
- dosing and sequence
- cost

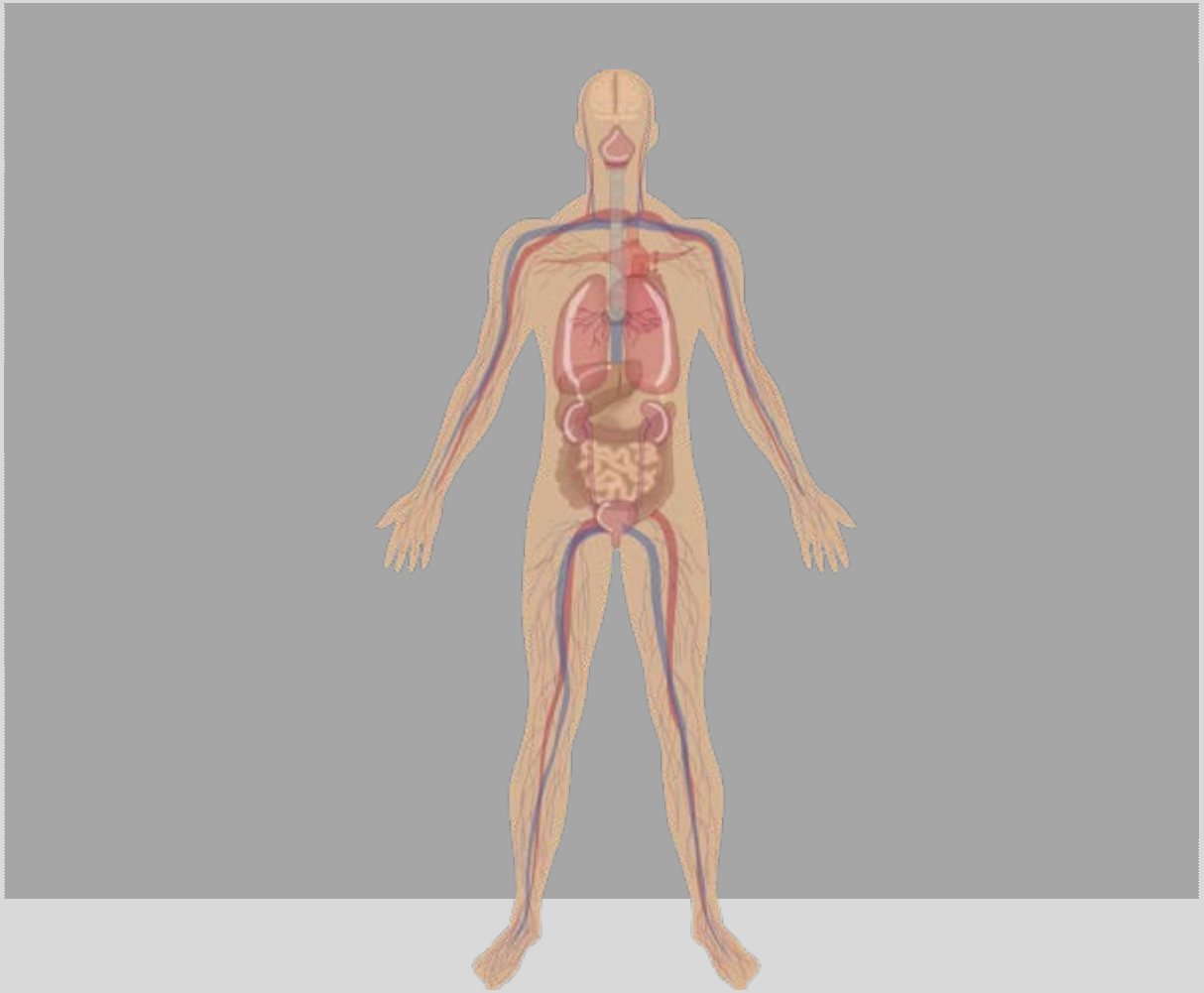

100
50
0
50%
40%
Ph 1 Pembrolizumab
100
50
0
0
6
12
18
24
68/74%
55%
Ph 3 Pembrolizumab
vs Ipilimumab
Ph 3 Dabrafenib + Trametinib
vs Dabrafenib
74%
52%
44%
0
6
12
18
24
30
36
42
48
Time, months

Effective Surveillance, Recognition, and Intervention Minimizes the Potential Impact of AEs[1,2]



1. Teply BA et al. *Oncology (Williston Park).* 2014;28 Suppl 3:30–38.
2. 2. Kannan R et al. *Clin J Onc Nurs*. 2015;18(3):311–317, 326.

irAEs Are Associated With Immuno-oncology Therapies[a]



[a] The AEs described here represent some but not all irAEs that may occur with immune checkpoint inhibitor therapies.

1. Teply BA et al. *Oncology (Williston Park).* 2014;28 Suppl 3:30–38. 2. Hodi FS et al. *N Engl J Med*. 2010;363(8):711–723. 3. Topalian SL et al. *N Engl J Med*. 2012;366(26):2443–2454. 4. Mellati M et al. *Diabetes Care*. 2015;38(9):e137–e138. 5. Forde PM et al. *Anticancer Res*. 2012;32(10):4607–4608.

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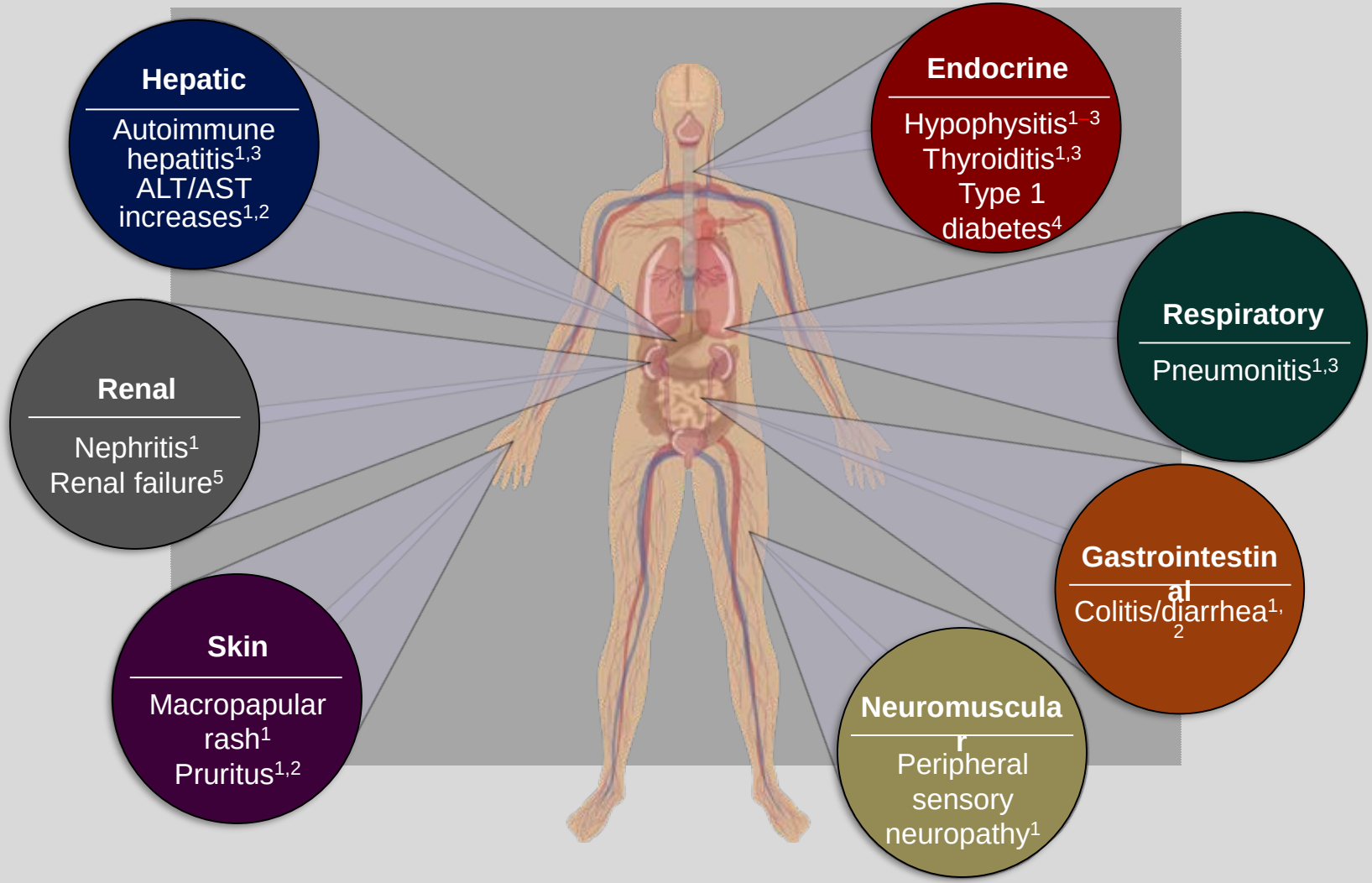

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Risk Evaluation and Management Strategy (REMS)

GASTROINTESTINAL

- Any changes in normal bowel habits or changes from baseline (eg, last week, last visit)
  - Diarrhea
  - Abdominal pain
  - Blood or mucus in stool with or without fever
  - Peritoneal signs consistent with bowel perforation
  - Ileus

LIVER

- Elevations in liver function tests
  - AST >2.5 times upper limit of normal (ULN)
  - ALT >2.5 times ULN
  - Total bilirubin >1.5 times ULN

SKIN

- Pruritus
- Rash (Maculopapular Rash)
- Viteligo

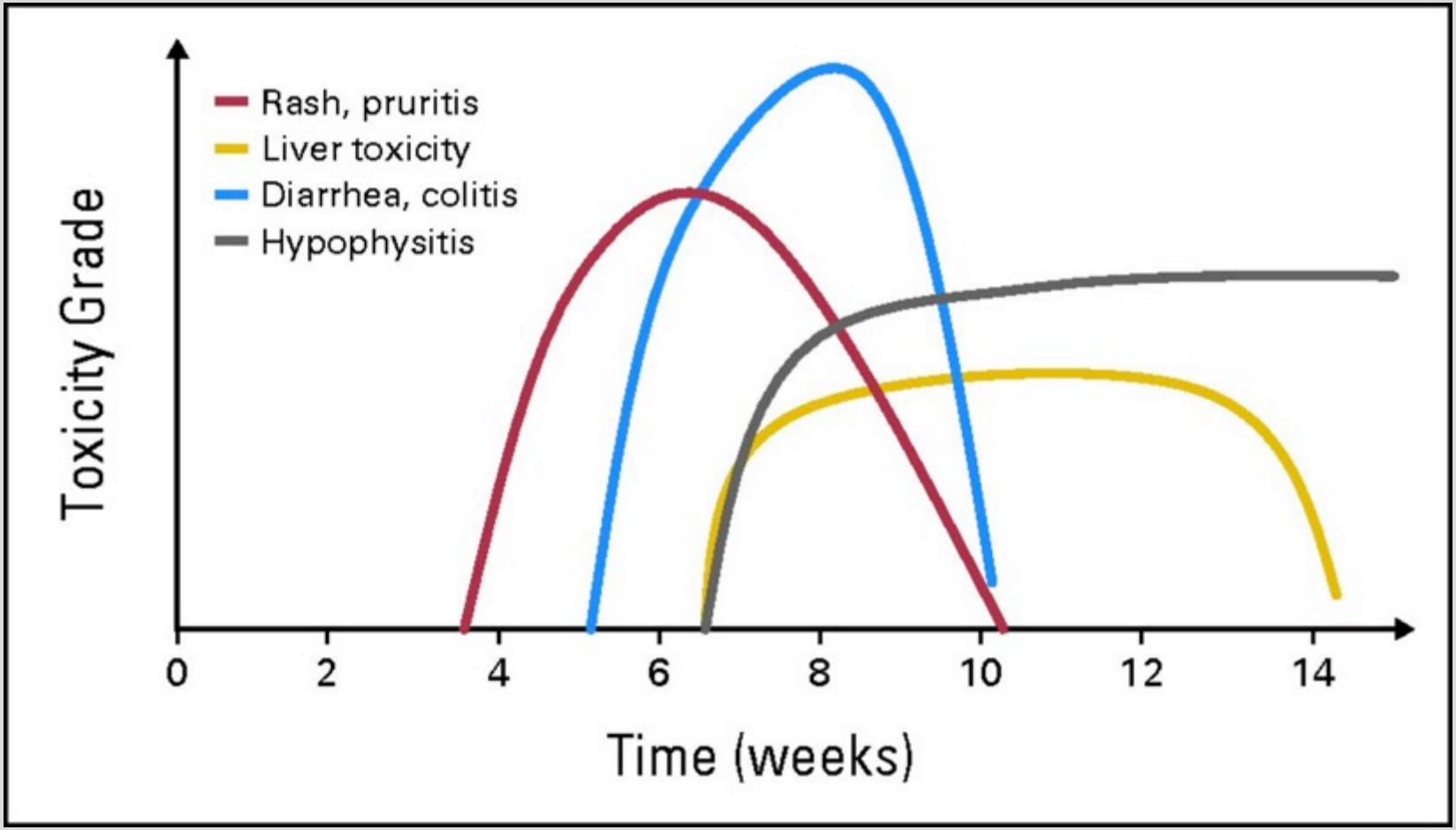
NEUROLOGIC

- Monitor for symptoms of motor and sensory neuropathy
  - Unilateral or bilateral weakness
  - Sensory alterations
  - Paresthesia

ENDOCRINE

- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries

Kinetics of appearance of immune-related adverse event



Weber J S et al. JCO 2012;30:2691-2697

Adverse Events

- CTLA-4: Rash, diarrhea, hepatitis, endocrine
  - 24% grade 3/4 (1)
- PD-1/PD-L1: Rash, fatigue, arthralgias, pnuemonitis
  - 6-12% grade 3/4 (2-4)
- Chemotherapy: Alopecia, nausea, myelosuppression
  - ~50% grade 3/4 (5)

(1) Hodi et al. *NEJM* 2010
(2) Hamid et al. *NEJM* 2013
(3) Topalian et al. *NEJM* 2012
(4) Weber et al. *Lancet Oncol* 2015
(5) Kelly et al. *JCO* 2001

Conclusions on Anti-PD1 Antibodies

- Anti-PD1 antibodies pembrolizumab and nivolumab are more active than ipilimumab[a,b,c,d]
- Analyses of QoL presented at SMR 2015 showed
  - Superior QoL with single-agent use of an anti-PD1 antibody vs single-agent ipilimumab[c]
  - Similar QoL with nivolumab/ipilimumab combination vs single-agent ipilimumab[d]
- Data from the CheckMate 067 trial suggest the tumor microenvironment may hold clues as to whether a PD1 inhibitor could be used alone or with ipilimumab in the frontline setting, although this is not entirely clear at this time and more data is needed[a]

a. Larkin J, et al. *N Engl J* Med. 2015;373:23-34; b. Postow MA, et al. *N Engl J* Med. 2015;372:2006-2017; c. Petrella T, et al. SMR 2015; d. Schadendorf D, et al. SMR 2015.

Immunotherapy Summary

- Immunotherapy continues to grow in importance in the care of patients with melanoma
- Response patterns to immunotherapy agents vary but can be durable
- Vigilance for adverse events by the patient, their family, and their healthcare team important
- Growing evidence indicates that chemotherapy treatment and the use of corticosteroids for immune-related toxicities do not reduce the efficacy of immunotherapies
- Patients education about expectations with immunotherapy is also important

Treatment of Advanced Malignant Melanoma 2016. Standard of care

- **BRAF V600E Positive**

- Vemurafenib (+ - Cobimet)
- Dabrafenib + Trametinib
- Ipilimumab
- Pembrolizumab / Nivolumab
- T-VEC
- Clinical trials

- **BRAF V600E Negative**

- Pembrolizumab/Nivolumab
- Ipilimumab
- Ipilimumab + Nivolumab
- T-VEC
- Clinical trials

Future Directions

Combination strategies including immunotherapy are currently being evaluated

Targeted agents + immunotherapy

Multiple immunotherapeutic agents

Patients selection using clinical and biological biomakers

Identification of additional tumor subtypes that can be effectively treated with immunotherapy

“In your case, Dave, there are choices, surgery, outpatient immunotherapy, anti BRAF, anti MEK, anti PDI or whatever is in the box that our lovely Carol is holding”.

‘THANK YOU’

SANDTON ONCOLOGY CENTRE

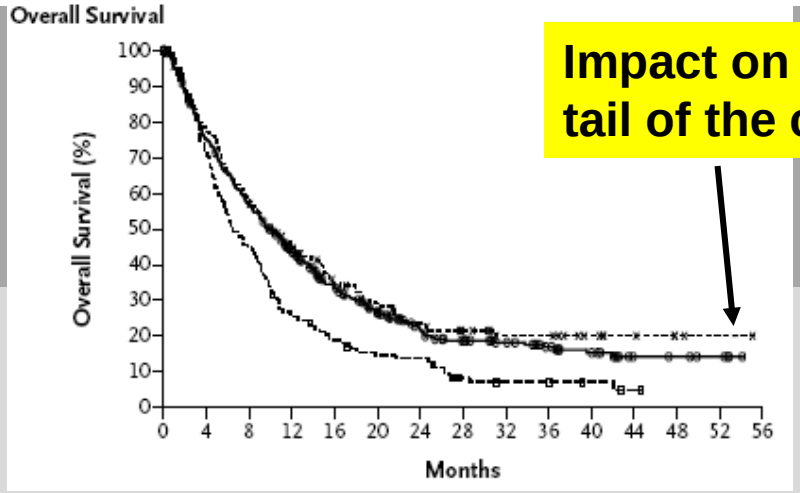
Ipilimumab
Major benefit is in durable tumor regressions

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.D., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.



Impact on the tail of the curve!