
SITC
2017
November 8-12
NATIONAL HARBOR
MARYLAND
Gaylord National Hotel
& Convention Center
sitc
Society for Immunotherapy of Cancer

November 8-12 • NATIONAL HARBOR, MD

Basic Principles of Tumor Immunotherapy

Michael K Wong MD PhD FRCPC
MD Anderson Cancer Center
mkwong@mdanderson.org

Presenter Disclosure Information

Michael K Wong MD PhD

The following relationships exist related to this presentation:

Vali Nanomedical, Founders Shares Received, Founder
Merck Pharmaceuticals, Honorarium , Advisory Board

Today's Goal: Provide a structured approach to ImmunoRx

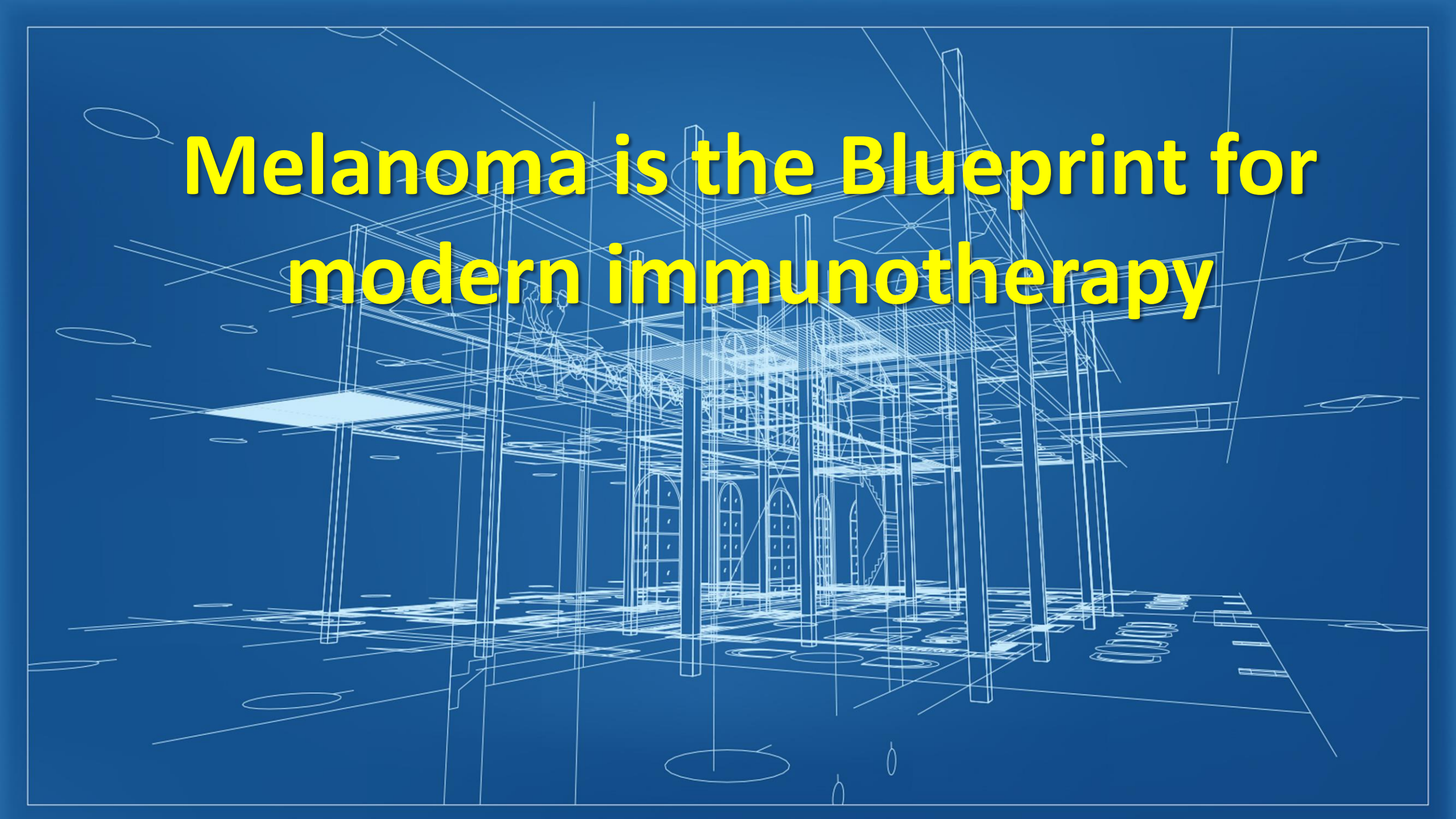

Jackson Pollack, MOMA, 2015


Douglas Coupland, Vancouver Museum of Art, 2015

Agenda

What are the principles that guide the use of immunotherapy?

- Who:
- Why :
- What :
- How:
- When:


Melanoma is the Blueprint for modern immunotherapy

Who: Immunotherapy's Expanding Footprint

2015

Nivolumab
11/2015: advanced **renal cell** carcinoma

Pembrolizumab
10/2015: PD-L1 positive advanced **non-small cell lung cancer**,

2016

Pembrolizumab
10/2016: **Head and neck** squamous cell cancer

Nivolumab
05/2016: Classical **Hodgkin lymphoma**
11/2016: **Head and Neck** squamous cell carcinoma

Atezolizumab
05/2016: **Urothelial** carcinoma
Metastatic **non-small cell lung cancer**

Who: Immunotherapy's Expanding Footprint

2017

Durvalumab
5/1/2017: platinum resistant locally advanced or metastatic **urothelial carcinoma**

Avelumab
3/23/2017: adults and pediatric patients 12 years and older with metastatic **Merkel cell carcinoma**

Pembrolizumab
3/14/2017: adult and pediatric patients with **refractory classical Hodgkin lymphoma** (cHL).

Nivolumab
2/2/2017: locally advanced or metastatic **urothelial carcinoma**

Nivolumab
7/31/2017: patients > = 12 years mismatch repair deficient (dMMR) and **microsatellite instability high** (MSI-H) metastatic colorectal cancer (post therapy)

Pembrolizumab
5/23/2017: adult and pediatric solid tumors with **microsatellite instability-high** (MSI-H) or mismatch repair deficient (dMMR).

Who: Immunotherapy's Expanding Footprint

2017

Nivolumab
9/22/2017: **hepatocellular carcinoma** (HCC) in patients who have been previously treated with sorafenib.

Pembrolizumab
9/22/2017: recurrent locally advanced or metastatic, **gastric, gastroesophageal junction adenocarcinoma** PD-L1+, >= 2 previous Rx (5FU, Platinum, EGFR)

Who: Selecting patients by PD-L1 Tumor Tissue Status

Principle: "+" = better response, outcomes

Table 1
Summary estimates according to PD-L1 status for clinical objective response and deaths.

Cancer Type	n. of estimates (n. of trials)	Subgroups	PD-L1 status	Summary Objective Response Rate (95% CI)	Odd Ratio	I^2%
MM	12 (10)		Positive	45% (35, 55)	2.14 (1.65, 2.77)	40
			Negative	27% (17, 39)		
	5 (6)	In anti-PD-1 treatment arms	Positive	46% (27, 65)	1.89 (1.35, 2.64)	0
			Negative	35% (19, 53)		
	5 (6)	In anti-PD-1 other treatment arms	Positive	16% (11, 2)	0.96 (0.5, 1.87)	5
			Negative	12% (5, 23)		
NSCLC	9 (8)		Positive	25% (20, 31)	2.12 (1.23, 3.66)	26
			Negative	14% (10, 18)		
	5 (5)	Squamous	Positive	26% (16, 38)	1.49 (0.48, 4.64)	0
			Negative	15% (8, 24)		
	4 (4)	Non-squamous	Positive	29% (19, 4)	3.78 (1.54, 9.24)	0
			Negative	11% (5, 19)		
RCC	4 (3)		Positive	29% (8, 57)	1.70 (0.32, 9.02)	33
			Negative	25% (0, 76)		
MM	6 (4)	Deaths			0.47 (0.30, 0.75)	0

Gandini, Sara, Daniela Massi, and Mario Mandalà. "PD-L1 expression in cancer patients receiving anti PD-1/PD-L1 antibodies: A systematic review and meta-analysis." Critical reviews in oncology/hematology 100 (2016): 88-98.

Cancer	PD-L1 status	Summary Objective Response Rate (95% CI)
MM	Positive	45% (35, 55)
	Negative	27% (17, 39)
	Positive	46% (27, 65)
	Negative	35% (19, 53)
	Positive	16% (11, 2)
	Negative	12% (5, 23)
NSCLC	Positive	25% (20, 31)
	Negative	14% (10, 18)
	Positive	26% (16, 38)
	Negative	15% (8, 24)
	Positive	29% (19, 4)
	Negative	11% (5, 19)
RCC	Positive	29% (8, 57)
	Negative	25% (0, 76)

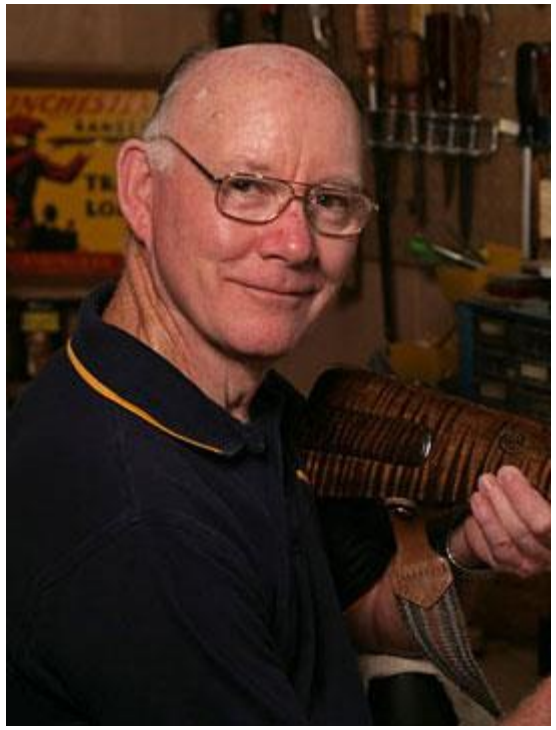
Gandini, Sara, Daniela Massi, and Mario Mandalà. "PD-L1 expression in cancer patients receiving anti PD-1/PD-L1 antibodies: A systematic review and meta-analysis." Critical reviews in oncology/hematology 100 (2016): 88-98.

Agenda

What are the principles that guide the use of immunotherapy?

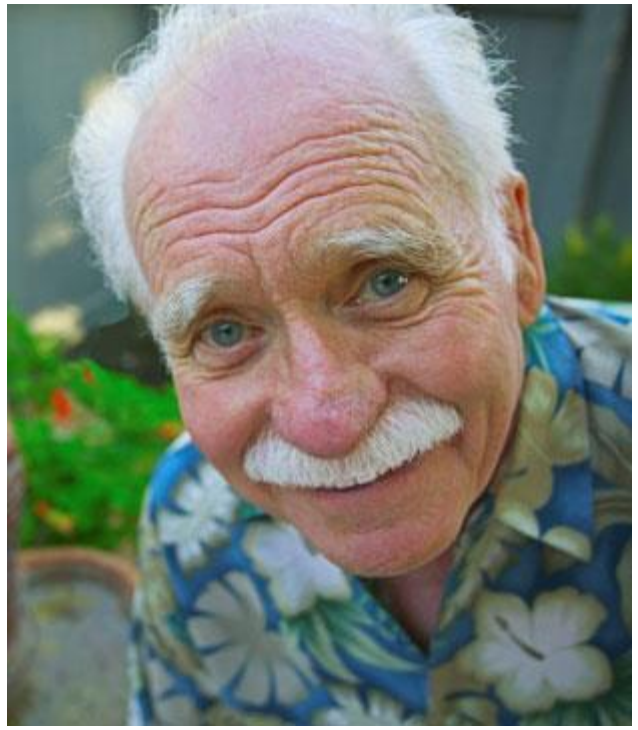
- Who: Expanding list of hematologic and solid tumors.
- Why :
- What :
- How:
- When:

Why is this important?

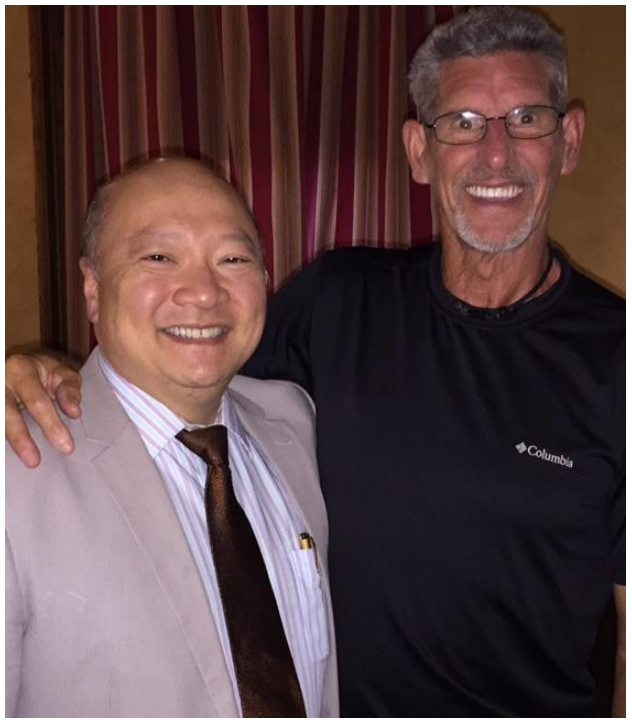


Cancer free 11 years

Cancer free 10 years



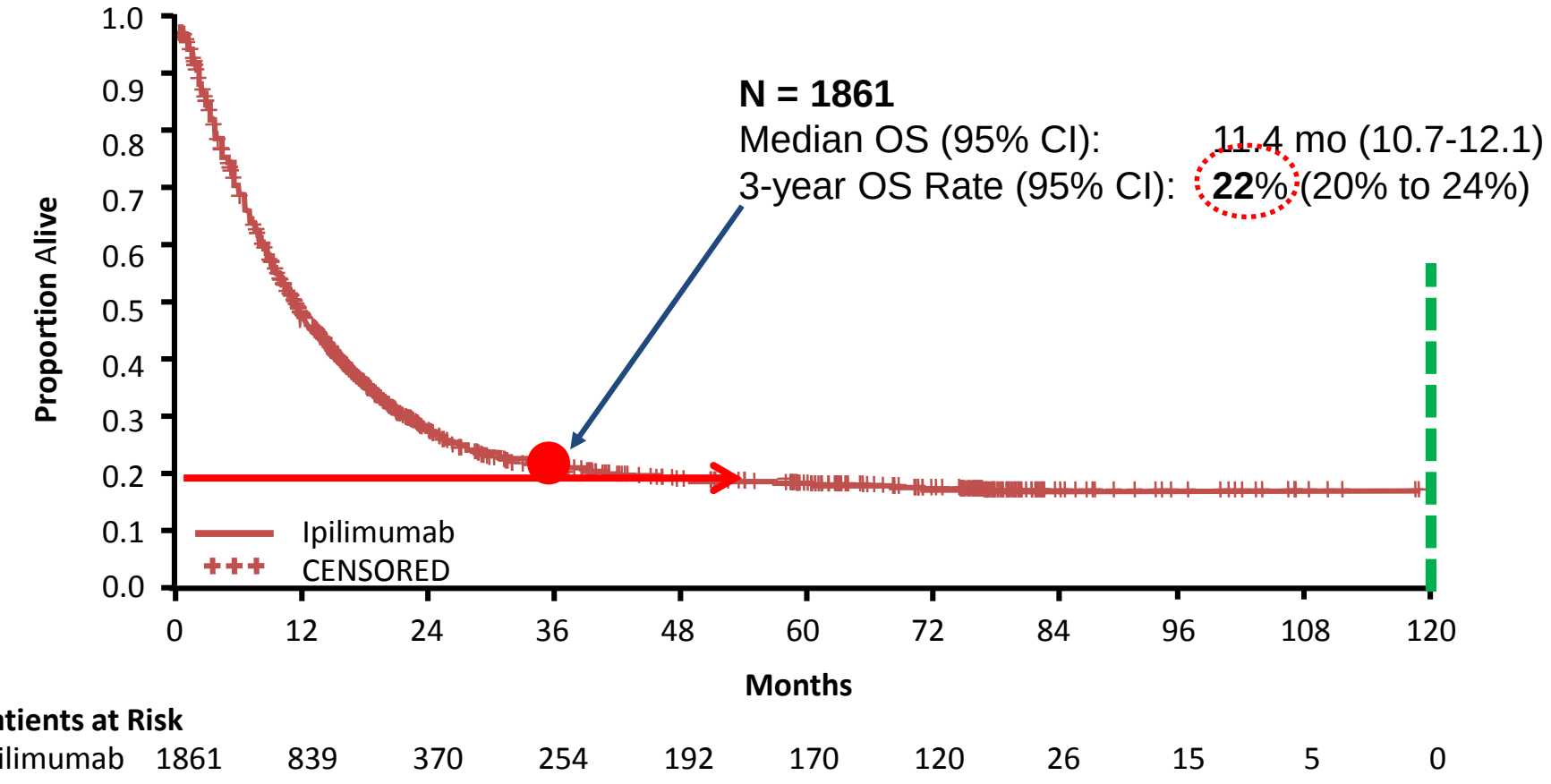
Cancer free 10 years



Cancer free 10 years

http://www.proleukin.com/ (patient stories) – accessed November 15, 2014

Ipilimumab (Yervoy™): Pooled Survival Analysis from Phase II/III Trials in Advanced Melanoma



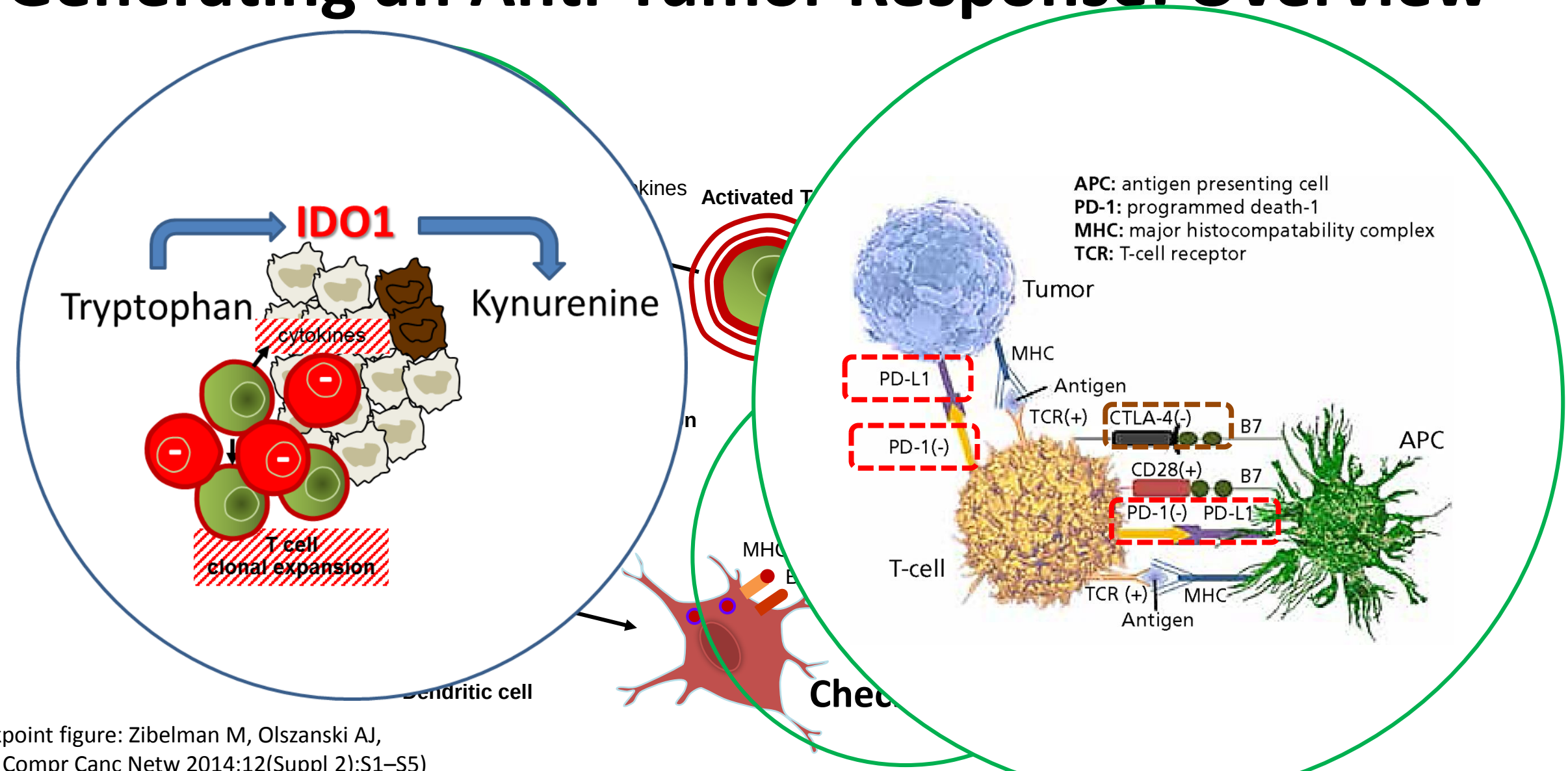
Hodi S, et al. 2013 European Cancer Congress. Abstract LBA 24.

Agenda

What are the principles that guide the use of immunotherapy?

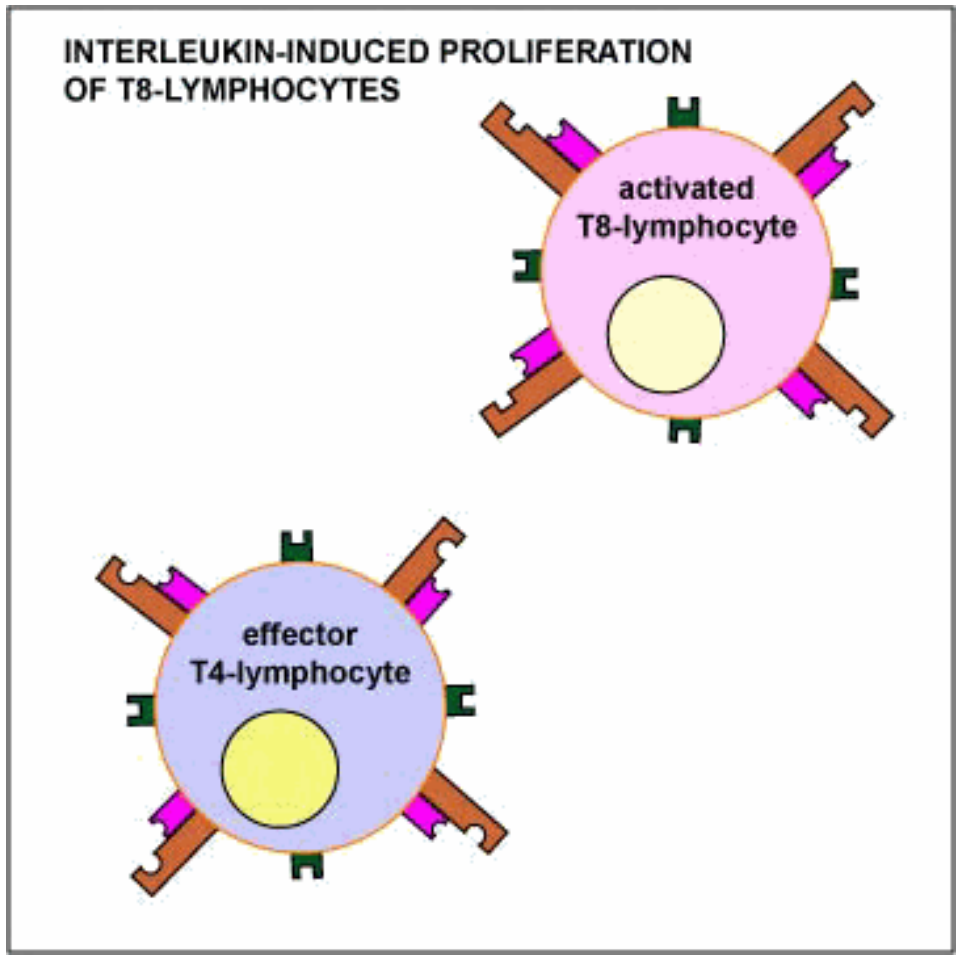
- Who: Expanding list of hematologic and solid tumors.
- Why : Long term responses.
- What :
- How:
- When:

Generating an Anti-Tumor Response: Overview

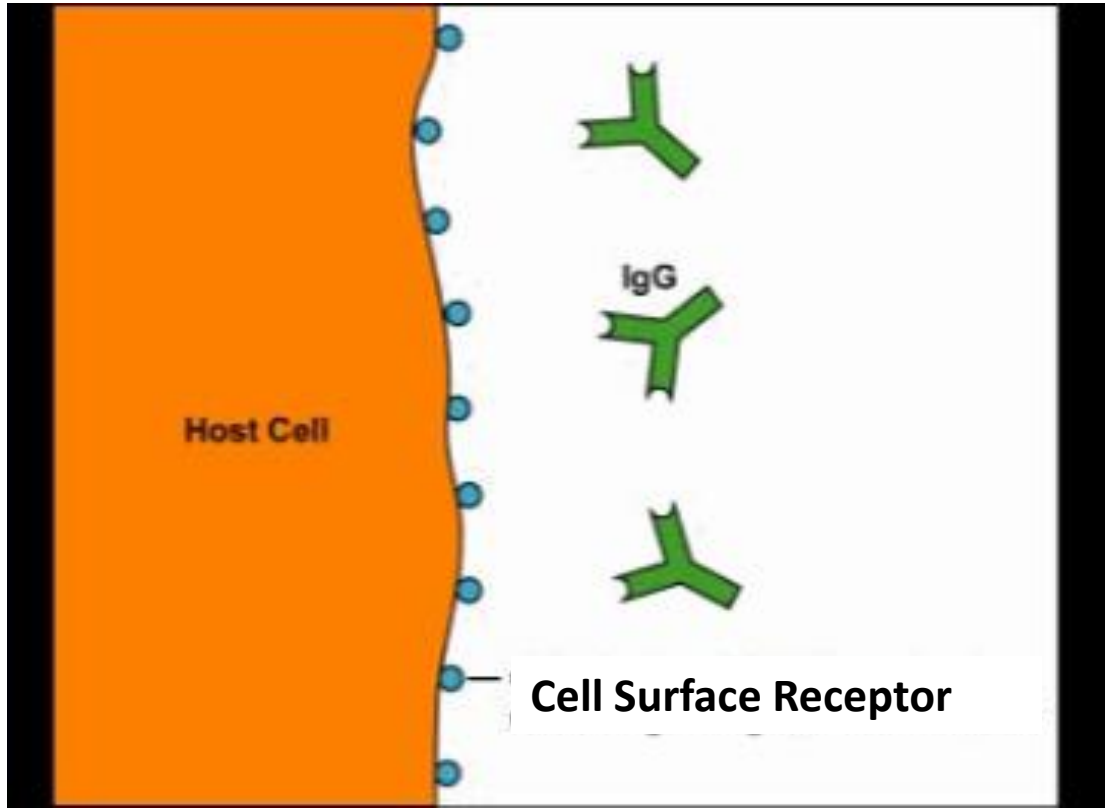


Checkpoint figure: Zibelman M, Olszanski AJ,
J Natl Compr Canc Netw 2014;12(Suppl 2):S1–S5)
IDO figure, modified from: clinicaloptions.com

Cytokine
(Interleukin – 2)



Blocking Antibody
Ipilimumab, Nivolumab, Pembrolizumab, Avelumab

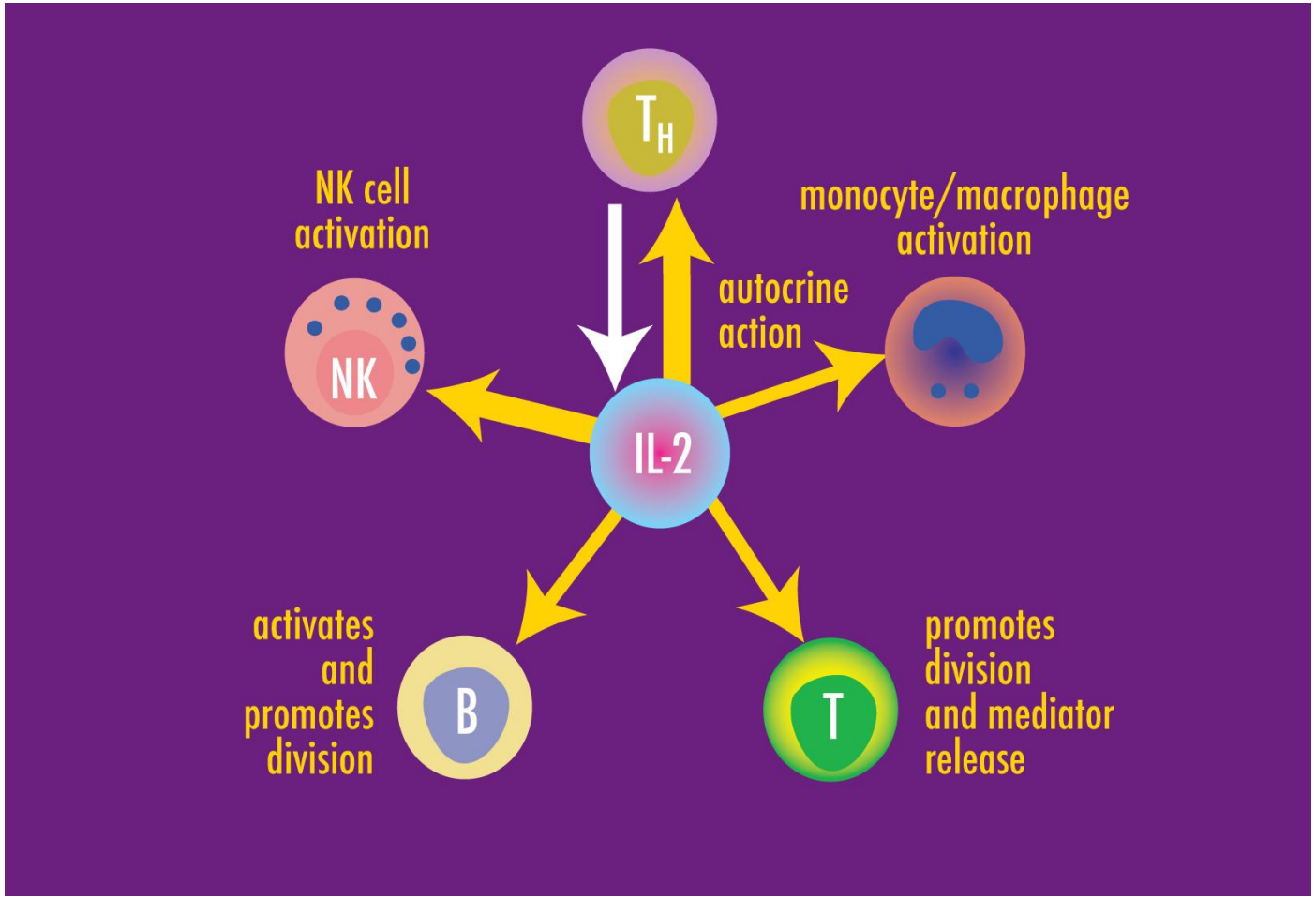


Agenda

What are the principles that guide the use of immunotherapy?

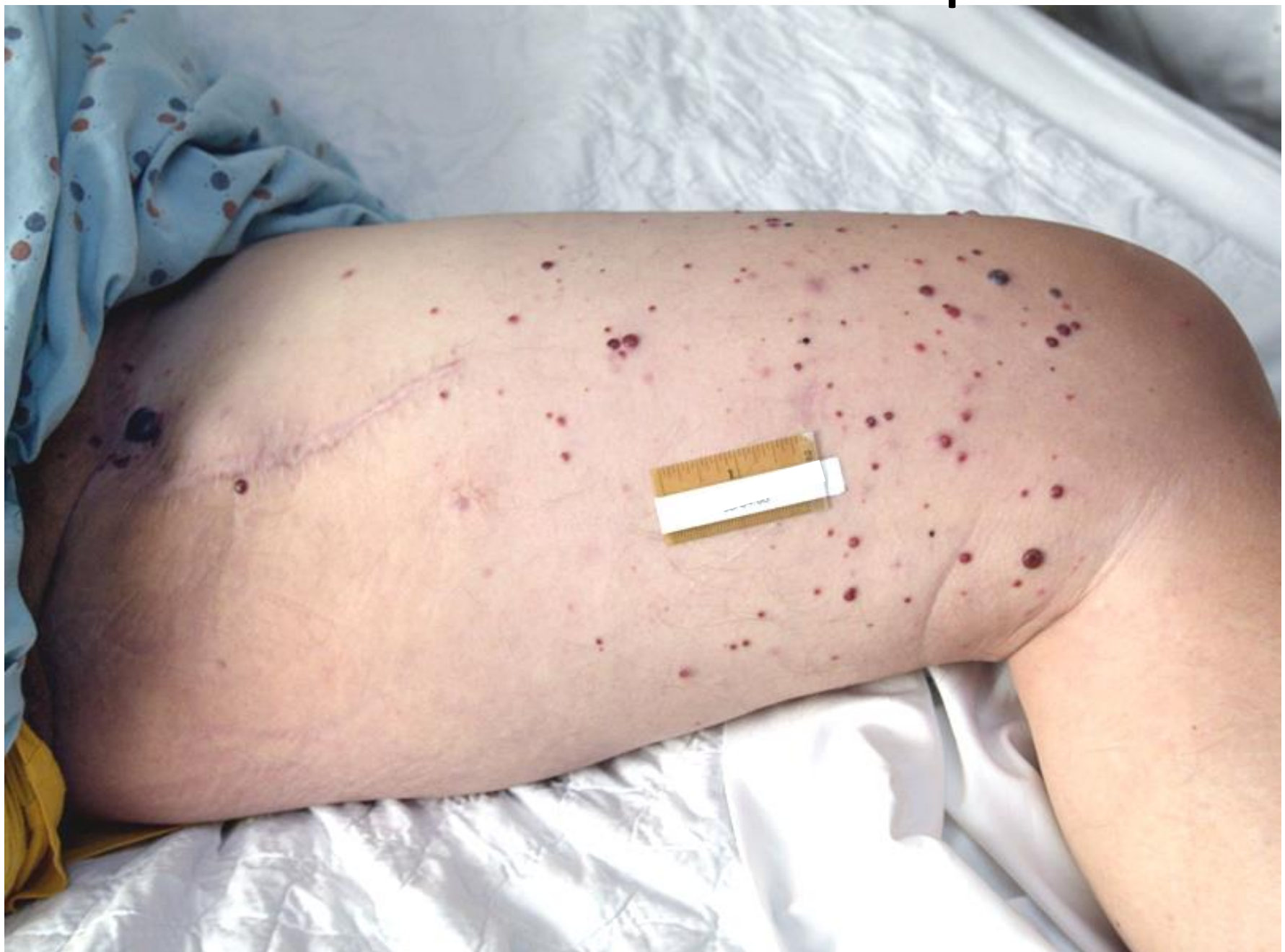
- Who: Expanding list of hematologic and solid tumors.
- Why : Long term responses.
- What : Checkpoints, Modulators, Vaccines, Cytokines.
- How:
- When:

IL-2 is in the center of the Immune Response

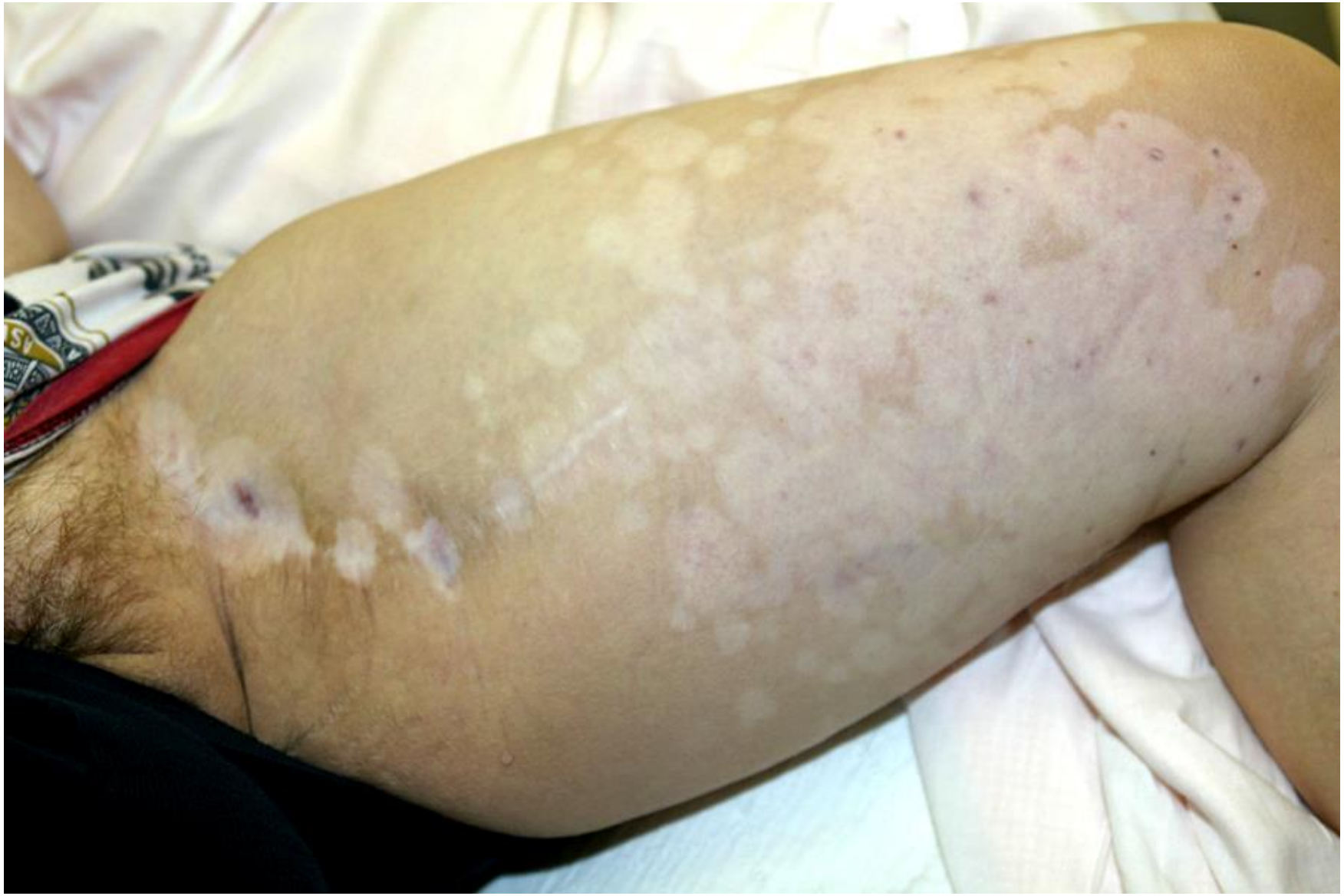


Roitt I, et al. *Immunology*. 1996;8:11.

Melanoma Case: IL-2 responses

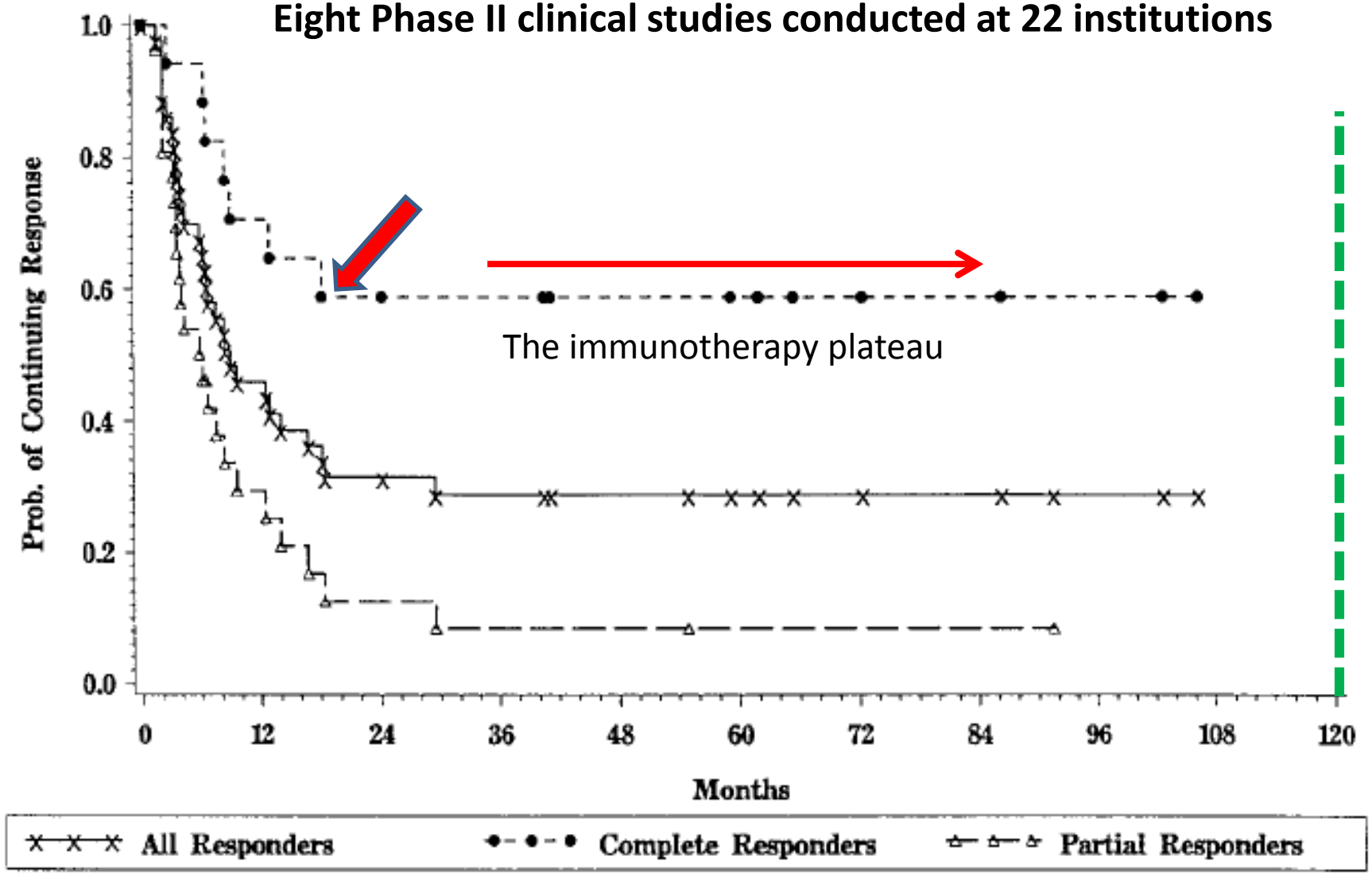


Melanoma Case: IL-2 responses



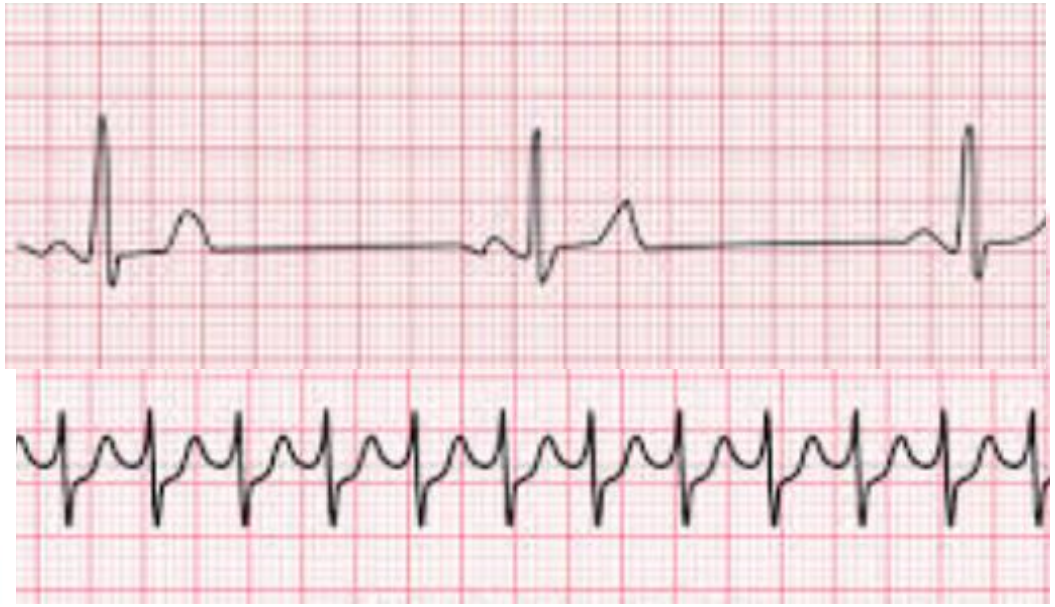
The Kaplan-Meier "Plateau": Durable responses with HD IL-2

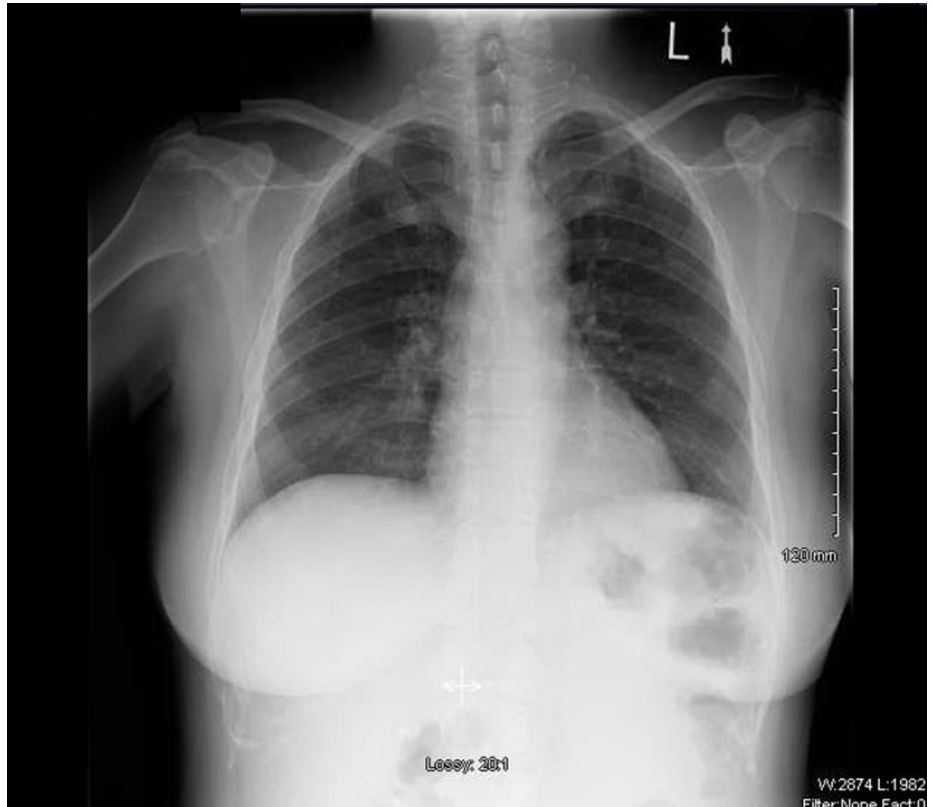
Eight Phase II clinical studies conducted at 22 institutions

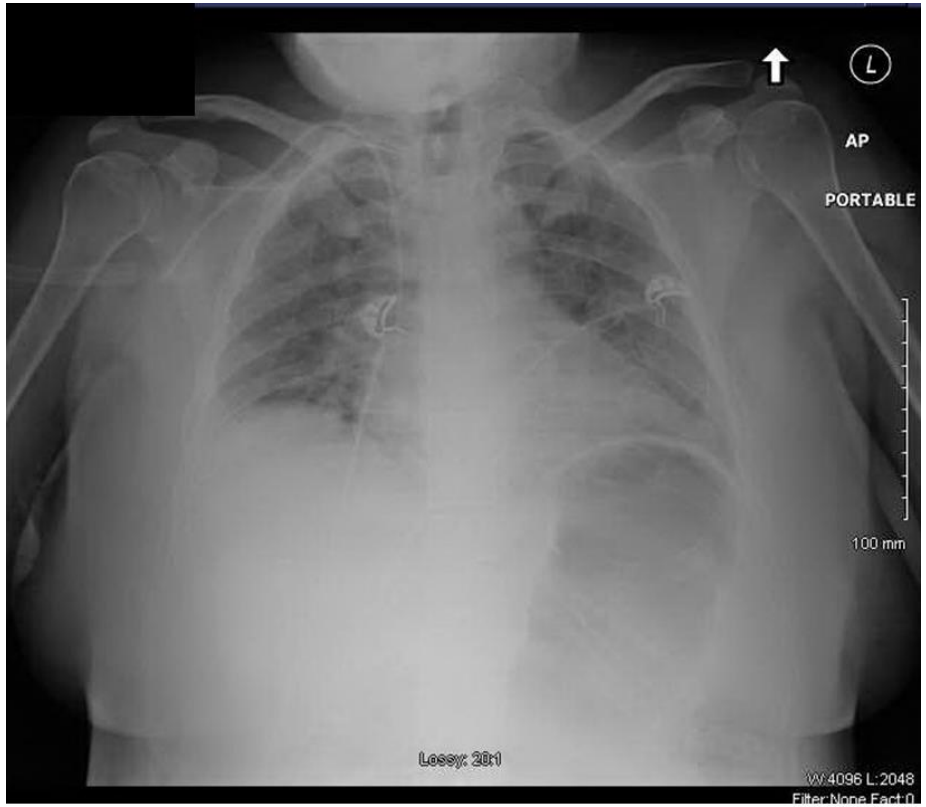


Atkins M et al., High-Dose Recombinant Interleukin 2 Therapy for Patients with Metastatic Melanoma: Analysis of 270 Patients Treated Between 1985 and 1993., J Clin Onc 17: 2105 (1999).


mooremedical



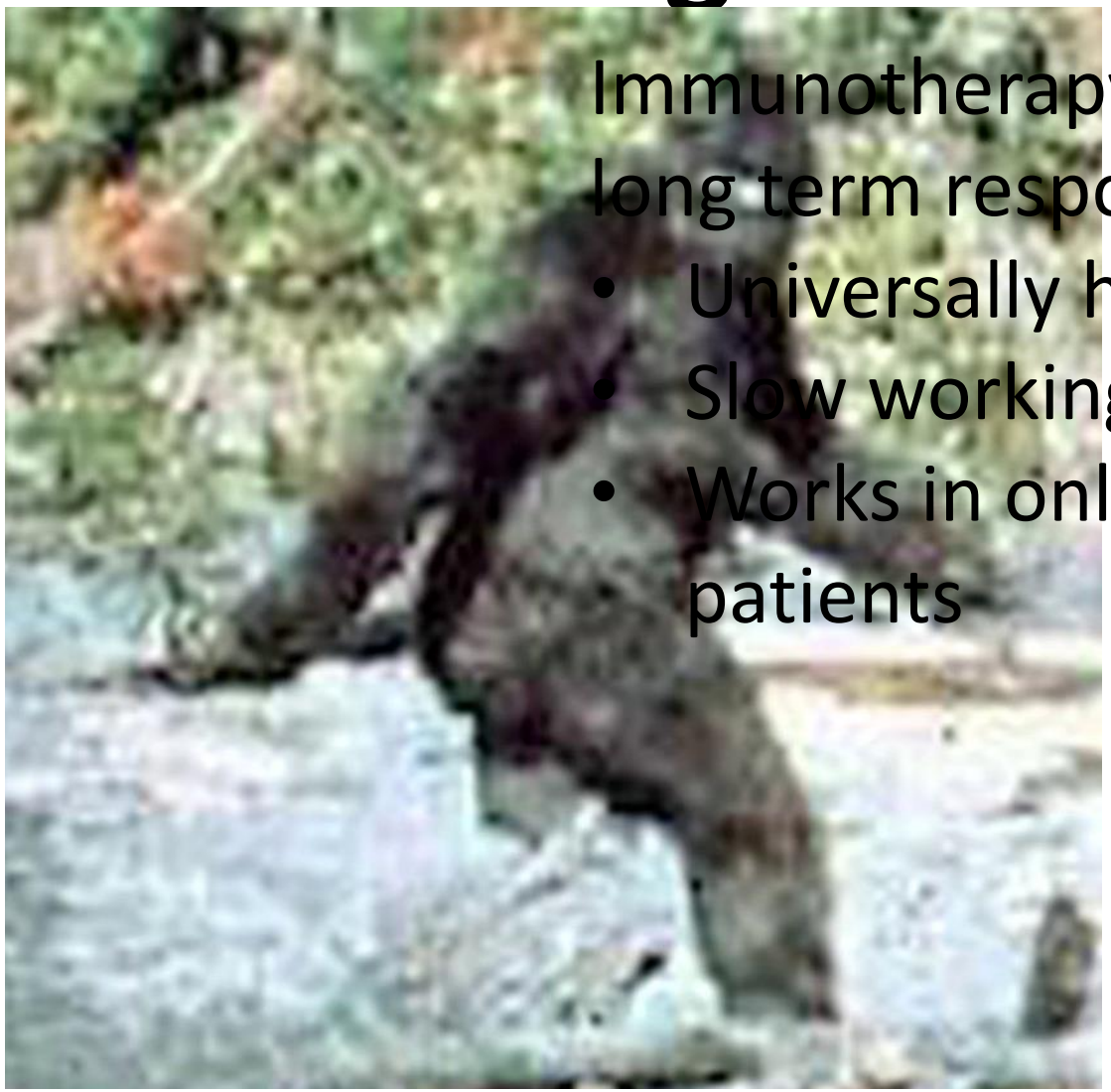

L
120 mm
Lossy: 20:1
W:2874 L:1982


L
AP
PORTABLE
100 mm
Lossy: 20:1
W:4096 L:2048

Cytokine Immunotherapy

- Requires a dedicated unit.
- **Highly selected populations**
- Decision point after 1-2 courses
- Can be durable!
- Current research:
  - Alternate schedule/dose
  - Combination therapy
  - Alternate forms of IL-2

Urban Legend



Immunotherapy can give rise to long term responders but it is:

- Universally highly toxic
- Slow working
- Works in only a small % of patients

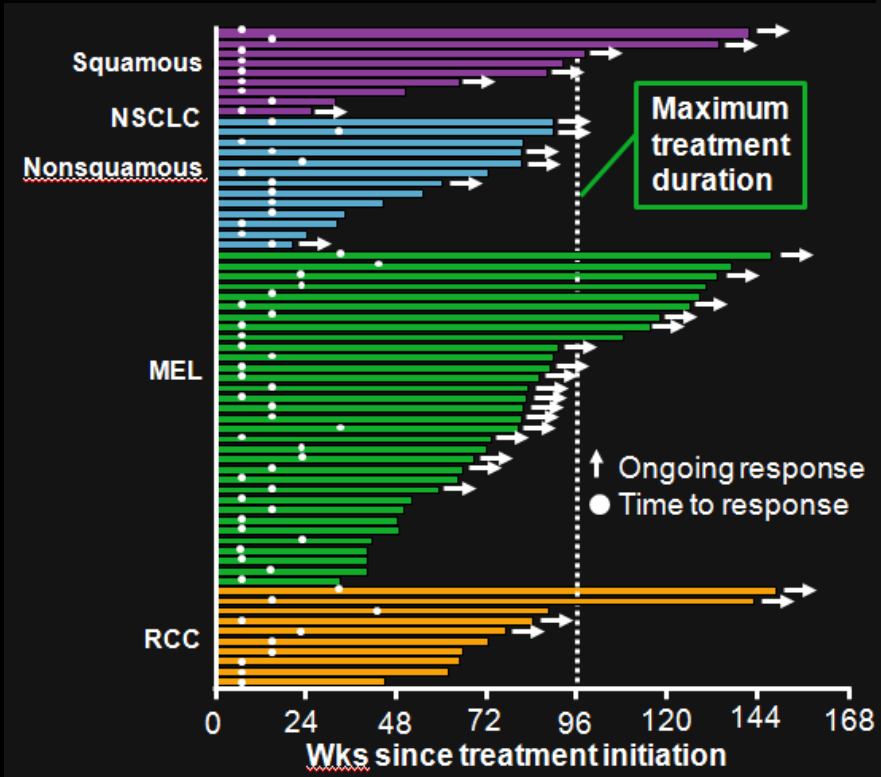
Table 1
Immune-related adverse event rates associated with immune checkpoint inhibitors in advanced melanoma.

	Pembrolizumab (2 mg/kg 2- and 3-weekly) [5]		Nivolumab (3 mg/kg 2-weekly) [7,8,10]		Ipilimumab (3 mg/kg 3-weekly) [5,10]		Ipilimumab + Nivolumab (3 mg/kg + 1 mg/kg every 3 weeks) [10]	
	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Diarrhoea (%)	14–17	1-3 %	11–19	2 %	23–33	9 %	44	9 %
Colitis (%)	2–4		1		8–12		12	
Hepatitis* (%)	1–2	1–2	3–6	2–3	1–7	0–2	30	19
Pruritus (%)	14	0	16–19	<1	25–35	<1	33	2
Rash (%)	13–15	0	9–22	<1	15–21	1–2	28	3
Vitiligo (%)	9–11	0	5–11		2–4	0	7	
Pneumonitis (%)	<1	<1 %	1–2	1 %	0–2	<1 %	6	1 %
Hypothyroidism (%)	9–10	<1	4–9	0	2–4	0	15	<1
Hyperthyroidism (%)	3–7	0	2–4	<1	1–2	<1	10	1
Hypophysitis (%)	<1	<1	<1		2–4	2	8	
Renal injury (%)	1	0 1 %	1	1 %	<1	<1 %	NR	1 %
Rheumatological (%)								
Myalgia	2–7	<1	4	0	2	<1	NR	NR
Arthralgia	9–12	<1	6–8	0	5	<1	11	<1
Arthritis	0–2	0		NR	0	0		NR
Myositis		0		NR	NR	NR		NR
Uveitis (%)	<1	0	NR	NR	0	0	NR	NR
Neurological (%)	1	0	1	NR	1	<1	NR	NR
Cardiac (%)	NR	1–2	0**	NR	NR	NR**	NR	NR
Fatigue (%)	19–21	0	34	0–1	15	1	35	4
Haematological (%)								
Anaemia	1–2	0	4	NR	<1	<1	NR	NR
Neutropenia	NR	NR	NR	0	0	0	NR	NR
Thrombocytopenia	NR	NR	NR	**0	NR	NR	NR	NR

NR = not reported
* Deemed to be any elevation of ALT or AST.
** G5 event.

Spain, Lavinia, Stefan Diem, and James Larkin. "Management of toxicities of immune checkpoint inhibitors." Cancer treatment reviews 44 (2016): 51-60.

Nivolumab

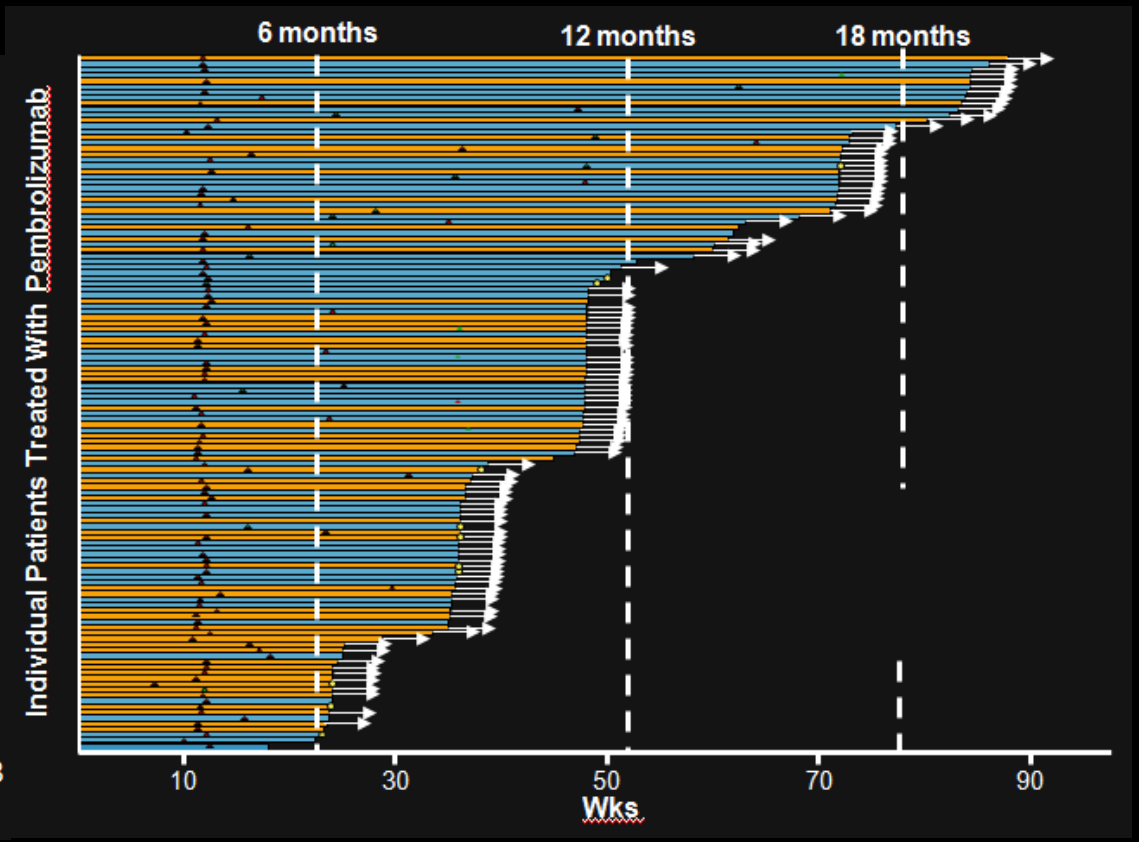


65 of 306 pts had ORR (CR/PR):

- 30 of 65 (46%) responses were evident at first tumor evaluation (8 wks)
- 35 of 65 (54%) responses were ongoing at time of data analysis
- Responses persisted off drug

Topalian SL, et al. ASCO 2013. Abstract 3002.

Pembrolizumab



- 88% of responses ongoing[a]
- Median response duration not reached (range, 6+ to 76+ weeks)

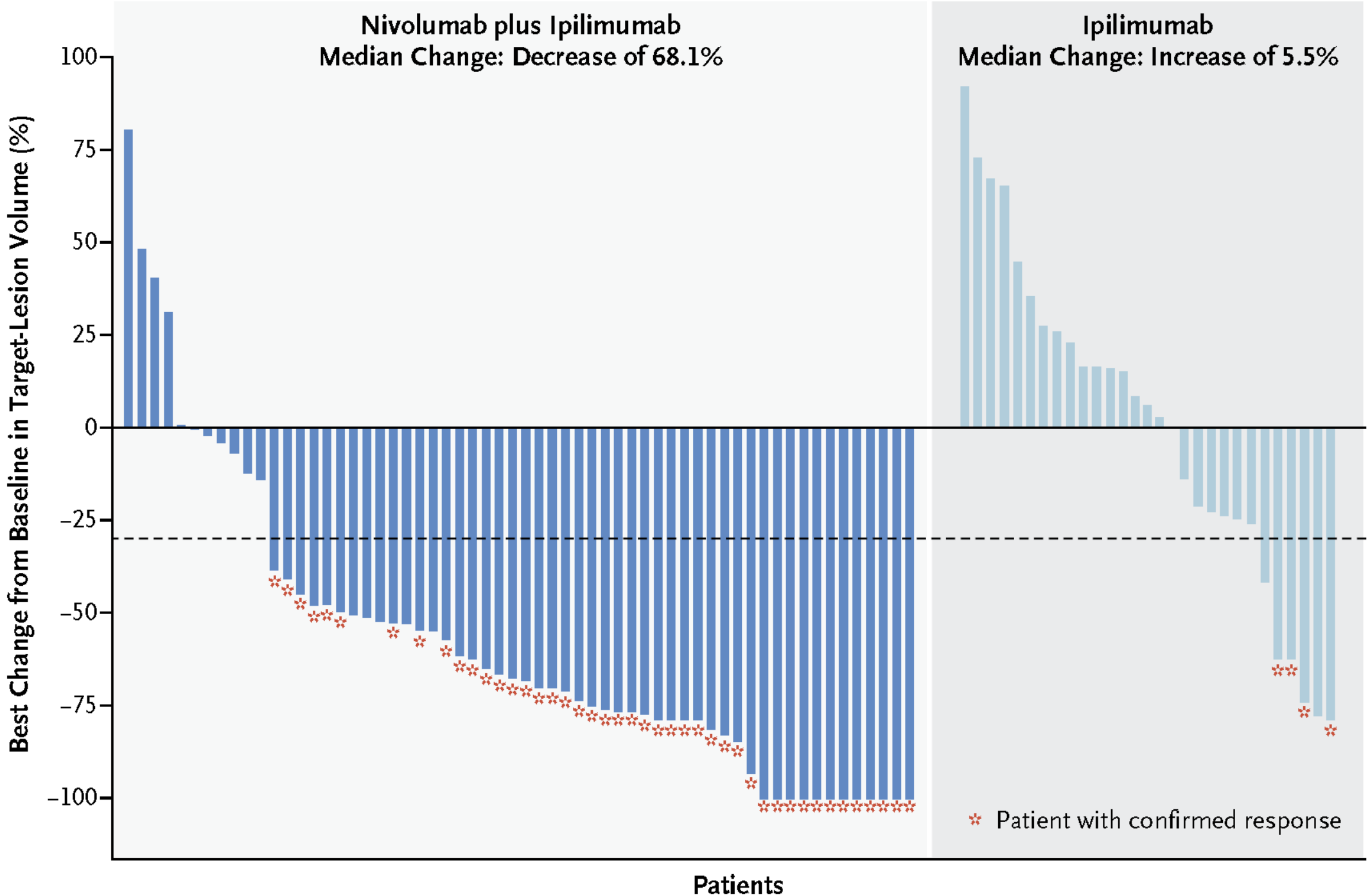
Ribas A, et al. ASCO 2014. LBA9000.

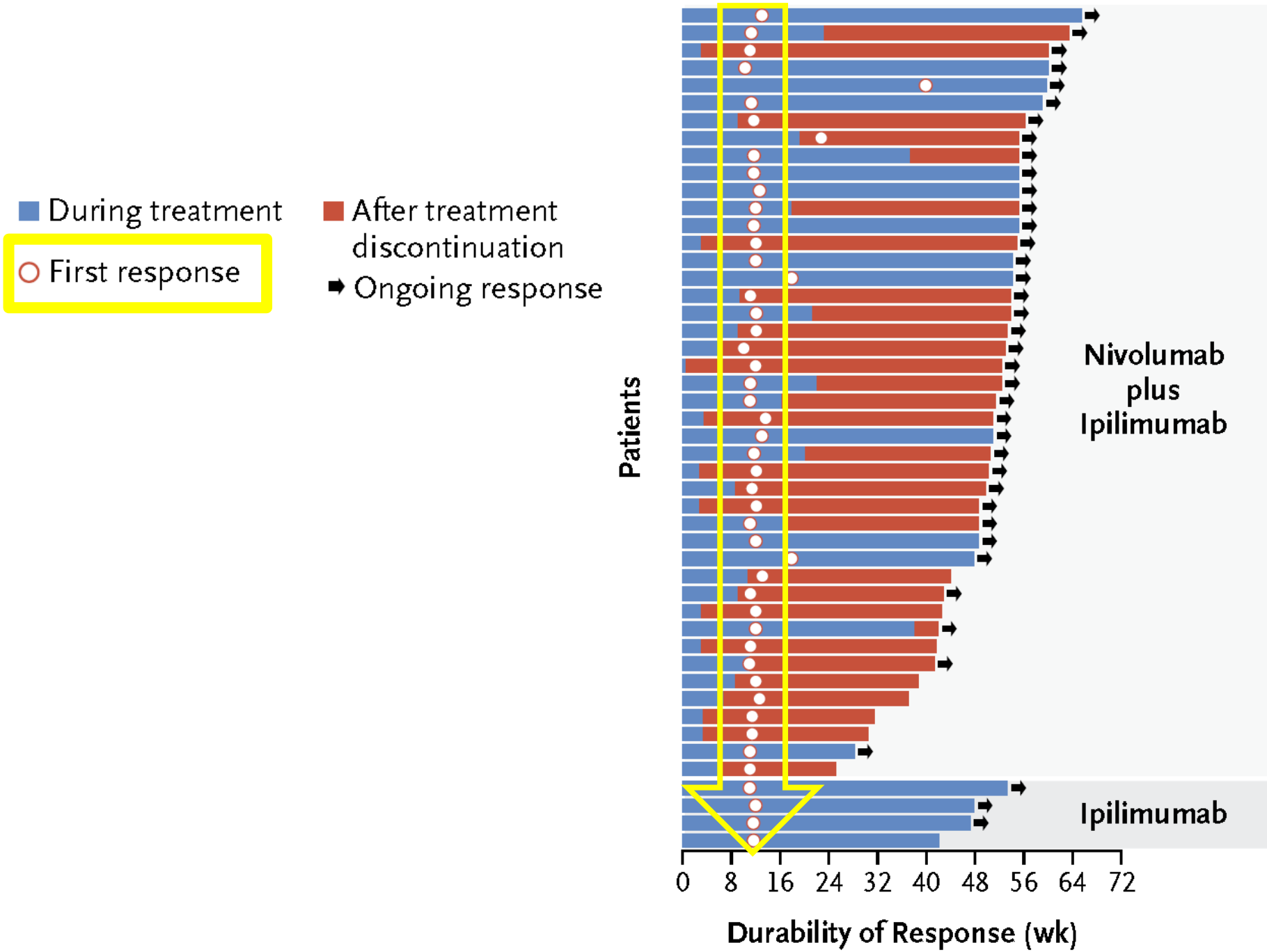
ORIGINAL ARTICLE

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

- 142 treatment naïve patients. 2:1 randomization to receive ipilimumab (3 mg/kg) + Nivolumab (1 mg/kg) or placebo, every 3 weeks X 4 doses.
- Followed by Nivolumab 3 mg/kg or placebo every 2 weeks.
- BRAF WT tumors: (combo vs placebo)
  - **RR: 61% vs 11%** ($P < 0.001$)
  - **CR: 22% vs 0**
- Toxicity: Grade III or IV in 54% vs 24%

Published April 20, 2015 at NEJM.org


Nivolumab plus Ipilimumab
Median Change: Decrease of 68.1%
Ipilimumab
Median Change: Increase of 5.5%
Best Change from Baseline in Target-Lesion Volume (%)
100
75
50
25
0
−25
−50
−75
−100
Patient with confirmed response
Patients


During treatment
After treatment discontinuation
First response
Ongoing response
Patients
Nivolumab plus Ipilimumab
Ipilimumab
0
8
16
24
32
40
48
56
64
72
Durability of Response (wk)

Urban Legend

Immunotherapy can give rise to long term responders but it is:

- Universally highly toxic
- Slow working
- Works in only a small % of patients

Urban Legend

Immunotherapy can give rise to long term responders but it is:

- ~~Universally highly toxic~~ → Small % of High Grade Toxicities
- ~~Slow working~~ → At 1st evaluation: 12 weeks
- ~~Works in only a small % of patients~~ → High % at landmark Year 1

Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

Pembrolizumab versus Ipilimumab in Advanced Melanoma

ECOG 0 ,1

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma

Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma

Immunotherapy has no DIRECT impact on the cancer

Therefore: the condition of the host, and any factor that impacts the host's ability to mount an immune response will impact your ability to mount an anti-tumor response.

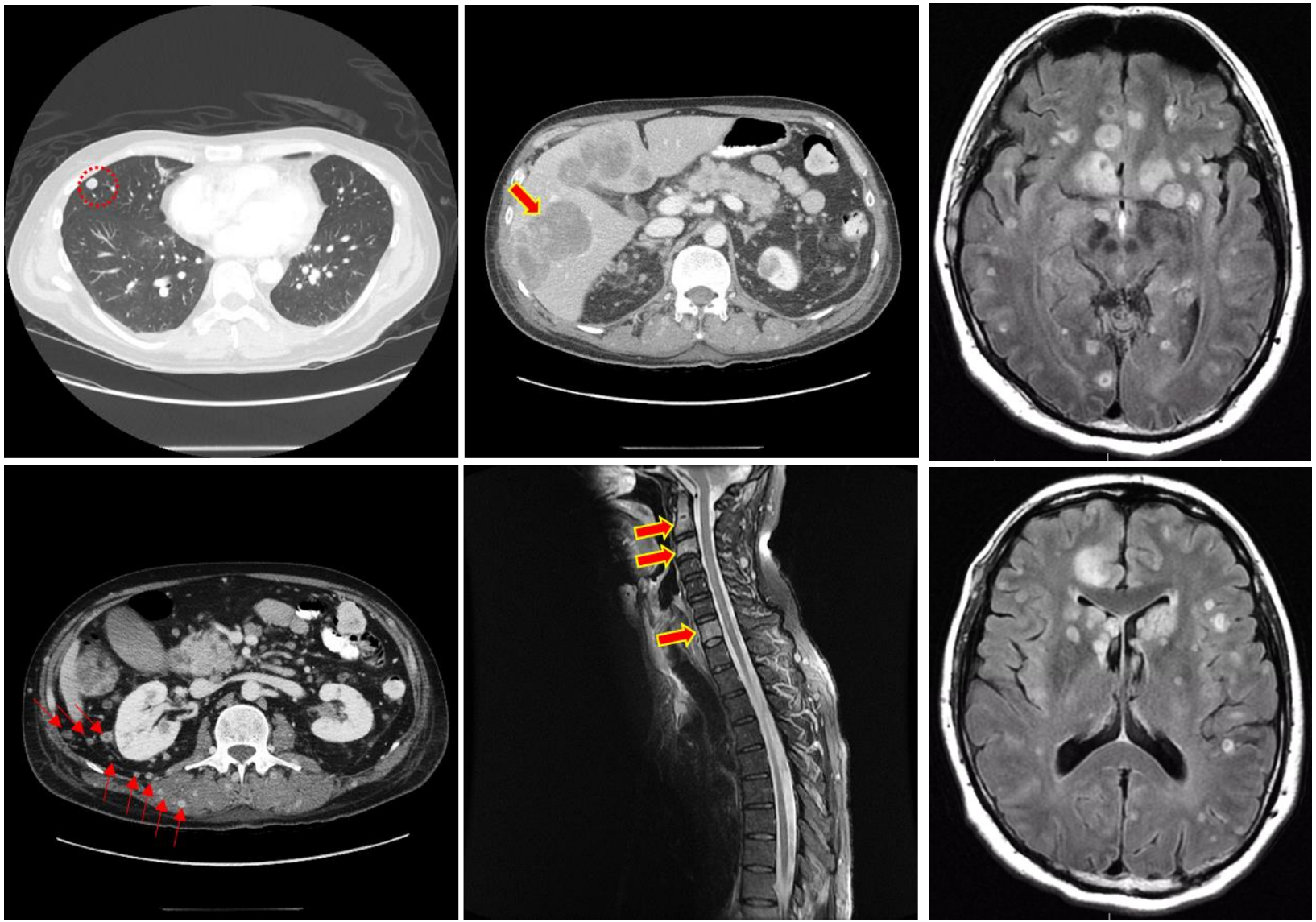
Pre-existing conditions

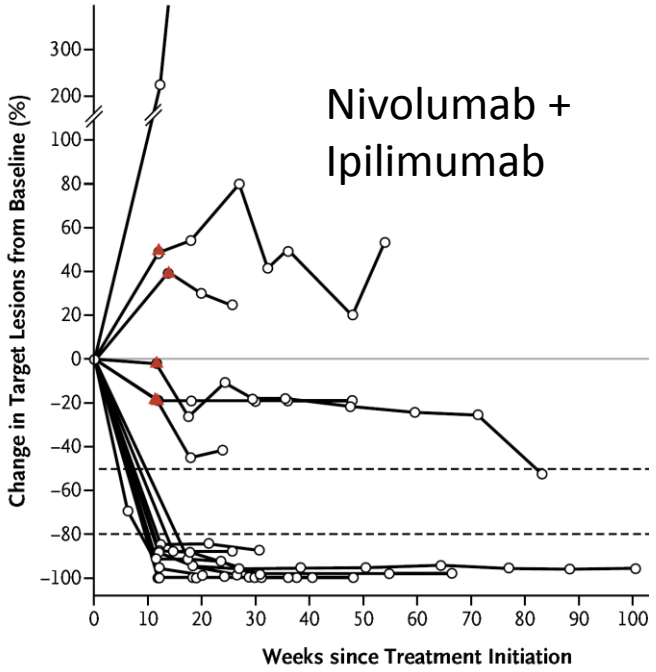
- Autoimmune diseases:
  i.e.: colitis, multiple sclerosis, rheumatoid arthritis, psoriasis, etc.

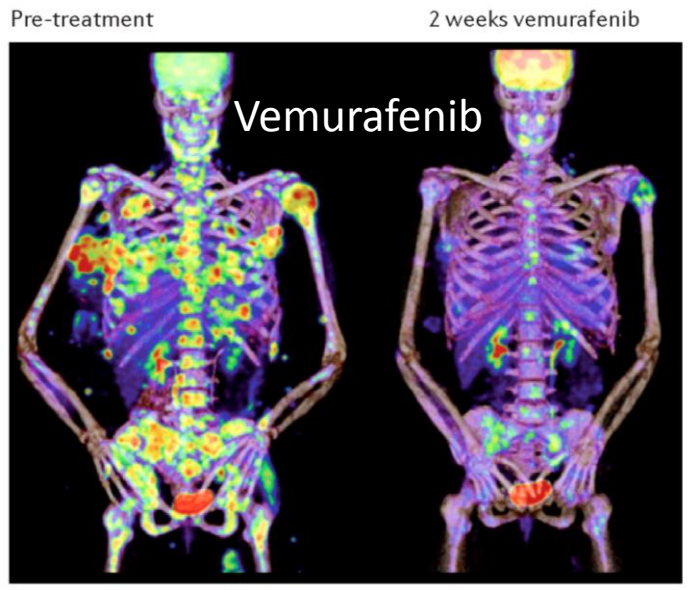
Acquired conditions

- Corticosteroid use :
  i.e.: raised intracranial pressure, autoimmune toxicities, allergies, etc.
- Hematologic conditions/malignancies
- Solid organ, Heme transplant

Immunotherapy requires time to work

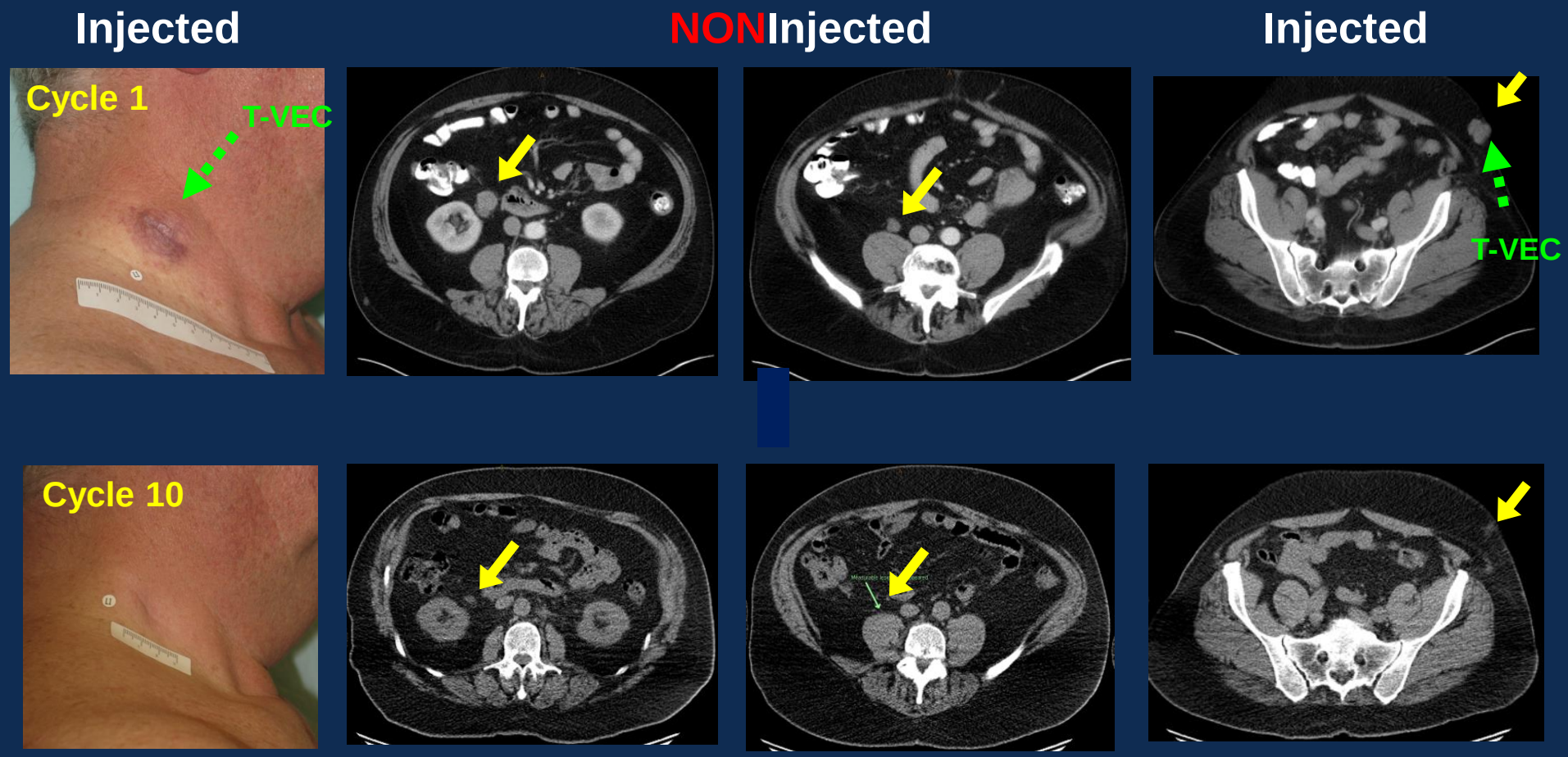






Wolchok, Jedd D., et al. "Nivolumab plus ipilimumab in advanced melanoma." New England Journal of Medicine 369.2 (2013): 122-133.
Bollog G, et al., Vemurafenib: the first drug approved for BRAF-mutant cancer NATURE REVIEWS DRUG DISCOVERY, 11:873, 2012
ra

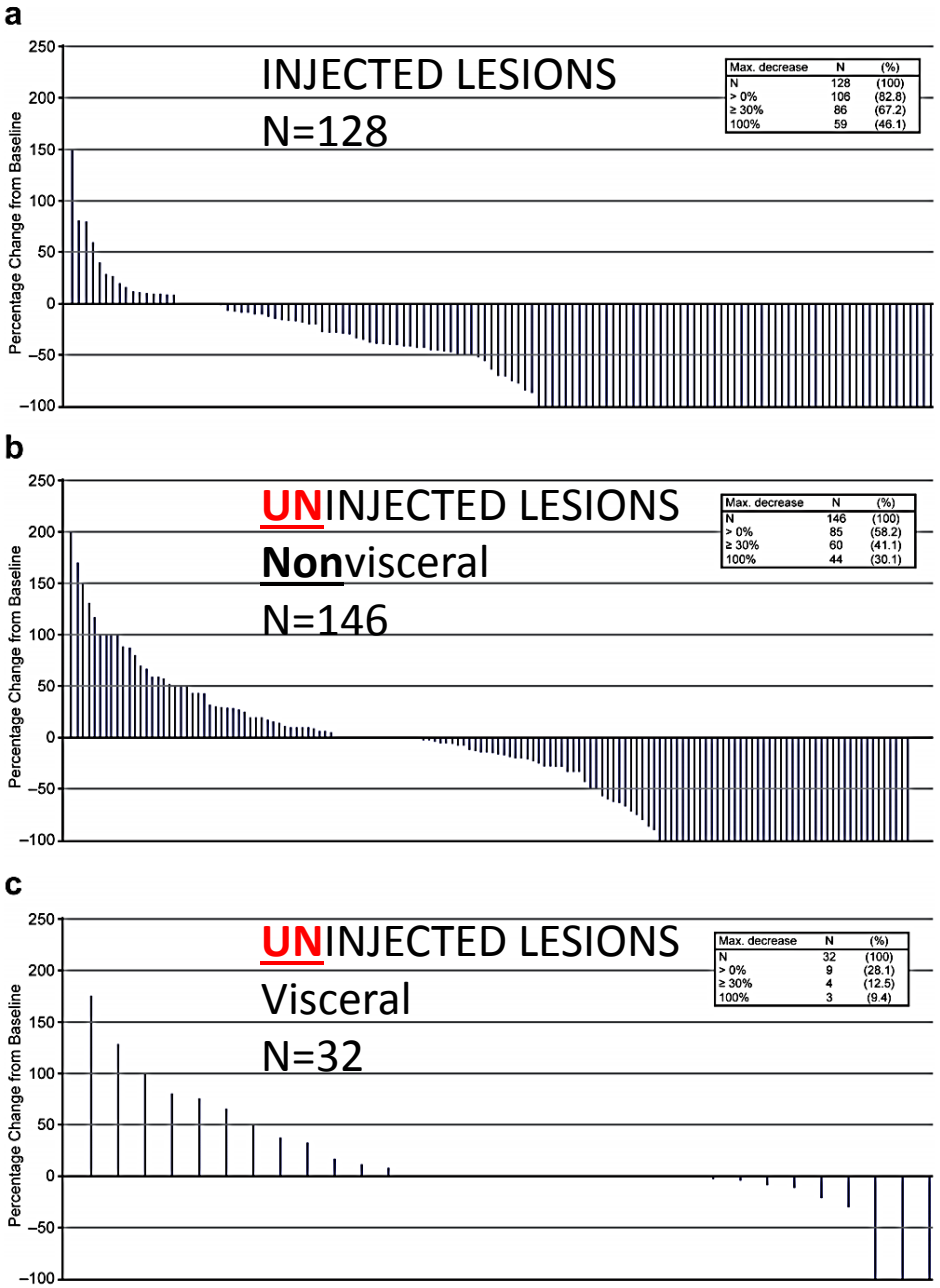
Immune Response Beyond the Locally Injected Lesion



There were 6 measurable lesions at baseline including 1 cutaneous neck lesion, 2 subcutaneous abdominal wall lesions (1 of which is shown), 2 intra-abdominal lesions (which are shown), and 1 in musculature of right thigh (which completely resolved). Both Injected lesions are indicated by a green arrow.

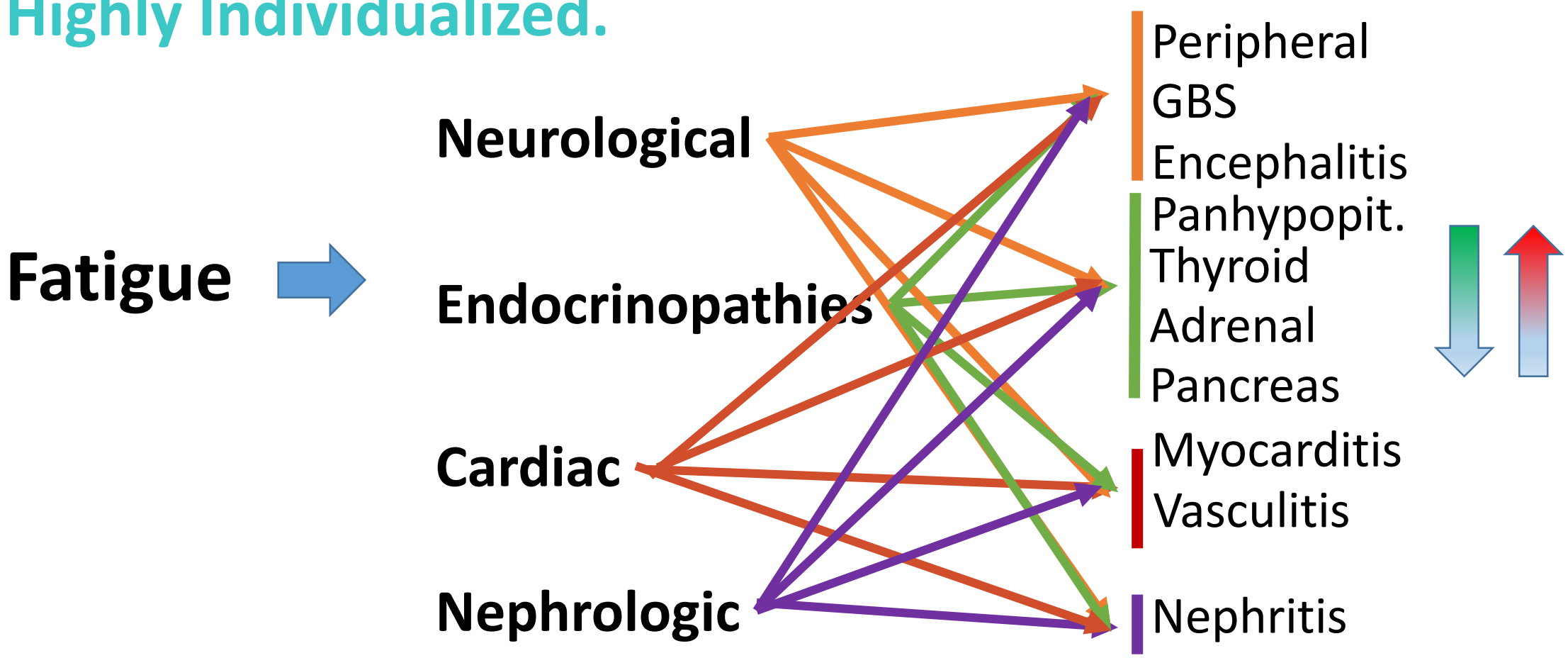
Multi-institutional single-arm open-label phase II clinical trial

Post hoc analysis of individual lesions (50 patients)



Kaufman et al. Journal for ImmunoTherapy of Cancer (2016) 4:12

The Presentation of Autoimmune Toxicity can be Highly Individualized.



Agenda

What are the principles that guide the use of immunotherapy?

- Who: Expanding list of hematologic and solid tumors.
- Why : Long term responses.
- What : Checkpoints, Modulators, Vaccines, Cytokines.
- How: Host dependent tumor activity and Toxicities.
  PS matters. Response propagates.
- When:

Immunotherapy and Melanoma Disease Stage

Brain Metastases ← **Stage IV Metastatic Melanoma** → **Adjuvant Therapy**

Checkmate 204: ipi+nivo brain mets

Response to Treatment – All Patients (N = 75)

	Global	Intracranial	Extracranial
Best overall response, n (%)			
Complete response	4 (5)	16 (21)	5 (7)
Partial response	36 (48)	25 (33)	32 (43)
Stable disease	4 (5)	4 (5)	2 (3)
Progressive disease[a]	18 (24)	18 (24)	16 (21)
Not evaluable[b]	13 (17)	12 (16)	20 (27)
Objective response rate, % (95% CI)	53 (41–65)	**55** (43–66)	49 (38–61)
Clinical benefit rate[c], % (95% CI)	59 (47–70)	**60** (48–71)	52 (40–64)

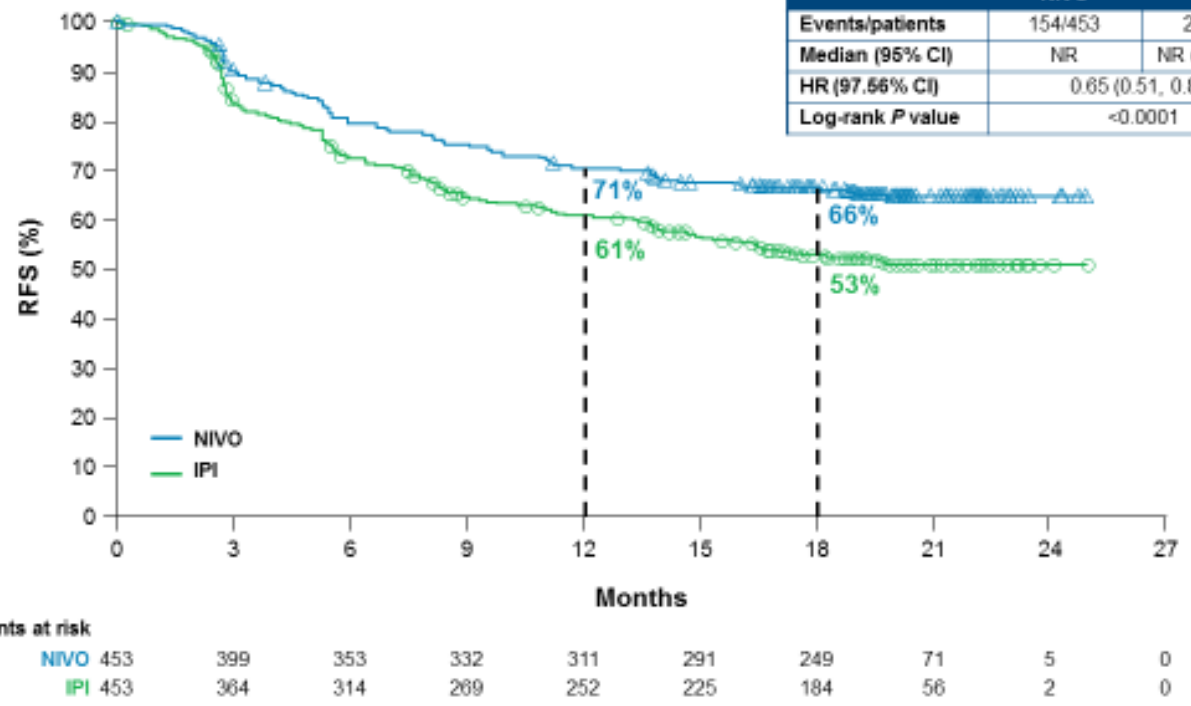
Journal of Clinical Oncology 35, no. 15_suppl (May 2017) 9507-9507

Checkmate 238

MADRID 2017 ESMO congress

Primary Endpoint: RFS

	NIVO	IPI
Events/patients	154/453	206/453
Median (95% CI)	NR	NR (16.6, NR)
HR (97.56% CI)	0.65 (0.51, 0.83)	
Log-rank *P* value	<0.0001	



Agenda

What are the principles that guide the use of immunotherapy?

- Who: Expanding list of hematologic and solid tumors.
- Why : Long term responses.
- What : Checkpoints, Modulators, Vaccines, Cytokines.
- How: Host dependent tumor activity and Toxicities.
  PS matters. Response propagates.
- When: Stage IV (Brain) -> Adjuvant -> Neoadjuvant

November 8-12 • NATIONAL HARBOR, MD

Basic Principles of Tumor Immunotherapy

Michael K Wong MD PhD FRCPC
MD Anderson Cancer Center
mkwong@mdanderson.org