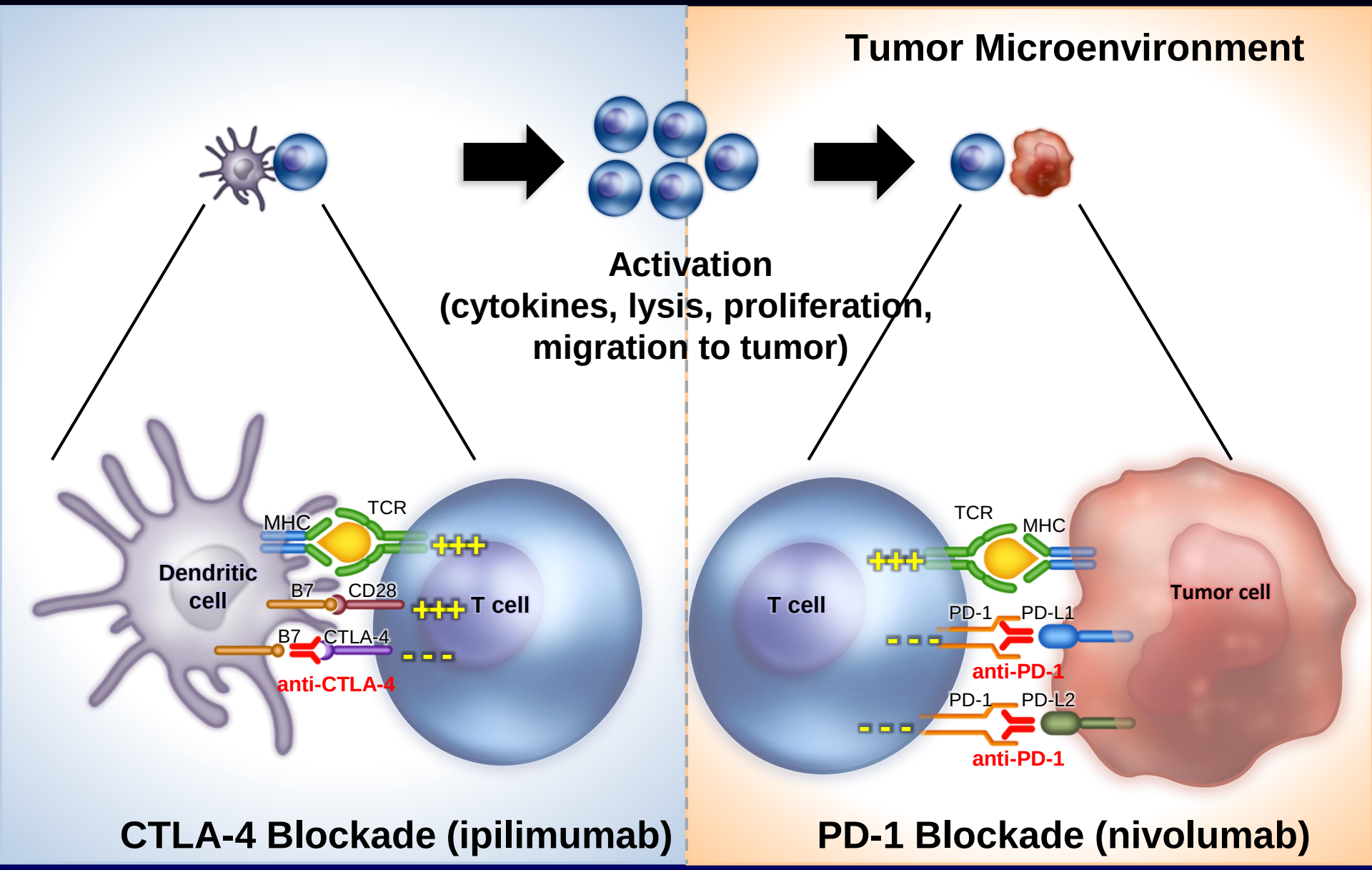
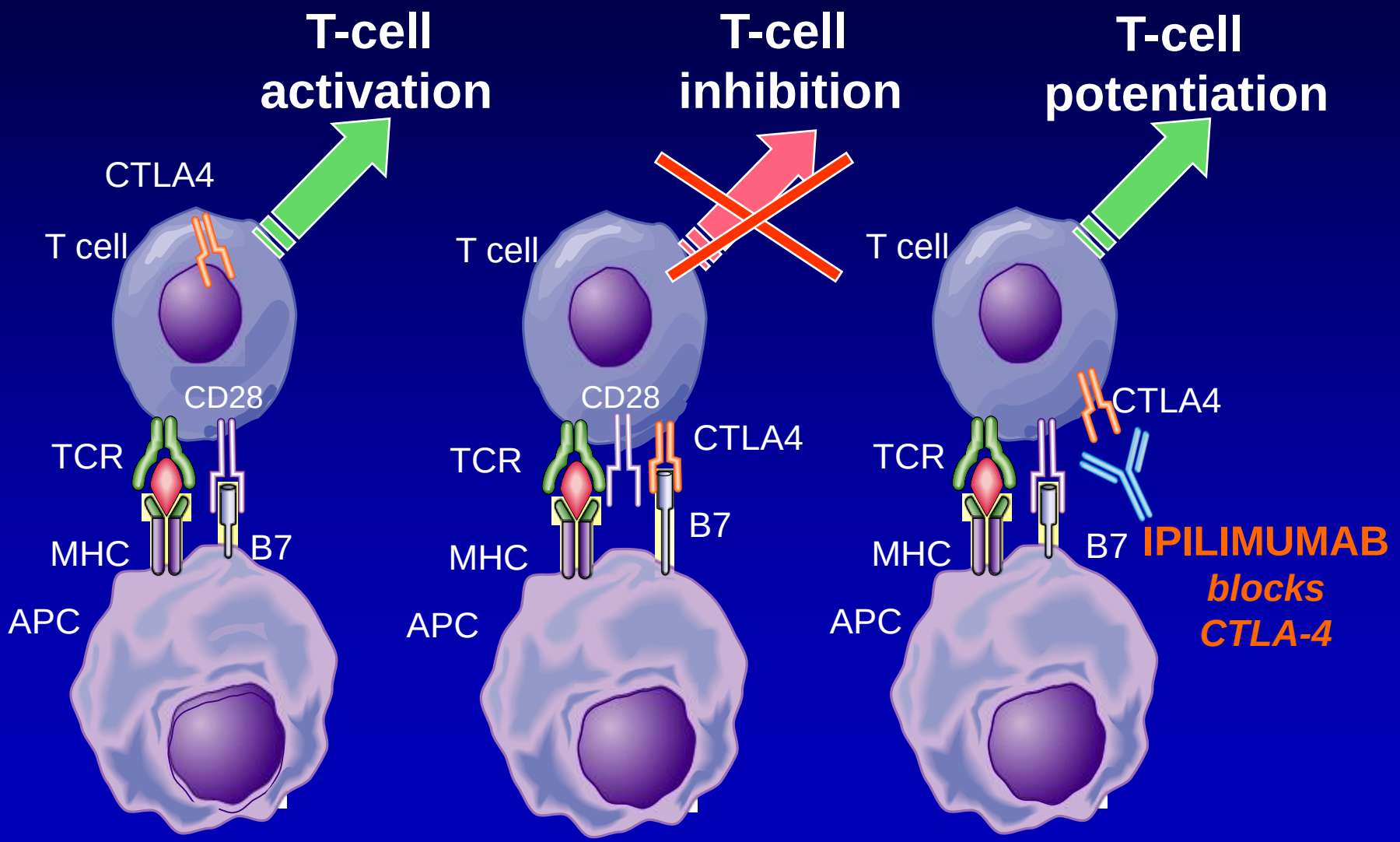
Featuring:

- Updates on immune checkpoint therapies
- Molecularly targeted therapies
- FDA approval for talimogene laherparepvec (T-VEC)

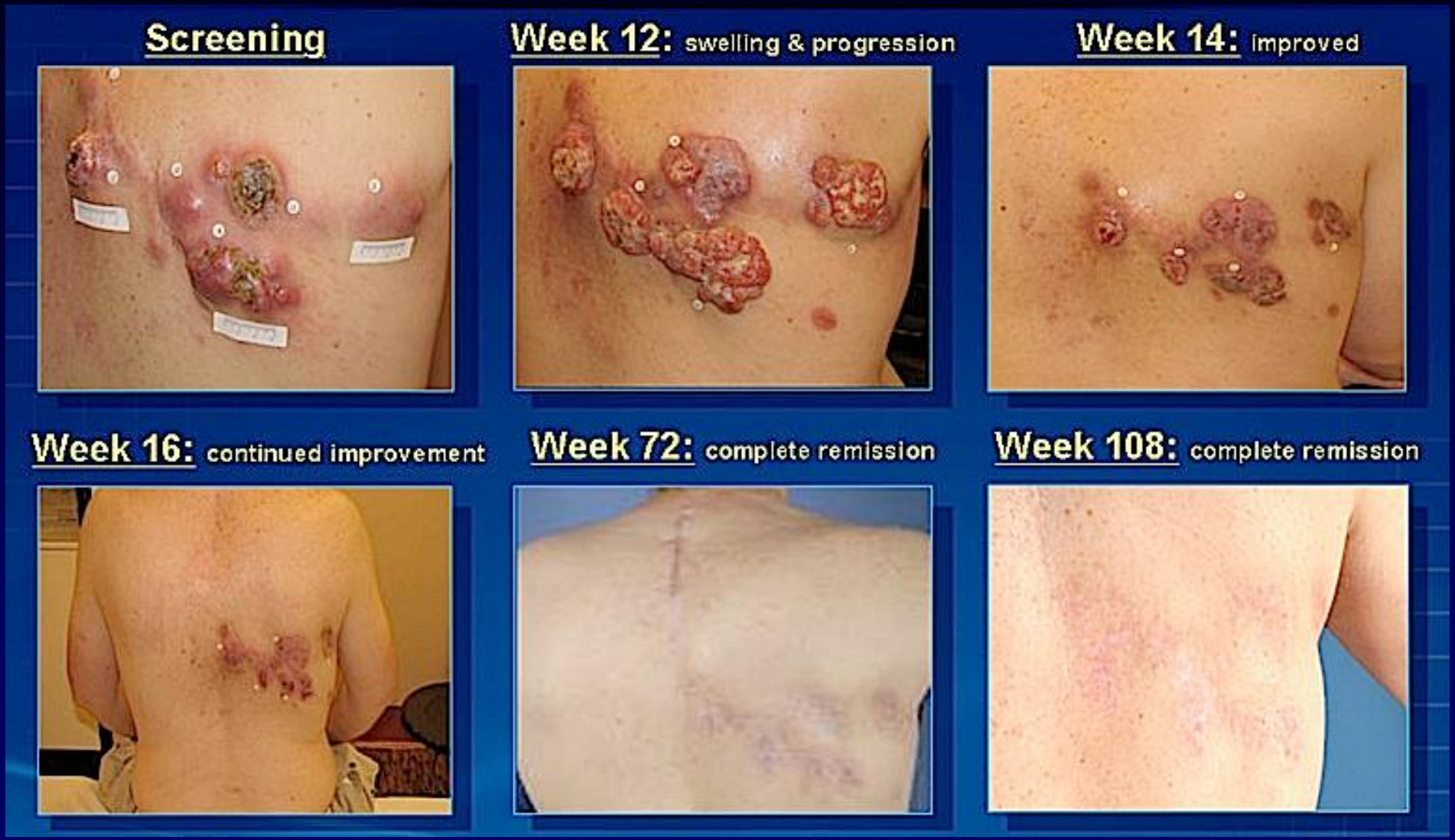
Mechanism of action of Ipilimumab and Nivolumab



Ipilimumab: Mechanism of Action



Ipilimumab Patterns of Response



Hoos A, et al. J Natl Cancer Inst 2010;102:1388-1397.

Immune-related Adverse Events (irAEs) Associated with Ipilimumab

Skin:
- Pruritus
- Rash

Gastrointestinal
- Diarrhea
- Abdominal Pain
- Blood in stool
- Bowel perforation
- Peritoneal signs

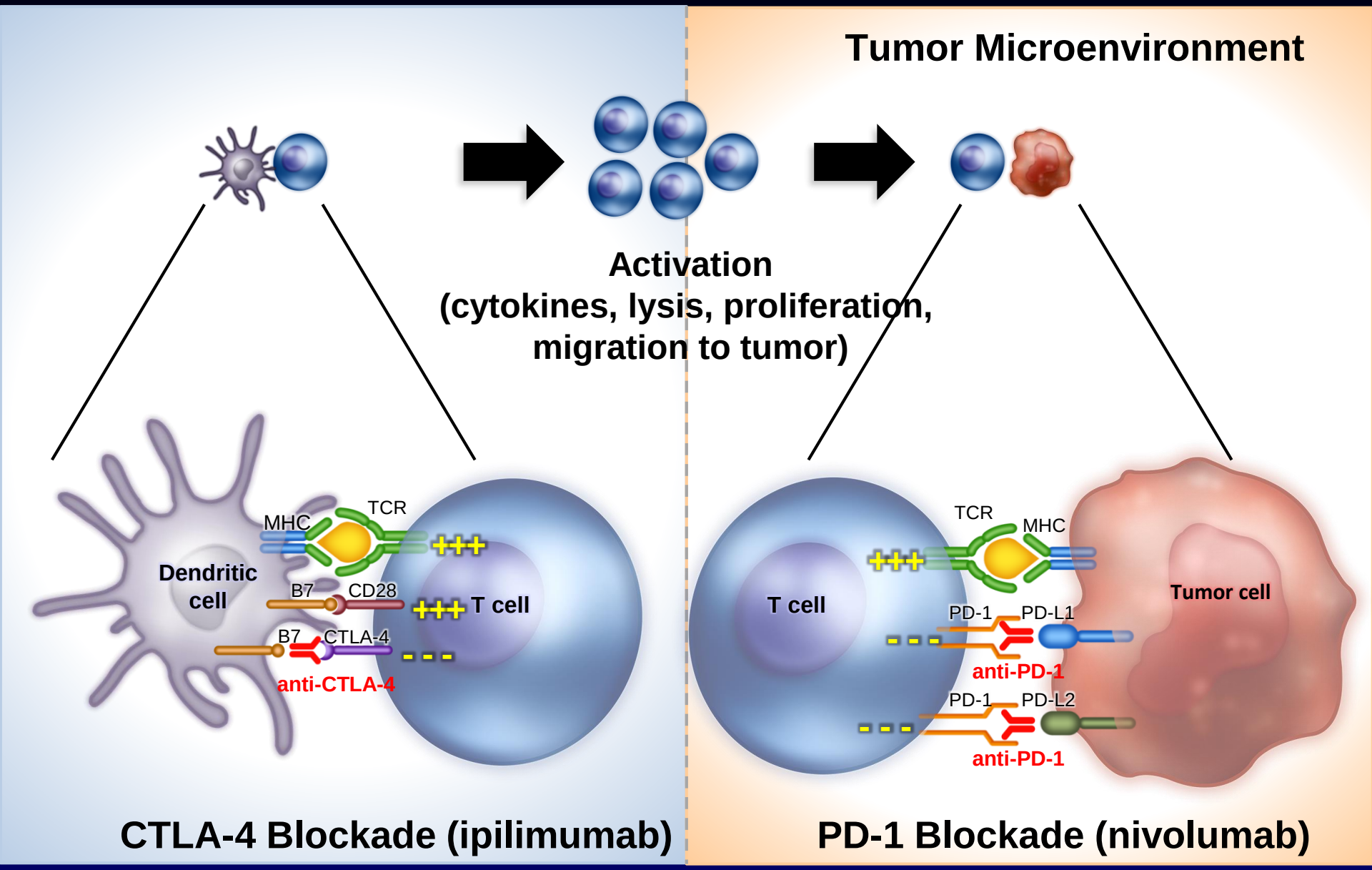
Liver
- ↑ AST/ALT, Bilirubin

Endocrine
- Fatigue
- Headache
- Mental status changes
- Hypotension
- Abnormal thyroid function tests/serum chemistries

Neurological
- Uni- or bilateral weakness
- Sensory alterations
- Paresthesias

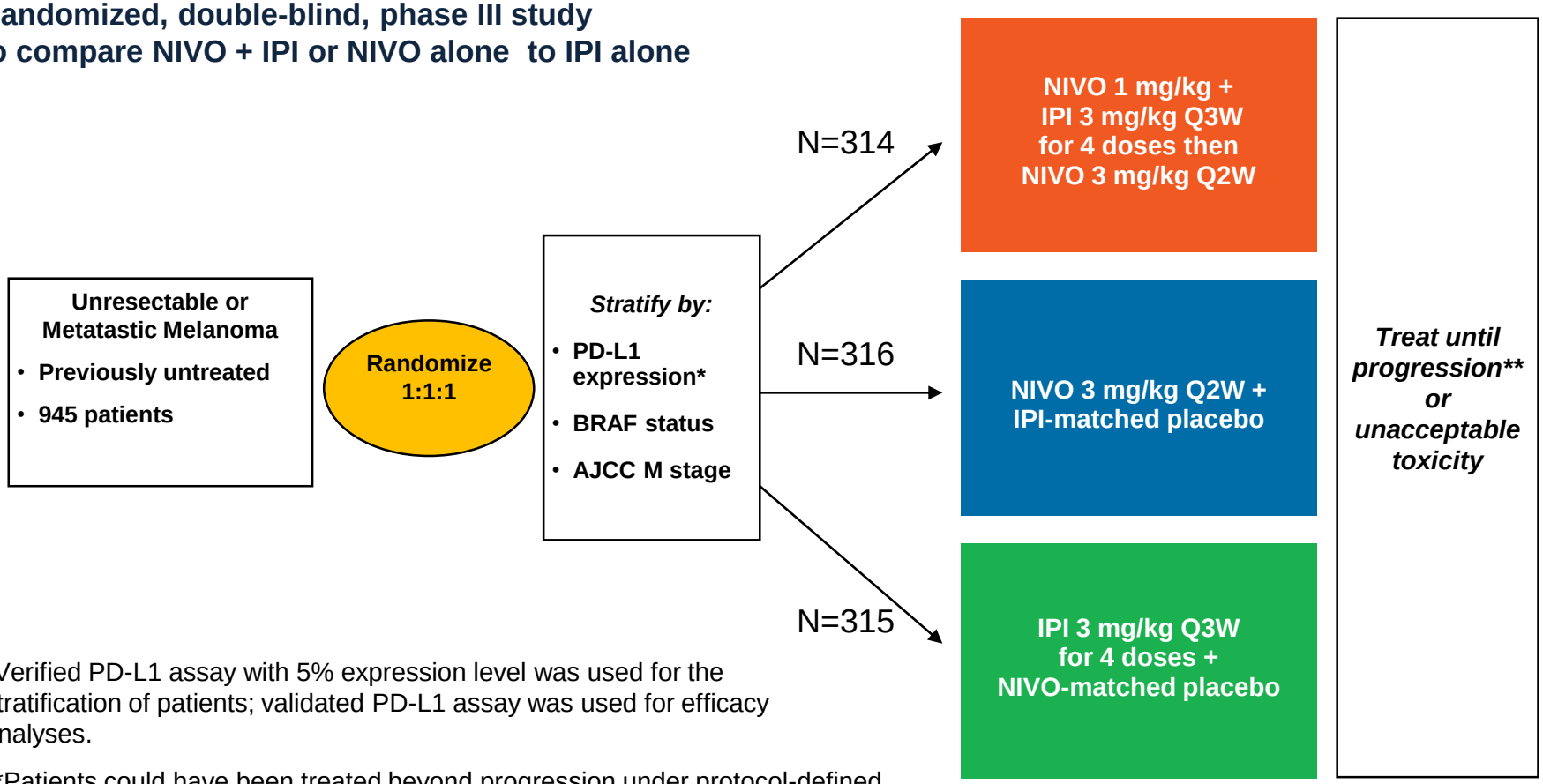
http://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=2265ef30-253e-11df-8a39-0800200c9a66&type=display.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Mechanism of action of Ipilimumab and Nivolumab



CA209-067 Study Design

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

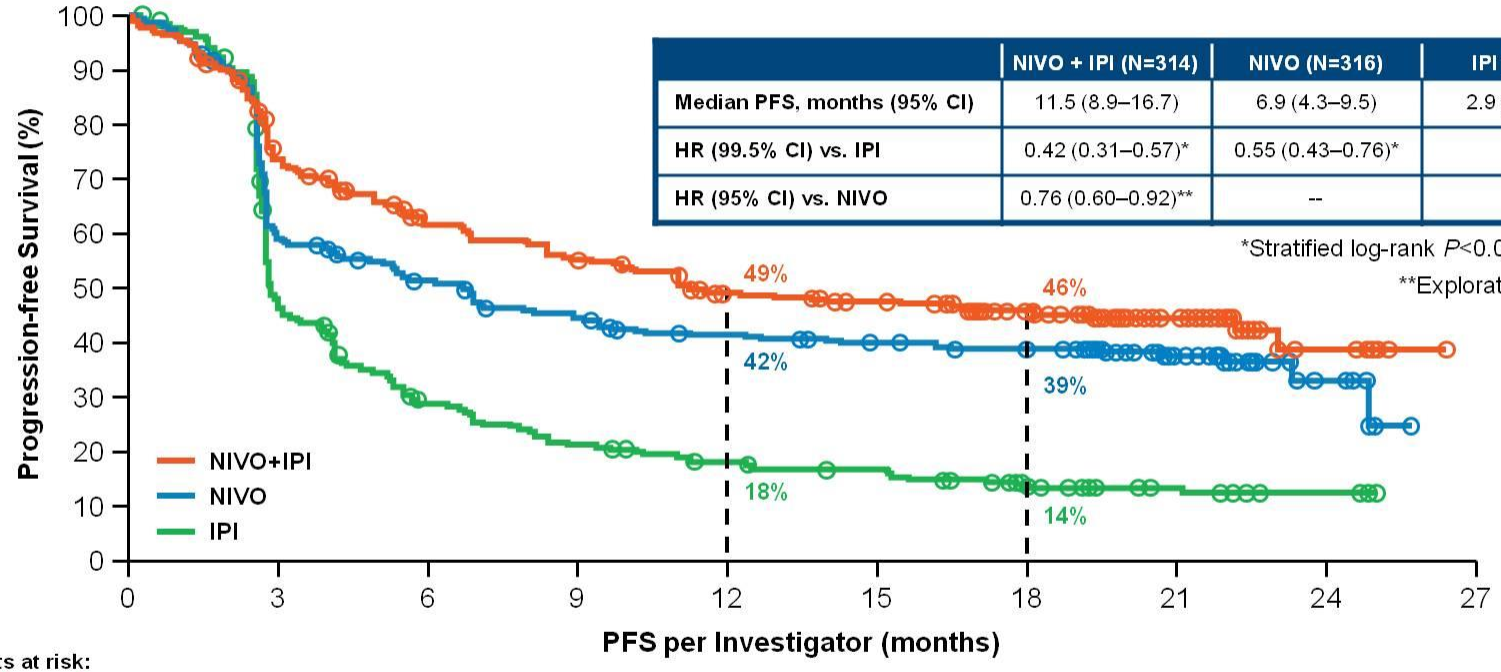


*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

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

Larkin J, et al. N Engl J Med 2015;373:23-34.

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

CA209-067 Response to Treatment

	NIVO + IPI (n=314)	NIVO (n=316)	IPI (n=315)
ORR, % (95% CI)*	**58** (52–63)	**44** (38–49)	**19** (14–24)
Two-sided *P* value vs IPI	<0.001	<0.001	--
Best response (%)			
Complete response	12	9	2
Partial response	46	35	17
Stable disease	13	11	22

Larkin J, et al. N Engl J Med 2015;373:23-34

CA209-067 Safety Summary

Patients Reporting Event, %	NIVO + IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse event (AE)	96	55	82	16	86	27
Treatment-related AE leading to discontinuation	36	29	8	5	15	13
Treatment-related death*	0		0.3		0.3	

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest)

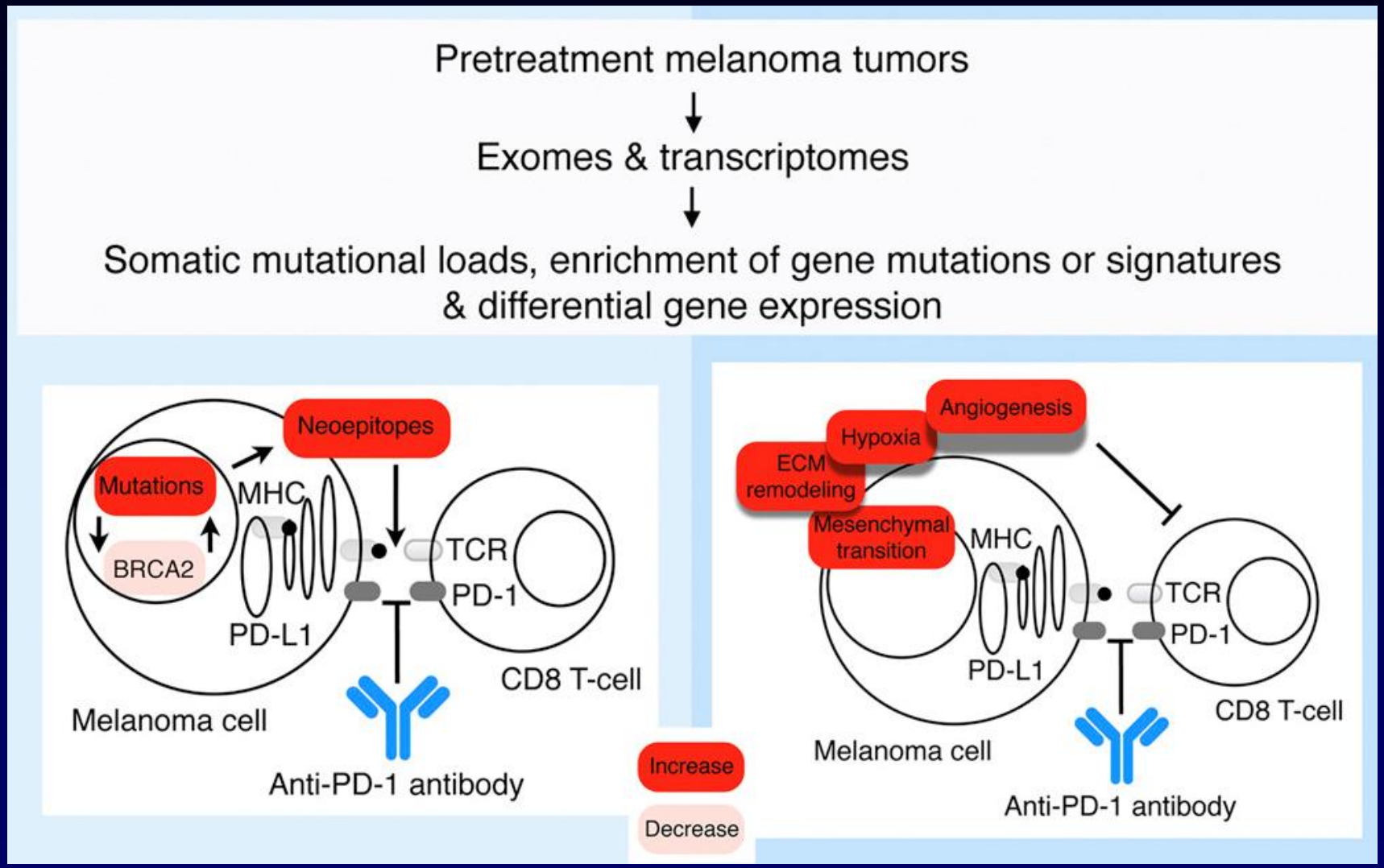
- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response

Tumor Staining for PD-L1: Correlation with Response to Therapy with Anti-PD-1 or Anti-PD-L1

	Overall Response Rate	
	PD-L1 Positive	PD-L1 Negative
Topalian (NEJM 2012)	13/31	0/18
Grosso (ASCO 2013)	7/17	3/21
Herbst (ASCO 2013)	13/36	9/67
Robert (NEJM 2015)	53%	33%

Topalian SL, et al. N Engl J Med 2012;366:2443-2454.
Grosso J, et al. ASCO Meeting Abstracts 2013;31:3016.
Herbst RS, et al. ASCO Meeting Abstracts 2013;31:3000.
Robert C, et al. N Engl J Med 2015;372:320-330.

Genomic and transcriptomic features of response to anti-PD-1 therapy of melanoma Hugo et al Cell 165:35, 2016

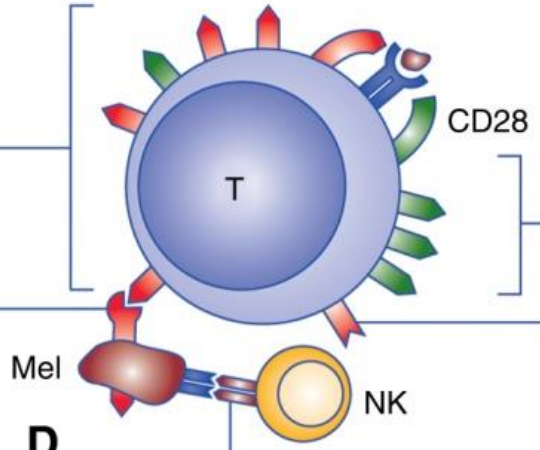


A

CD28/CTLA-Ig family	
Target	Status
CTLA-4	Approved
PD-1	Phase III accruing
BTLA	Preclinical
LAG3	Preclinical
ICOS	Preclinical

B

TNF superfamily	
Target	Status
CD40	Ph I
OX40	Ph I accruing
CD137	Ph II
GITR	Ph I accruing
CD27	Ph I accruing



C

PD-1	Phase III accruing

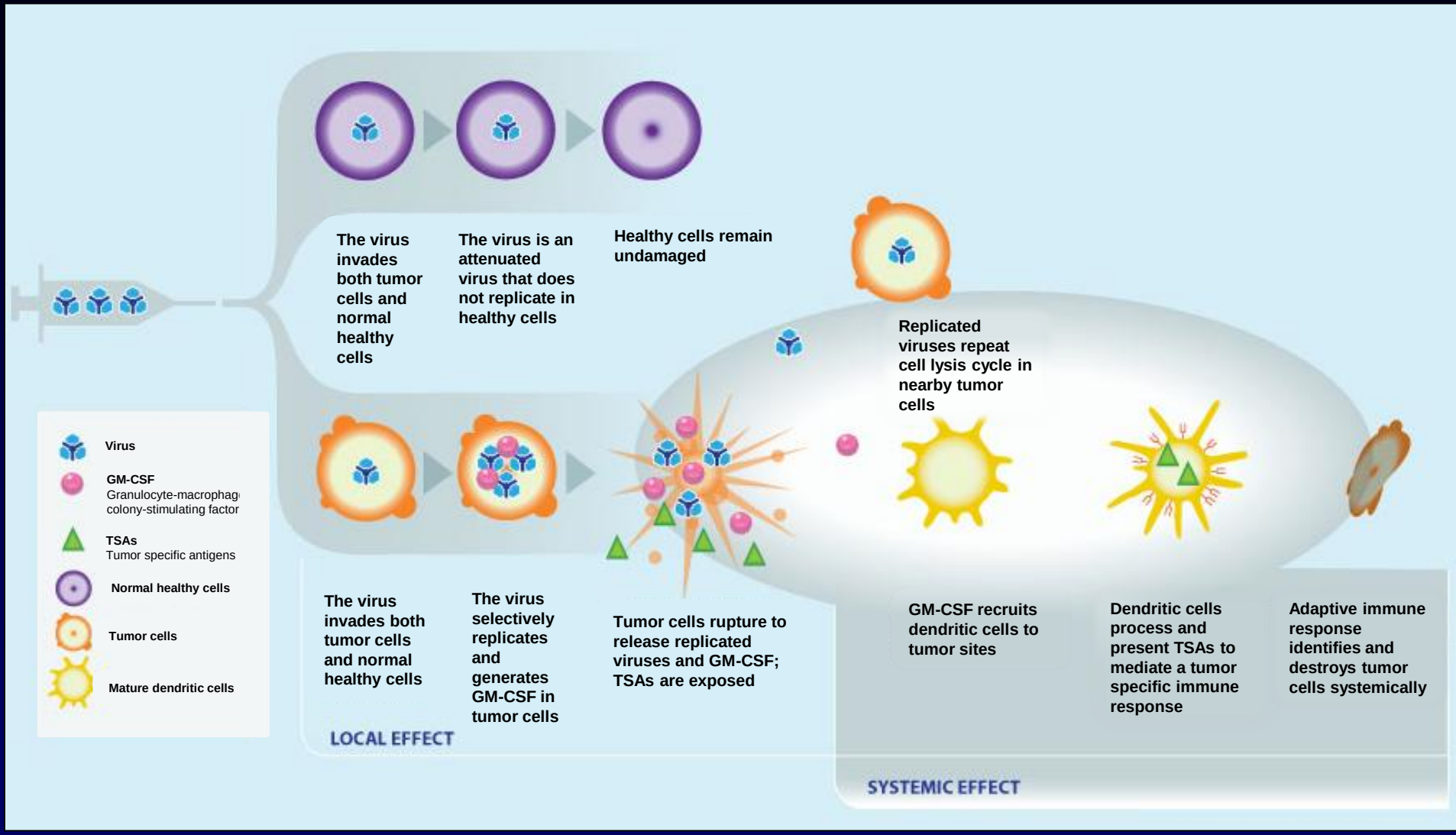
D

KIR	Ph II accruing

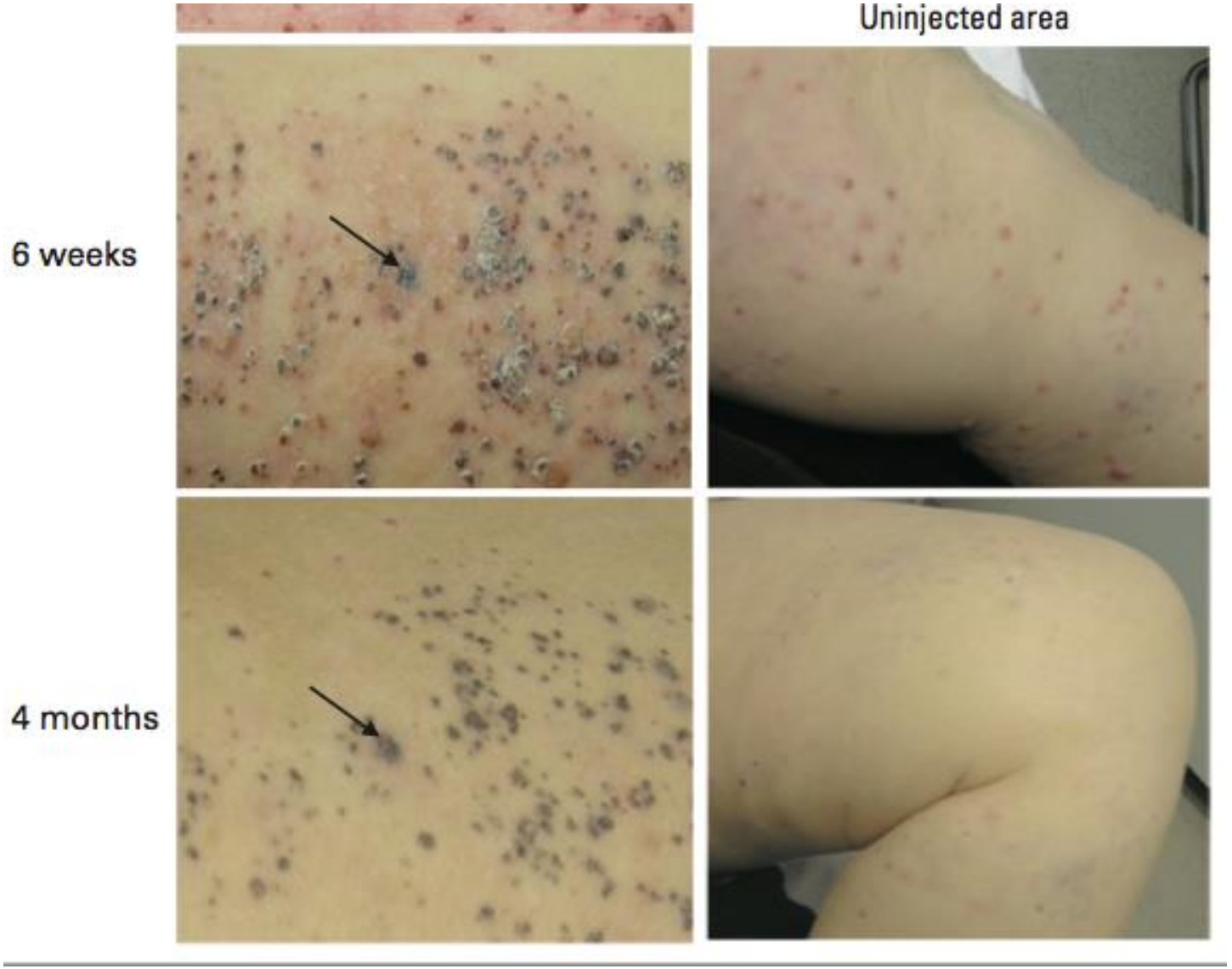
E

TIM-3	Preclinical

Figure 1 from J Naidoo
British Journal of Cancer Advance Online Publication
11 September 2014 doi:10.1038/bjc.2014.348


Virus
GM-CSF
Granulocyte-macrophag
colony-stimulating factor
TSAs
Tumor specific antigens
Normal healthy cells
Tumor cells
Mature dendritic cells
The virus invades both tumor cells and normal healthy cells
The virus is an attenuated virus that does not replicate in healthy cells
Healthy cells remain undamaged
The virus invades both tumor cells and normal healthy cells
The virus selectively replicates and generates GM-CSF in tumor cells
Tumor cells rupture to release replicated viruses and GM-CSF; TSAs are exposed
Replicated viruses repeat cell lysis cycle in nearby tumor cells
GM-CSF recruits dendritic cells to tumor sites
Dendritic cells process and present TSAs to mediate a tumor specific immune response
Adaptive immune response identifies and destroys tumor cells systemically
LOCAL EFFECT
SYSTEMIC EFFECT

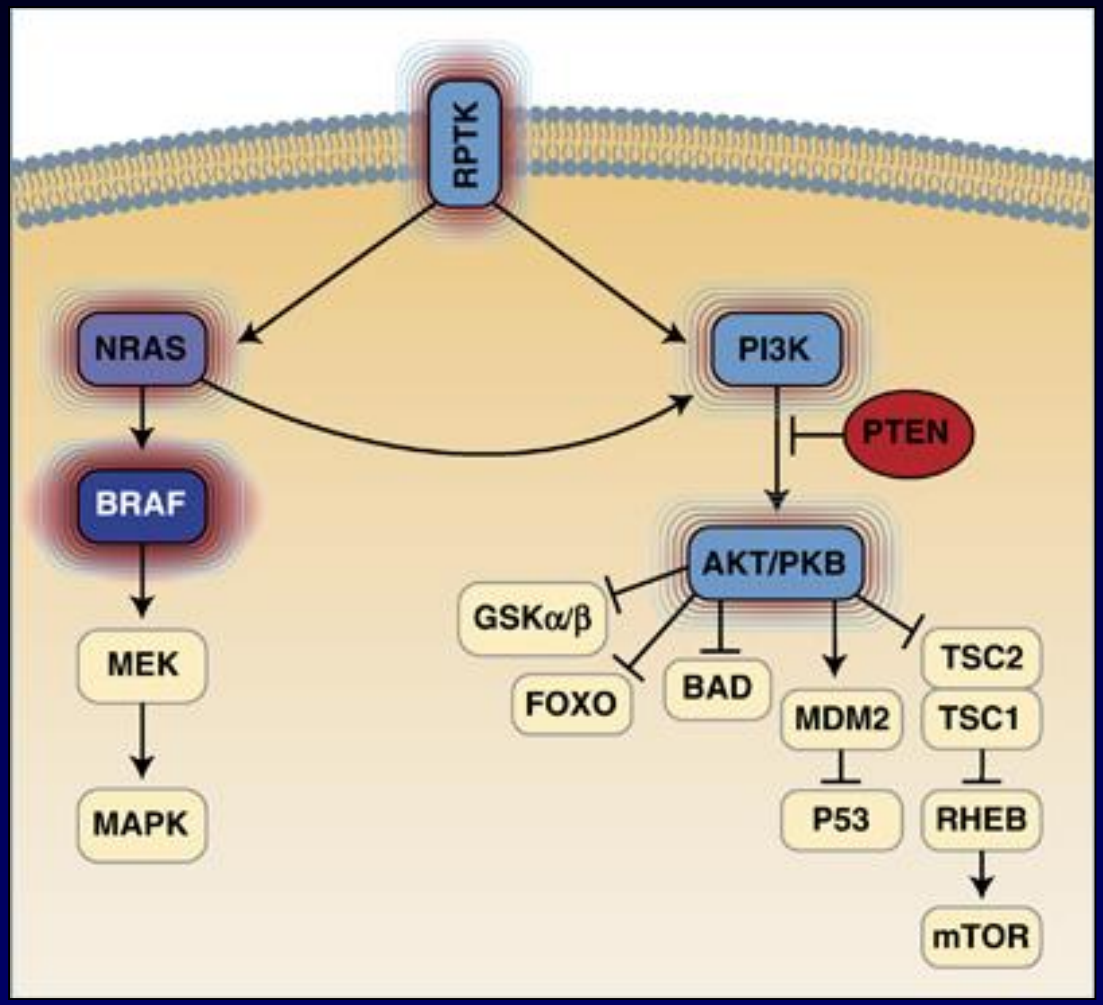
Phase 2 results with OncoVEX^{GMCSF}



[Senzer NN. *JCO* 2009]

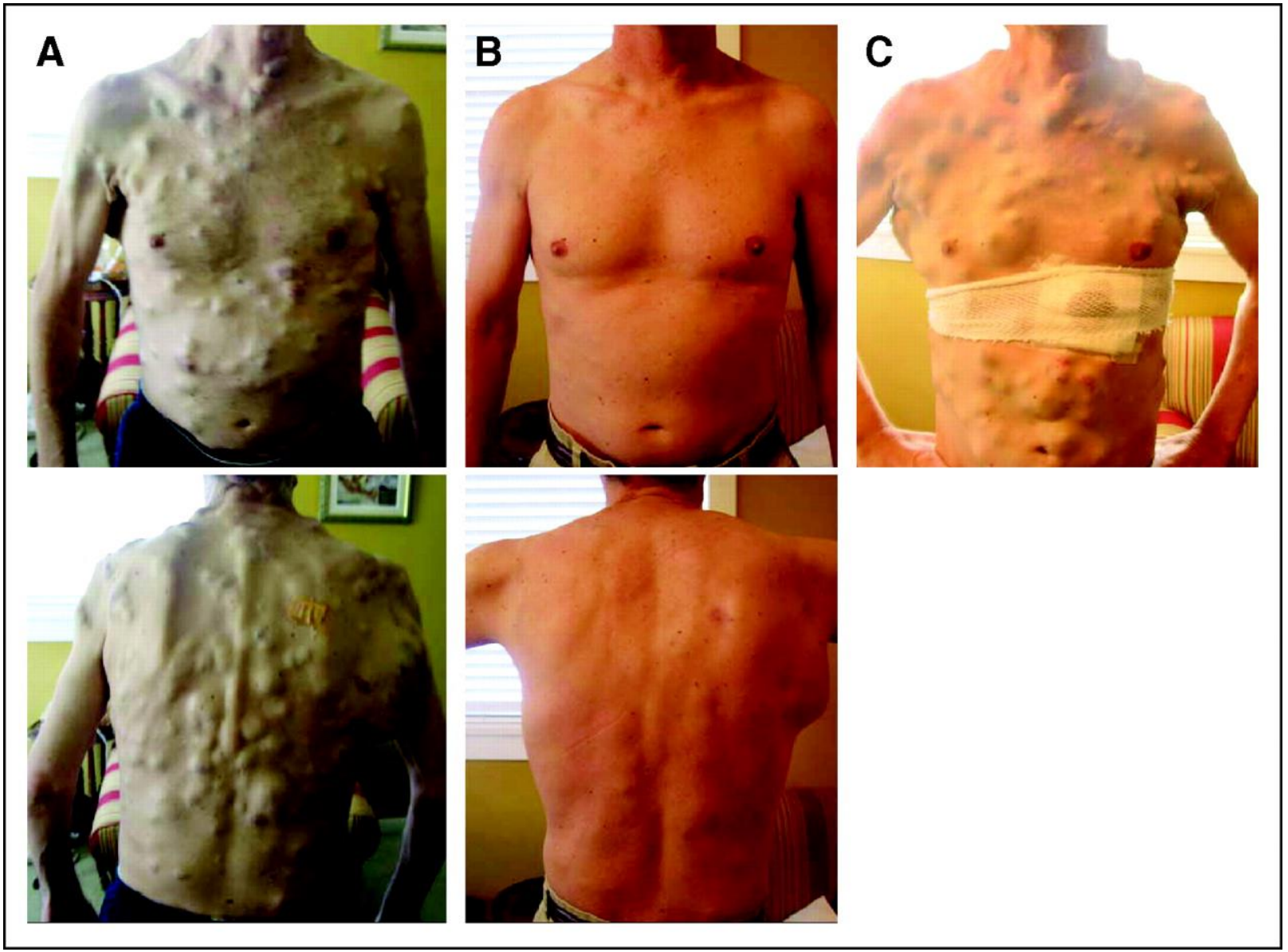
signaling pathways in melanoma.

Kinase Signaling Pathways in Melanoma



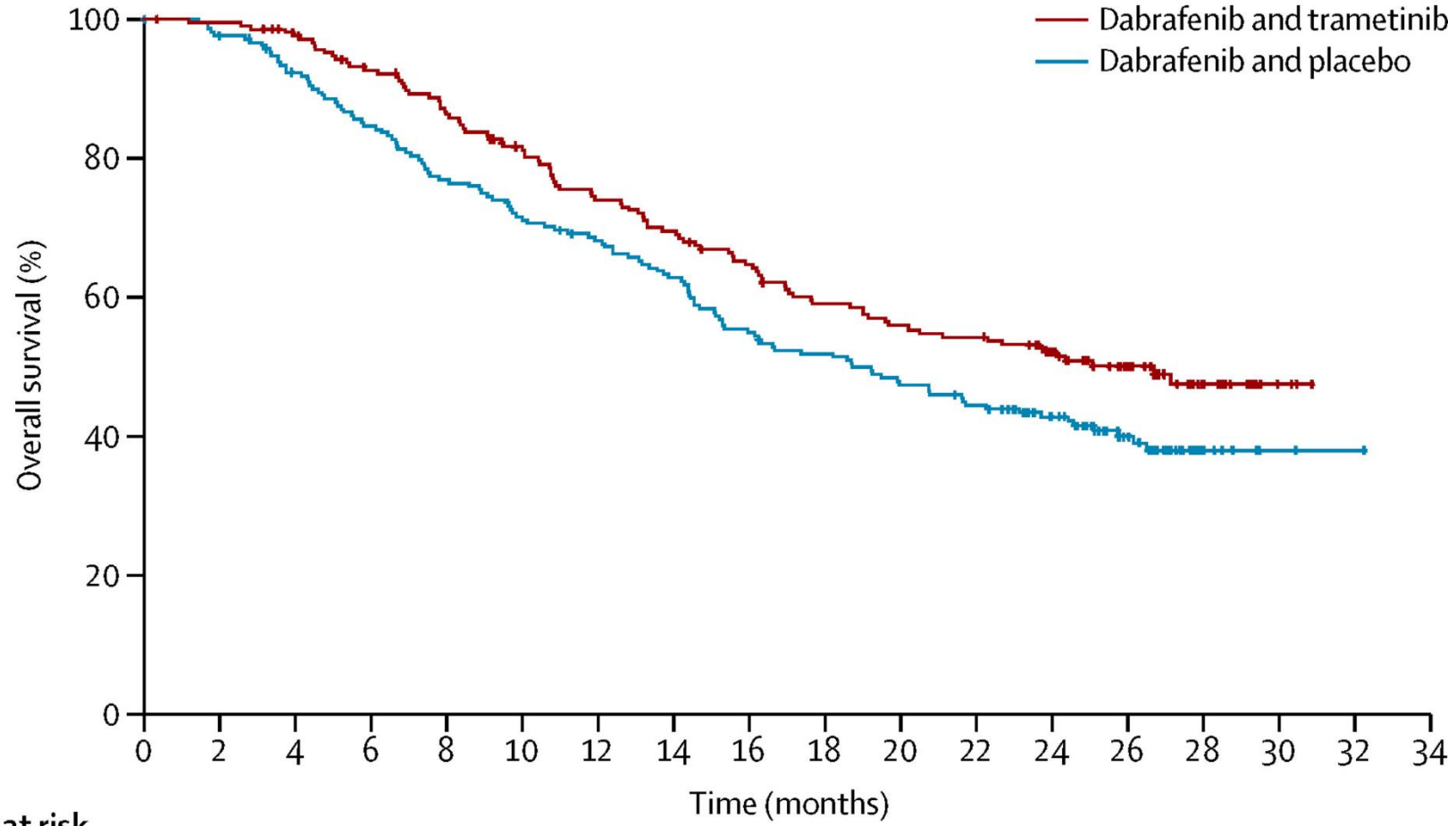
Davies MA, et al. Oncogene 2010;29:5545-5555.

A 38-year-old man with BRAF-mutant melanoma and miliary, subcutaneous metastatic deposits.



Nikhil Wagle et al. JCO 2011;29:3085-3096

A



Number at risk																	
Dabrafenib and trametinib	211	208	200	187	174	159	144	135	124	112	106	103	88	53	21	3	0	0
Dabrafenib and placebo	212	206	191	175	159	147	138	127	111	104	95	88	70	42	10	2	1	0

Long GV, et al. Lancet 2015;386:444-451.

Unanswered questions:

Optimal duration of therapy?

Biomarkers to predict response?

Combination vs sequential therapy?

Role of T-cell therapies?