ISTITUTO NAZIONALE TUMORI
IRCCS – Fondazione Pascale

LA QUARTA ARMA CONTRO IL CANCRO

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Disclosure

- **Employment or Leadership Position:** None
- **Consultant/Advisory Role:** Bristol-Meyers Squibb, Roche-Genentech, Merck Sharp & Dohme, Novartis, Amgen, Array, Merck Serono, Pierre Fabre, Incyte, NewLink Genetics, Genmab, Medimmune
- **Stock Ownership:** None
- **Research Funding:** Bristol-Meyers Squibb, Roche-Genentech, Array
- **Expert Testimony:** None
- **Other Remuneration:** None

Immunotherapy:
The third important wave in the history of oncology

1940s

Chemotherapy
alkylating agents, antimetabolites, CDDP, taxanes…

end of 1990s

Targeted Therapy
rituximab, trastuzumab, imatinib…

2011–present

Immunotherapy
ipilimumab, nivolumab, pembrolizumab…

CDDP, cisplatin

History of Intralesional Immunotherapy: "Coley's Toxins"

William Bradford Coley

- Late 19th Century, NY Surgeon
- Unresectable sarcomas regress after superinfection with erysipelas
- Injections of mixed toxins of erysipelas and bacillus prodigiousus
- Dose to 102-103º fever

THE TREATMENT OF INOPERABLE SARCOMA WITH THE MIXED TOXINS OF ERYSIPELAS AND BACILLUS PRODIGIOSUS.

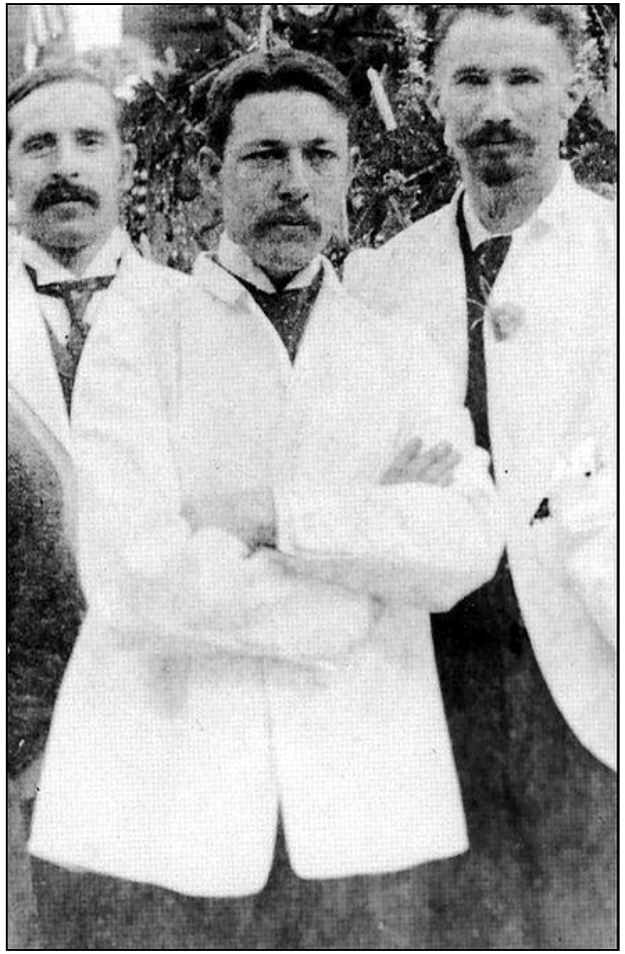
IMMEDIATE AND FINAL RESULTS IN ONE HUNDRED AND FORTY CASES.

Presented to the Section on Surgery and Anatomy, at the Forty-ninth Annual Meeting of the American Medical Association, held at Denver, Colo., June 7–10, 1898.

BY WILLIAM B. COLEY, M.D.

ATTENDING SURGEON TO THE NEW YORK CANCER HOSPITAL; ASSISTANT SURGEON TO THE HOSPITAL FOR RUPTURED AND CRIPPLED.

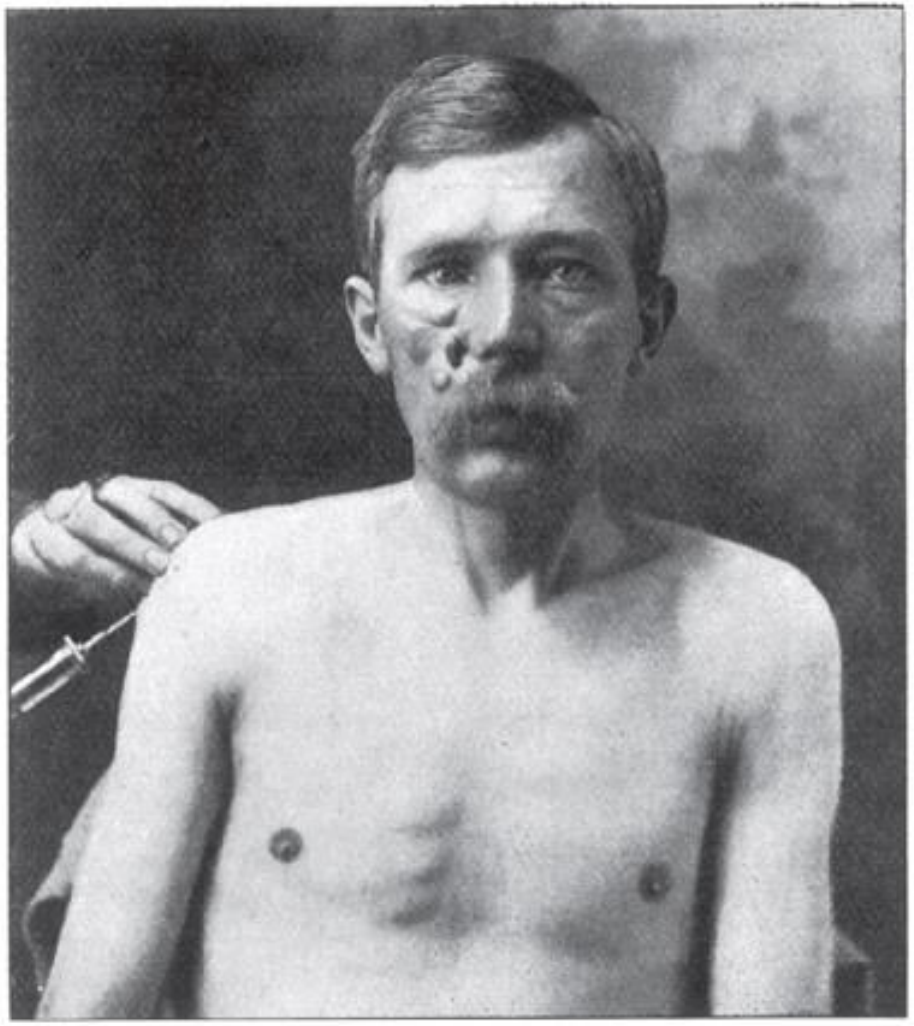
NEW YORK, N. Y.



Courtesy of Mike Faries

Coley's Toxins: Example
Round cell sarcoma 1899

After 63 injections with Coley's toxins



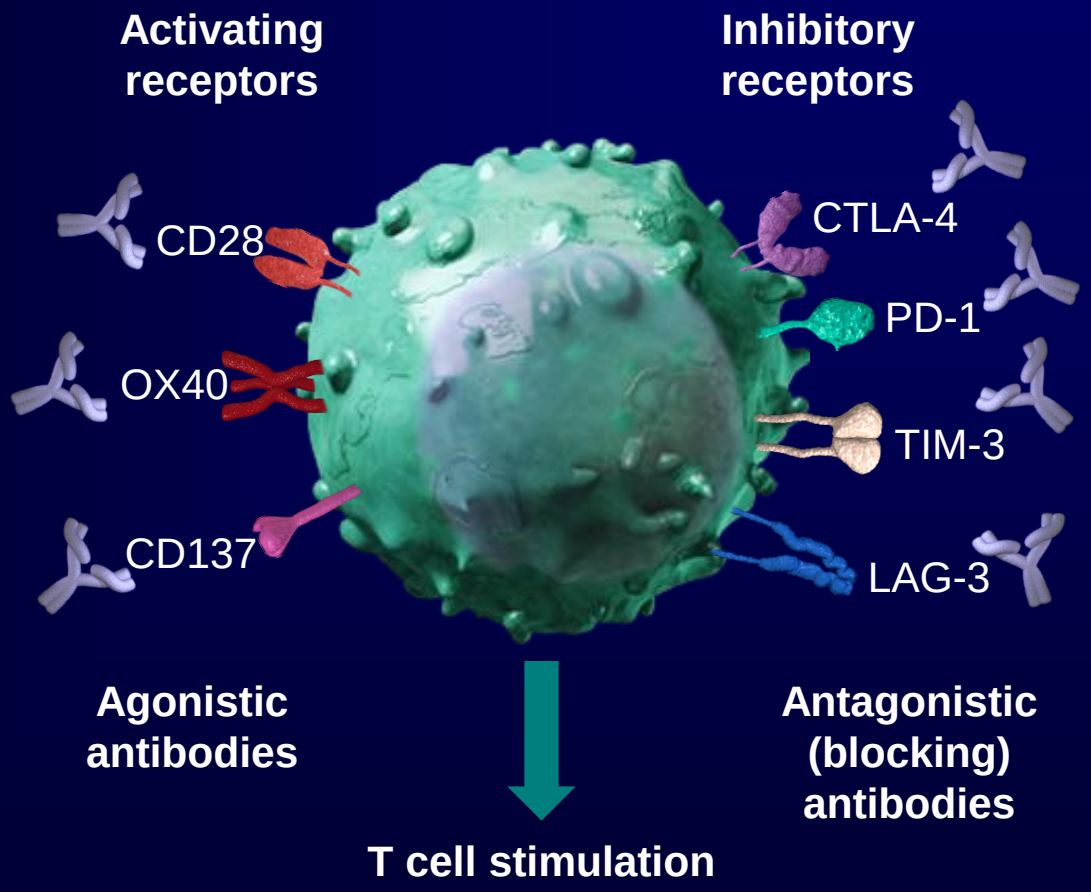
After additional injections

Balkwill Nat Rev Cancer 2010.

Alive and well in 1910.

Courtesy of Mike Faries

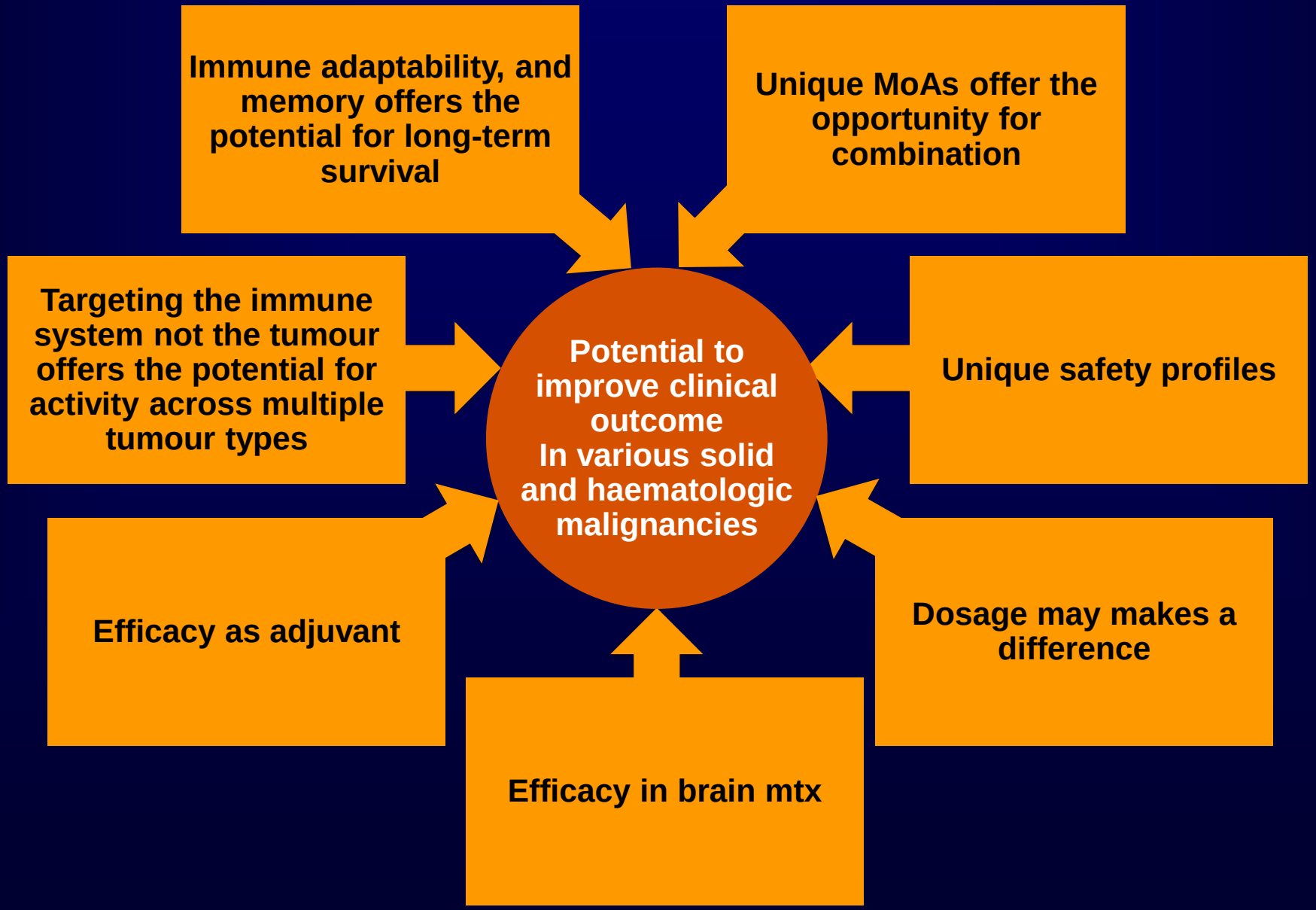
Regulating the T cell immune response[1,2a]



- T cell responses are regulated through a complex balance of inhibitory (‘checkpoint’) and activating signals
- Tumours can dysregulate checkpoint and activating pathways, and consequently the immune response
- Targeting checkpoint and activating pathways is an evolving approach to cancer therapy, designed to promote an immune response

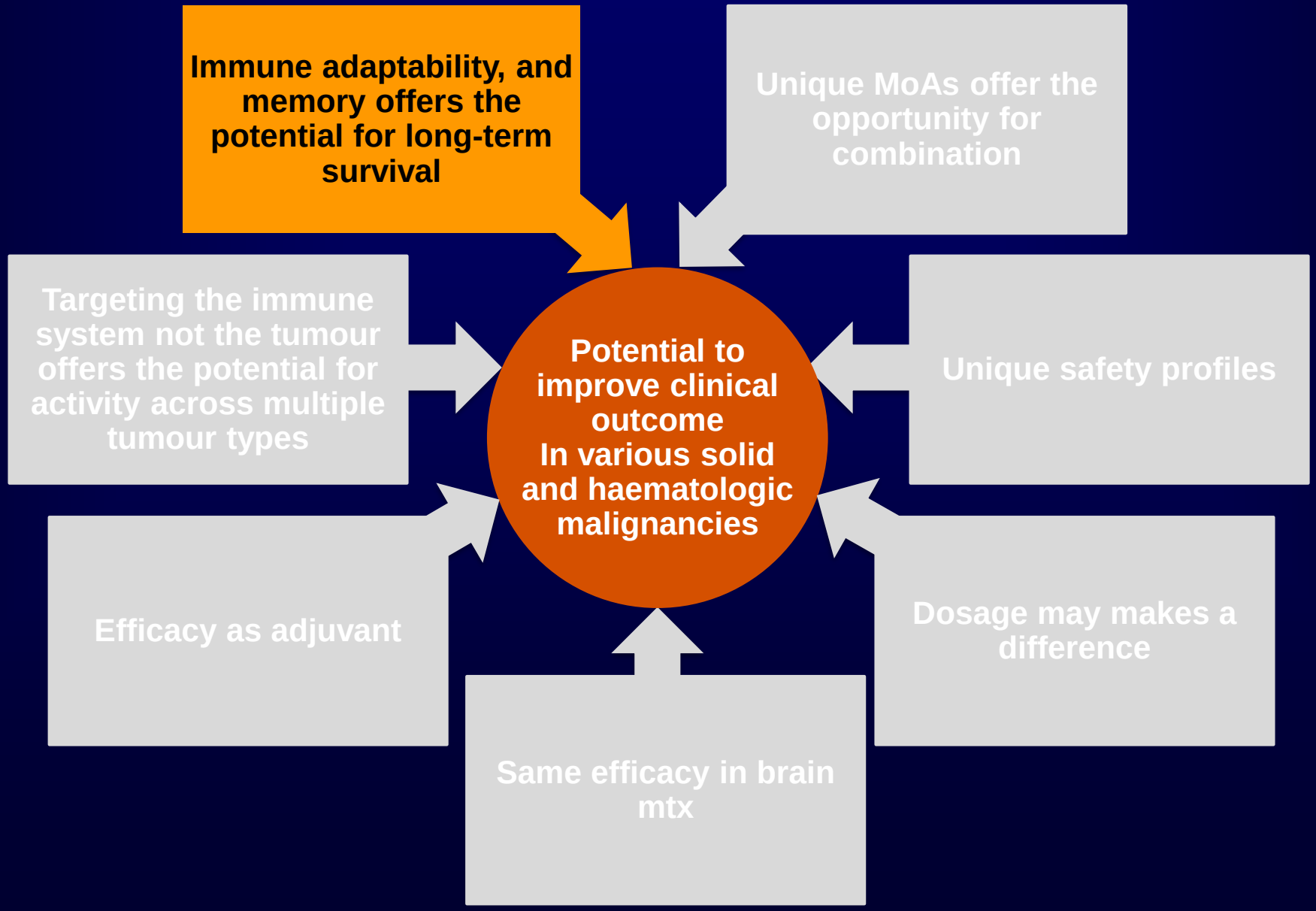
[a]The image shows only a selection of the receptors/pathways involved
LAG-3 = lymphocyte-activation gene 3
1. Adapted from Mellman I, et al. Nature 2011:480;481–489; 2. Pardoll DM. Nat Rev Cancer 2012;12:252–264

What we learned from Immuno-therapy in melanoma

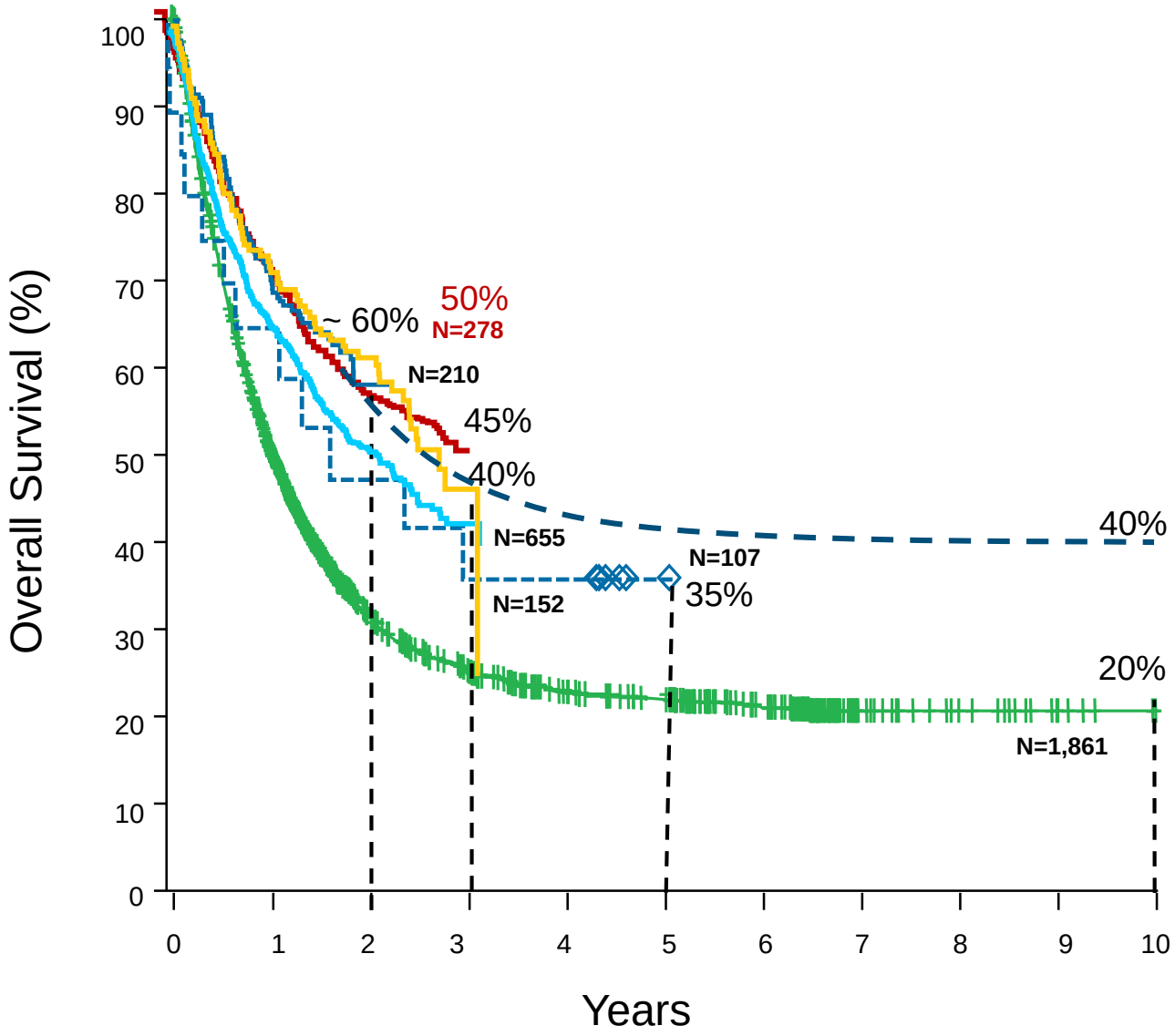


Cosa abbiamo imparato dall'immunoterapia negli ultimi anni

What we learned from Immuno-therapy in melanoma



Immune Checkpoint Inhibitors Provide Durable Long-term Survival for Patients with Advanced Melanoma

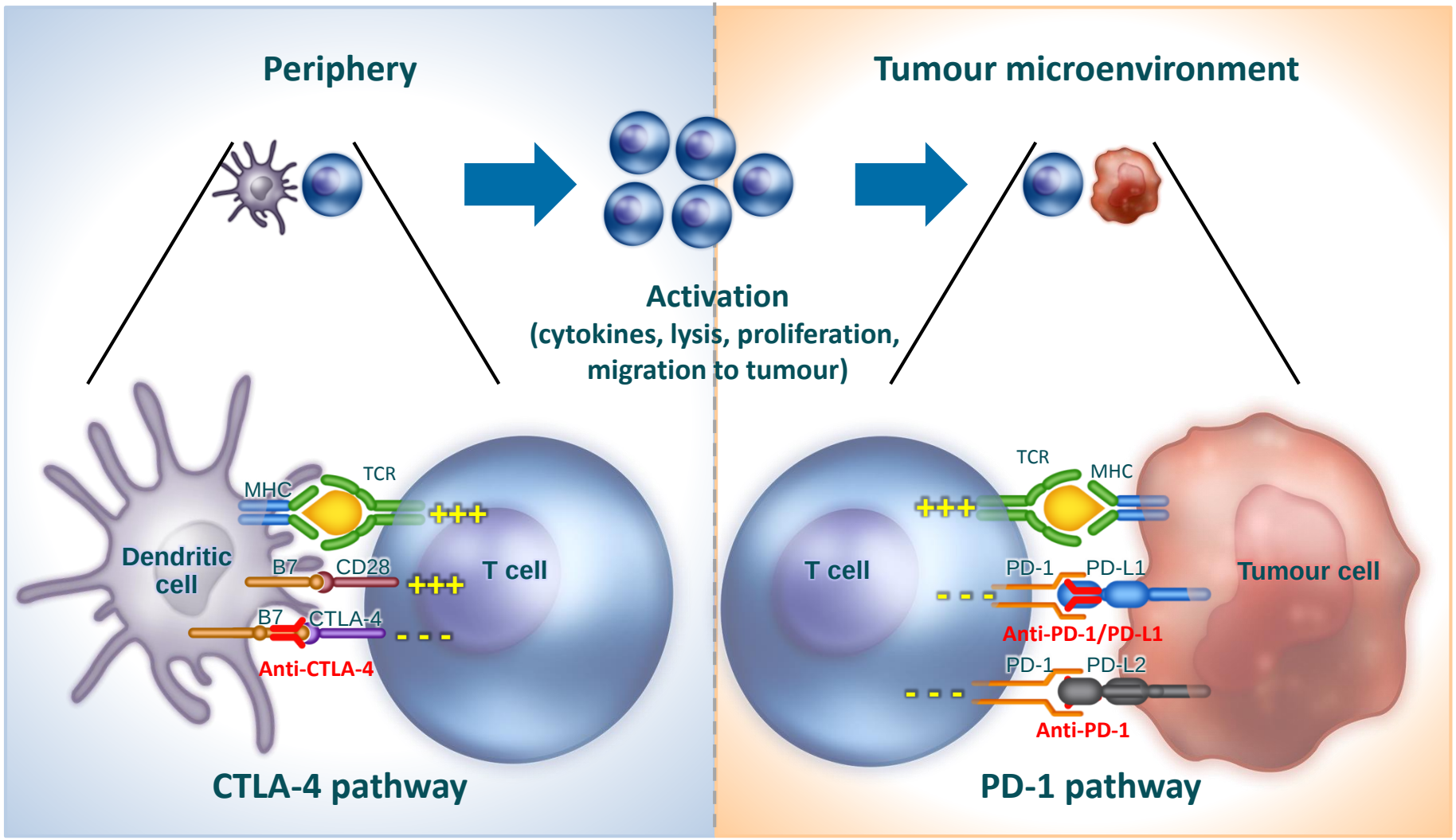


- IPI (Pooled analysis)[1]
- NIVO Monotherapy (Phase 1 CA209-003)[2]
- NIVO Monotherapy (Phase 3 Checkmate 066)[3]
- PEMBRO Monotherapy (Phase 1 Keynote-001)[4] Naïve Patients
- PEMBRO Monotherapy (Phase 1 Keynote-001)[4] Pretreated and Naïve Patients
- PEMBRO Monotherapy (Phase 3 Keynote-006)[7]

Study	mOS (mos)	1-yrs OS%	2-yrs OS%	3-yrs OS%	5-yrs OS%
CA209-003	20,3	65%	47%	41%	35%
CA209-066	NR	70,7%	57,7%	NA	NA
Keynote-001 All Pts	24,4	66%[5]	50%	40%	NA
Keynote-006	32,3	~70%	55%	50%[7]	NA
Keynote-001 Naive Pts	32,2	73%[5]	61%	45%	NA

1. Schadendorf et al. *J Clin Oncol* 2015;33:1889-1894; 2. Current analysis;
2. Hodi FS. AACR 2016
3. Poster presentation by Dr. Victoria Atkinson at SMR 2015 International Congress.
4. Robert et al. Oral presentation ASCO 2016
5. Daud et al. Oral presentation ASCO 2015
6. Larkin et al NEJM 2015
7. Robert et al. ASCO 2017

Targeting CTLA-4 and PD-1 pathways



Wolchock J, et al. JCO 2013 Volume 31, Issue 15_suppl ; abstr 9012^

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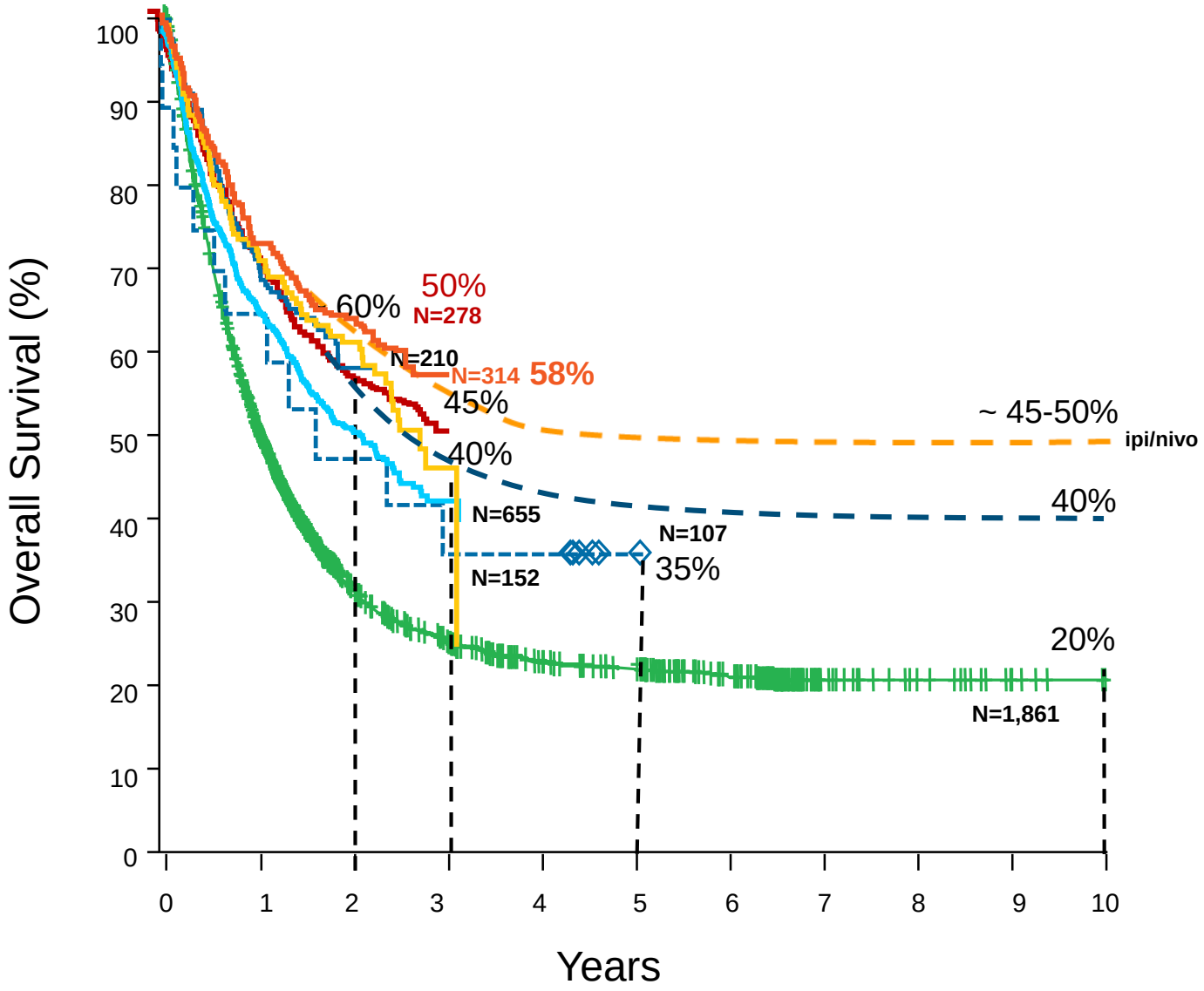

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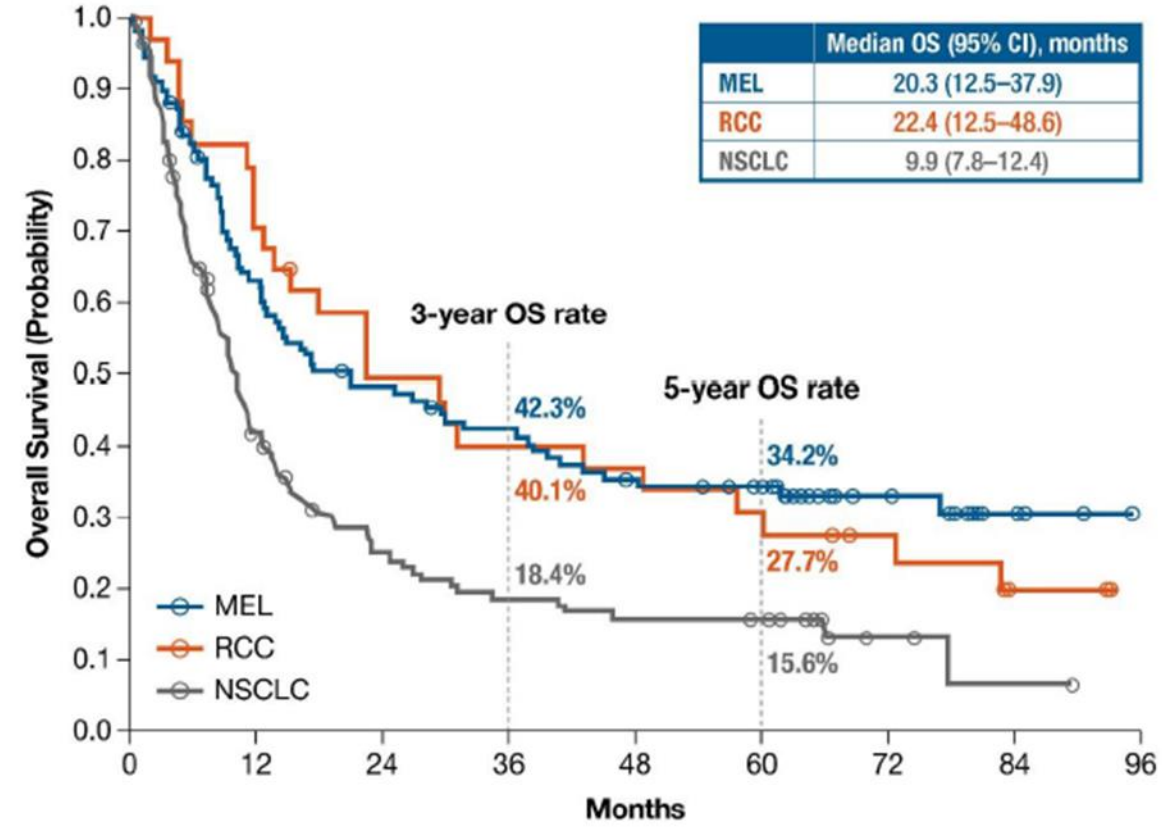
Cross Tumor CA209-003 phase I LTS data

Figure 1. OS estimates for patients with advanced MEL, RCC, or NSCLC

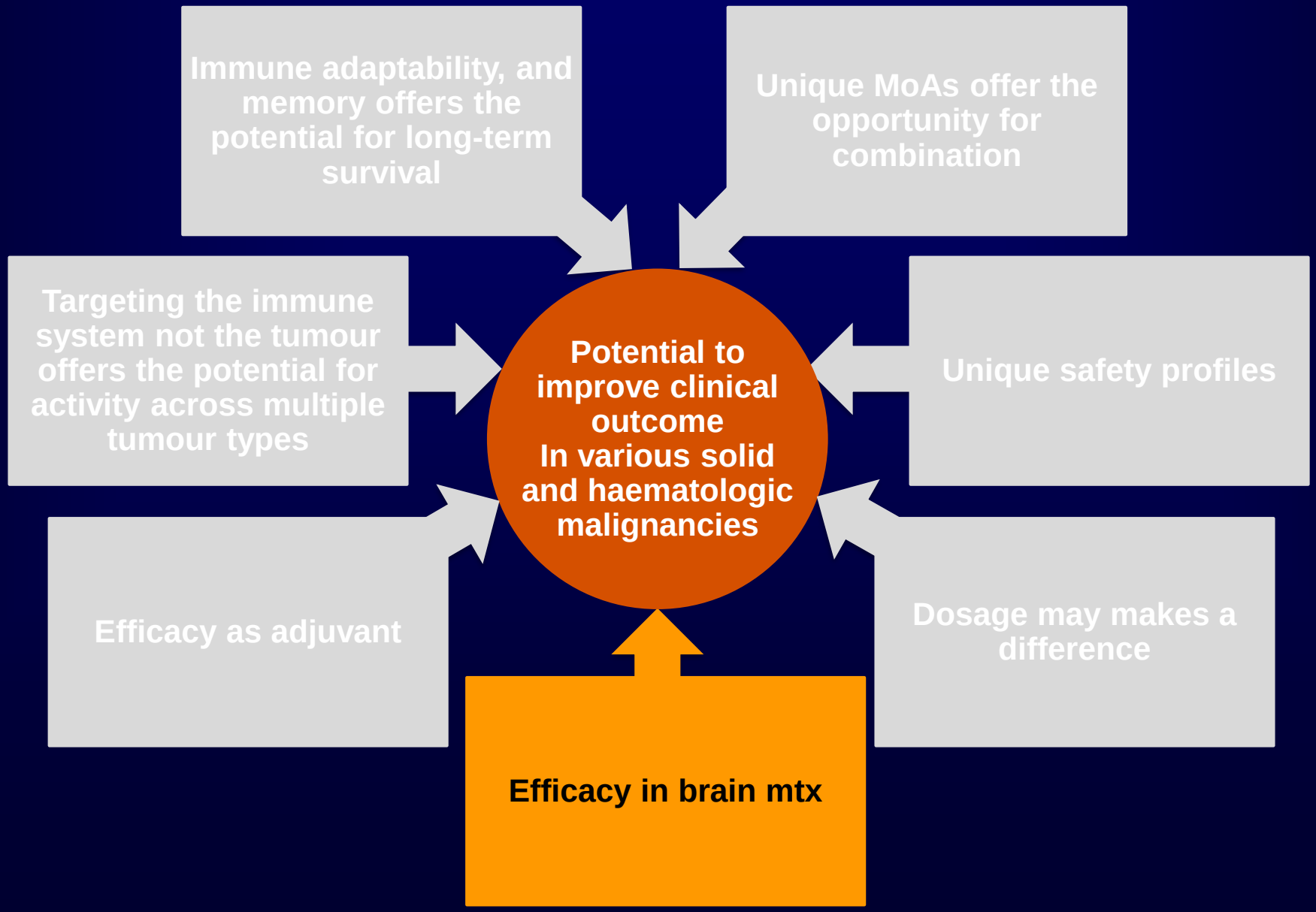


No. of patients at risk								
MEL 107	65	49	42	34	30	14	4	0
RCC 34	24	16	13	12	9	7	2	0
NSCLC 129	49	27	20	17	16	3	1	0

CI = confidence interval

Topalian et al; SITC 2017

What we learned from Immuno-therapy in melanoma

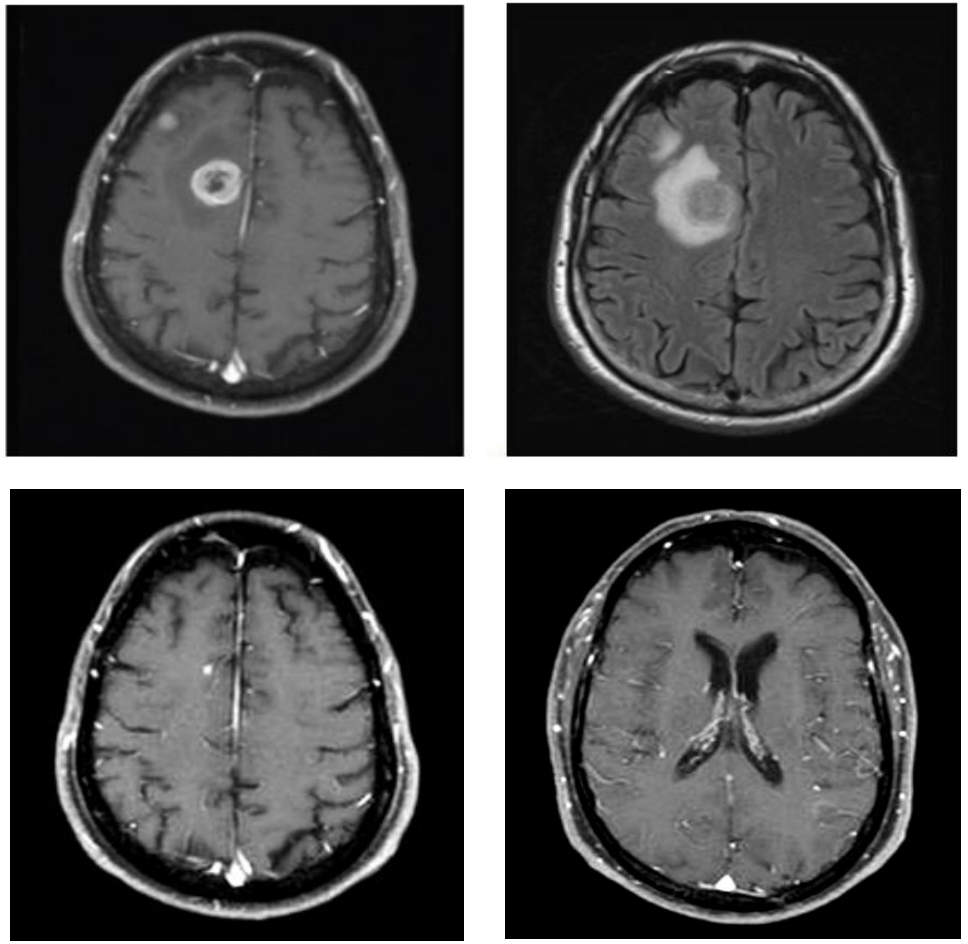


Patient Case

71 year old male with *BRAF* V600E-mutated MEL, ~7 brain mets, no steroids or SRT

Baseline

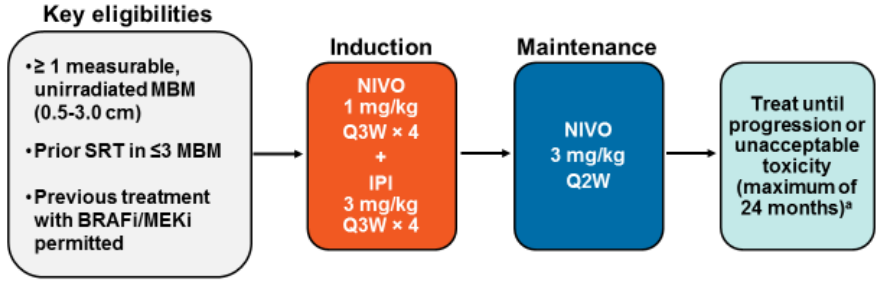
1 year



Tawbi et al ASCO 2017

Ipilimumab + nivolumab in Brain Metastases

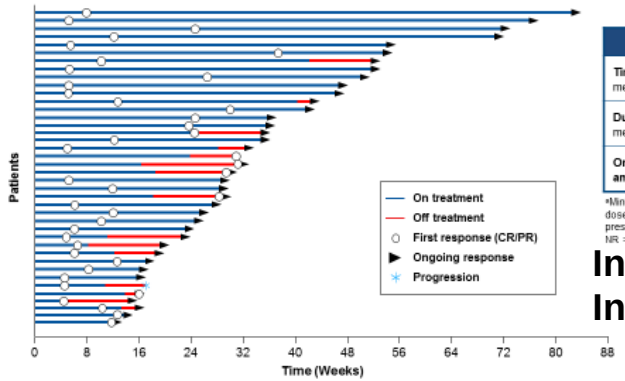
Trial Design



- Exclusion criteria included neurological symptoms; steroids > 10 days; WBRT; prior treatment with checkpoint inhibitors; leptomeningeal disease
- Original planned enrollment of 110 asymptomatic patients

Q2W = every 2 weeks; Q3W = every 3 weeks
[a]Patients with grade 3-4 adverse events (AEs) during NIVO+IPI induction could resume NIVO when toxicity resolved; all patients who discontinued proceeded to follow-up

Swimmer Plot: Time to and Duration of Intracranial Response



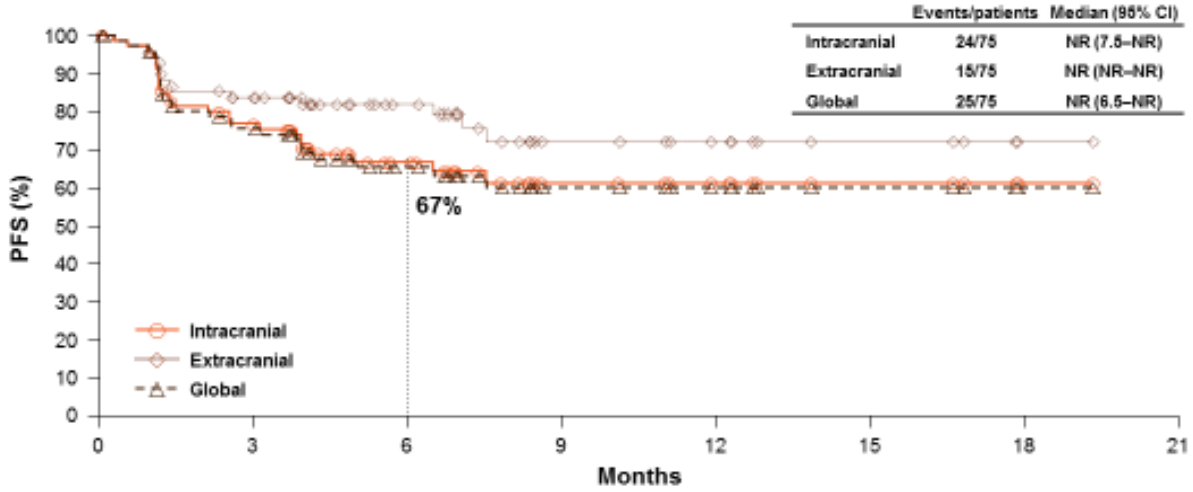
	N = 41
Time to response,[a] median (range), months	2.8 (1.0–11.0)
Duration of response,[a] median (95% CI), months	NR (NR-NR)
Ongoing response among responders[a]	38/41 (93%)

[a]Minimum follow-up of 6 months from date of first dose; 1 patient undergoing further evaluation and not present on plot
NR = not reached

First tumor assessment was at 6 weeks (+/- 2 weeks)

Intracranial ORR: 55%
Intracranial DCR: 60%

PFS



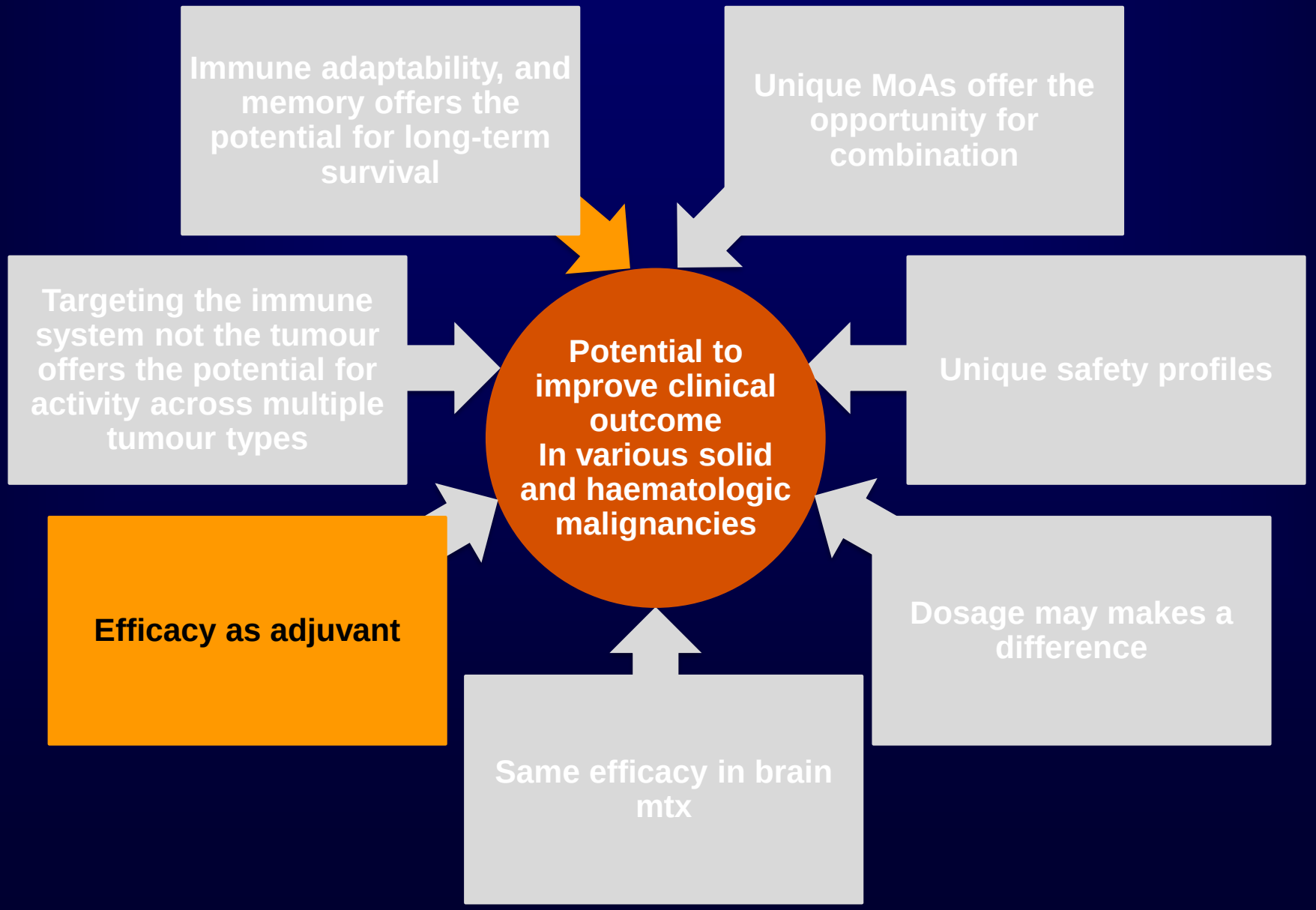
	Events/patients	Median (95% CI)
Intracranial	24/75	NR (7.5–NR)
Extracranial	15/75	NR (NR–NR)
Global	25/75	NR (6.5–NR)

Number of patients at risk

Intracranial	75	50	30	14	10	5	1	0
Extracranial	75	52	31	14	10	5	1	0
Global	75	49	29	14	10	5	1	0

Tawbi et al. ASCO 2017

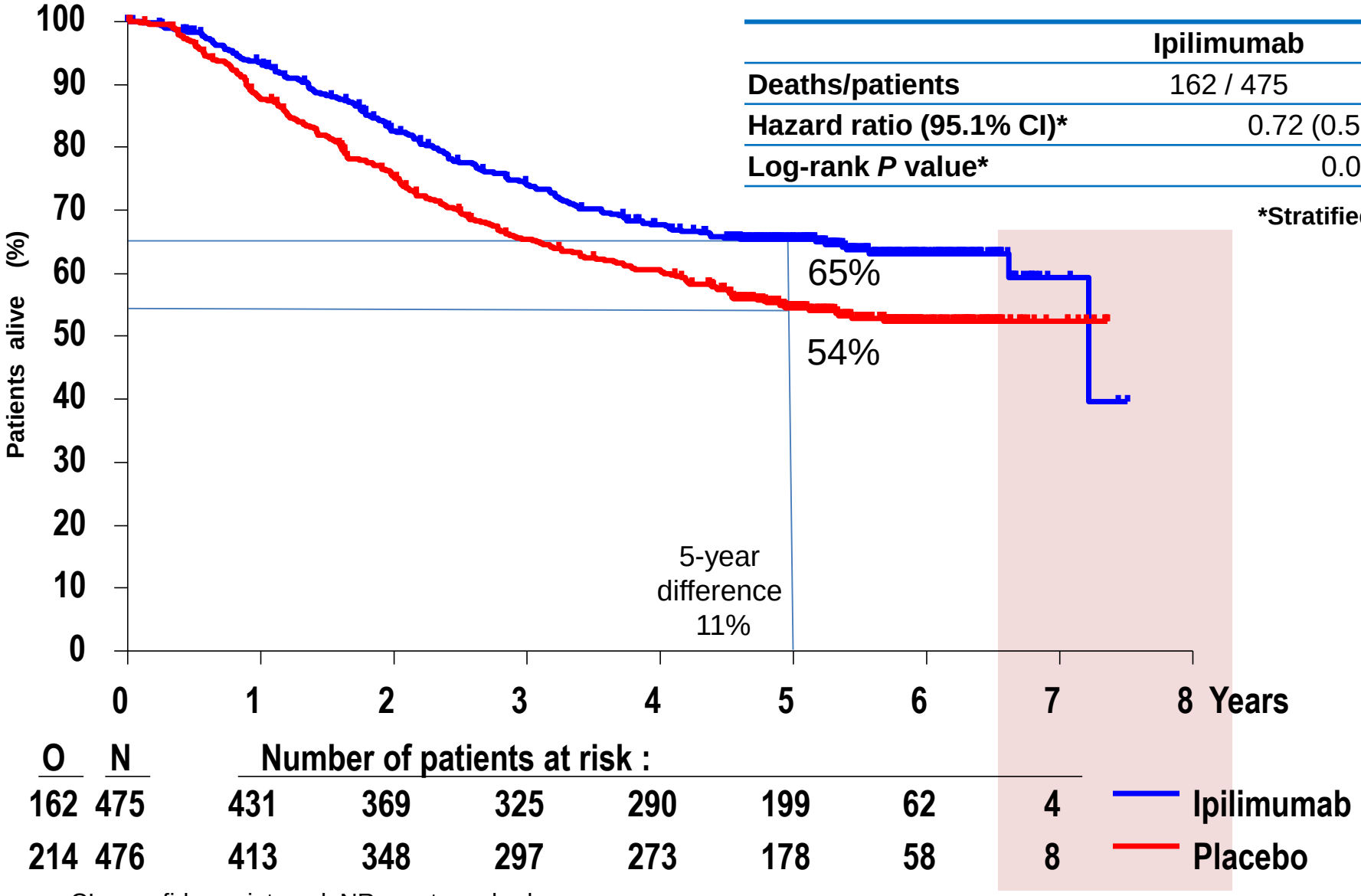
What we learned from Immuno-therapy in melanoma



EORTC 1807: Overall Survival

	Ipilimumab	Placebo
Deaths/patients	162 / 475	214 / 476
Hazard ratio (95.1% CI)*	0.72 (0.58 - 0.88)	
Log-rank *P* value*	0.001	

***Stratified by stage at randomization**

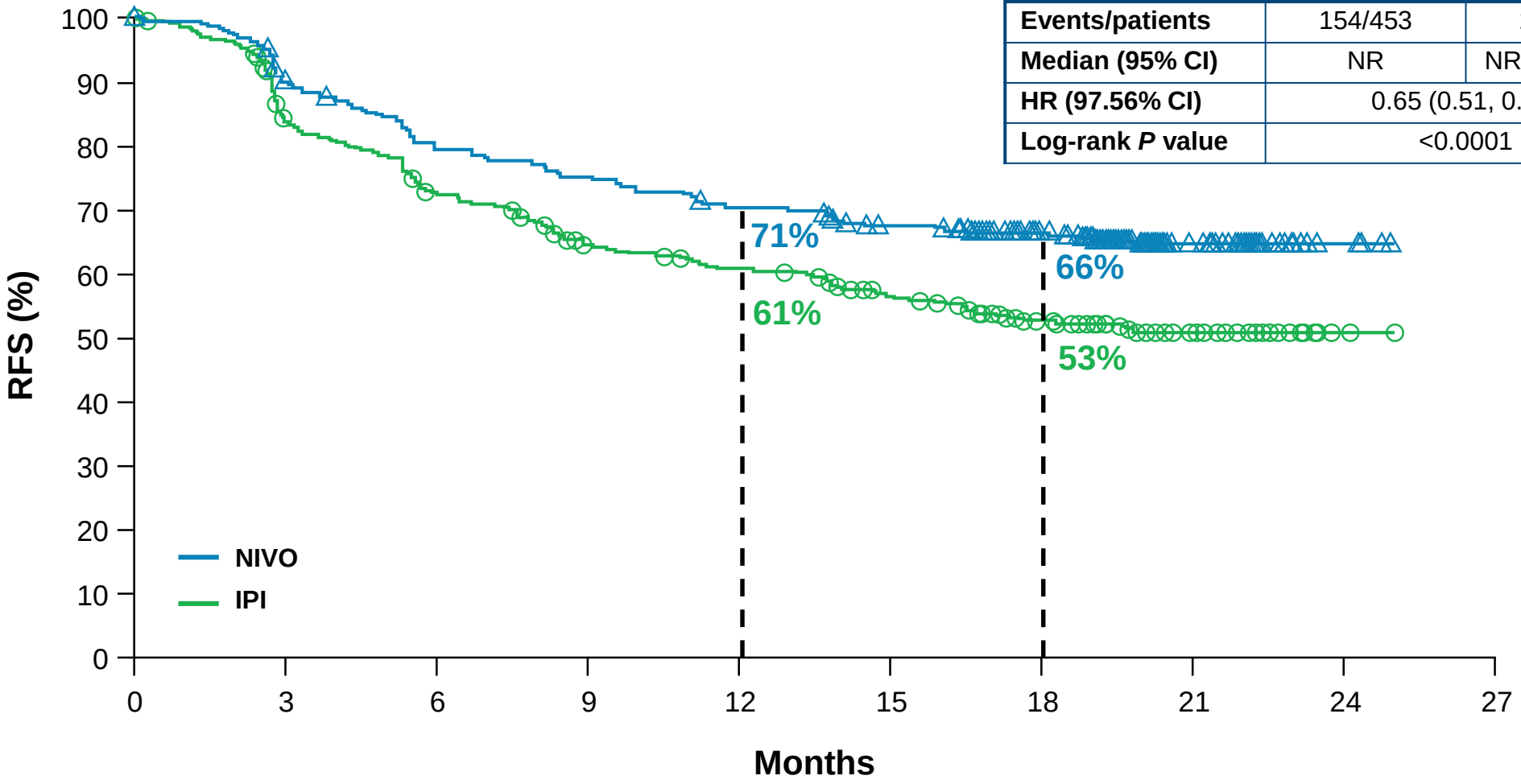


CI = confidence interval; NR = not reached.

Eggermont et al. NEJM 2016

Checkmate 238: 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	

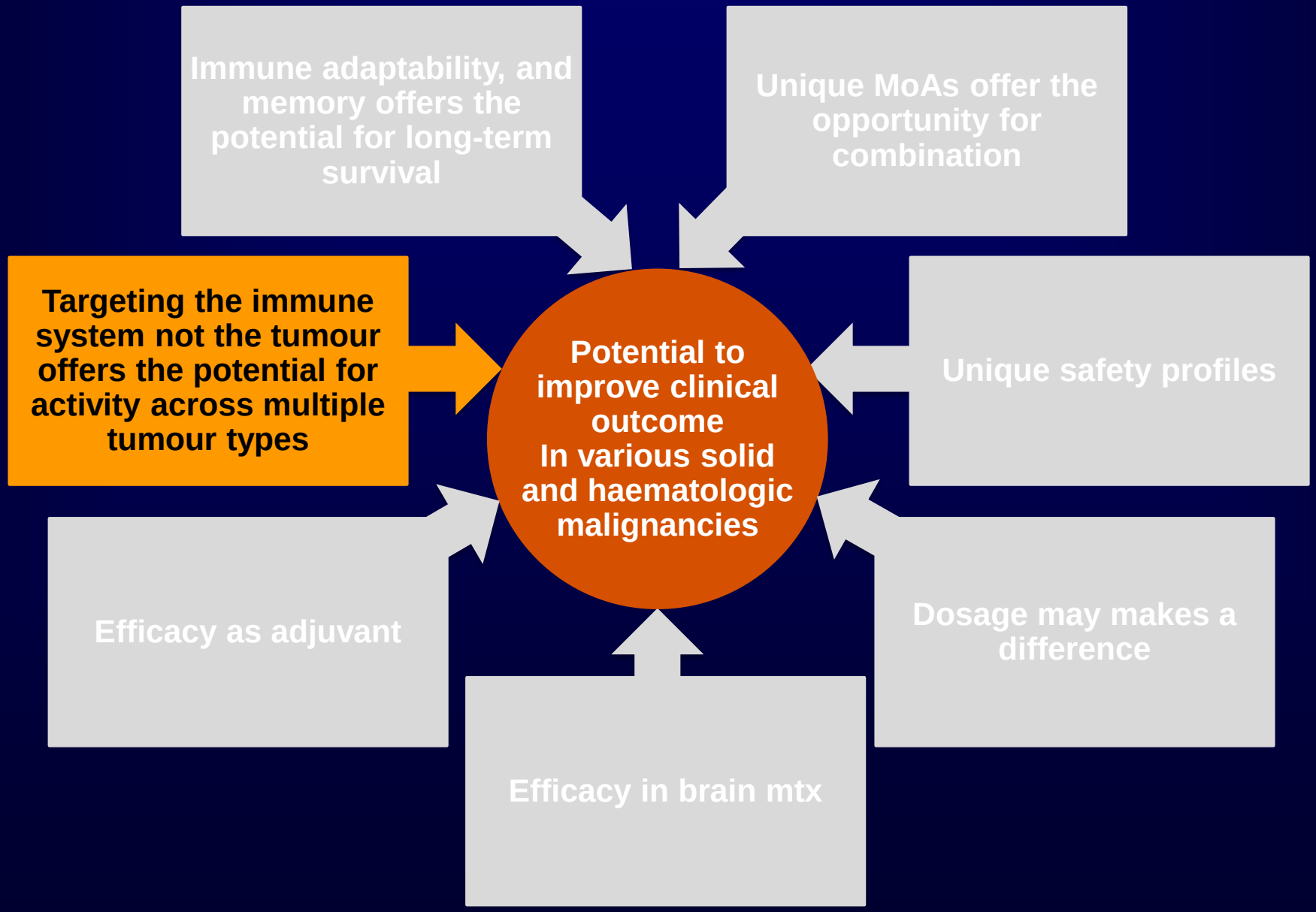


Number of patients at risk

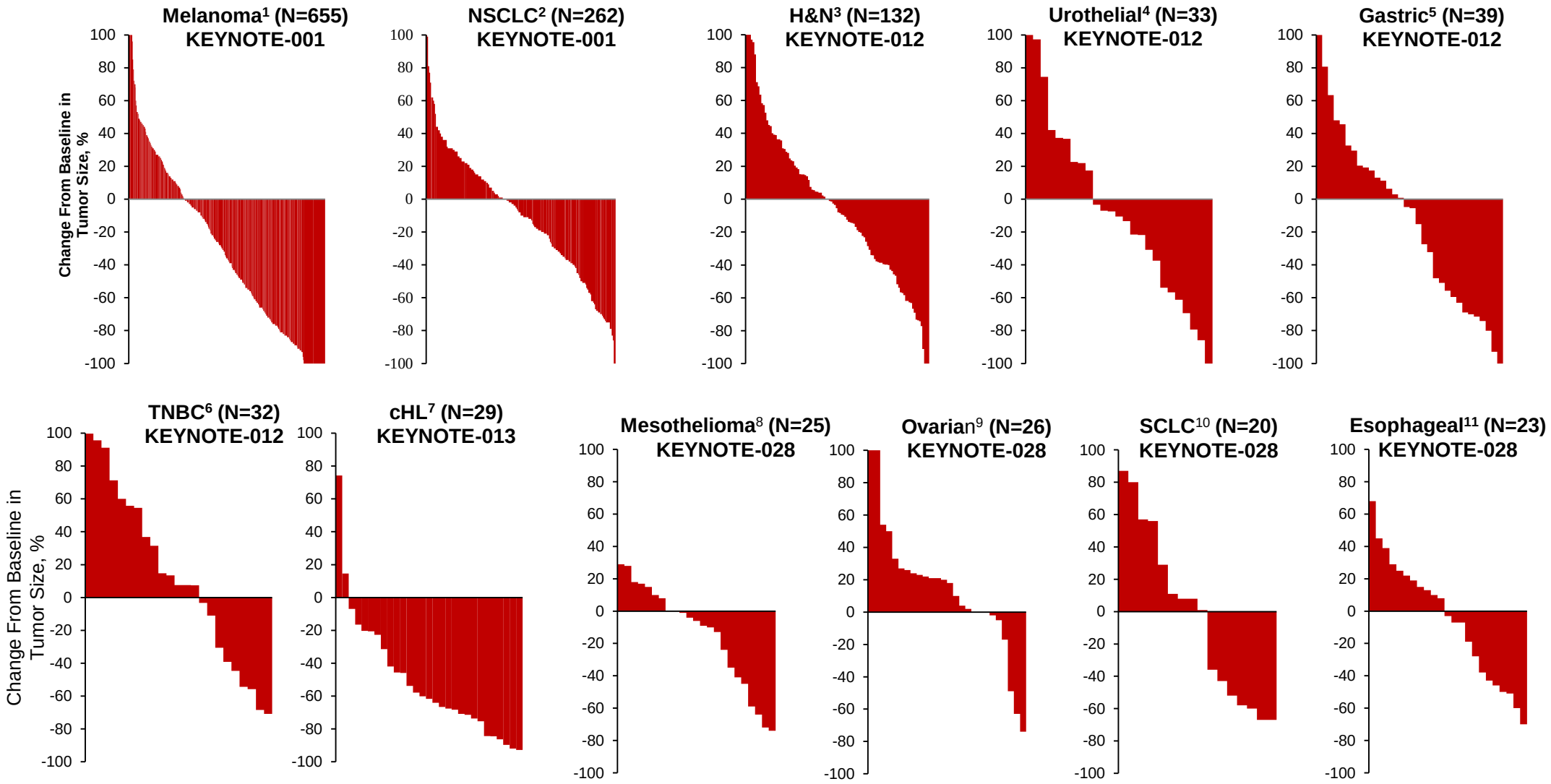
NIVO	453	399	353	332	311	291	249	71	5	0
IPI	453	364	314	269	252	225	184	56	2	0

Weber et al. NEJM 2017

What we learned from Immuno-therapy in melanoma



Pembrolizumab Demonstrates Broad Antitumor Activity



1. Daud A et al. 2015 ASCO; 2. Garon EB et al. ESMO 2014; 3. Seiwert T et al. 2015 ASCO; 4. Plimack E et al. 2015 ASCO; 5. Bang YJ et al. 2015 ASCO; 6. Nanda R et al. SABCS 2014; 7. Moskowitz C et al. 2014 ASH Annual Meeting; 8. Alley EA et al. 2015 AACR; 9. Varga A et al. 2015 ASCO; 10. Ott PA et al. 2015 ASCO; 11. Doi T et al. 2015 ASCO.

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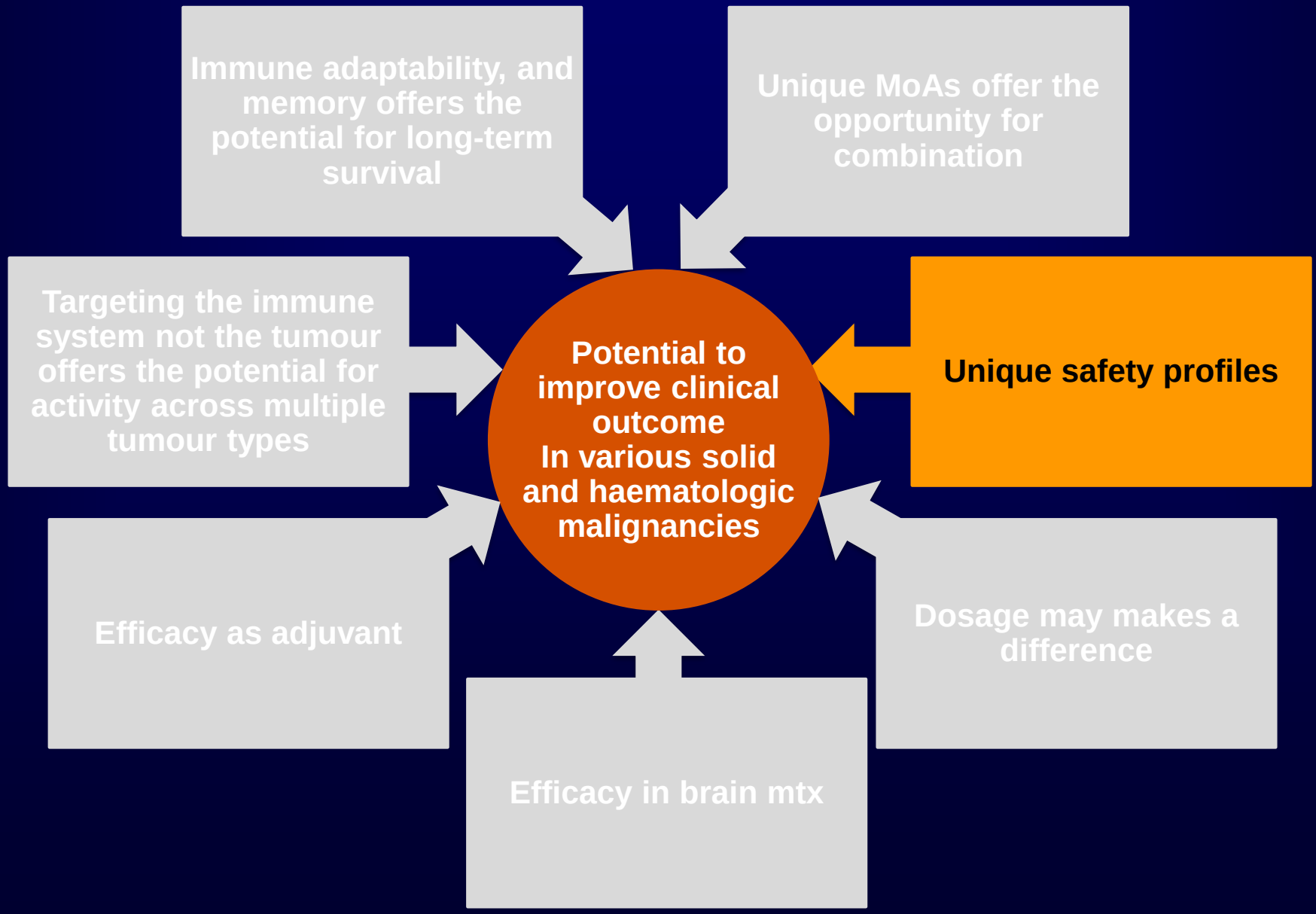
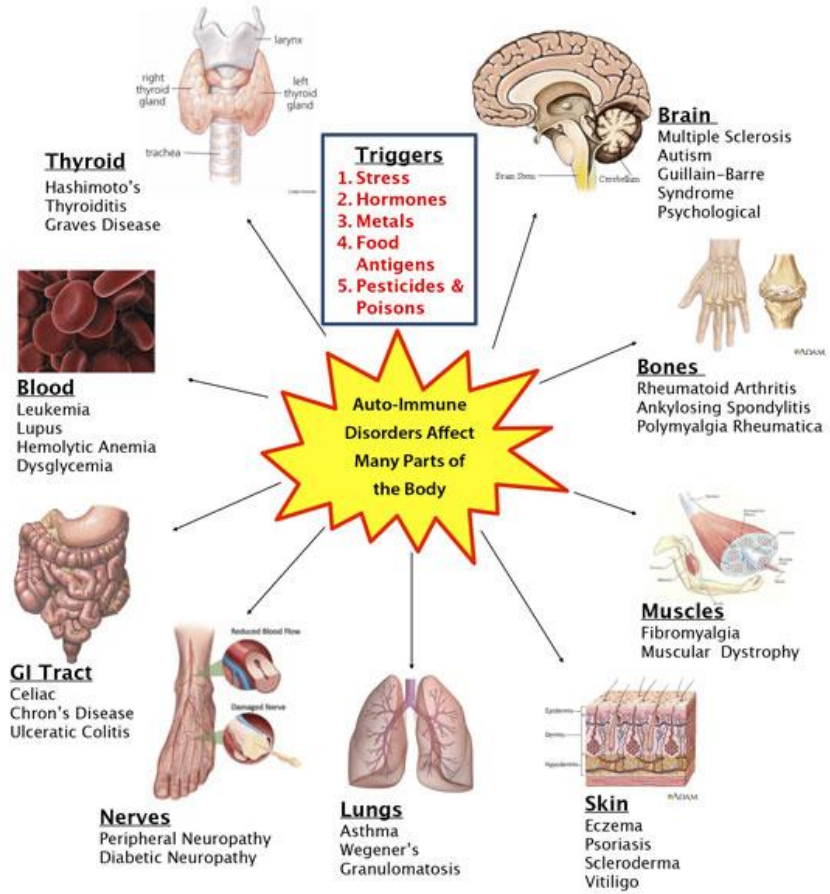
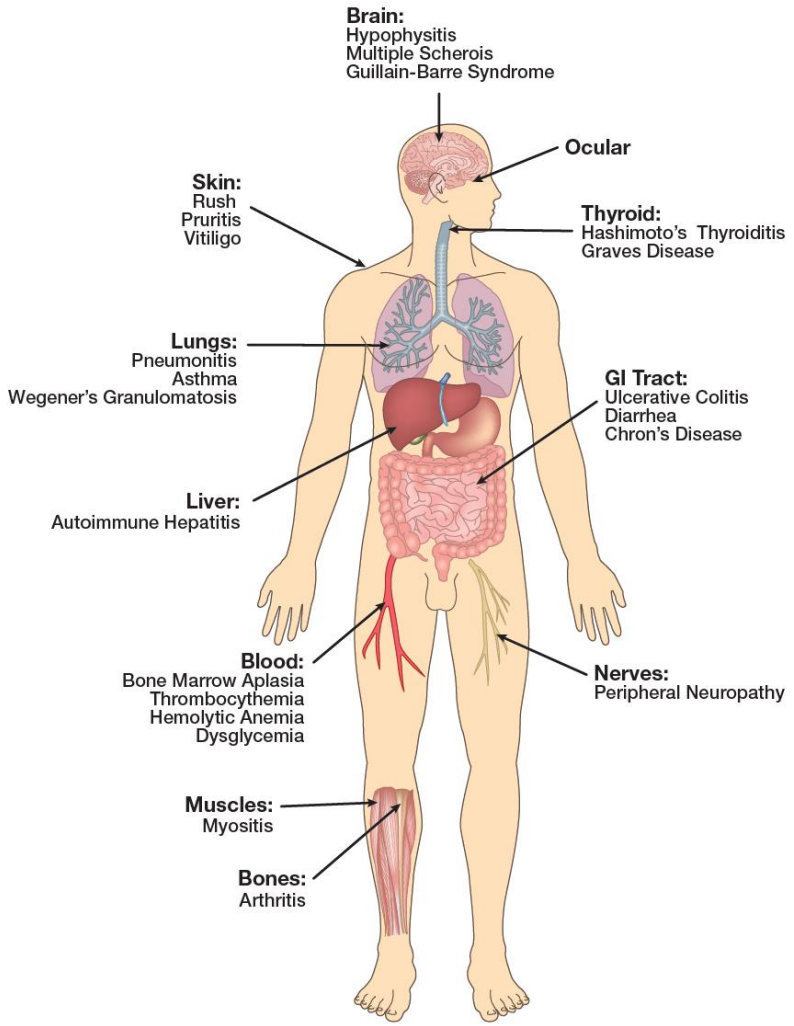


Tissues of the body affected by autoimmune attack



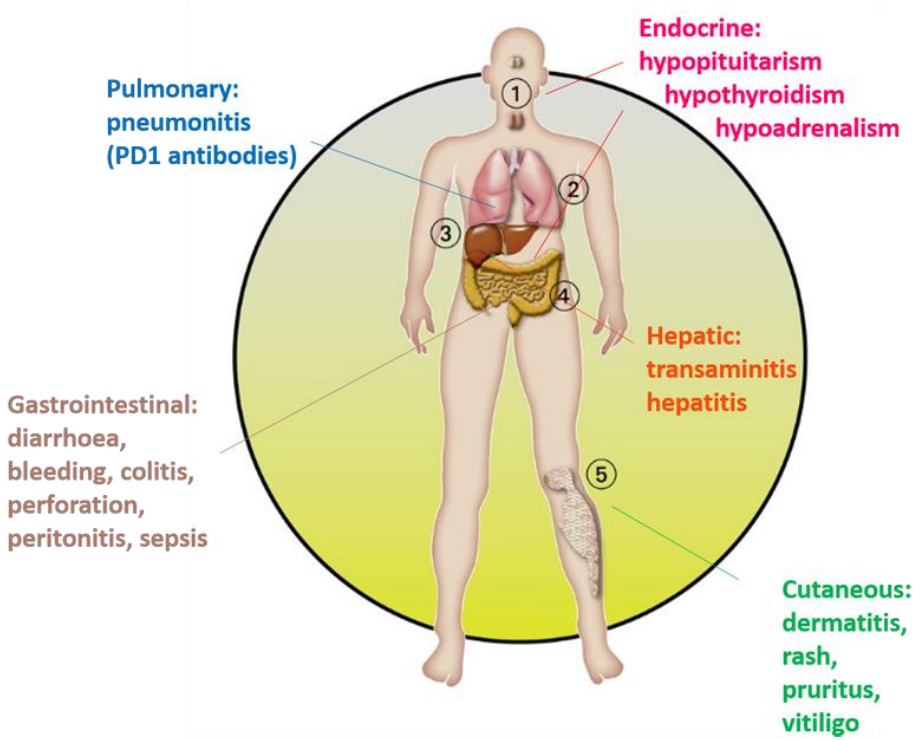
The clinical spectrum of IRAEs (immune-related adverse events)



Festino and Ascierto. Oncoimmunology Eds 2017

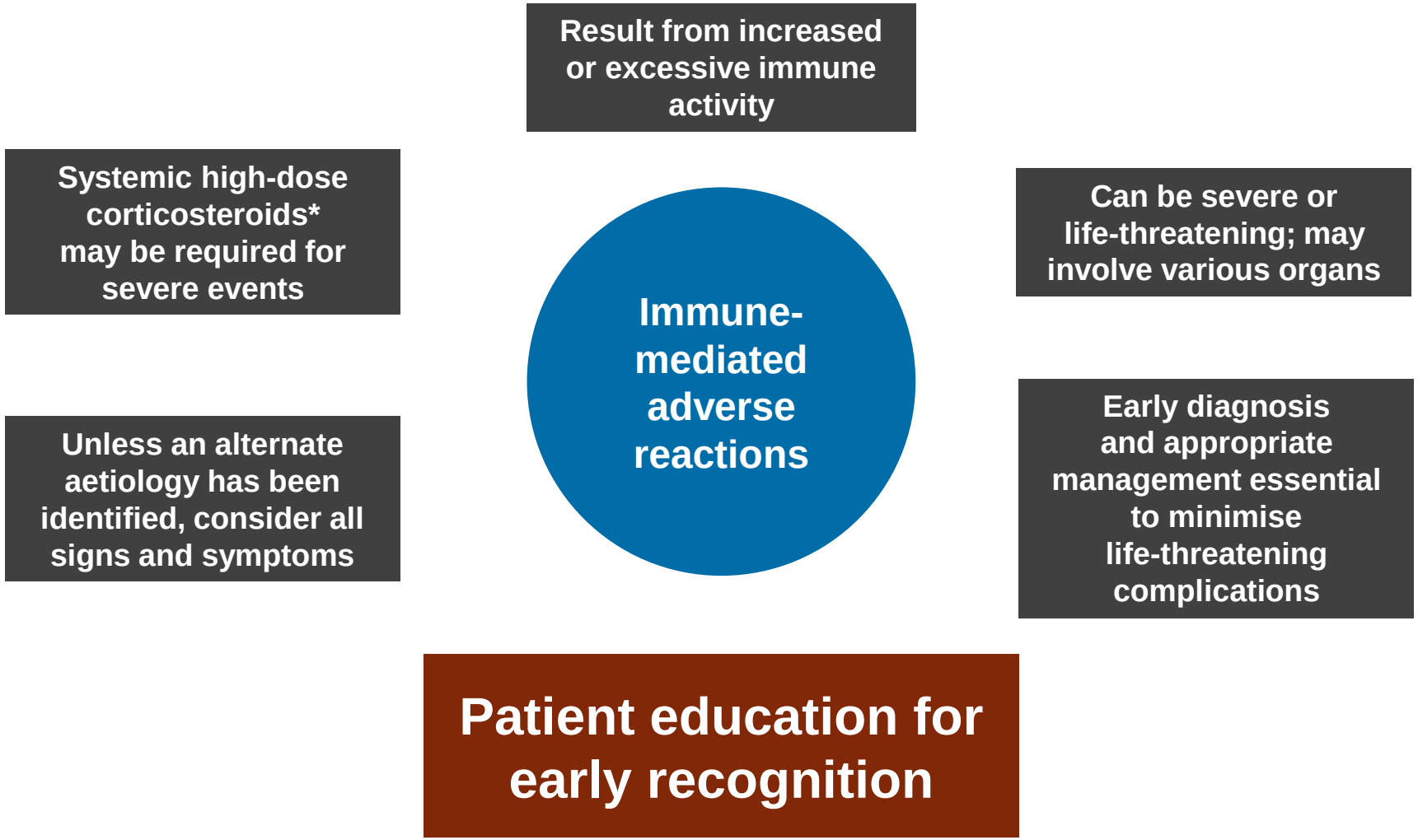
Most frequent irAEs

	Grade 3-4 AEs %	% of Pts who permantely discontinued for any grade
Ipilimumab 3 mg/kg[1]	27	15.4
Ipilimumab 10 mg/kg[1]	34	31
Nivolumab[2]	13	6
Pembrolizumab 2 mg/kg[3]	13.5	4.5
Ipilimumab/Nivolumab[4]	56.5	38.7



1. Ascierto et al. ESMO 2016
2. Atkinson et al. SMR 2015
3. Hamid ESMO 2016
4. Wolchock et al ASCO 2016

Treatment algorithms/experience aid early diagnosis and management of immune-mediated adverse reactions



**With or without additional immunosuppressive therapy*

What’s the next ……

NeoAdjuvant

Better combos with less side effects

The right duration of treatments

Combination or sequencing

Thank you!

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