Update on Management of Melanoma

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Disclosures

- Attended an advisory board meeting for Array BioPharma; Denver 11/2018

Case presentation

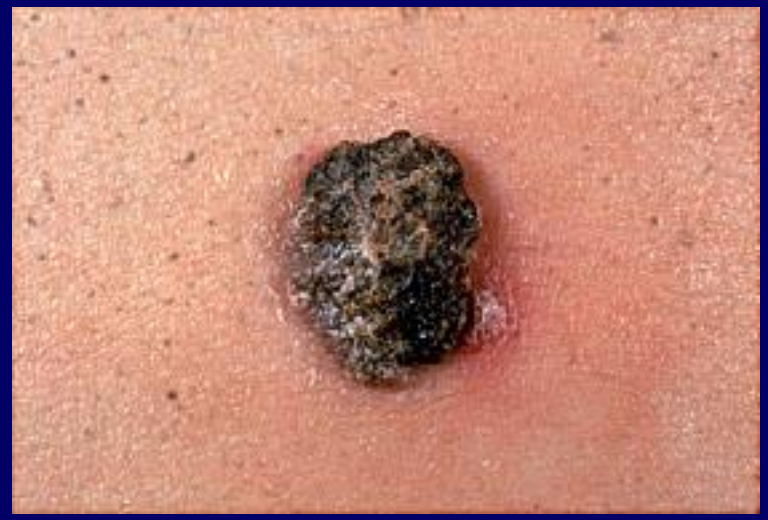
- Mr. K is a 63 year old male who presented to his primary care physician with a rapidly growing pigmented lesion on his right shoulder blade. The primary care physician suspects melanoma. This is most likely:

A- Superficial spreading melanoma

B- Nodular melanoma

C- Acral-lentiginous melanoma

D- Lentigo maligna melanoma



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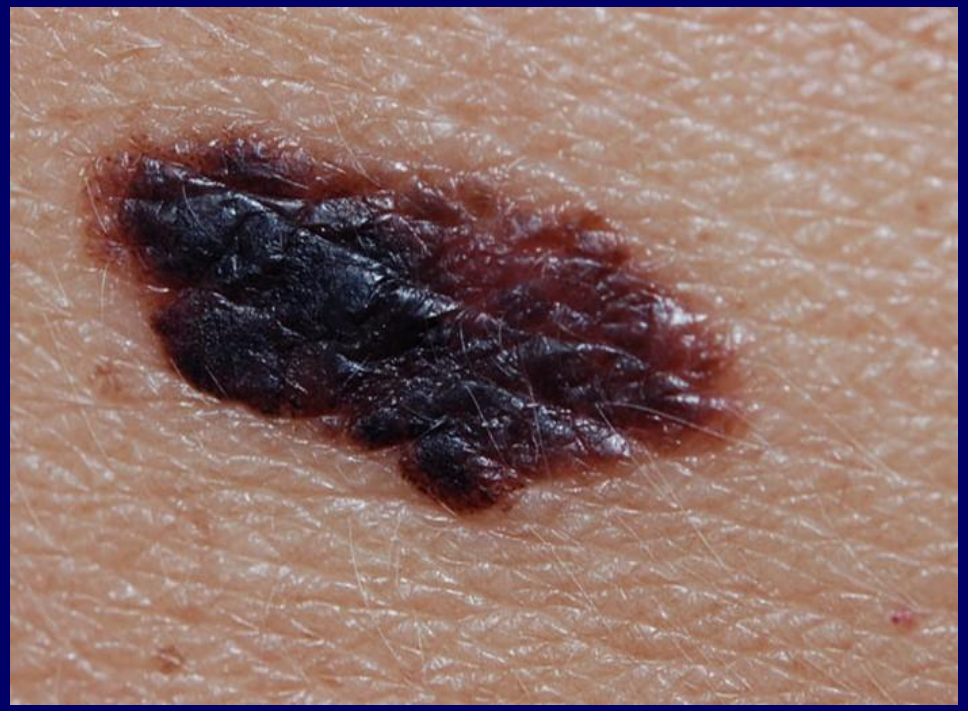
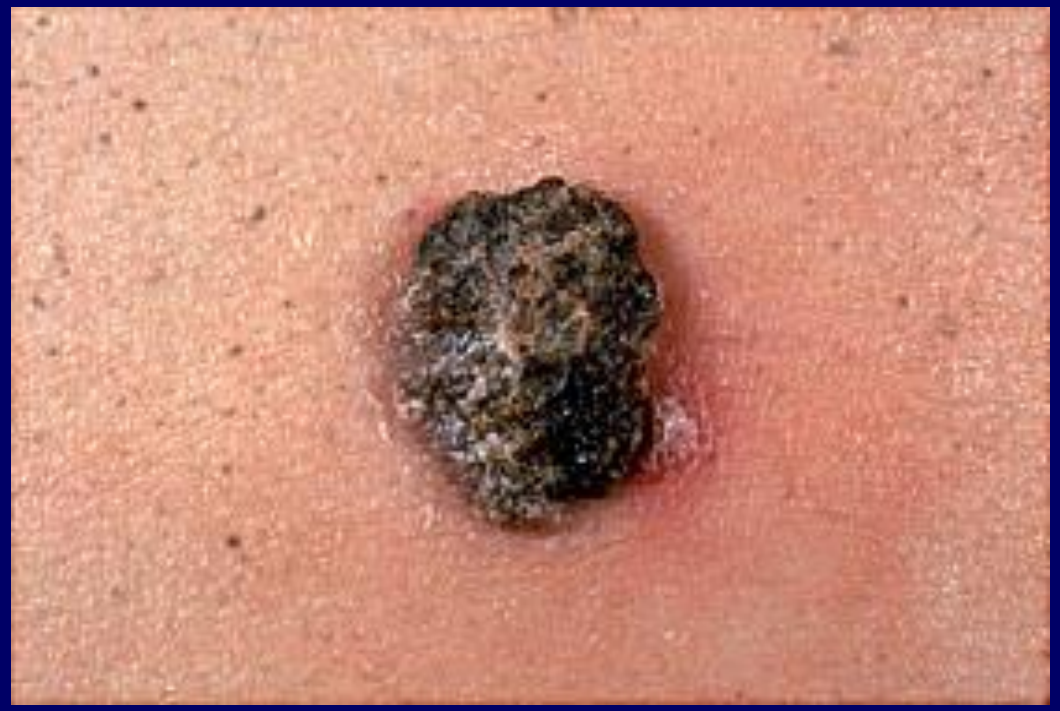
Types of melanoma



Superficial spreading melanoma

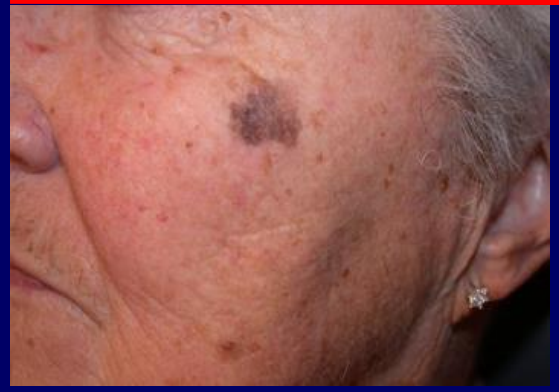
- Most common type of skin melanoma 70%
- Asymptomatic black or brown macule
- Radial growth phase before becoming invasive.



Nodular melanoma

- Second most common type of skin melanoma 15%
- Nodular shape
- Vertical not radial growth
- Rapid progression over months

Types of melanoma

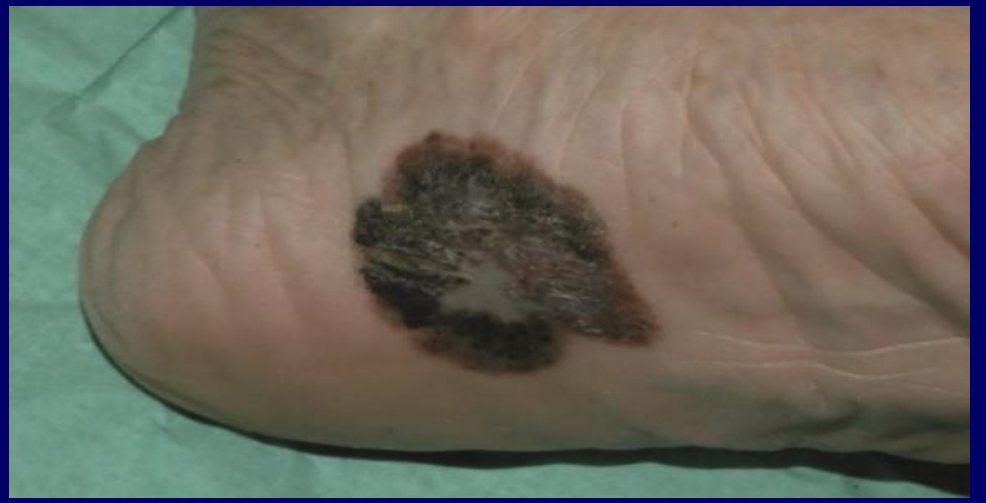


Lentigo maligna

- Irregularly shaped macule
- In situ melanoma
- Slowly grows over 5-15 years before becoming invasive
- Invasive changes (lentigo maligna melanoma)

can be evident with the formation of bumps (papules)

Lentigo maligna melanoma



Acral-lentiginous melanoma

- 2-8% of melanomas in white people
- 75% of melanomas in black and Asian people

Subungual melanoma

0.7 to 3.5% of all melanomas

The ABCDE


Asymmetry.
One half is unlike the other half.
Border.
An irregular, scalloped, or poorly defined border.
Color.
Is varied from one area to another; has shades of tan, brown, or black; is sometimes white, red, or blue.
Diameter.
Melanomas are usually greater than 6mm (the size of a pencil eraser) when diagnosed, but they can be smaller.
Evolving.
A mole or skin lesion that looks different from the rest or is changing in size, shape, or color.

Case presentation....

- Patient was referred to a dermatologist who performed an excisional biopsy. Final pathology confirmed malignant melanoma, Breslow depth 3 mm and a close surgical margin of 1 cm. What would be the next step.

A- Wide local excision

B- Wide local excision and sentinel lymph node biopsy

C- PET CT or CT chest/abdomen/pelvis to rule out metastatic disease

D- No further intervention needed as the dermatologist already excised the melanoma lesion

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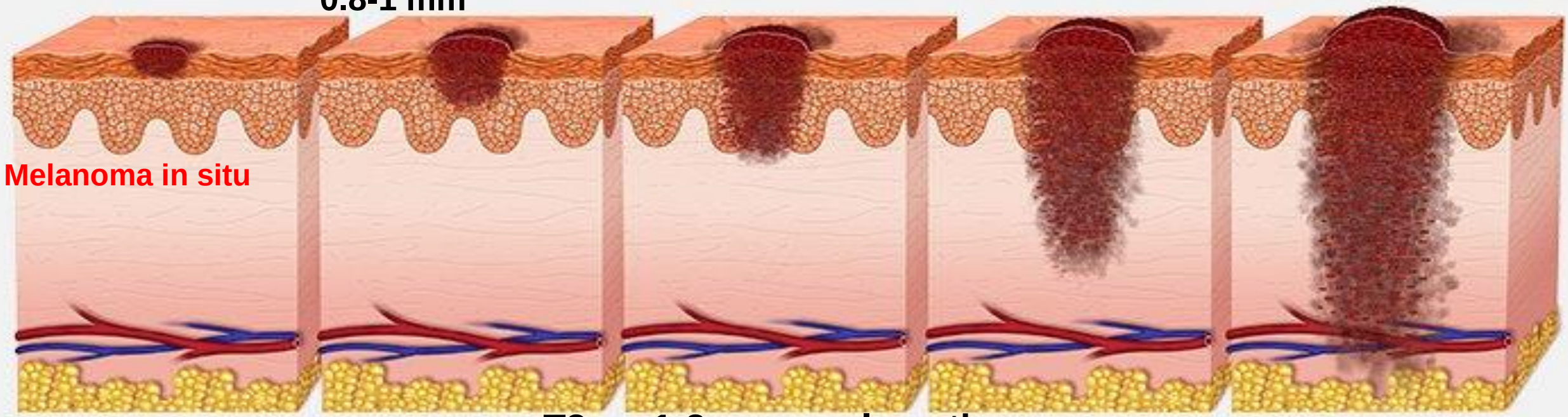
Breslow depth & T stage

T1a:<0.8 mm no ulceration
T1b: <0.8 mm with ulceration
0.8-1 mm

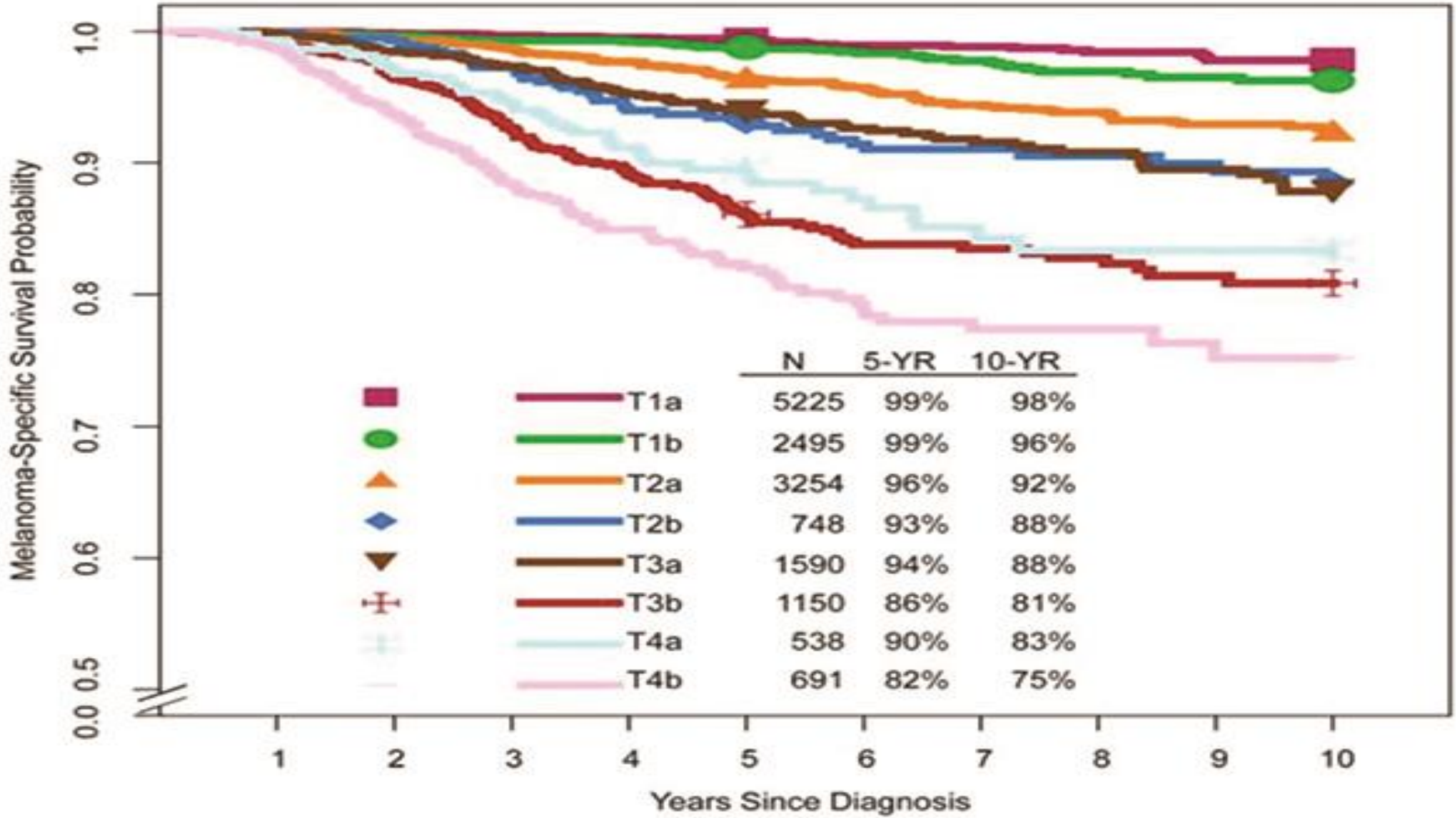
T3a: >2-4mm no ulceration
T3b: >2-4mm with ulceration



Melanoma in situ

T2a: >1-2mm no ulceration
T2b: >1-2mm with ulceration

T4a: >4mm no ulceration
T4b: >4mm with ulceration


Melanoma-Specific Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.0
1
2
3
4
5
6
7
8
9
10
Years Since Diagnosis
N 5-YR 10-YR
T1a 5225 99% 98%
T1b 2495 99% 96%
T2a 3254 96% 92%
T2b 748 93% 88%
T3a 1590 94% 88%
T3b 1150 86% 81%
T4a 538 90% 83%
T4b 691 82% 75%

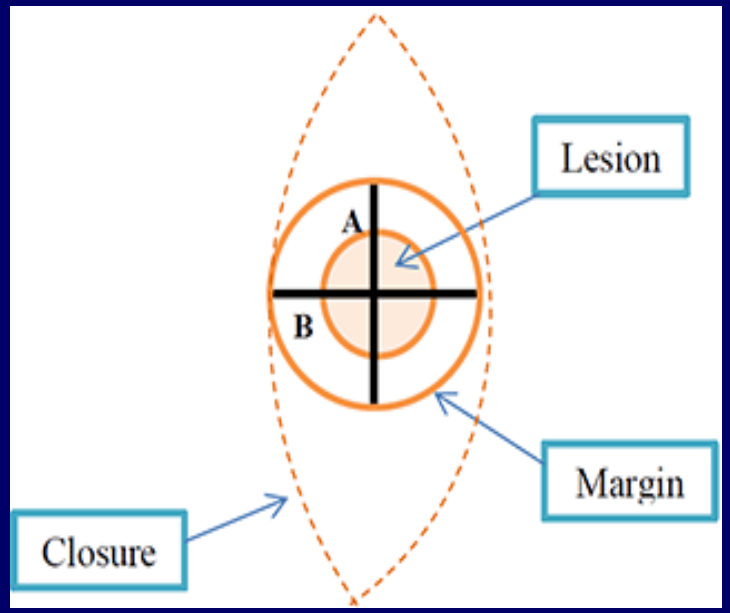
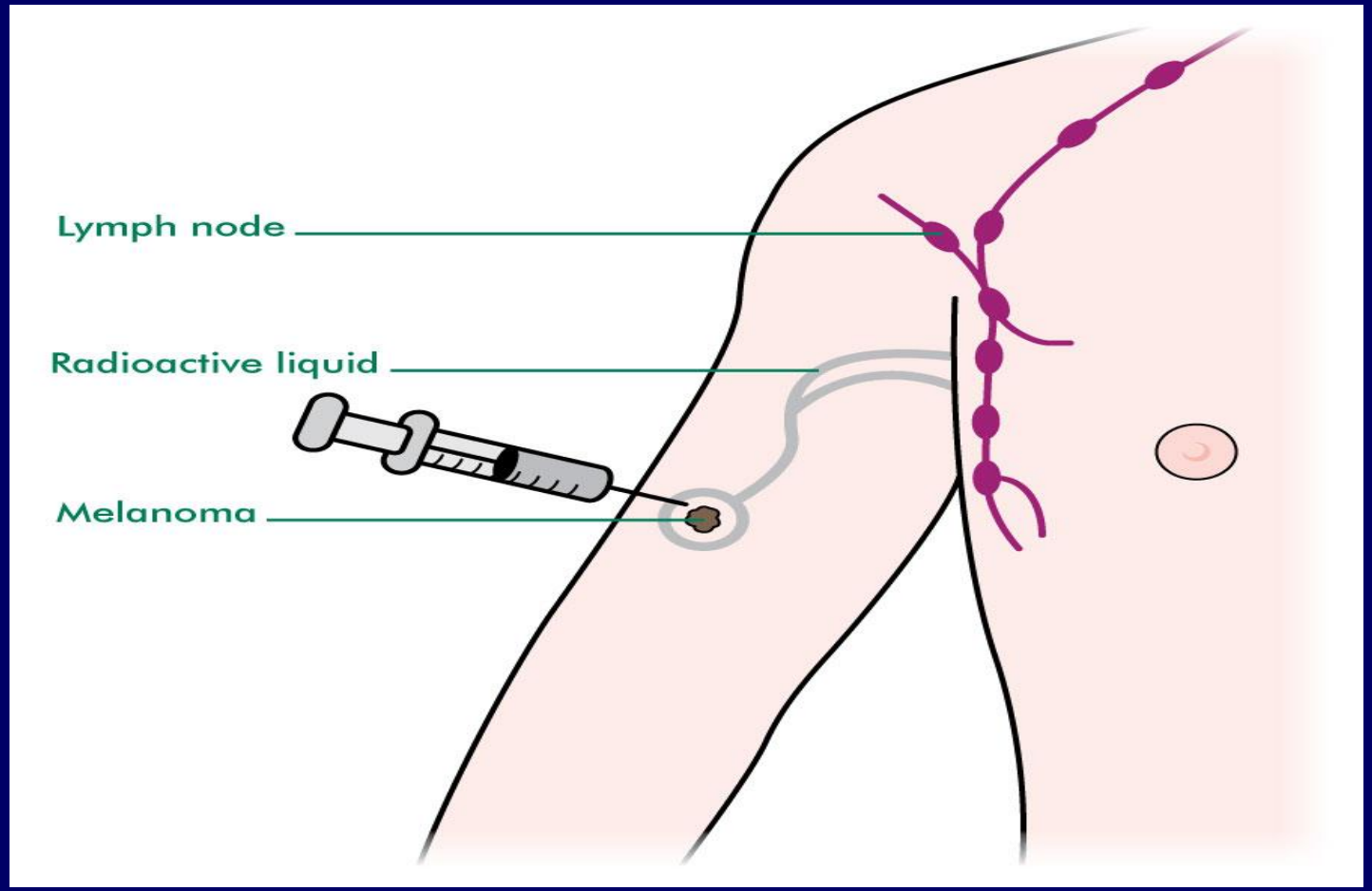


Table 4: NCCN-Recommended Surgical Margins for Melanoma

Tumor Thickness	Recommended Margin
In situ	0.5 cm
≤ 1.0 mm	1.0 cm
1.01–2 mm	1–2 cm
2.01–4 mm	2.0 cm
> 4 mm	2.0 cm

NCCN = National Comprehensive Cancer Network.



ASCO/SSO guidelines recommend

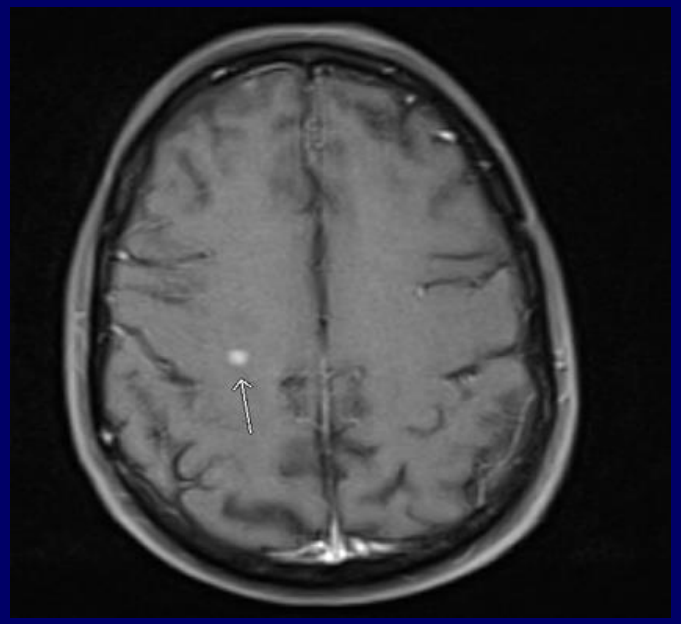
- **SLNB for all patients with >=1mm melanoma**
- **Should be considered in patients with T1b melanomas (0.8–1 mm or < 0.8 mm with ulceration).**
- **Routine sentinel node biopsy is not recommended for T1a melanomas (< 0.8 mm, nonulcerated).**

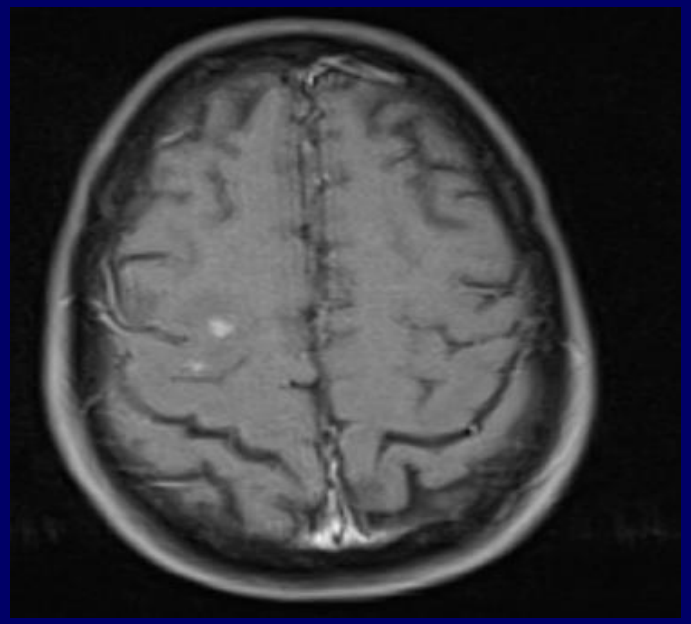
Case presentation....

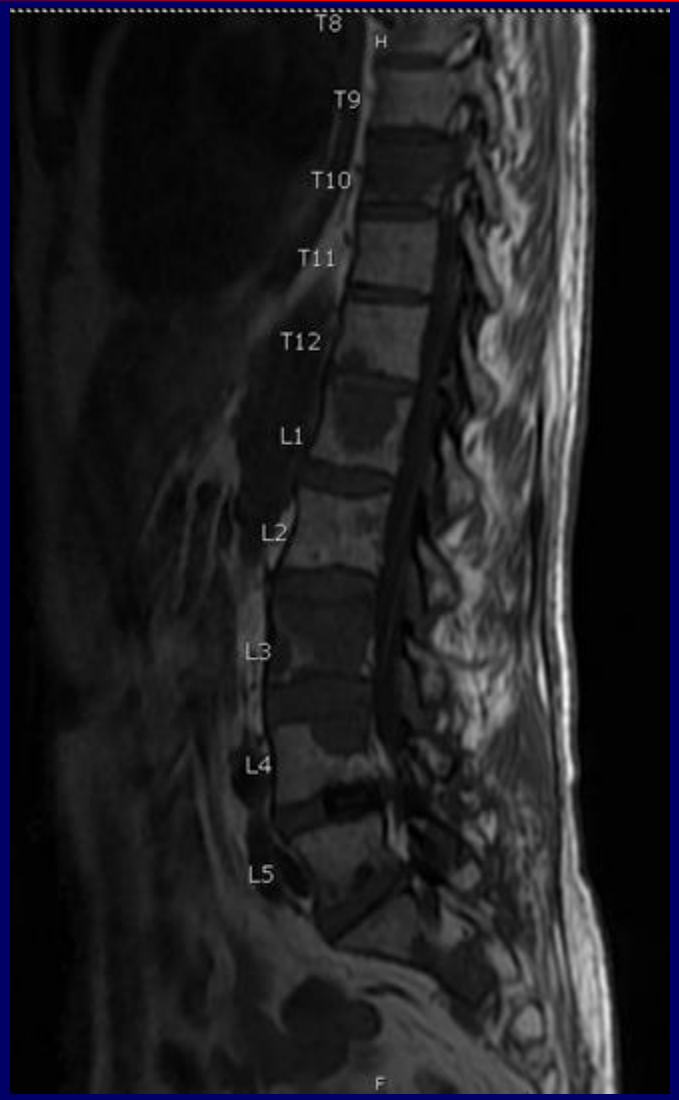
- Patient underwent wide local excision and SLNB. No residual melanoma was detected and 2 lymph nodes were removed none were involved with metastatic melanoma. Patient was scheduled for every 3 month follow up exam with his dermatologist and surgical oncologist.

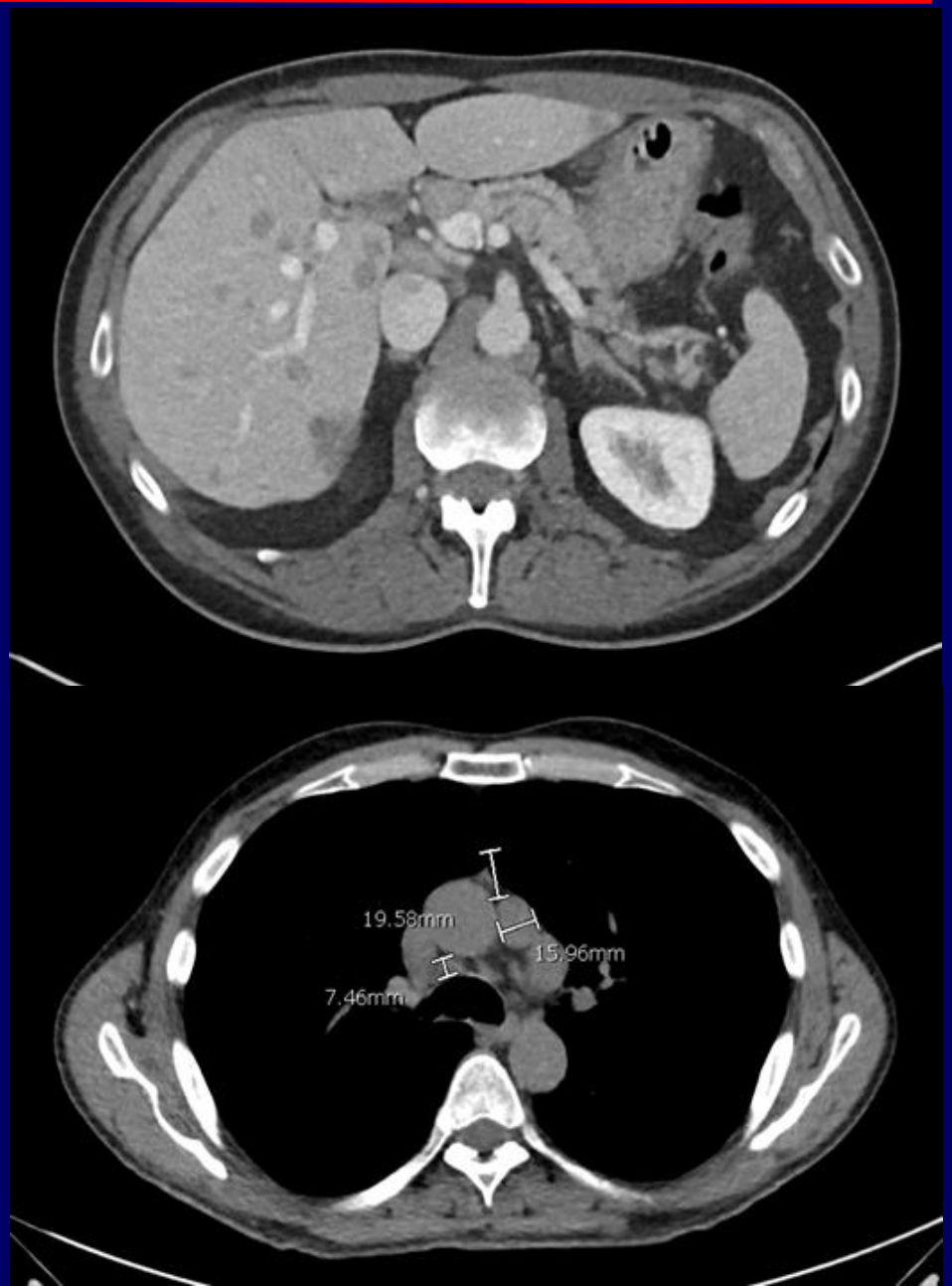
- 2 years later he presented with fatigue, severe pain in the right upper quadrant and mid-back, and 20 lbs weight loss the last 3 months.
- CT c/a/p, MRI spine and MRI brain revealed metastatic disease to mediastinal lymph nodes, liver, brain, and spine. Initial serum LDH level was 200.
- US-guided liver biopsy and pathology confirmed metastatic melanoma.

Images 04/2018-Case 1









Case presentation....

- What is the most appropriate next step:

A- Initiate immunotherapy with ipilimumab and nivolumab

B- Refer to whole brain radiation therapy

C- High dose IL2

D- Chemotherapy

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THE TOXINS OF WILLIAM B. COLEY AND THE TREATMENT OF BONE AND SOFT-TISSUE SARCOMAS

Edward F. McCarthy, M.D.

ABSTRACT

In 1891, William B. Coley injected streptococcal organisms into a patient with inoperable cancer. He thought that the infection he produced would have the side effect of shrinking the malignant tumor. He was successful, and this was one of the first examples of immunotherapy. Over the next forty years, as head of the Bone Tumor Service at Memorial Hospital in New York, Coley injected more than 1000 cancer patients with bacteria or bacterial products. These products became known as Coley's Toxins. He and other doctors who used them reported excellent results, especially in bone and soft-tissue sarcomas.

Despite his reported good results, Coley's Toxins came under a great deal of criticism because many doctors did not believe his results. This criticism, along with the development of radiation therapy and chemotherapy, caused Coley's Toxins to gradually disappear from use. However, the modern science of immunology has shown that Coley's principles were correct and that some cancers are sensitive to an enhanced immune system. Because research is very active in this field, William B. Coley, a bone sarcoma surgeon, deserves the title "Father of Immunotherapy."

Figure 1. William B. Coley (1862-1936) from *Trans Am Surg Assoc* 54(1936):415. Courtesy of the Welch Library of the History of Medicine.

patient's immune system can be stimulated or enhanced to attack the malignant tumors. The first systematic

New York Times - July 29, 1908

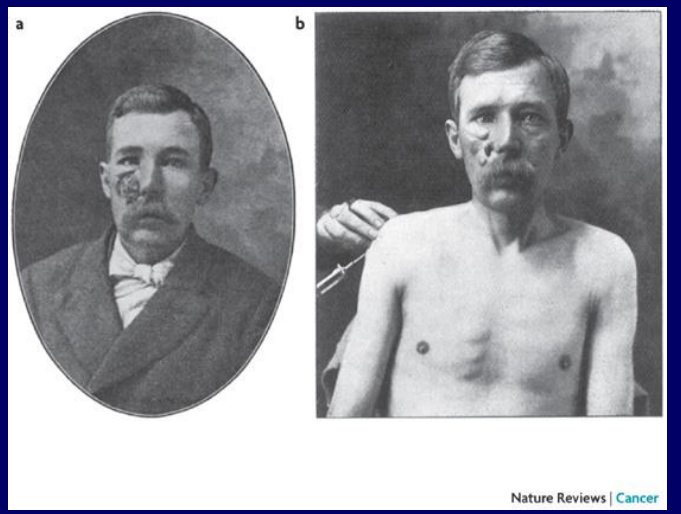
ERYSIPELAS GERMS AS CURE FOR CANCER

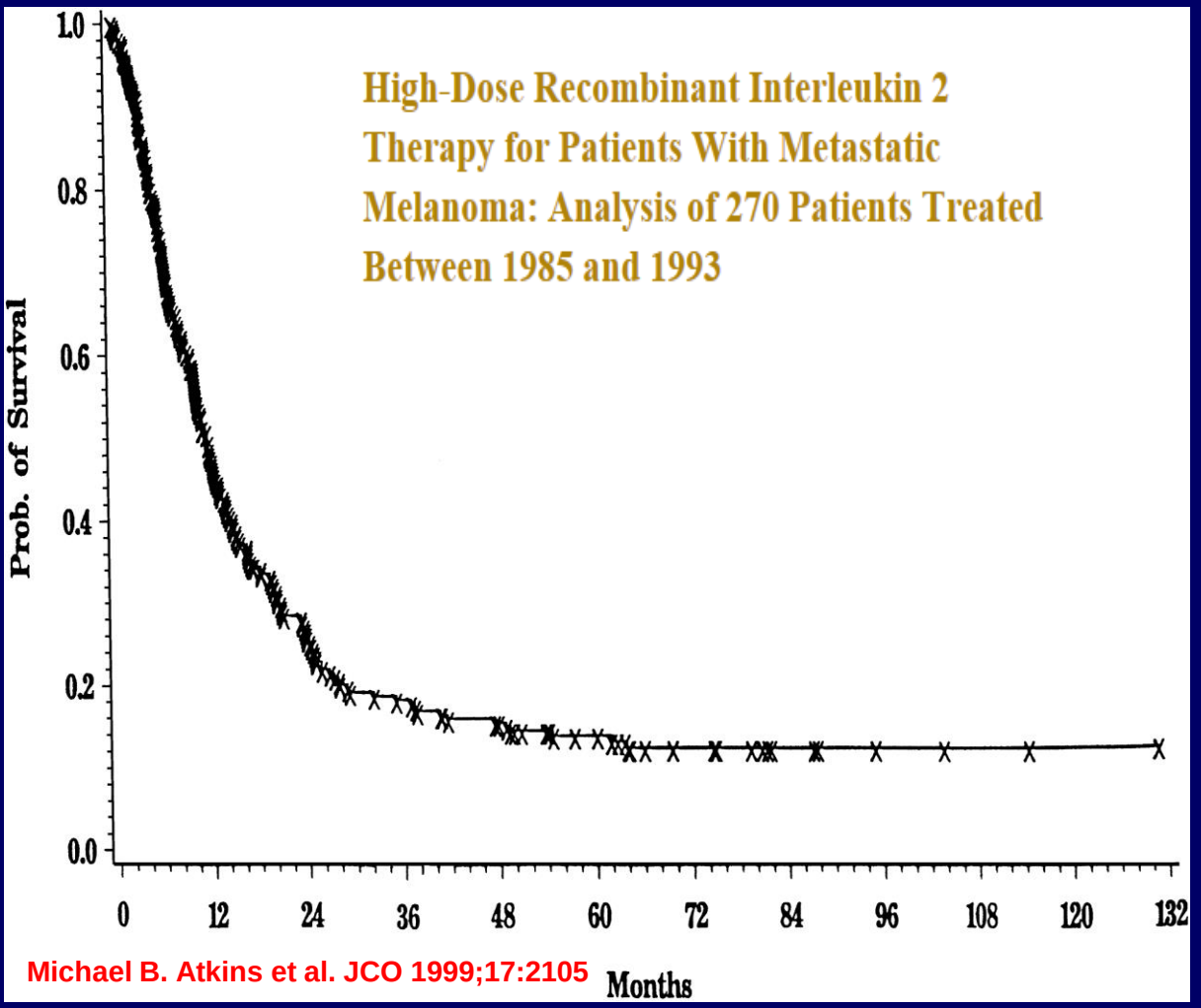
Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

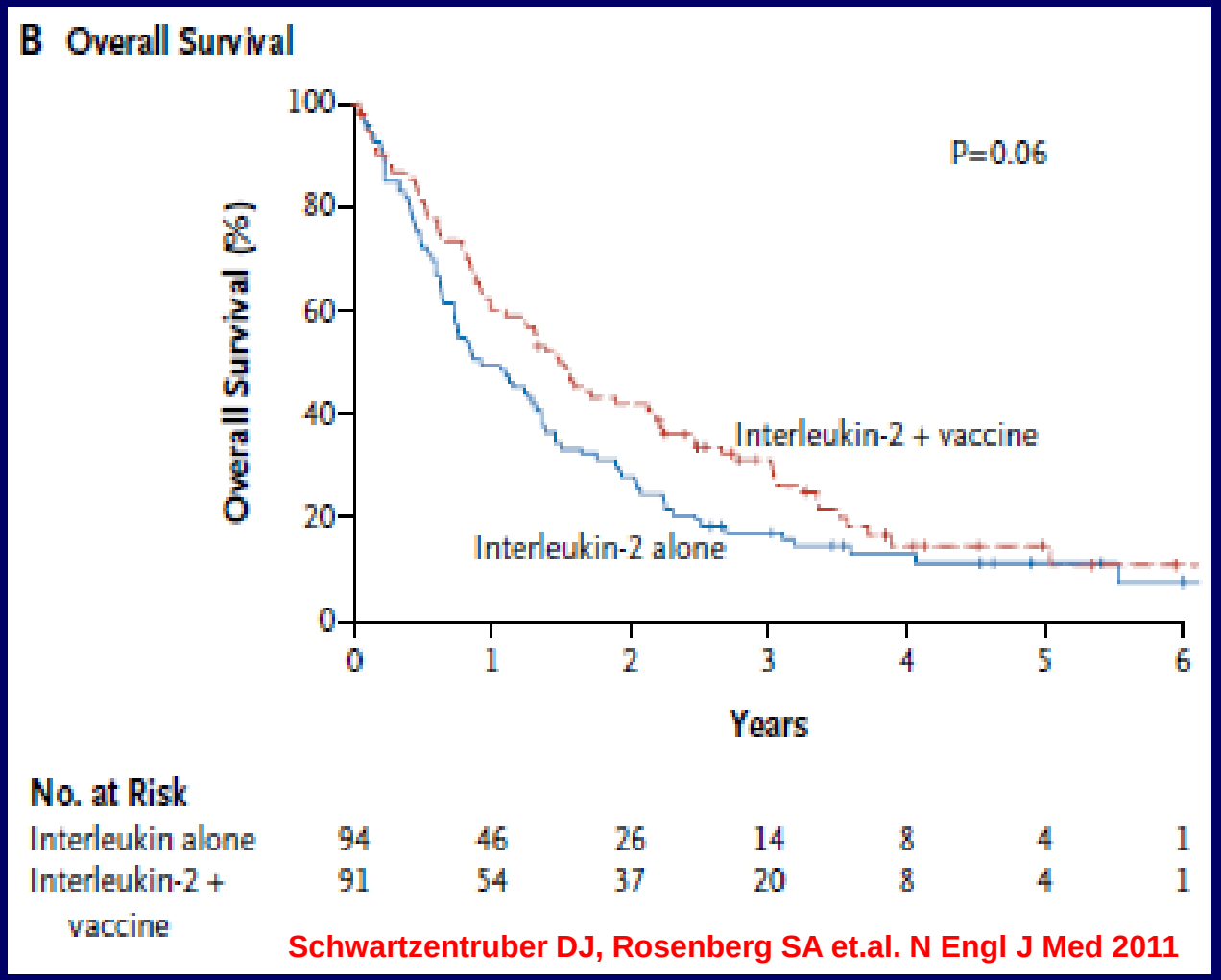
Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yester-



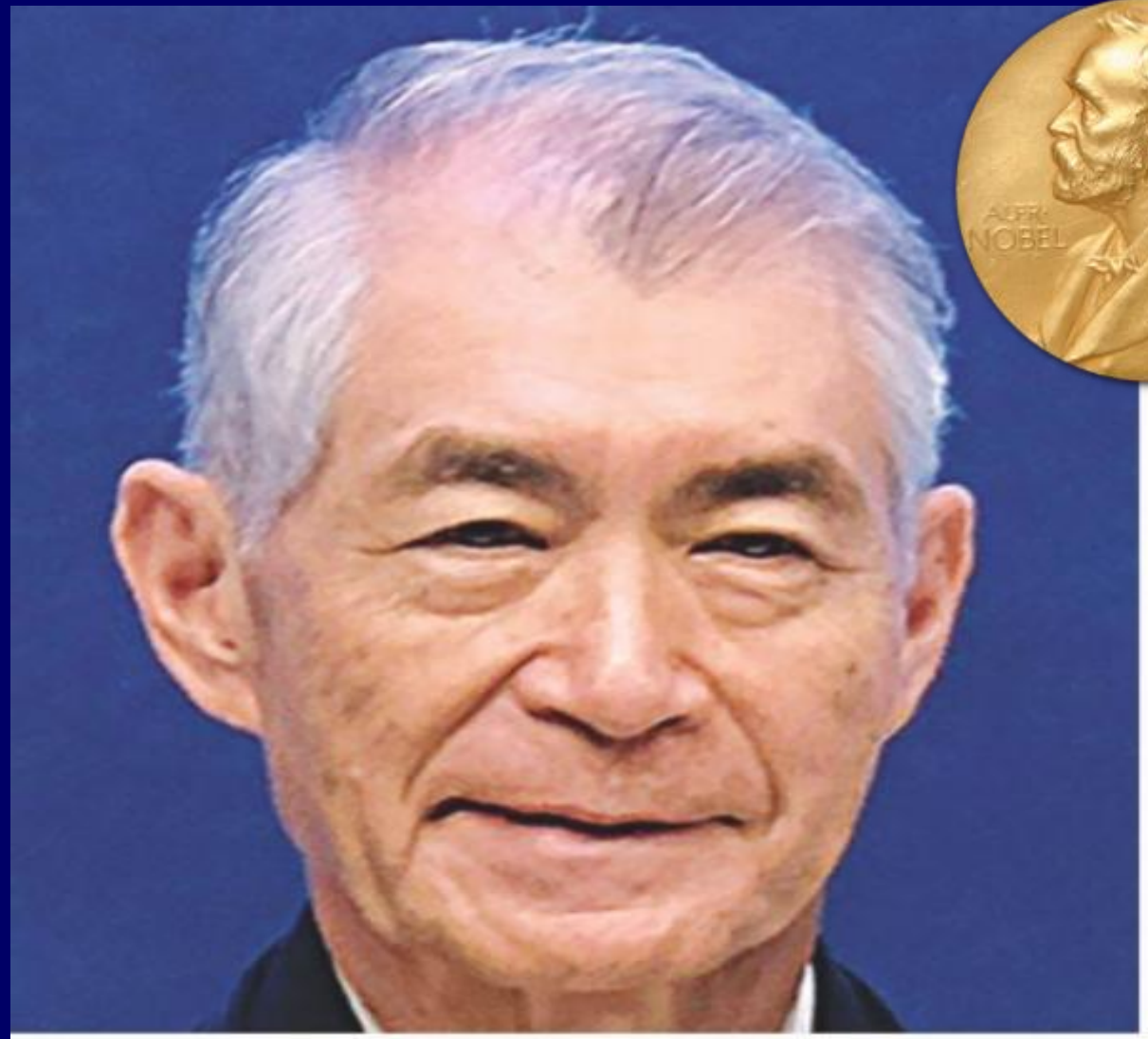


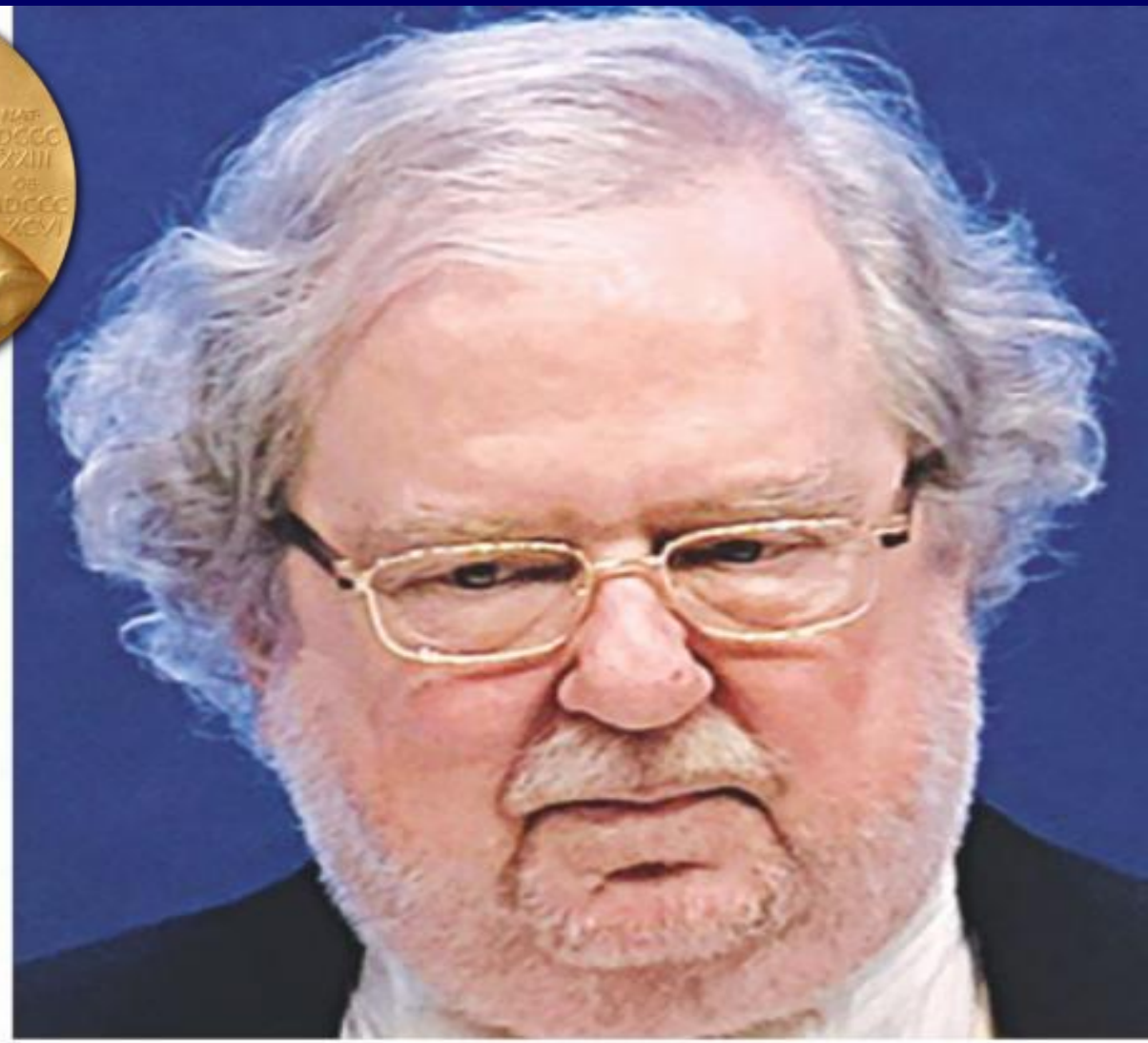
Michael B. Atkins et al. JCO 1999;17:2105



Schwartzentruber DJ, Rosenberg SA et.al. N Engl J Med 2011

CHECKPOINT INHIBITORS





Tasuku Honjo

James Allison

Quiz

Which of the following agents is a CTLA4 inhibitor:

A- Pembrolizumab
B- Nivolumab
C- Ipilimumab
D- Atezolizumab

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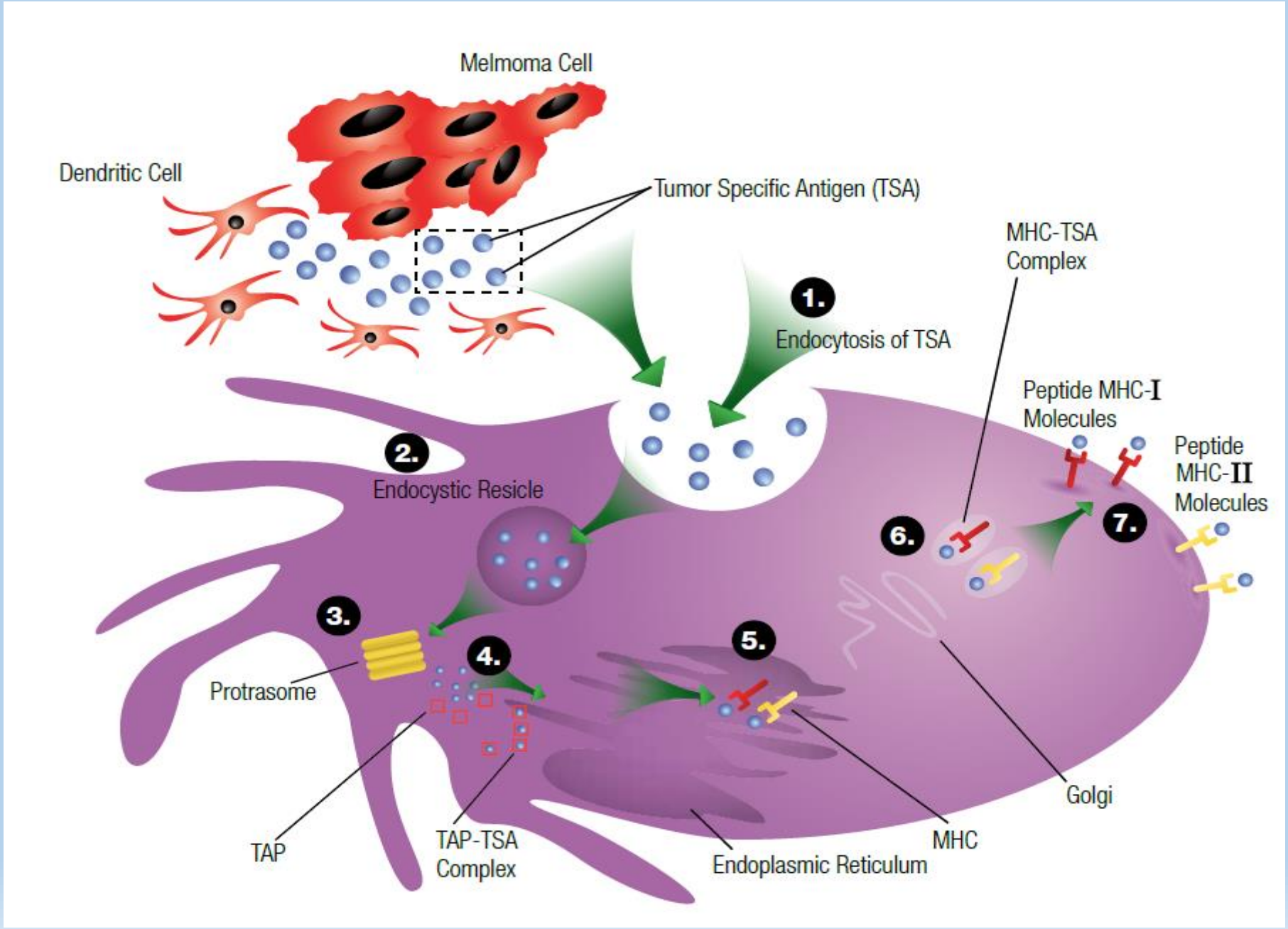


Immune Surveillance in Melanoma: *From immune attack to melanoma escape and even counterattack*.
Fade Mahmoud, Bradley Shields et.al.
Cancer Biol Ther. 2017 Jul 3:18(7):451-469.

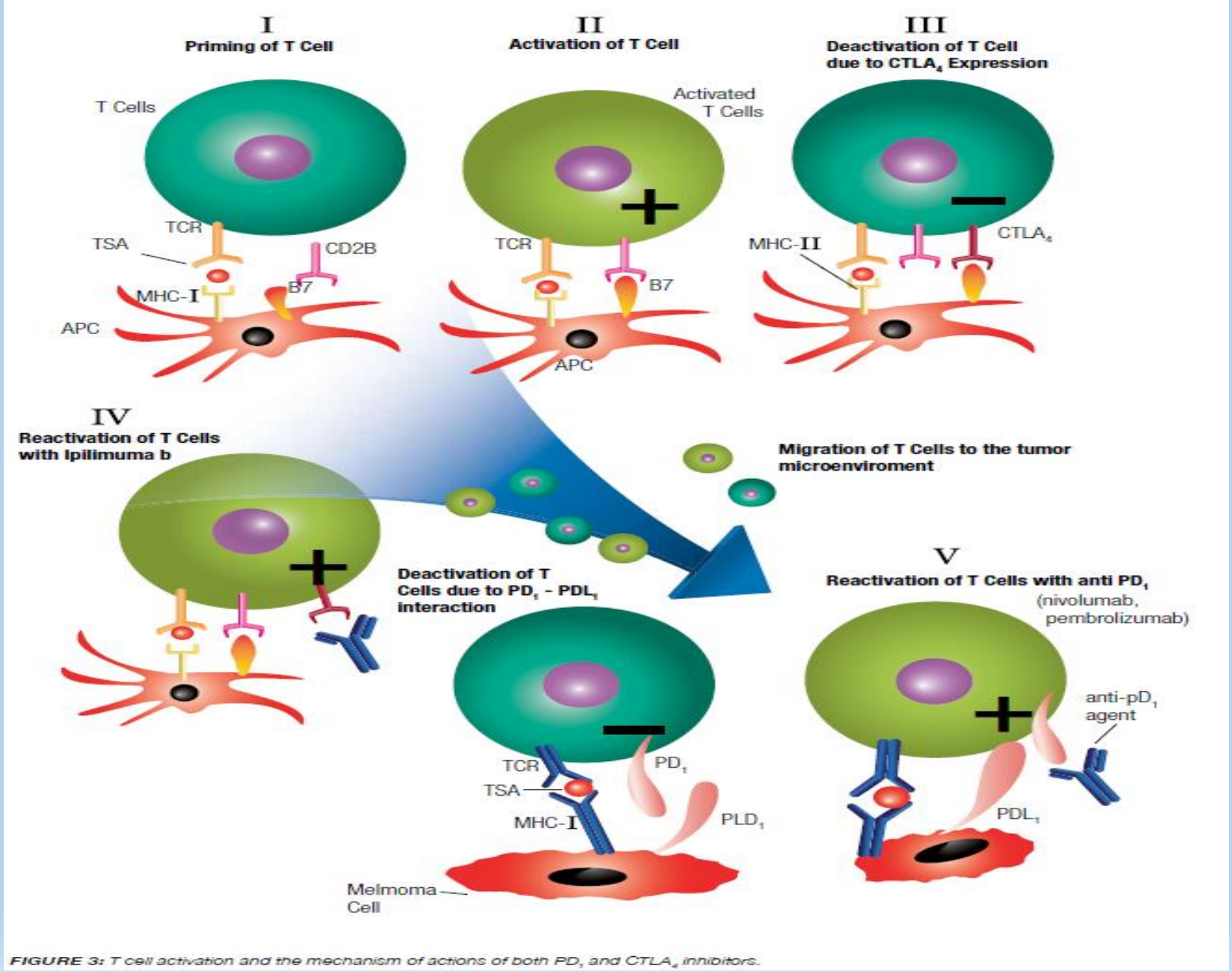
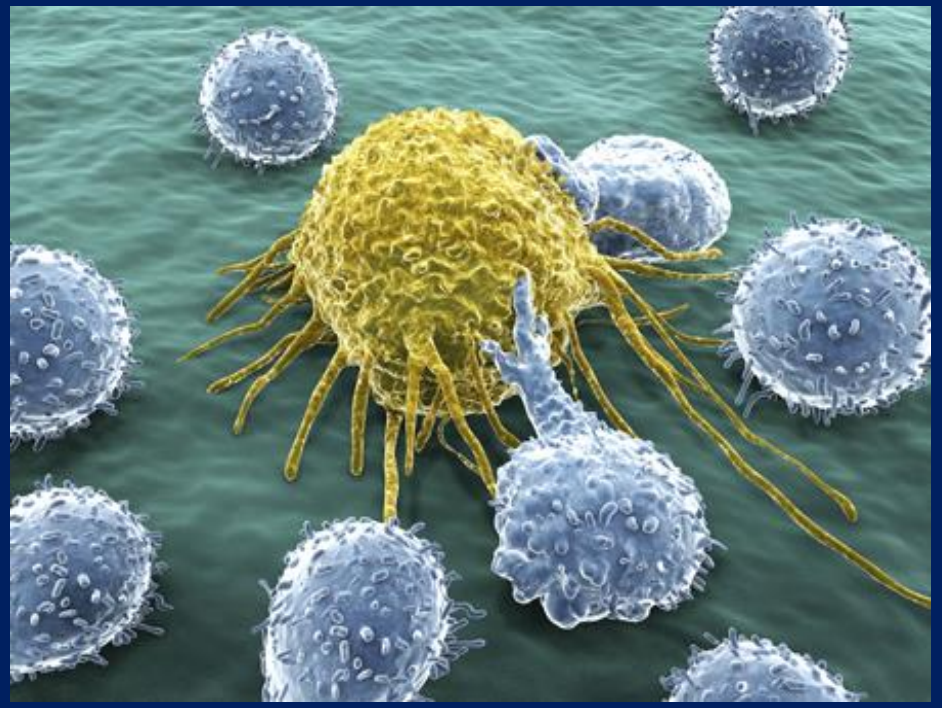


FIGURE 3: T cell activation and the mechanism of actions of both PD_1 and $CTLA_4$ inhibitors.

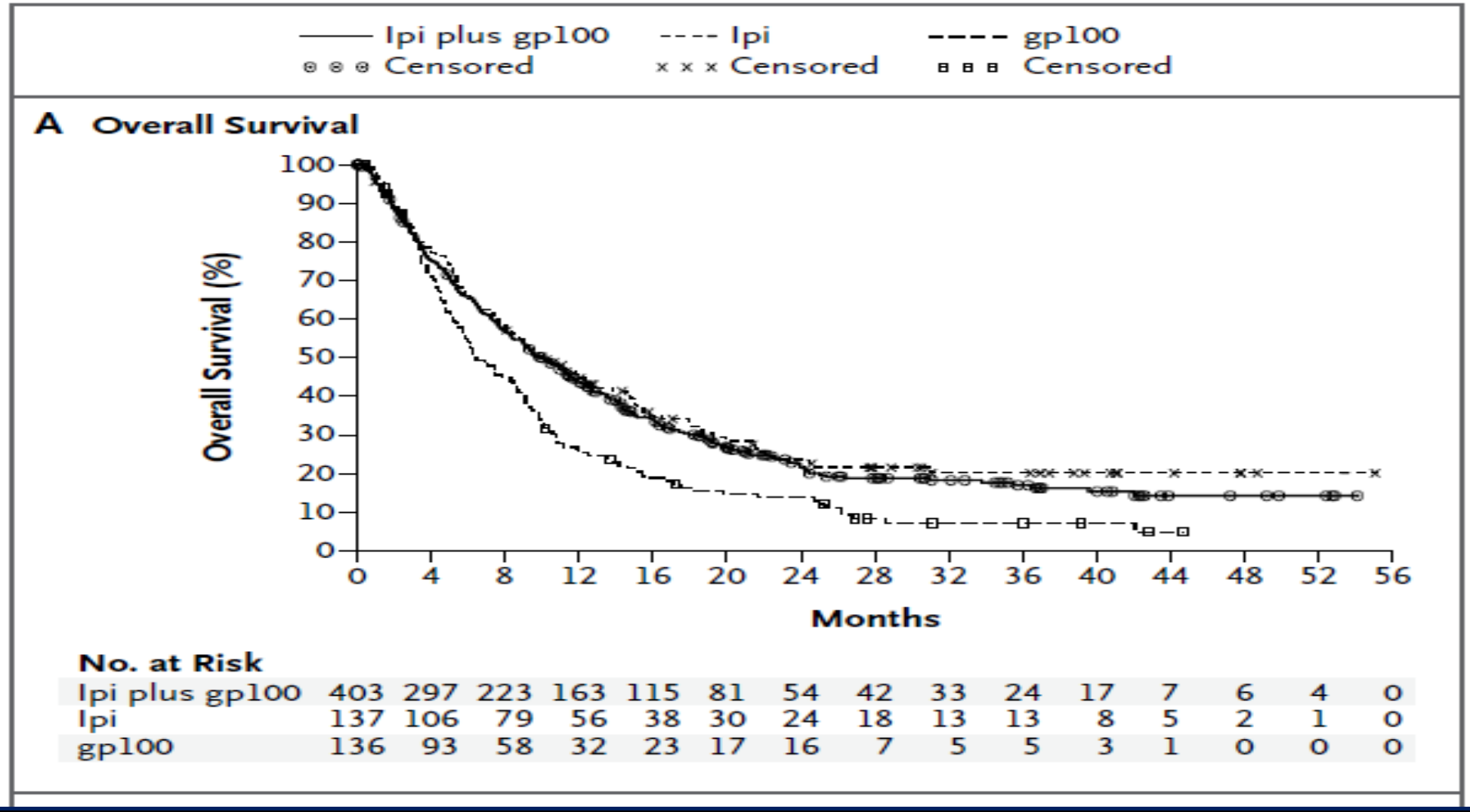
Immune Surveillance in Melanoma: *From immune attack to melanoma escape and even counterattack*.
Fade Mahmoud, Bradley Shields et.al.
Cancer Biol Ther. 2017 Jul 3;18(7):451-469.

Cytotoxic T cells attack melanoma

- Apoptosis
- The granule exocytosis pathway

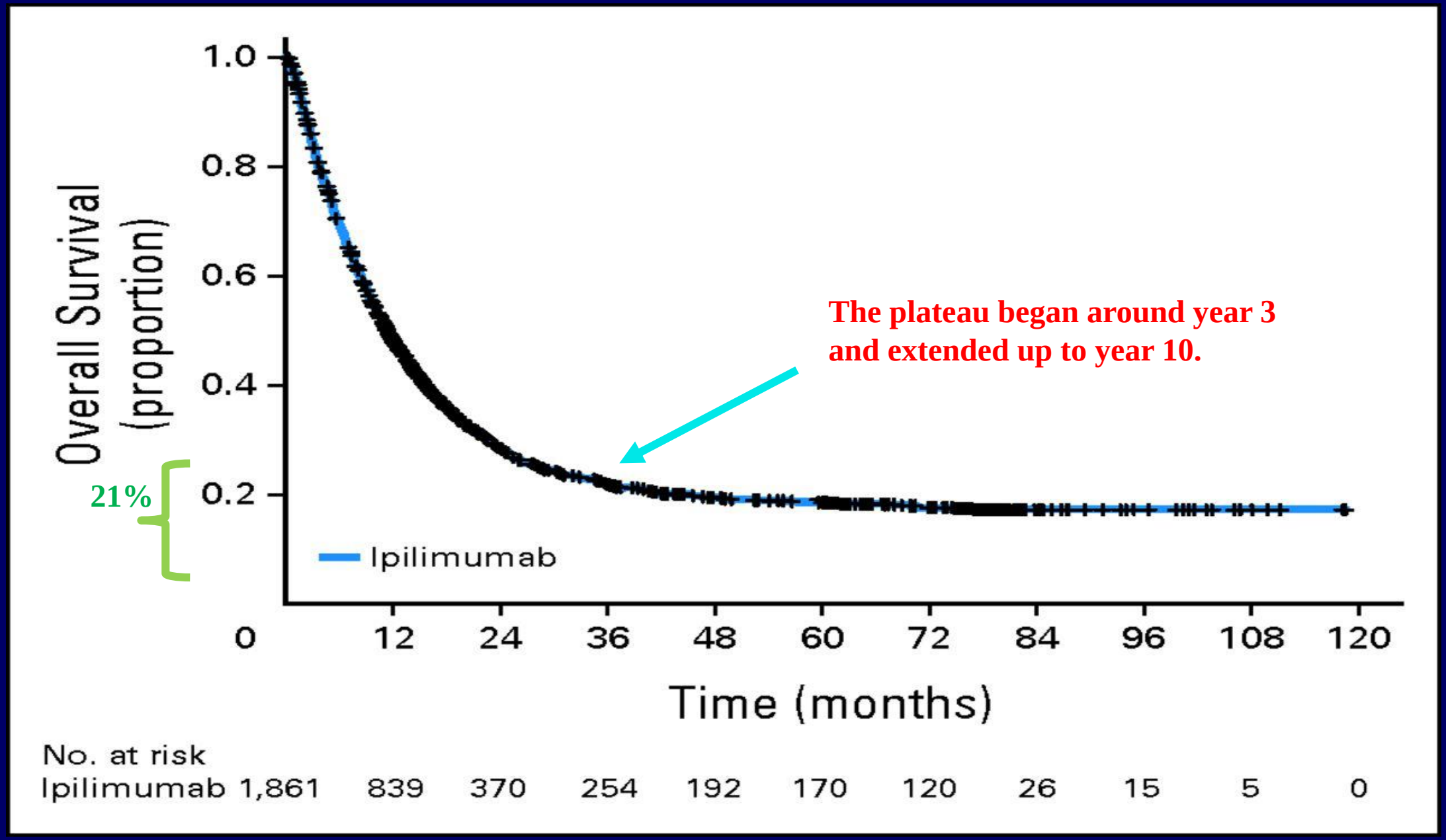


https://www.youtube.com/watch?v=jgJKaP0Sj5U



Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

Hodi et.al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010 Aug 19;363(8):711-23



Dirk Schadendorf et al. JCO doi:10.1200/JCO.2014.56.2736

KEYNOTE-006: final overall survival results

CANCER
IMMUNOTHERAPY
MONTH

FACT OF THE DAY

"[After immunotherapy] ... they didn't find any cancer at all."

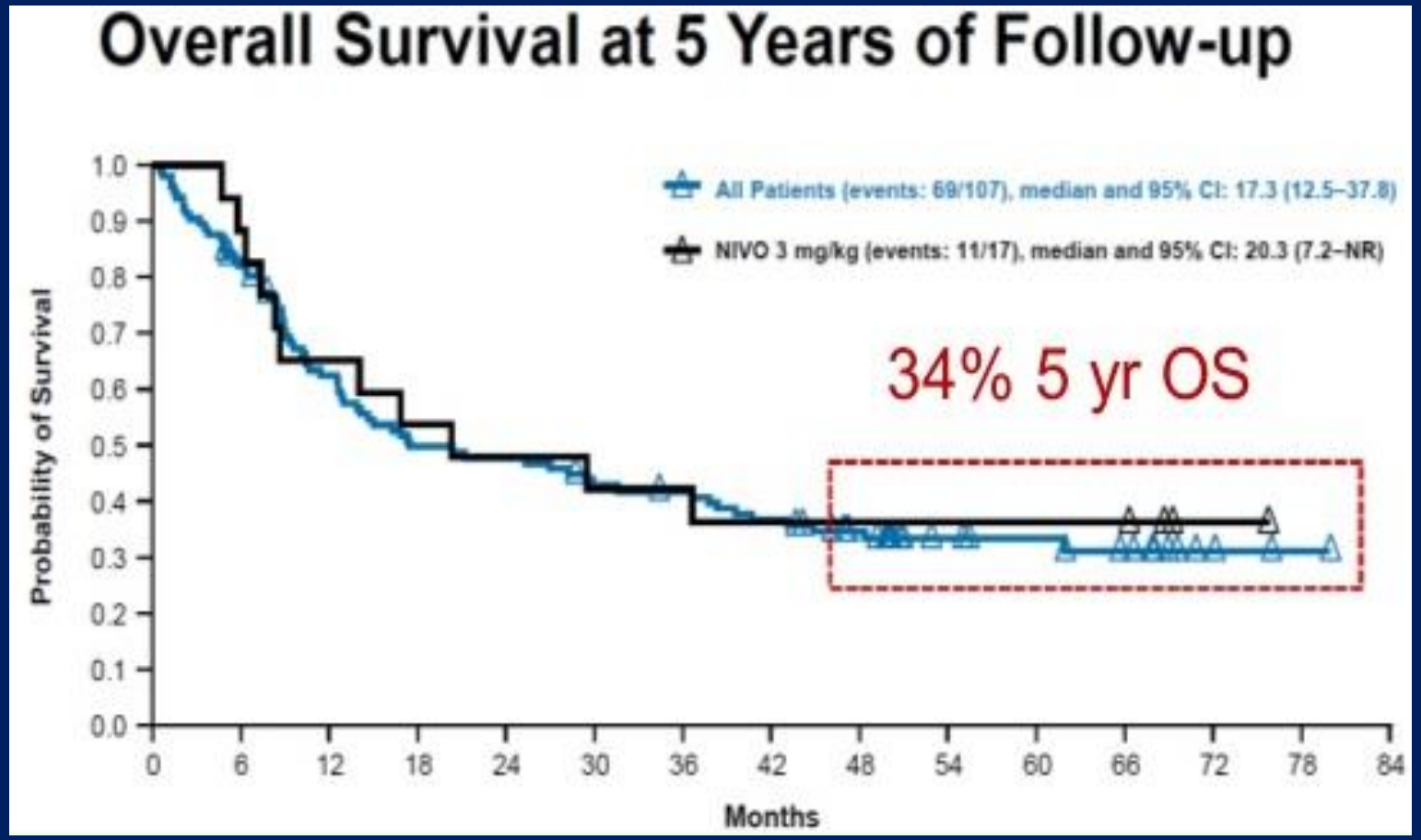
– **JIMMY CARTER**
Former U.S. President

#CIM17

CANCER RESEARCH INSTITUTE

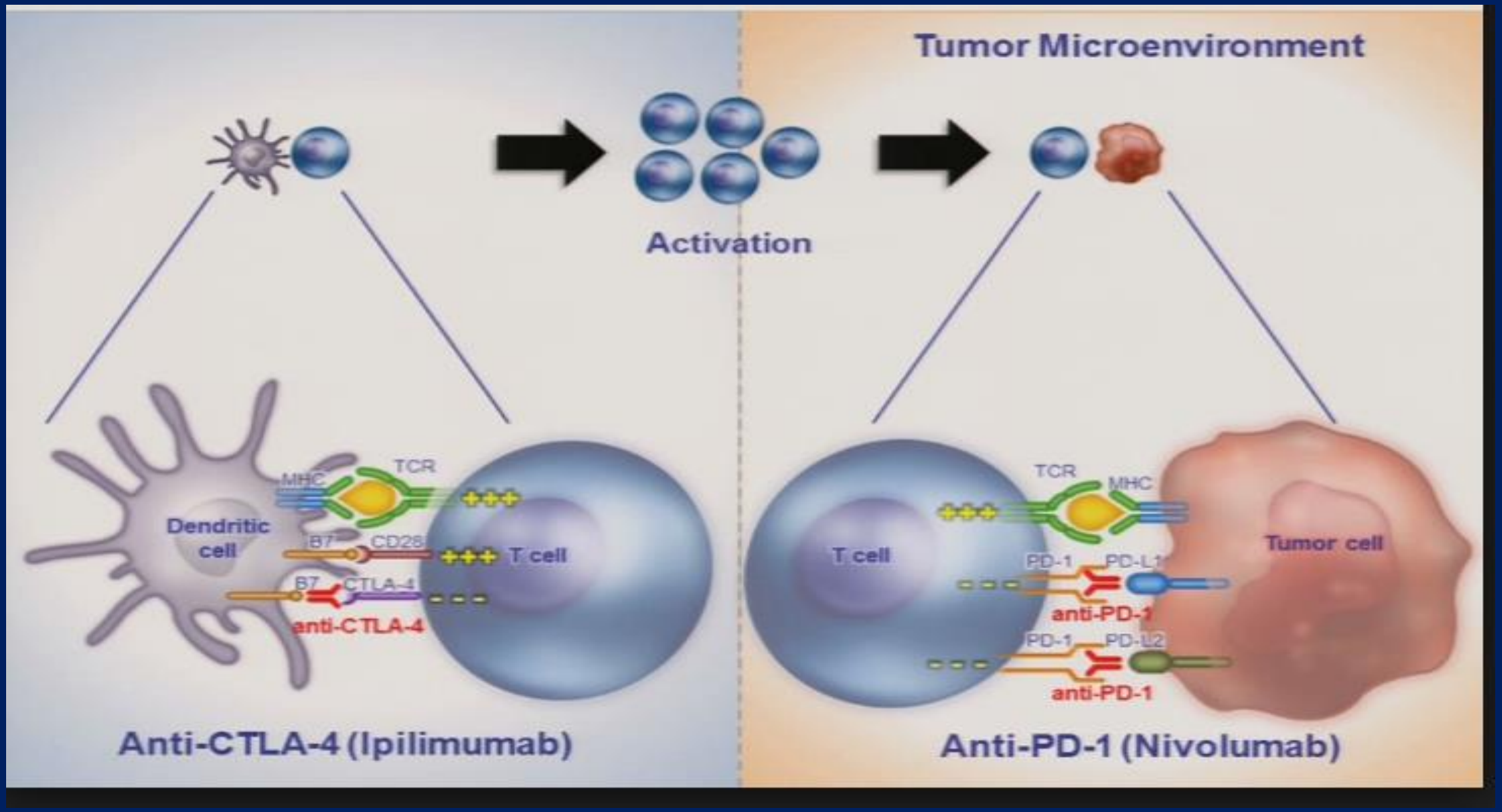
AACR 2016: 5-Year Survival Rates for Patients With Metastatic Melanoma Treated With Nivolumab Much Higher Than Historical Rates

By The ASCO Post
Posted: 4/20/2016 10:02:26 AM



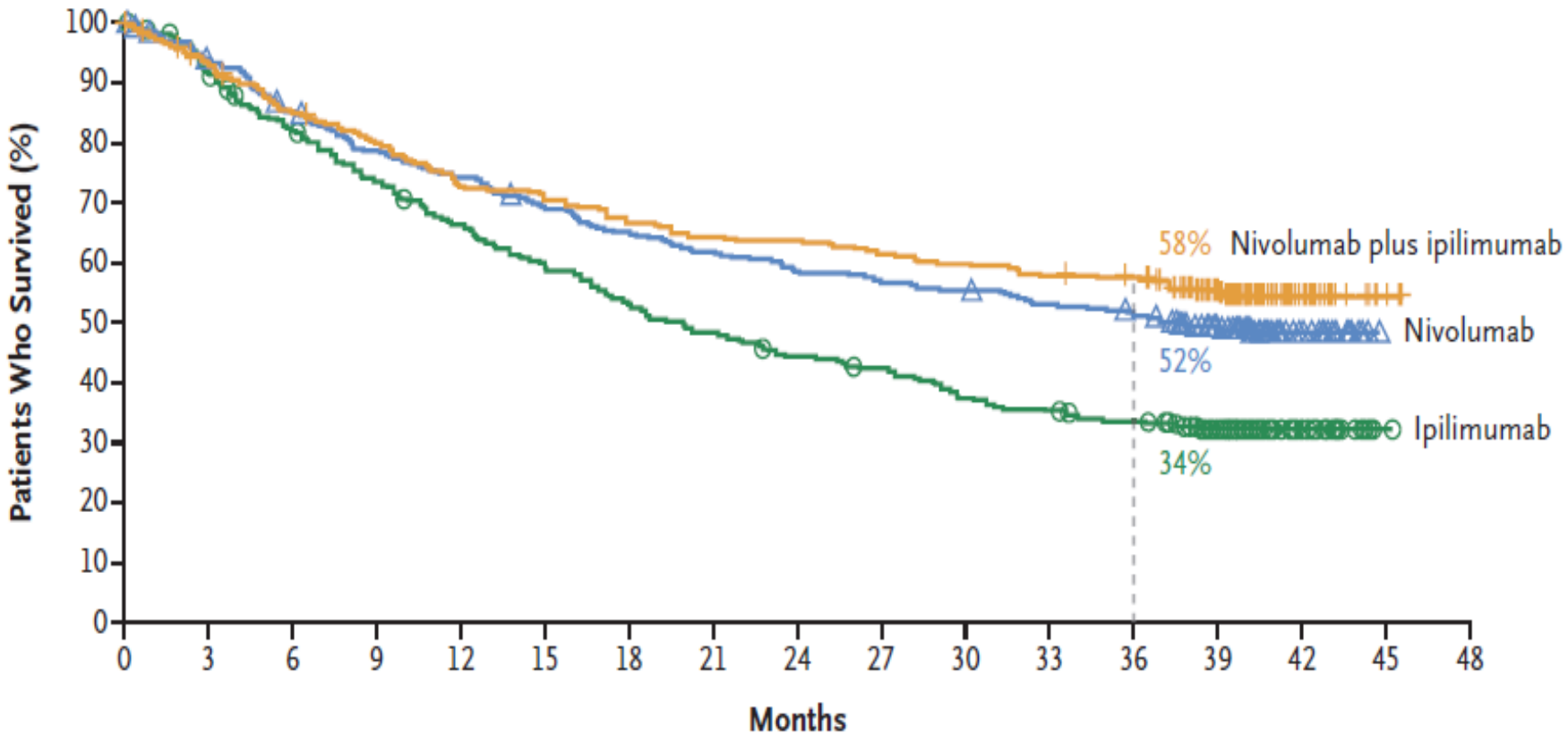
Hodi, AACR April 2016

Combination Therapy (Anti PD1 + Anti-CTLA-4)



CheckMate 067

B Overall Survival



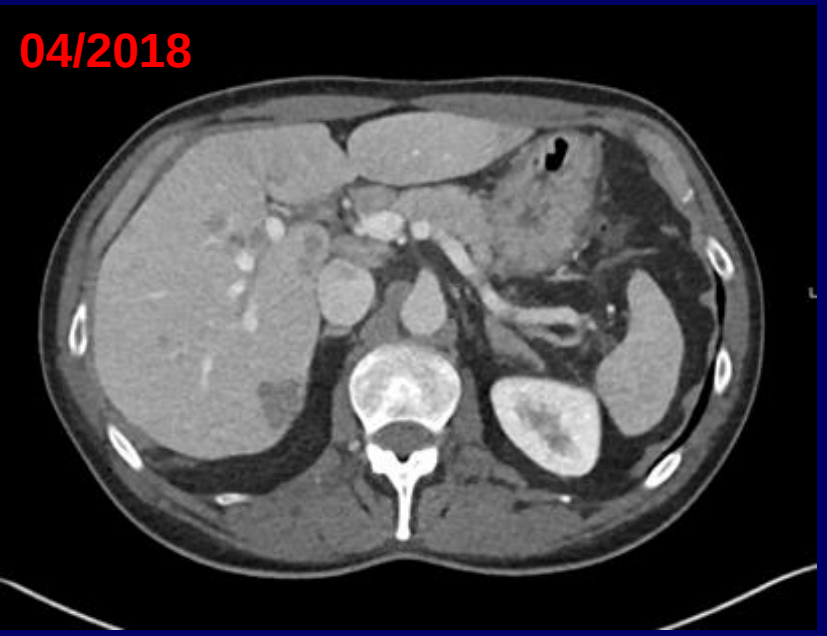
No. at Risk

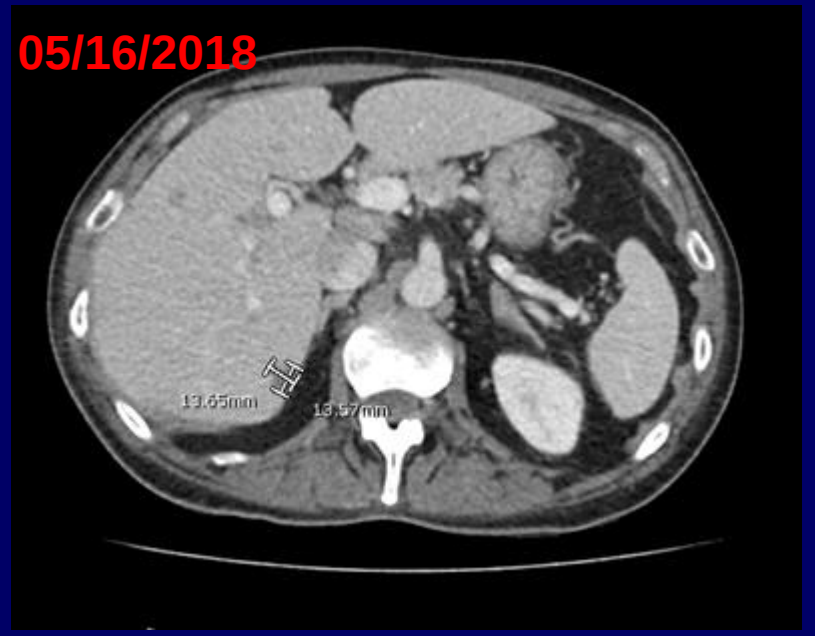
Nivolumab plus ipilimumab	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0
Nivolumab	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	117	107	100	68	20	2	0

Wolchok JD, Chiarion-Sileni V, et al. N Engl J Med. 2017 Sep 11. doi: 10.1056/NEJMoa1709684

Case presentation....

- 04/20/2018 Ipilimumab and nivolumab C1
- 05/07/2018 Stereotactic radiation to brain lesions
- 05/10/2018 Ipilimumab and nivolumab C2
- 5/15/2018 BRAF V 600 was detected
- 5/16/2018 Fatigue (cortisol, TSH, ACTH normal), fever and generalized grade II skin rash. Symptoms resolved with corticosteroids.





Case presentation....

- 05/31/2018 Nivolumab C3

- 06/2018 Severe diarrhea >8 watery stools daily.

The most appropriate next step in management is to:

A- Admit to hospital and start solumedrol 125 mg IV every 8 hours

B- Prescribe over the counter Imodium and prescribe flagyl

C-Prescribe Imodium and have the patient seen in the clinic the following day.

D- Schedule the patient to have an outpatient colonoscopy with biopsy

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Case presentation....

- 06/2018 Hospitalized due to grade III diarrhea (colitis confirmed by colonoscopy), recurrent fever, and recurrent diffuse skin rash. He received solumedrol 125 mg IV every 8 hours. Symptoms improved within 24 hours and in 48 hours he was discharged home on prednisone 1 mg/kg p.o daily taper over 6 weeks.
- After completing 6 weeks of prednisone therapy he feels better except for grade I fever and generalized skin rash.

What would be your next step

A- Resume nivolumab

B- Stop nivolumab but initiate combination BRAFi/MEKi therapy.

C- Obtain CT c/a/p and MRI brain; if no signs of progression continue surveillance only.

D- Give another course of corticosteroids. When adverse events are completely gone, then resume nivolumab.

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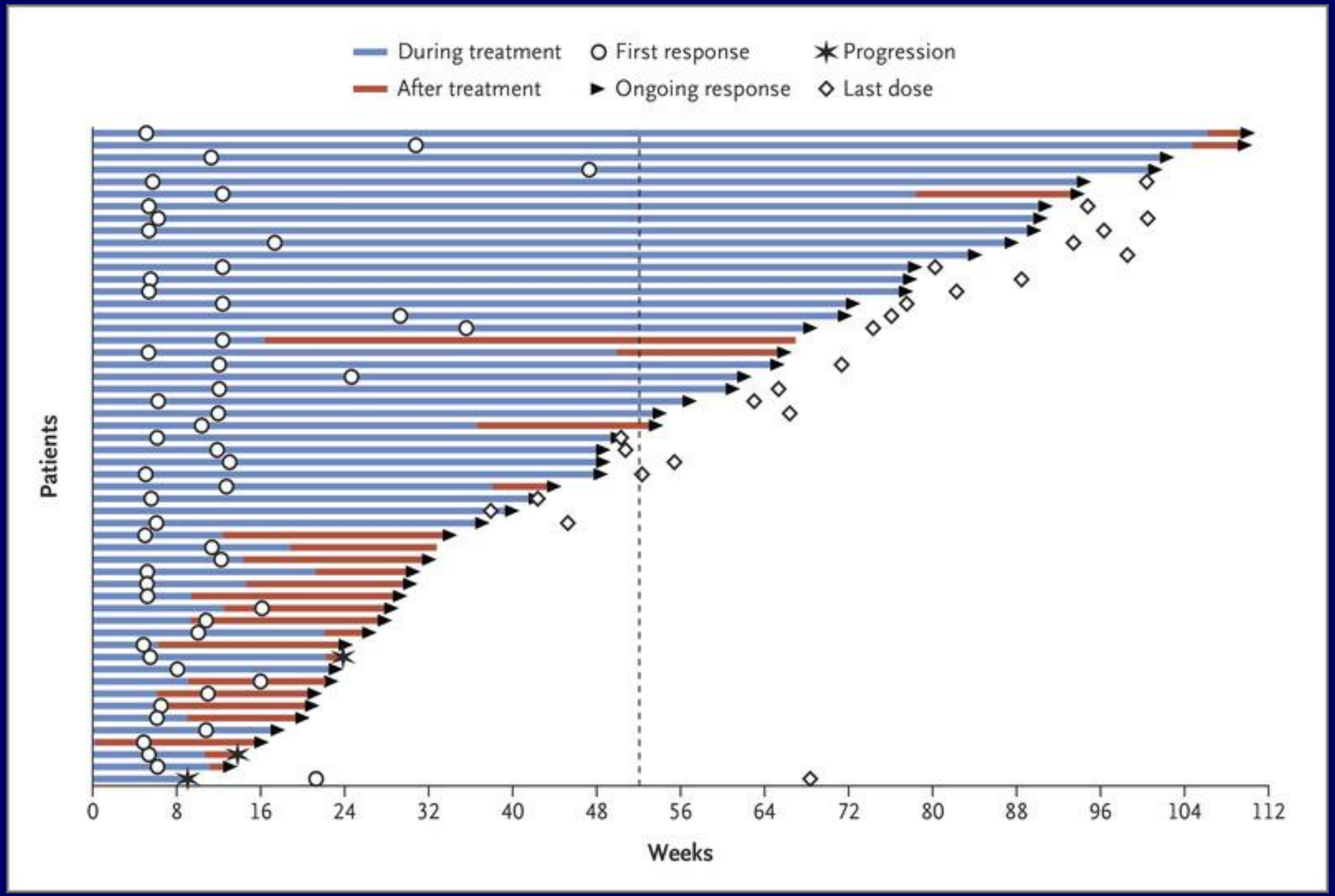
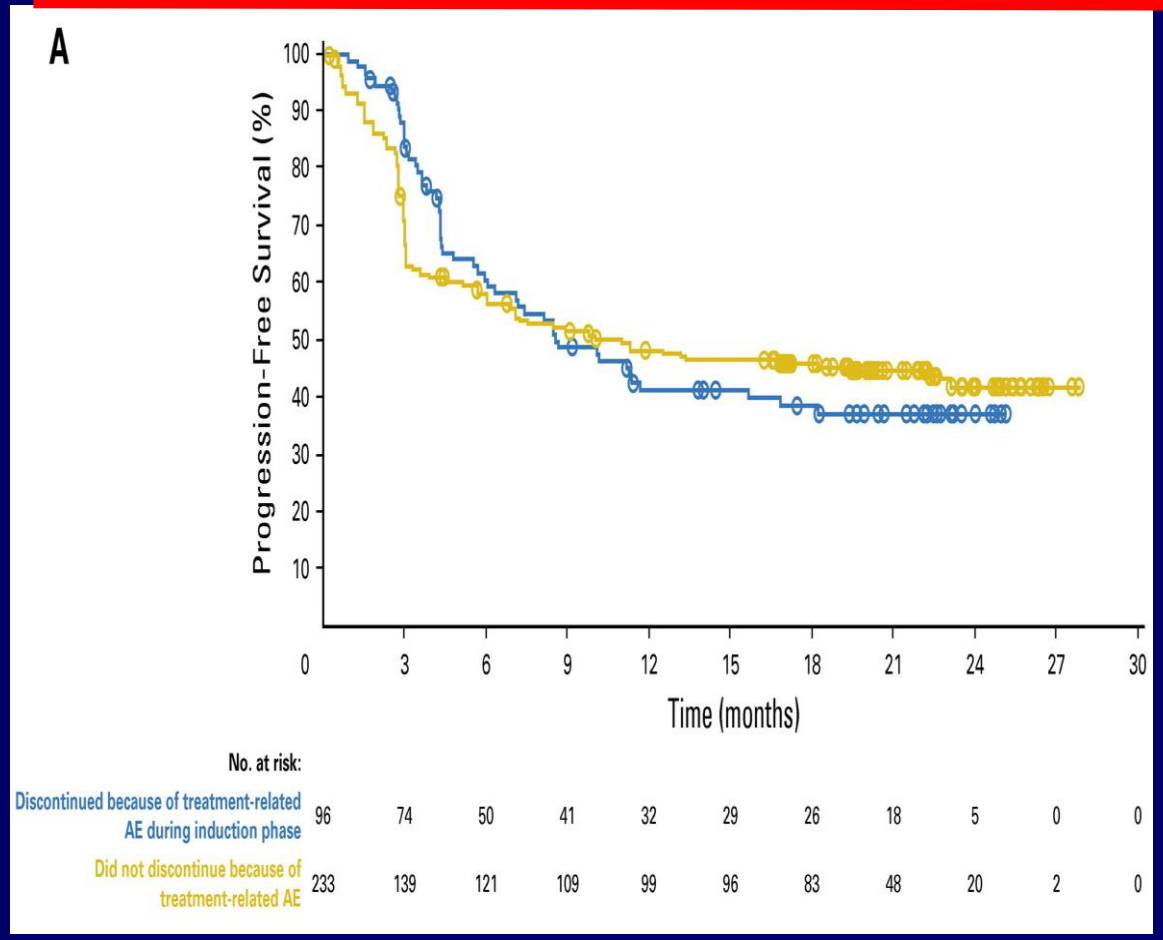
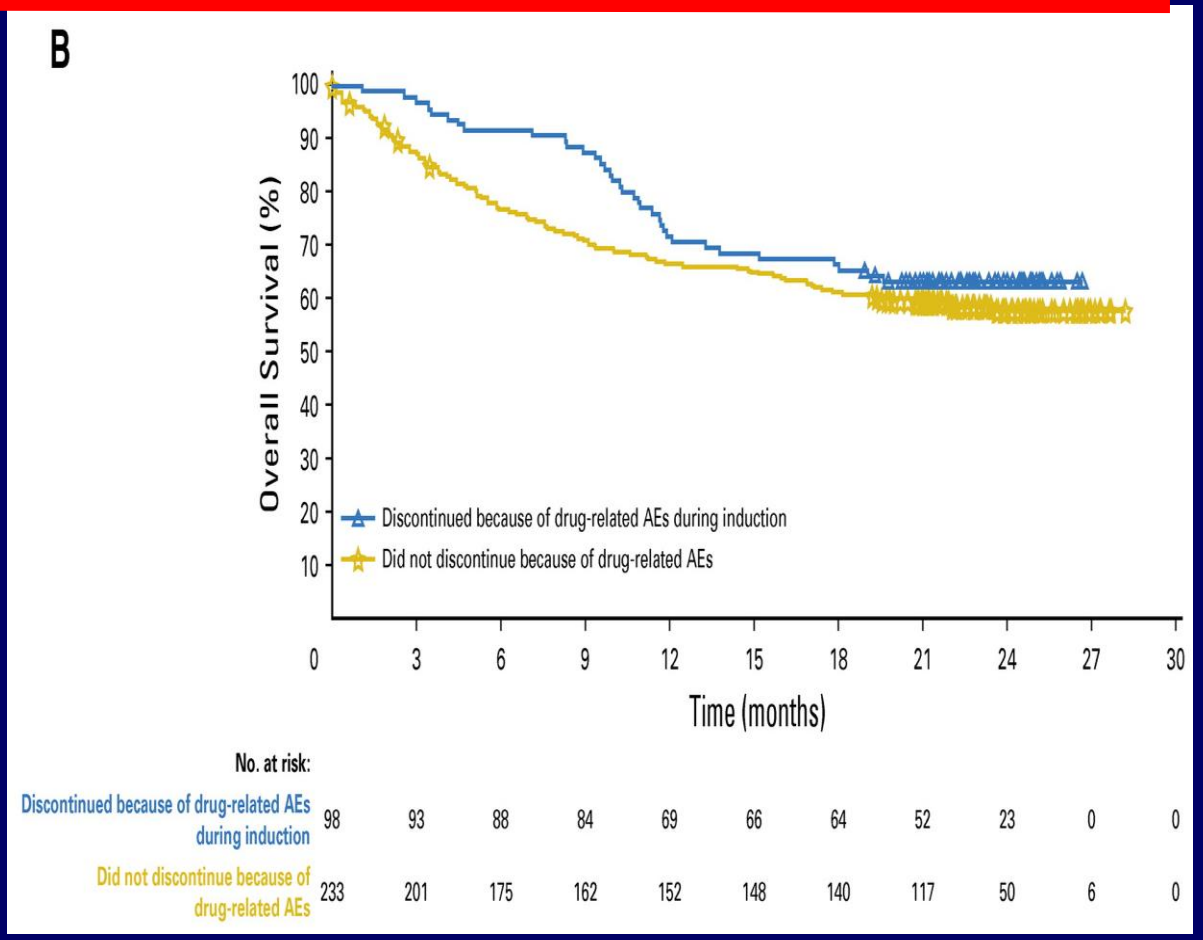

During treatment
After treatment
First response
Ongoing response
Progression
Last dose
Patients
0
8
16
24
32
40
48
56
64
72
80
88
96
104
112
Weeks

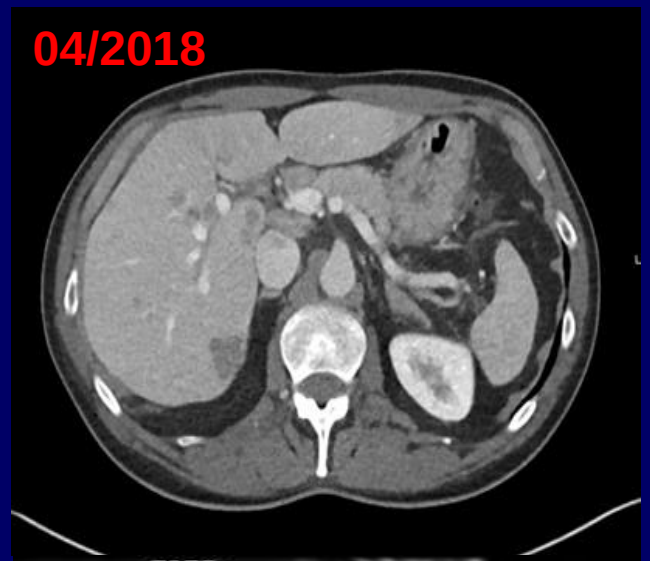
- **Pooled analysis of patients treated with Ipi (3mg/kg) + Nivo (1 mg/kg) in Checkmate-067 (phase III) and -069 (phase II), which did not allow resumption of PD-1 if developed SAEs during Ipi + Nivo induction**
  - **Patients that discontinued treatment during induction due to AEs: n= 96 (24%)**
  - **Patients that did not discontinue treatment due to AEs: n=233 (57%)**

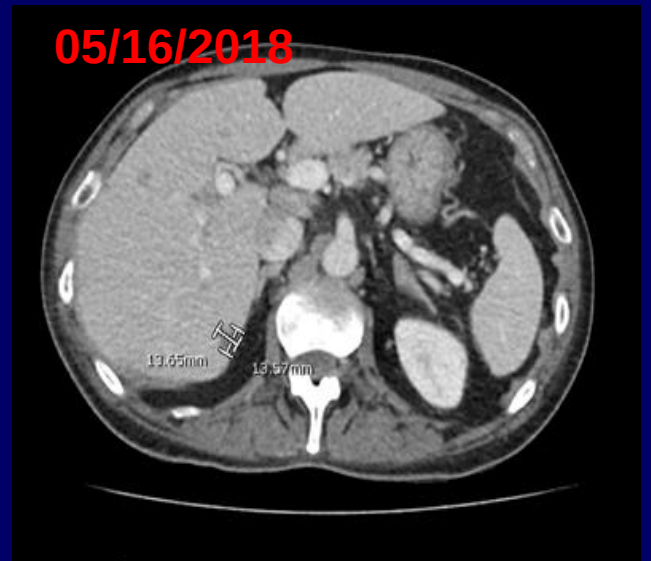


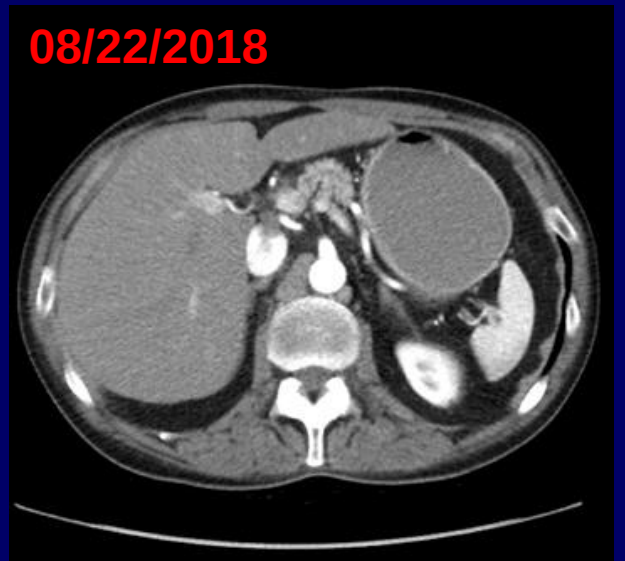


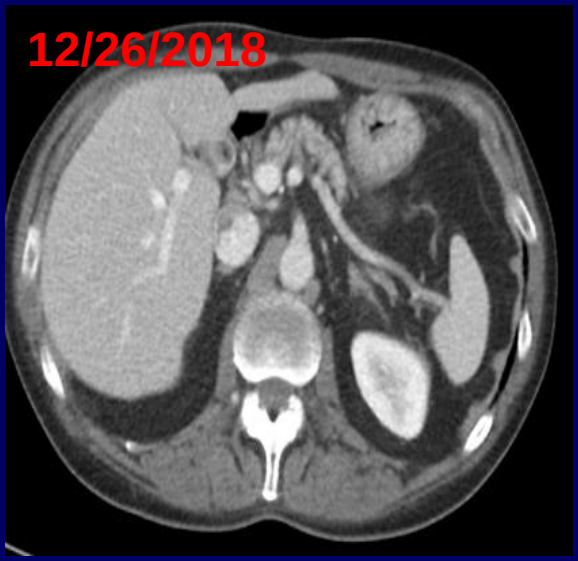
Schadendorf D, Wolchok J et.al. JCO 2017

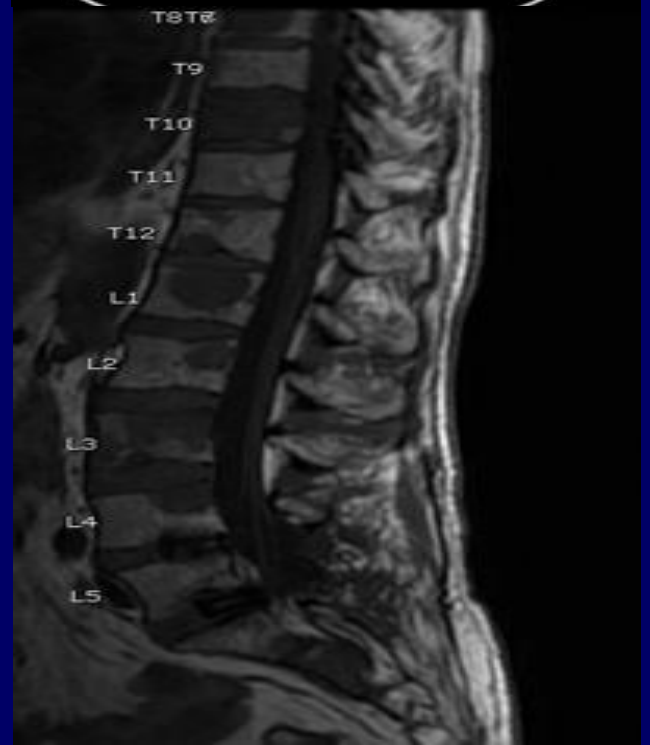
Case 1

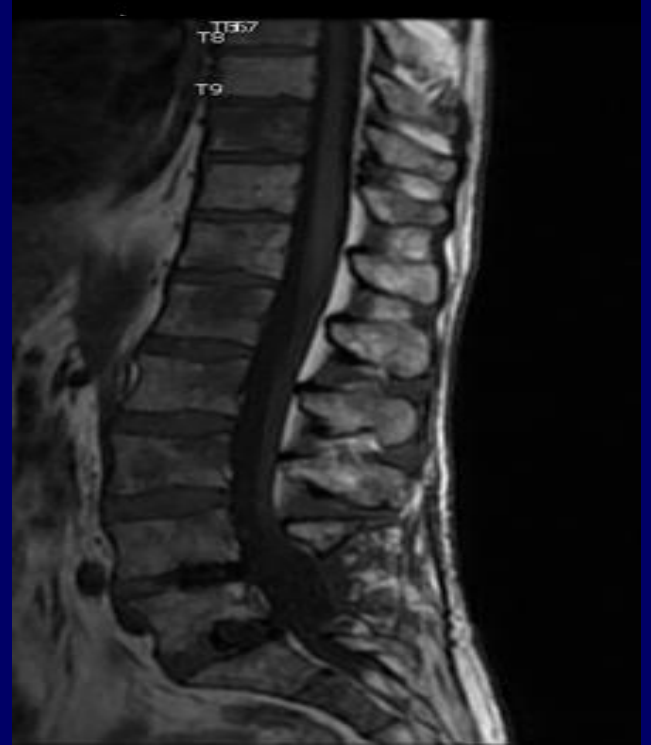


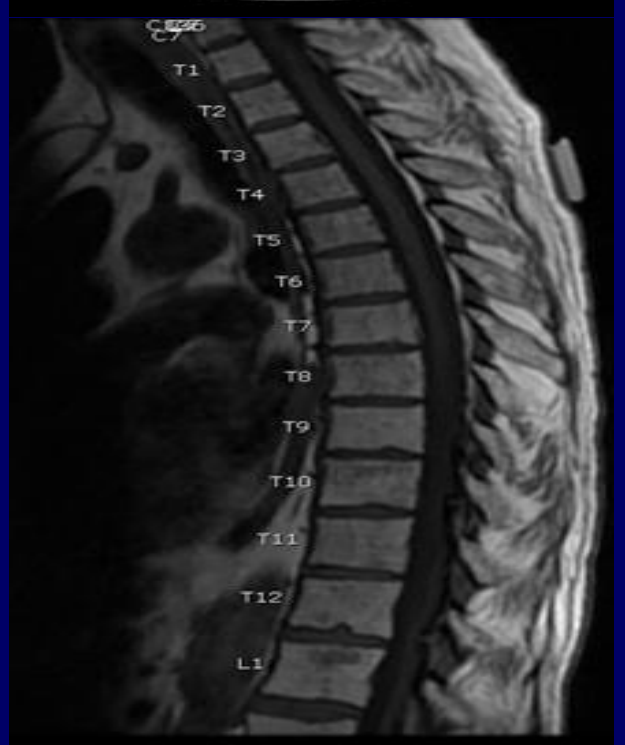












12/26/2018: MRI Brain: Continued therapeutic response.

Quiz

Ipilimumab is a CTLA4 inhibitor. All of the following are potential adverse events of ipilimumab except one which is less likely to be induced by ipilimumab and more likely to occur in the setting of anti PD1 therapy:

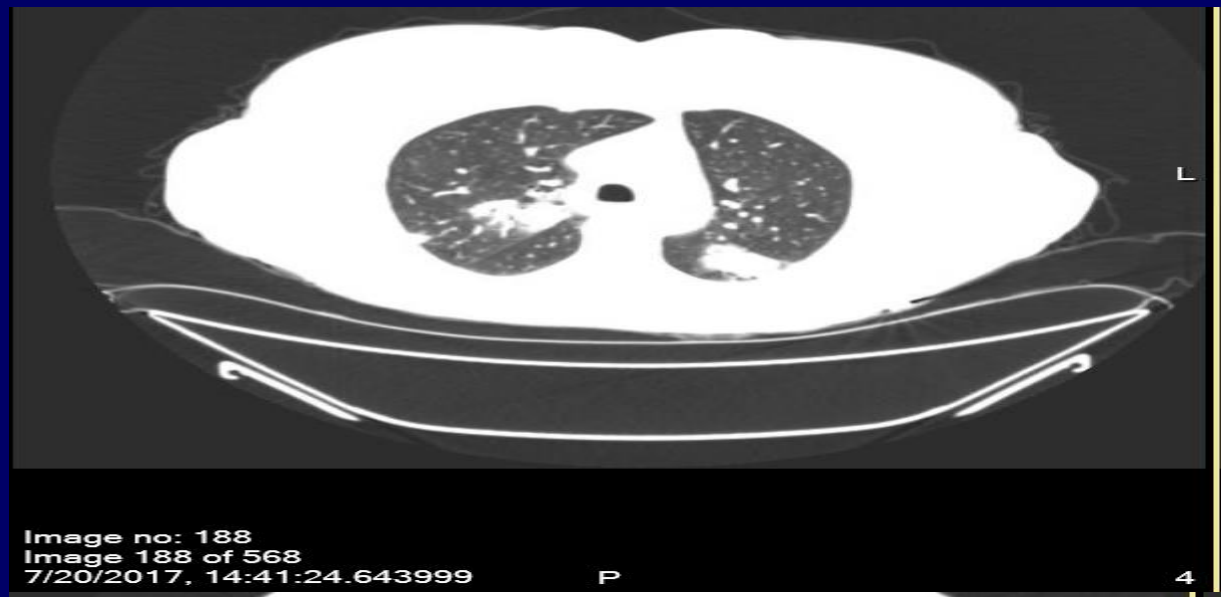
A- Hypophysitis

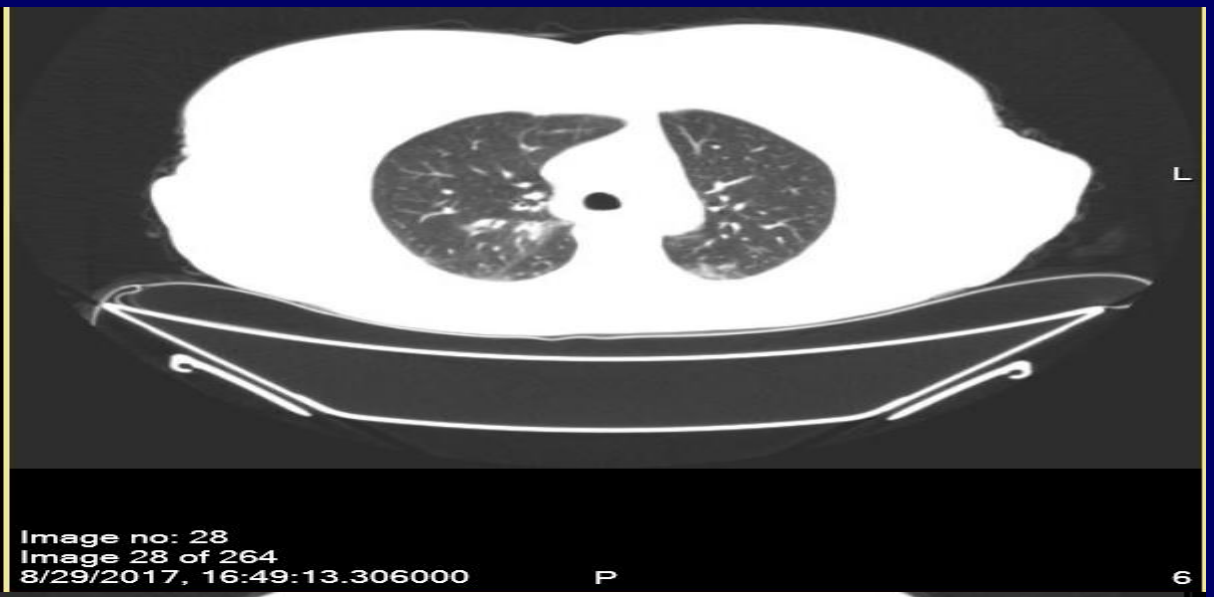
B- Colitis

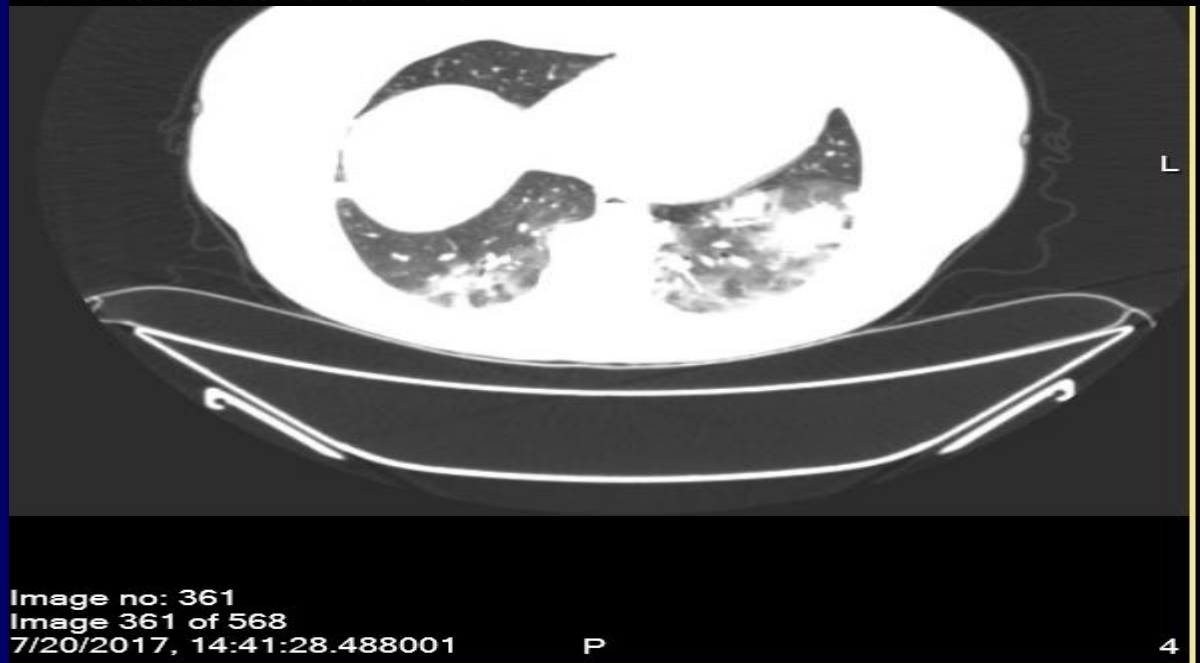
C- Pneumonitis

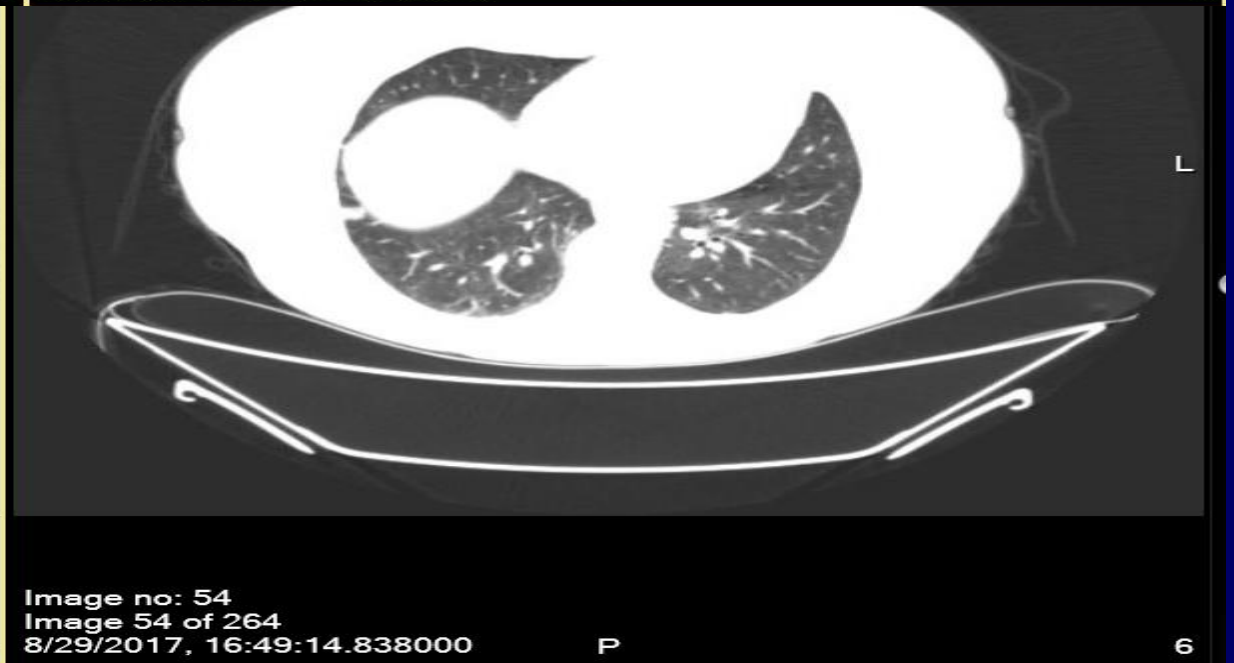
D- Skin rash

Immune mediated pneumonitis









Immune mediated Hypophysitis

ACTH

Status: **Final result** Visible to patient: **This result is not viewable by the patient.** Next appt:
09/01/2015 at 09:00 AM in Radiology (UAMS OPC05) Dx: **Hypopituitarism**

Newer results are available. Click to view them now.

	Ref Range	1yr ago (4/17/14)	2yr ago (8/14/12)	2yr ago (8/4/12)
ACTH	7 - 69 pg/mL	<5 (L)	<2 (L) R	4 (L) R

Results **Cortisol, Serum (Order 10958304)**

Cortisol, Serum

Status: **Final result** Visible to patient: **This result is not viewable by the patient.** Next appt:
09/01/2015 at 09:00 AM in Radiology (UAMS OPC05) Dx: **Hypopituitarism**

Newer results are available. Click to view them now.

	Ref Range	1yr ago
Cortisol	ug/dL	0.7
Comments: AM: 5 – 23 PM: 3 – 16		

Results **Cortisol, 60 min (Order 10958306**

Cortisol, 60 min

Status: **Final result** Visible to patient: **This result is not viewable by the patient.** Next appt:
09/01/2015 at 09:00 AM in Radiology (UAMS OPC05) Dx: **Hypopituitarism**

	Ref Range	1yr ago
Cortisol, 60 Min	ug/dL	2.2
Comments: AM: 5 – 23 PM: 3 – 16		
Resulting Agency	Softlab	

Immune mediated hypothyroidism

56 year old female with metastatic melanoma developed abnormal thyroid function tests after 2 cycles of combined ipilimumab and nivolumab.

	Ref Range	8:53 AM (2/9/16)	3wk ago (1/19/16)	1mo ago (12/30/15)	1mo ago (12/15/15)	2mo ago (11/25/15)	3mo ago (11/6/15)
TSH	0.34-5.60 uIU/mL	48.23 (H)	80.46 (H)	49.14 (H)	0.26 (L)	0.03 (L)	1.68

68 year old male developed abnormal thyroid function tests after 4 cycles of combined ipilimumab and nivolumab

	Ref Range	1d ago (3/7/17)	4wk ago (2/7/17)	1mo ago (1/24/17)	1mo ago (1/10/17)
TSH	0.34-5.60 uIU/mL	6.92 (H)	0.06 (L)	0.04 (L)	0.09 (L)
Resulting Agency		UAMS LAB	UAMS LAB	UAMS LAB	UAMS LAB

A phase of acute autoimmune thyroiditis with transient hyperthyroidism

Sarcoidosis-like syndrome and lymphadenopathy due to checkpoint inhibitors

Belal Firwana, Rahul Ravilla, Mihir Raval, Laura Hutchins and Fade Mahmoud

J Oncol Pharm Practice
0(0) 1–5

DOI: 10.1177/1078155216667635
opp.sagepub.com
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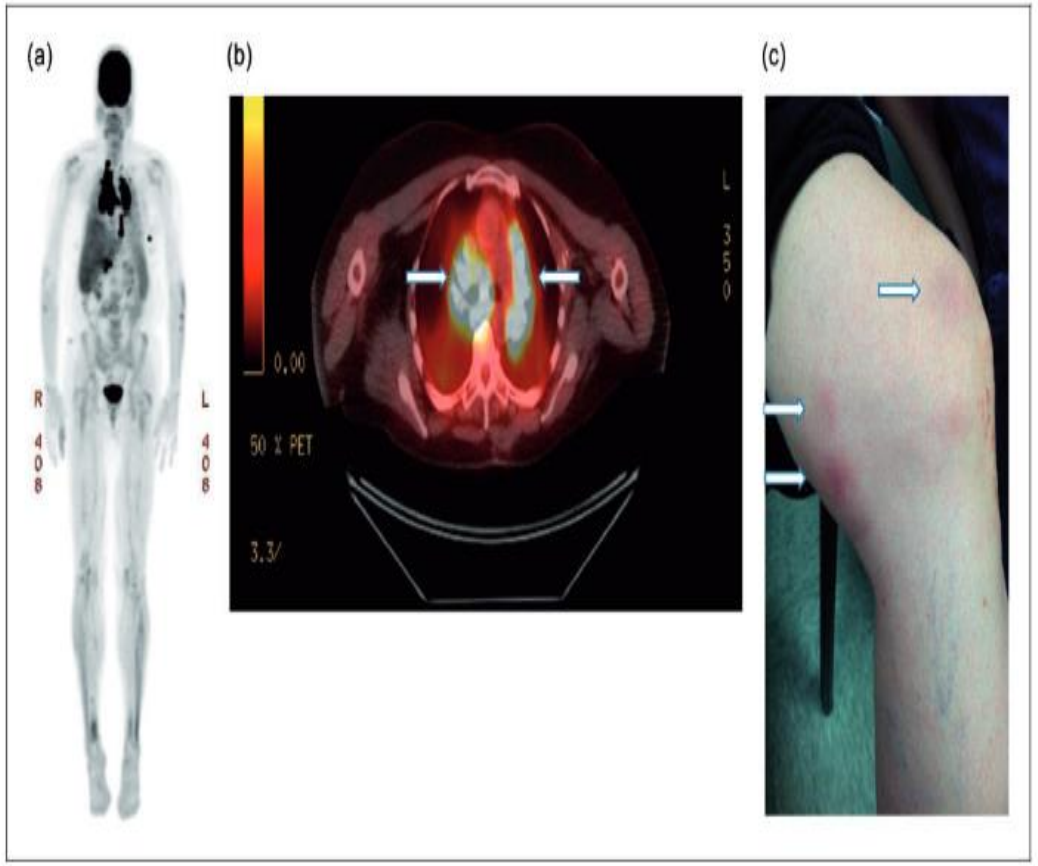


Figure 3. Full body PET CT; (a) Sagittal image shows diffuse mediastinal and hilar lymphadenopathy; (b) Axial fused FDG-PET/CT image shows new FDG-avid mediastinal and hilar lymphadenopathy; (c) erythema nodosum.

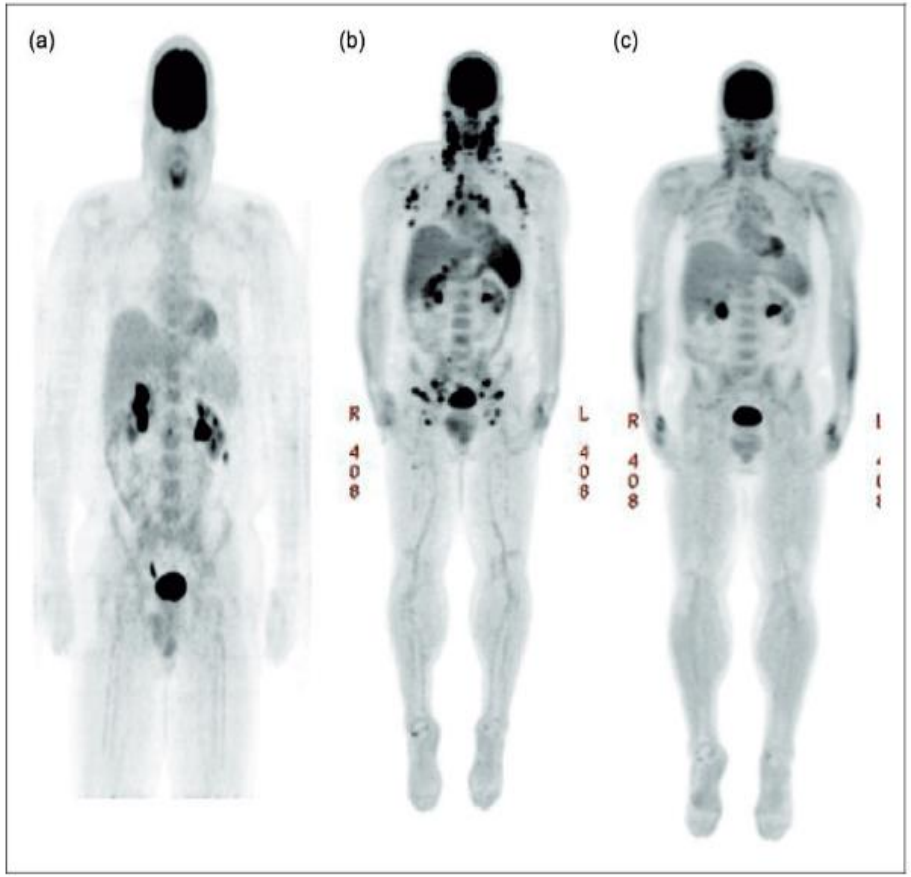


Figure 1. Sagittal PET CT scan images of total body. (a) initial PET CT, (b) Diffuse lymphadenopathy throughout the body on PET CT obtained one week after the third cycle of ipilimumab, (c) PET CT scan obtained three months later which showed resolution of the lymphadenopathy.

CLINICAL MEDICINE

Pembrolizumab-Induced Pancytopenia: A Case Report

Dinesh Atwal, MD; Krishna P Joshi, MD; Rahul Ravilla, MD; Fade Mahmoud, MD

Perm J 2017;21:17-004

E-pub: 07/07/2017

https://doi.org/10.7812/TPP/17-004

	3/28/16	10/18/16	10/22/16	11/2/16	11/25/16	12/15/16	12/19/16	1/11/17	2/19/17	2/11/17	2/12/17	3/7/17
WBC	4.83	1.22	0.71	0.93	1.32	1.82	2.2	3.92	4.07	1.8	1.8	3.9
HGB	12.3	5.6	7.5	8.6	7.2	7.6	10	8.7	8	7.4	6.5	9.3
HCT	35.1	16.5	21.7	25.2	21.3	22.3	35.6	26.2	23.9	21.8	19.2	27.3
PLT	231	28	31	19	16	22	32	64	55	46	56	85

IVIG: 1 g/kg daily X 5 days

Prednisone 1 mg/kg tapered over 6 weeks

10/19: Bone marrow cellularity 20%

11/29: Bone marrow cellularity 40%

Figure 2. Screenshot from the patient's electronic medical record showing the timeline of the case with relevant laboratory tests results. Dates are month/day/year.

HCT = hematocrit (%); HGB = hemoglobin (g/dL); IVIG = intravenous immunoglobulins; PLT = platelets (× 10^9/L); WBC = white blood cells (× 10^9/L);
▲ = 1 U of red blood cell transfusion, ▲ = 1 U of platelet transfusion.

Quiz

The patient presented in our case has metastatic melanoma that harbors the BRAF V600 mutation. He is currently in remission after immunotherapy but let us assume that he presents to you now with weight loss and restaging scans chest/abdomen/and pelvis revealed progression of his disease. What be an appropriate next step:

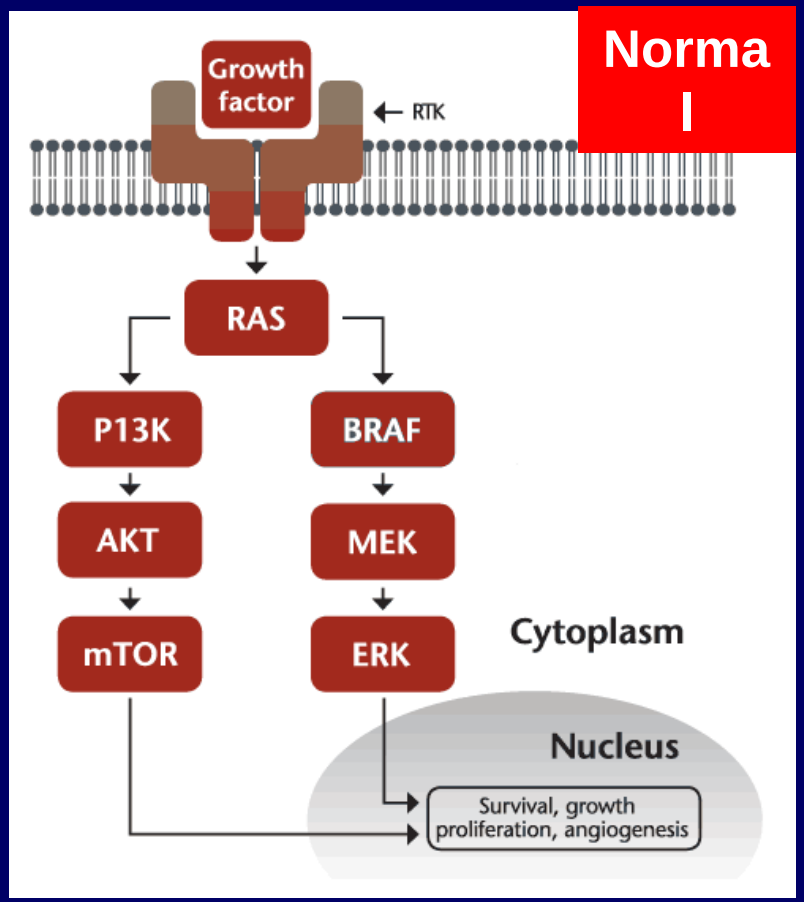
A- Repeat ipilimumab and nivolumab.

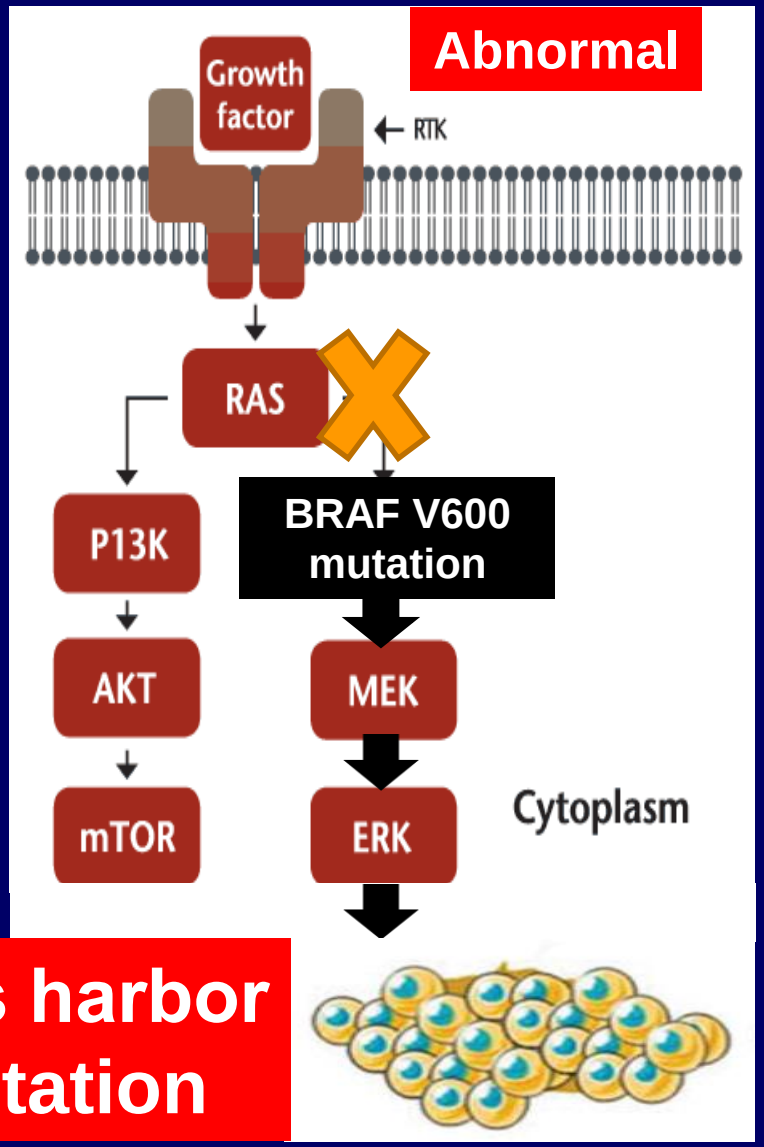
B- Proceed with nivolumab alone.

C- Dabrafenib and Trametinib

D- Dabrafenib alone

MAPK PATHWAY AND BRAF MUTATION

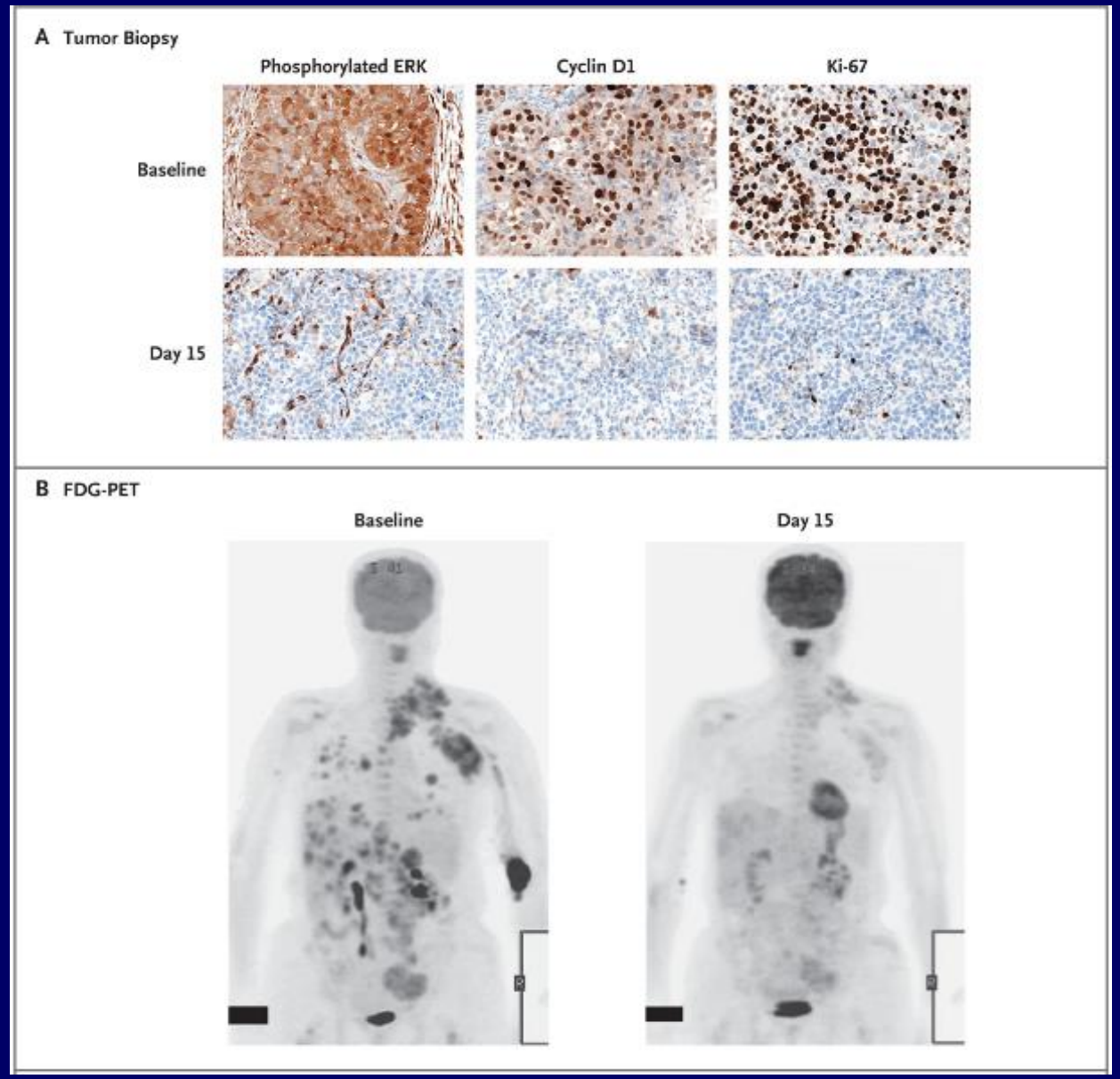


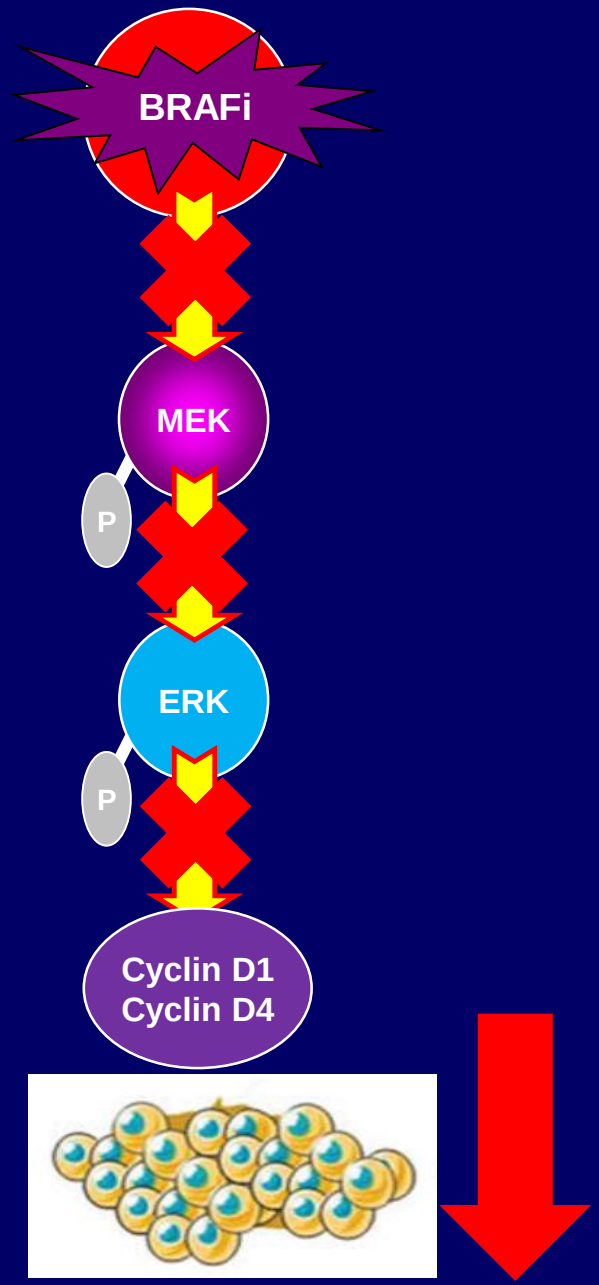


≈ 50% of melanomas harbor the BRAF V600 mutation

Hong S, Han SB. *Arch Pharm Res* 2011;34(5):699–701

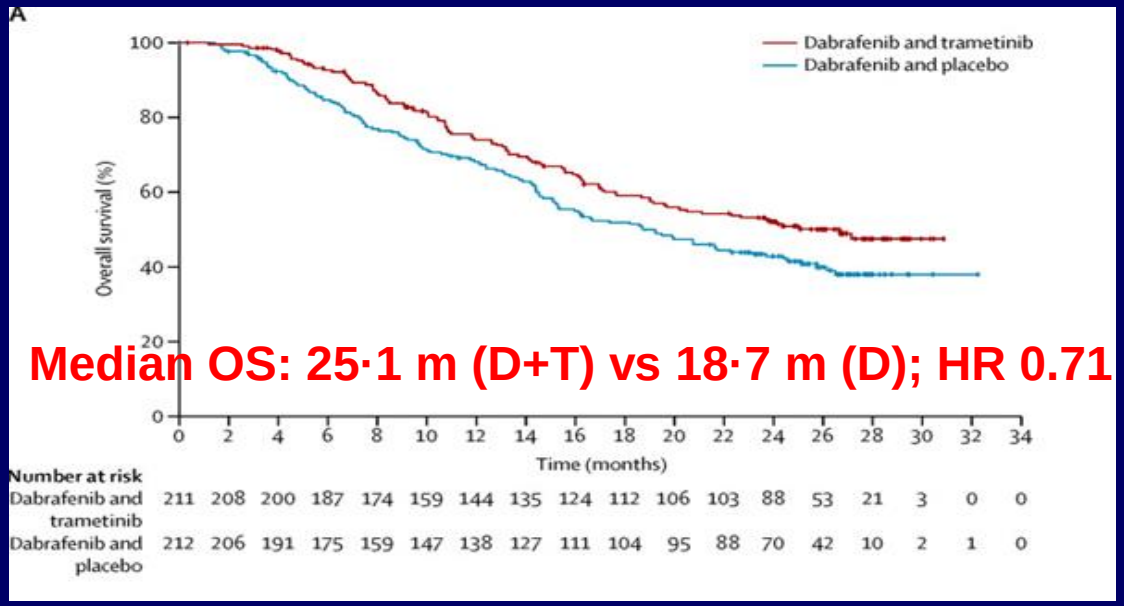
Effect of Vemurafenib in BRAF mutated Melanoma





Flaherty et.al. N Engl J Med 2010

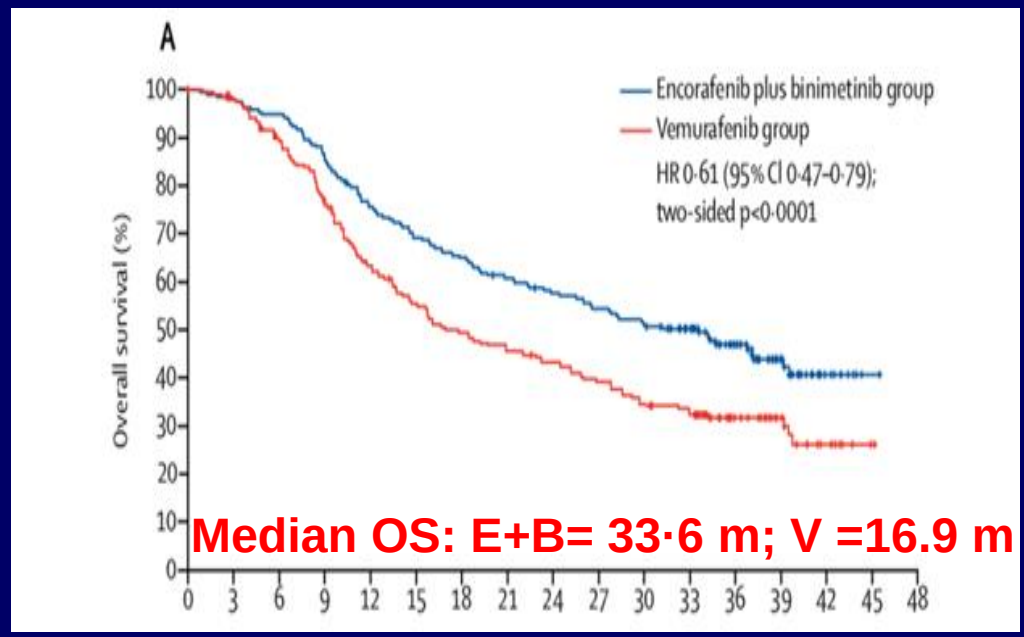
Dabrafenib+trametinib



Median OS: 25·1 m (D+T) vs 18·7 m (D); HR 0.71

Long GV et.al. Lancet. Aug 2015.

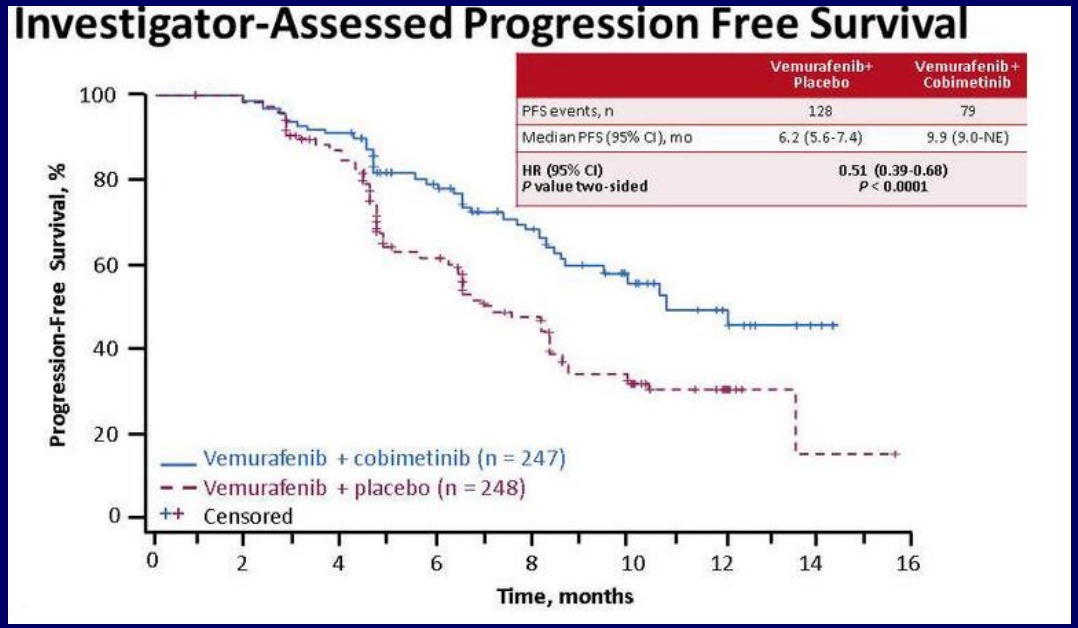
Encorafenib+Binimetinib



Median OS: E+B= 33·6 m; V =16.9 m

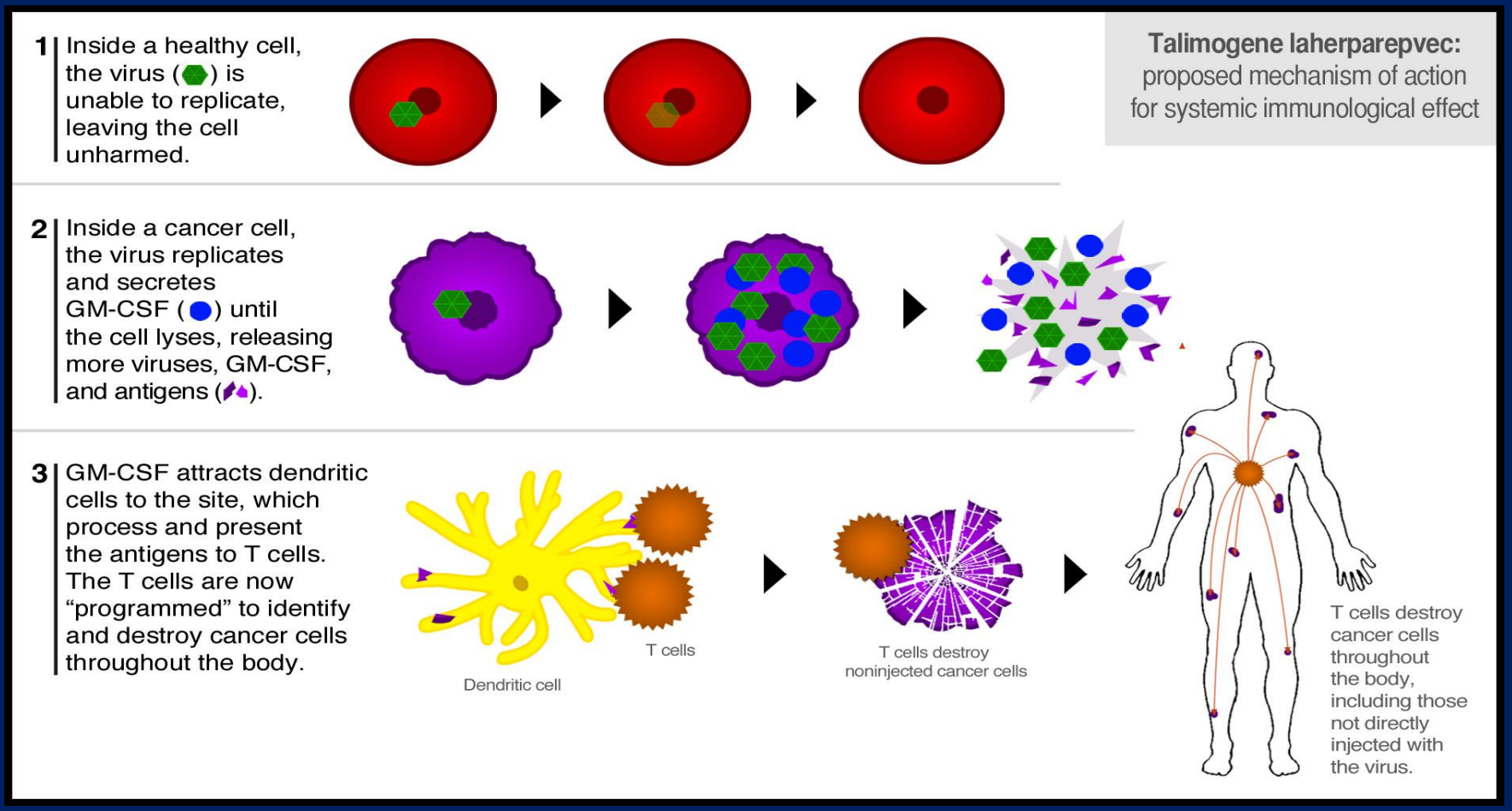
Dummeret al. Lancet Oncol Sept 2018

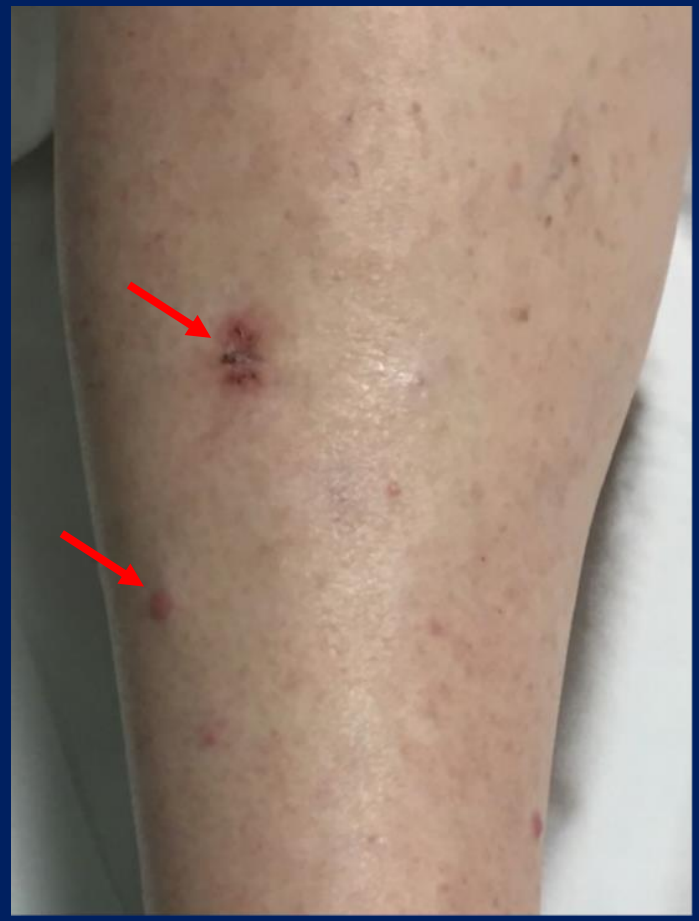
Vemurafenib+Cobimetinib



Ascierto PA al. Lancet Oncol Jul 2016

Oncoloytic Immunotherapy





Metastatic Melanoma Treatment Landscape 2019