Update on Management of Melanoma

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Disclosures

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

Case presentation

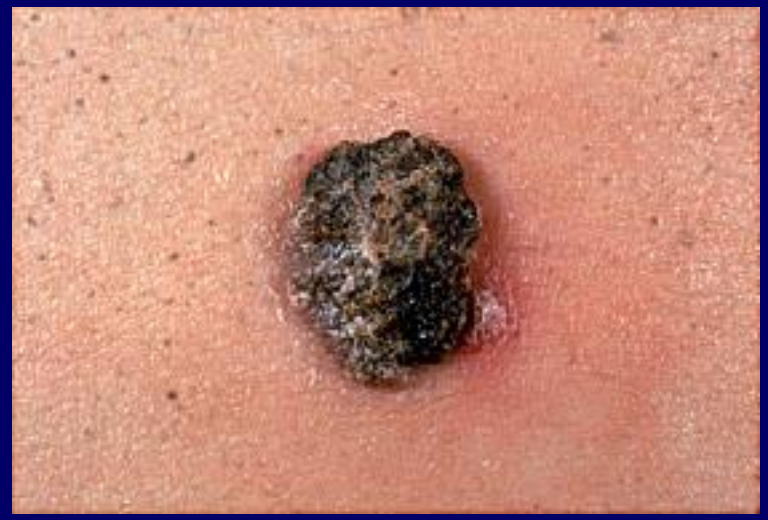
- Mr. K is a 63 year old male presented with a rapidly growing “berry-like” pigmented lesion on the skin of his right shoulder. This is most likely:

A- Superficial spreading melanoma

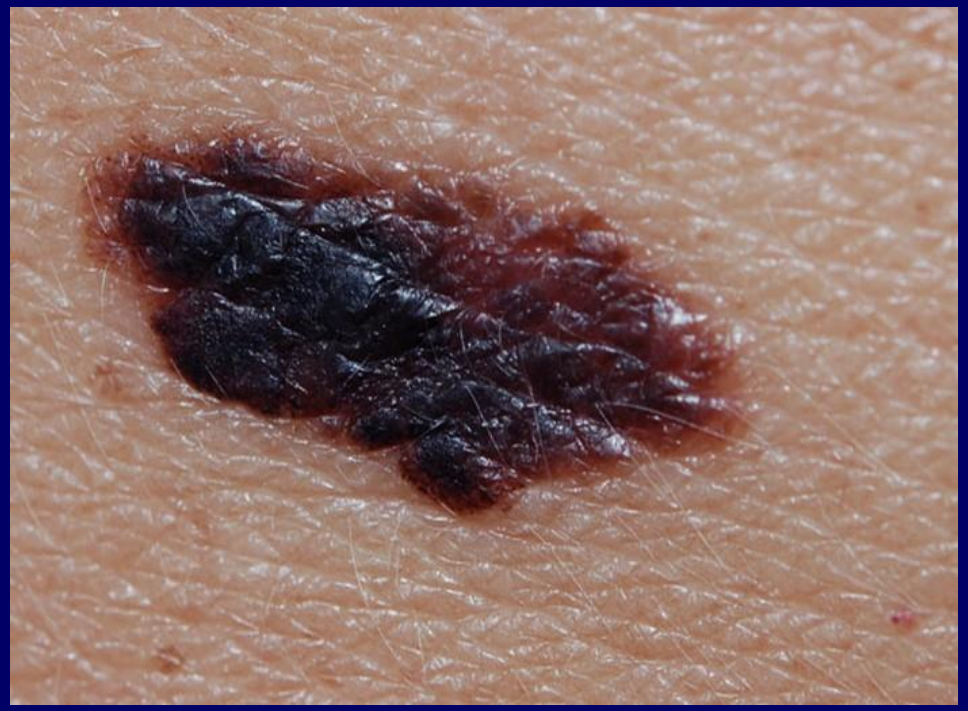
B- Nodular melanoma

C- Acral-lentiginous melanoma

D- Lentigo maligna melanoma

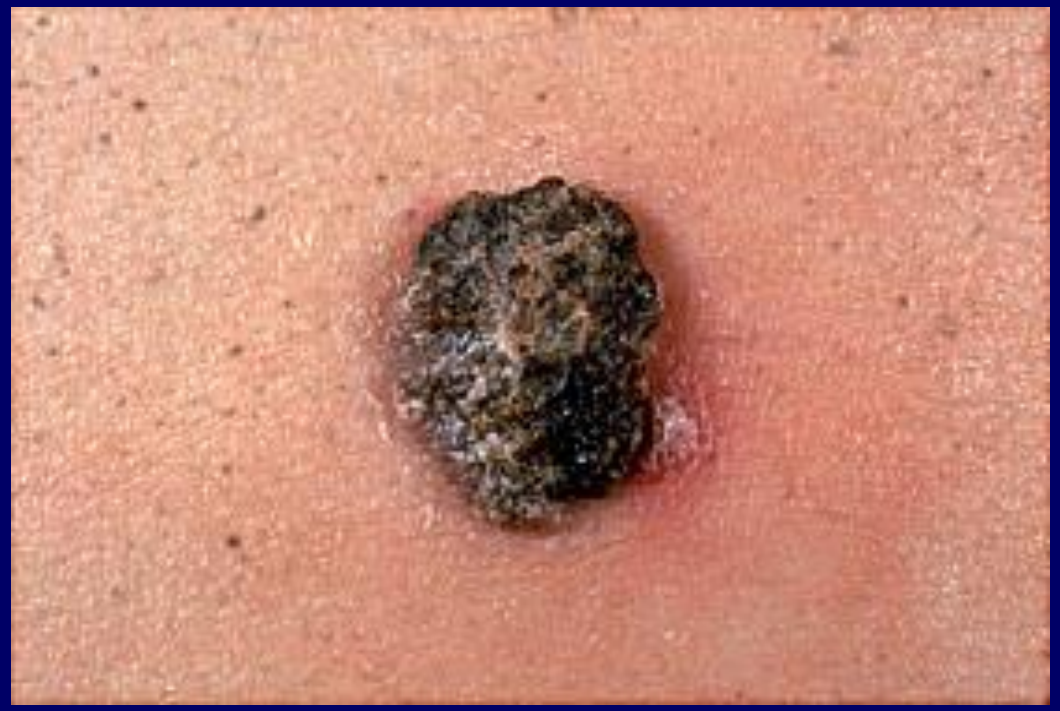


Types of melanoma



Superficial spreading melanoma

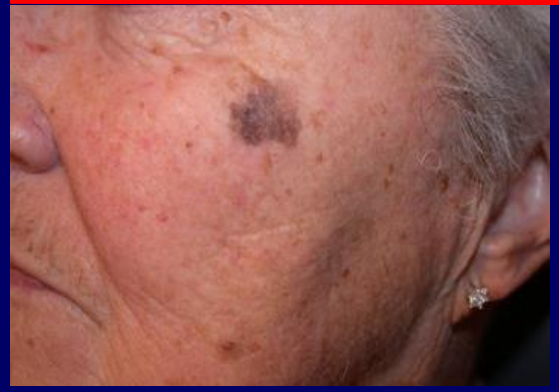
- Most common type of skin melanoma (70%)
- Asymptomatic black or brown macule
- Radial growth phase before becoming invasive.



Nodular melanoma

- Second most common type of skin melanoma (15%)
- Blue-black “berry-like” nodular lesion
- Vertical not radial growth
- Rapid progression over months

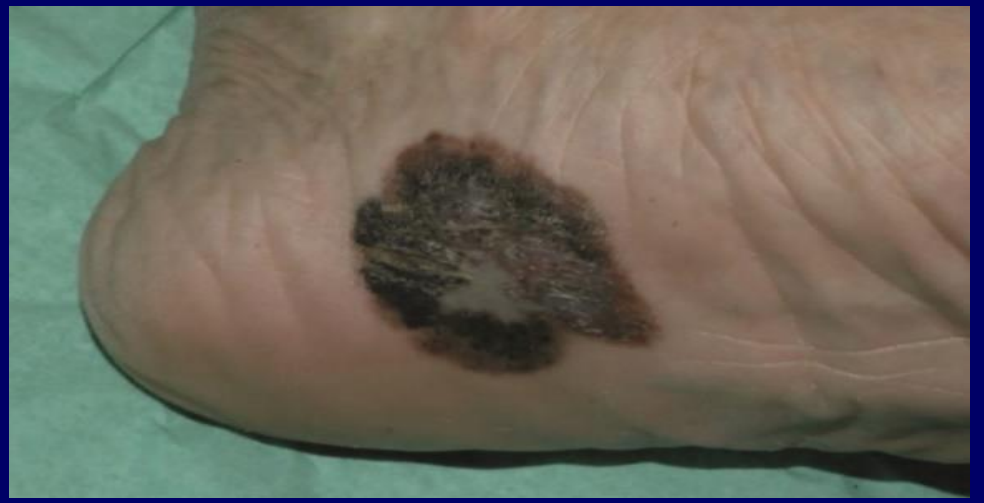
Types of melanoma



Lentigo maligna

- Irregularly shaped macule, older patients, size: up to 5-7 cm
- In situ melanoma
- Slowly grows over 5-15 years before becoming invasive
- Invasive changes (lentigo maligna melanoma): the formation of bumps (papules), change in color.

Lentigo maligna melanoma



Acral-lentiginous melanoma

- Occurs on the palms and soles.
- 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

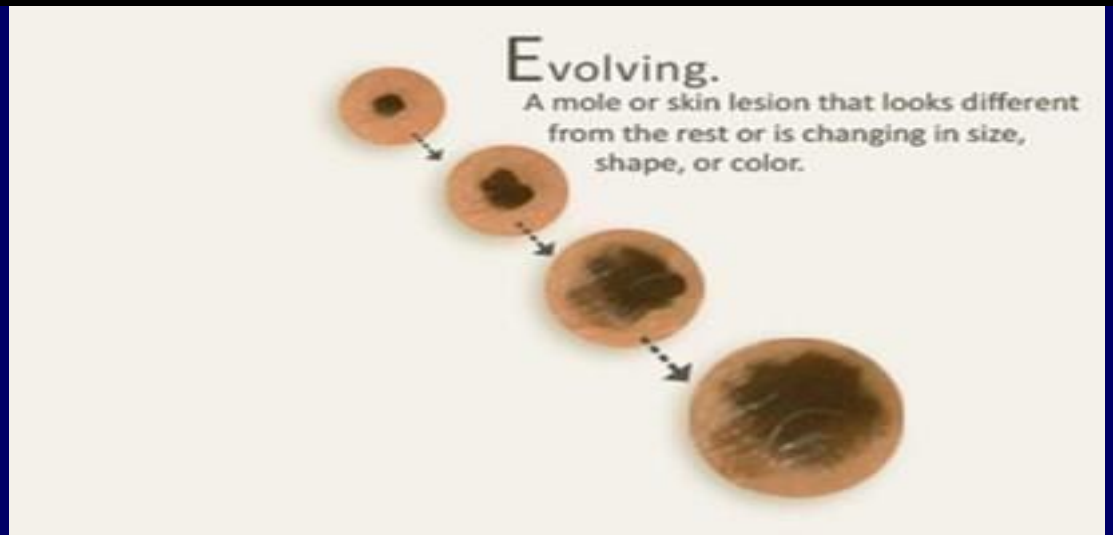
The ABCDE

You evaluated the patient presented in this case. All of the following are acceptable methods to biopsy a suspected melanoma lesion except:

A- Excisional biopsy with 1-2 mm margin

B- Shave biopsy should be avoided due to risk of transecting a melanoma and preventing true staging of the lesion

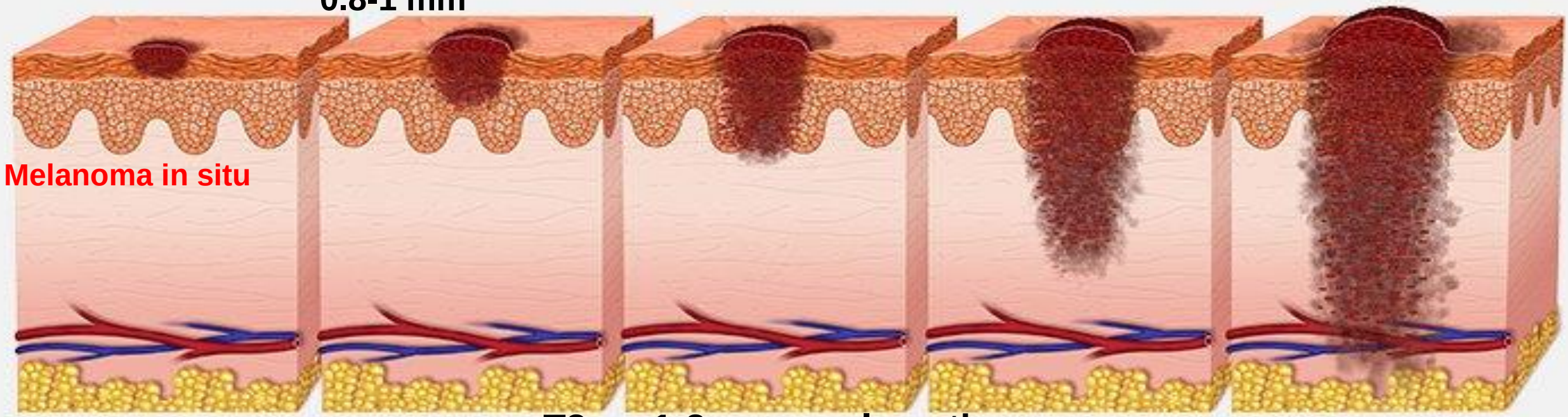
D- Incisional biopsy



Breslow depth & T stage

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

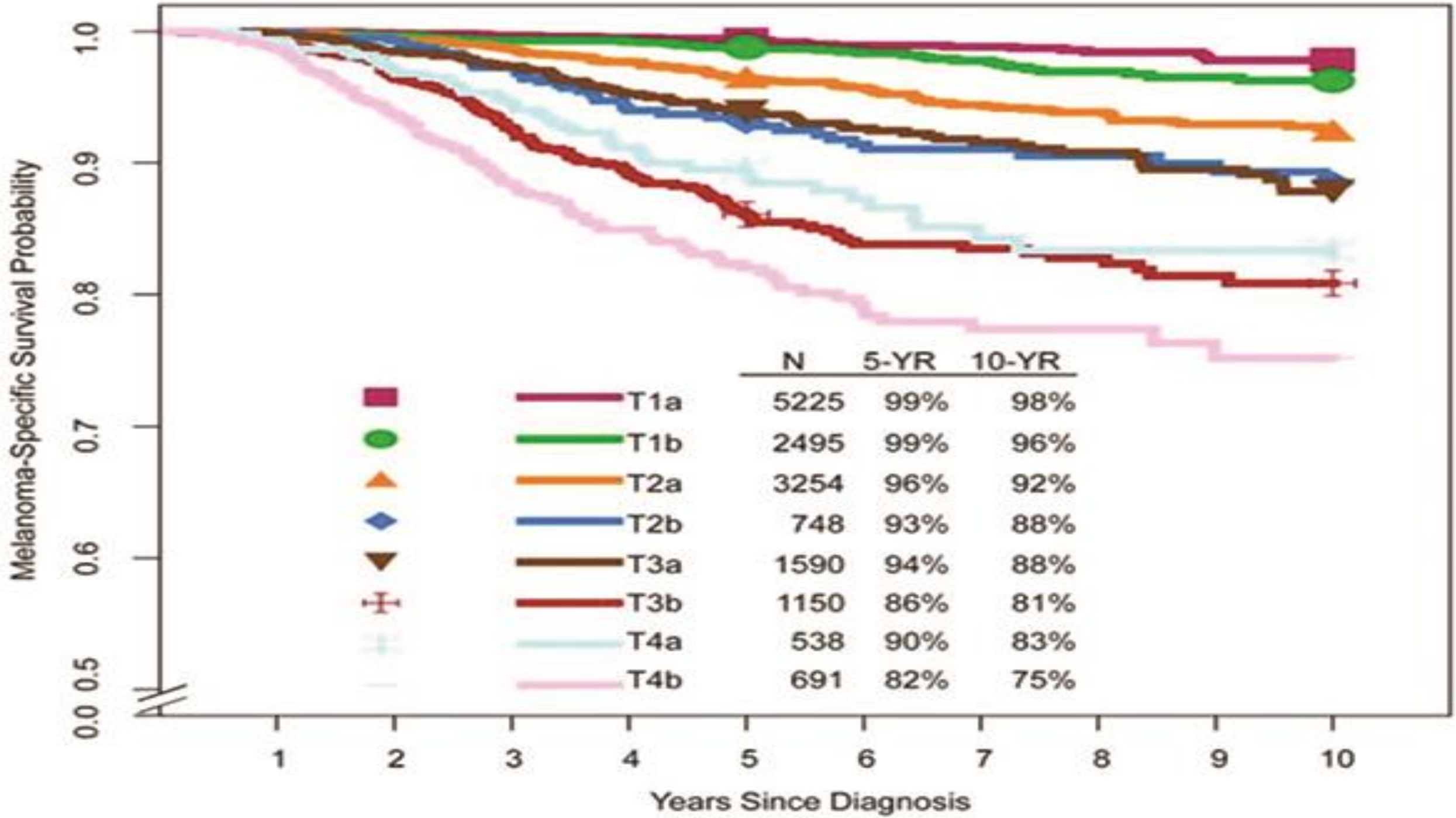
T3a: >2-4mm no ulceration
T3b: >2-4mm with ulceration



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%

Case presentation....

- An excisional biopsy was done. 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

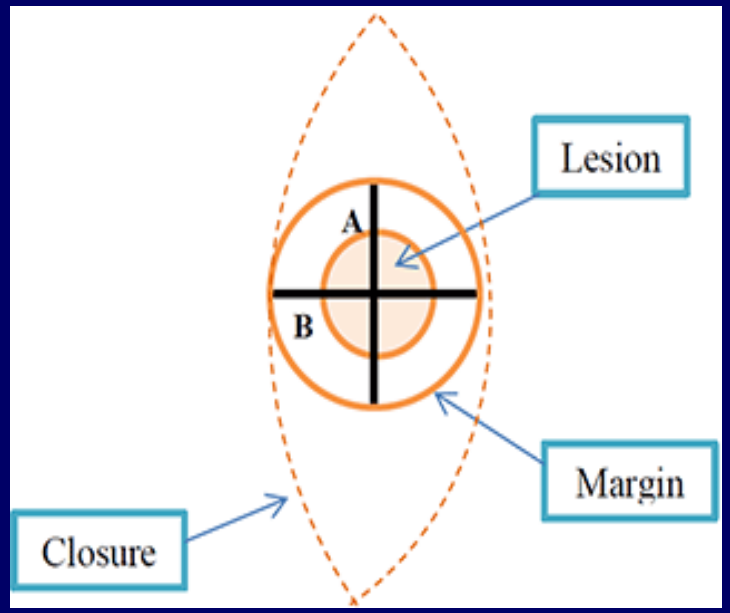
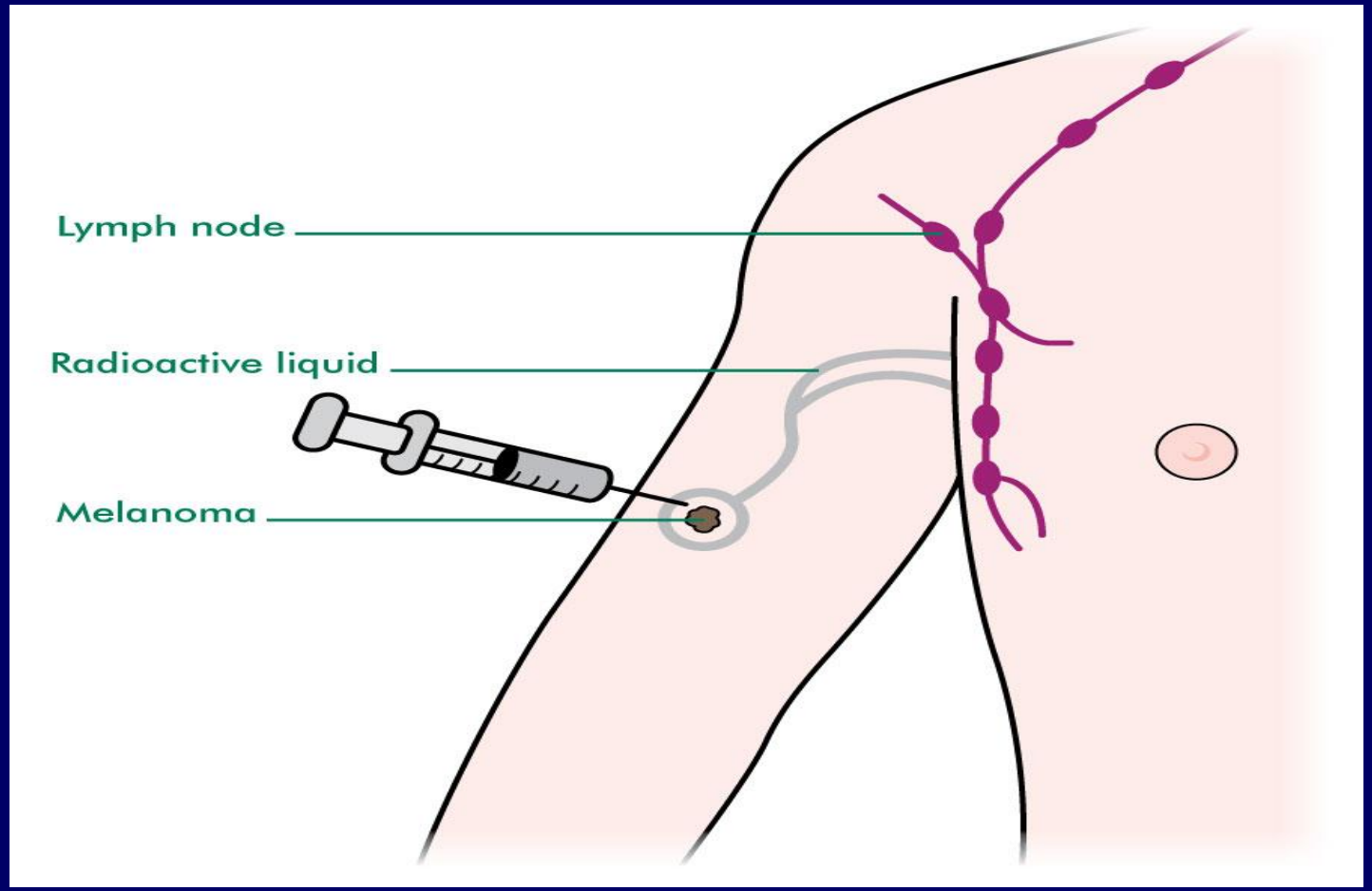


Table 4: NCCN-Recommended Surgical Margins for Melanoma

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.



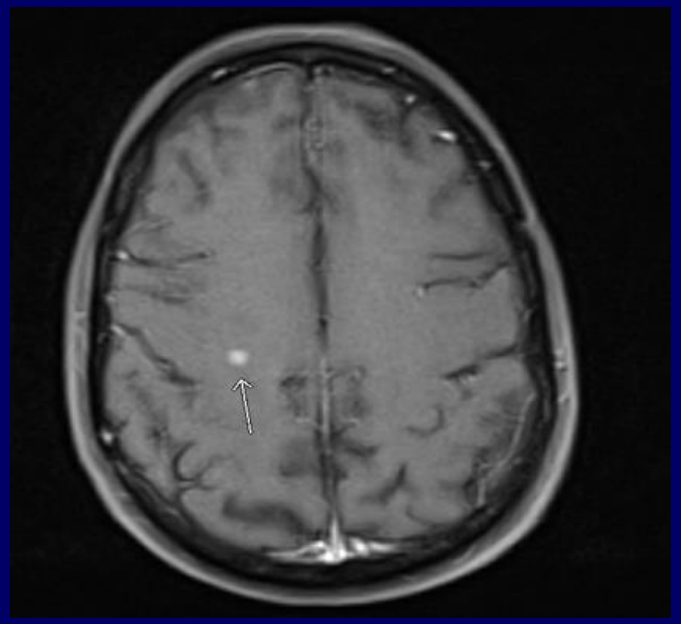
ASCO/SSO guidelines recommend

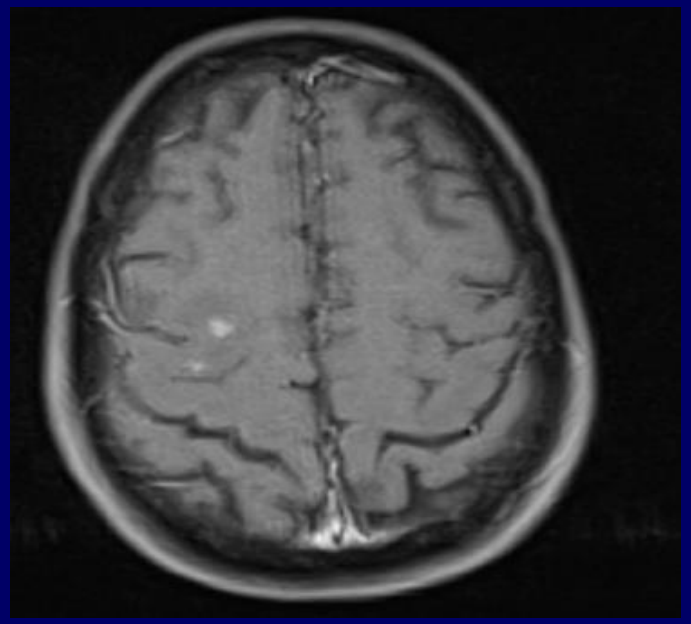
- **SLNB for all patients with >=1mm melanoma**
- **Should be considered in patients with T1b melanomas (0.8–1 mm or < 0.8 mm with ulceration).**
- **Routine sentinel node biopsy is not recommended for T1a melanomas (< 0.8 mm, nonulcerated).**

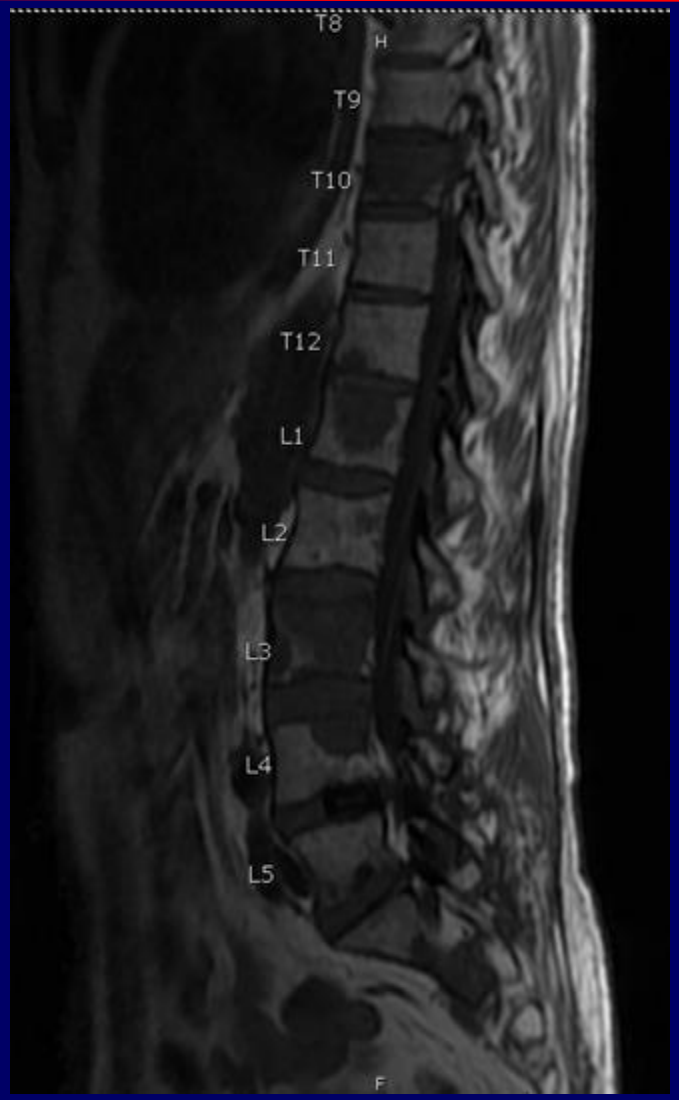
Case presentation....

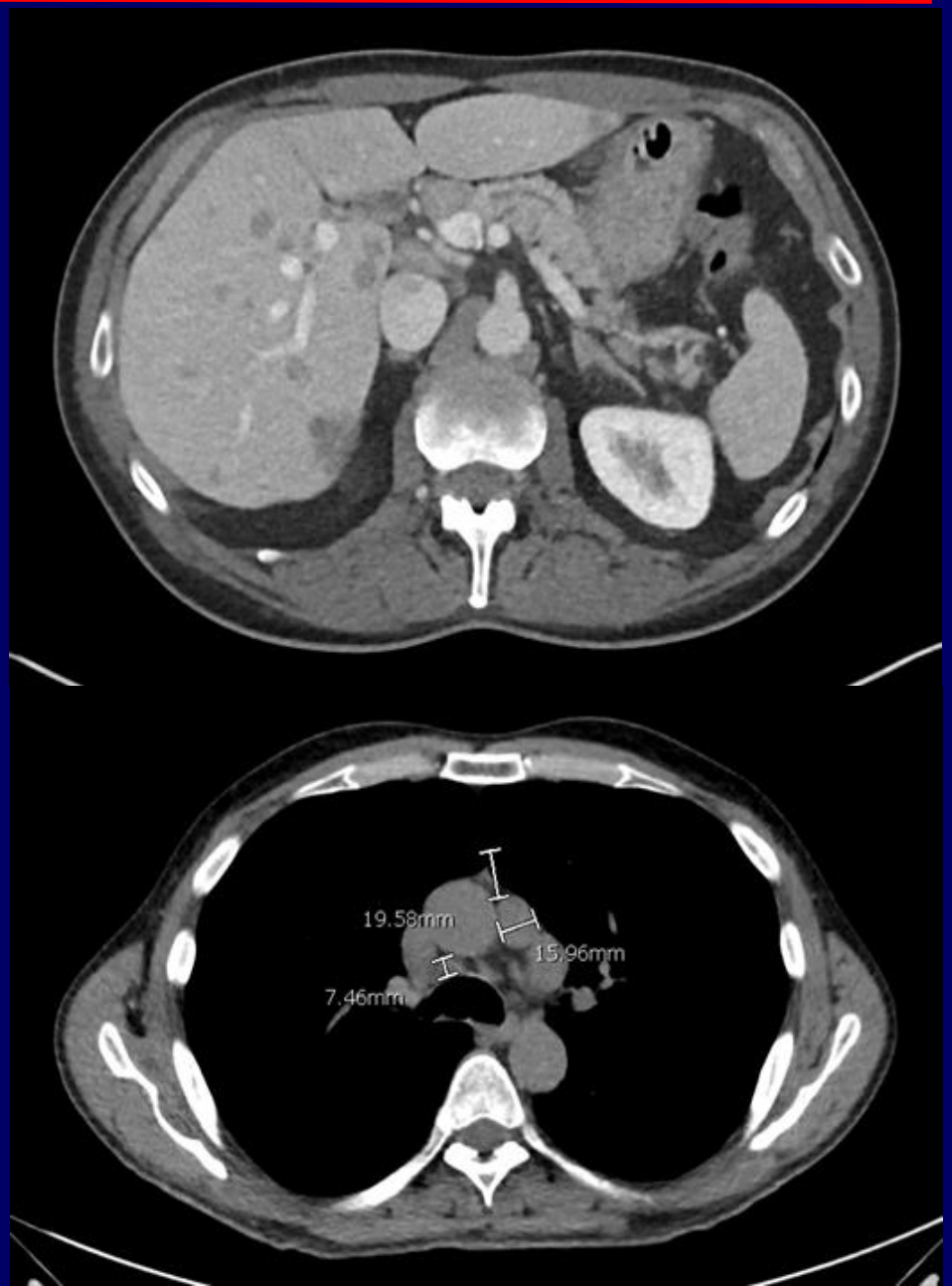
- Patient underwent wide local excision and SLNB.
- No melanoma was detected in the 2 sentinel LNs.
- Patient was scheduled for every 3 month follow up exam with his dermatologist and surgical oncologist.
- 2 years later he presented with fatigue, severe pain in RUQ and mid-back, anorexia, and 20 lbs 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

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

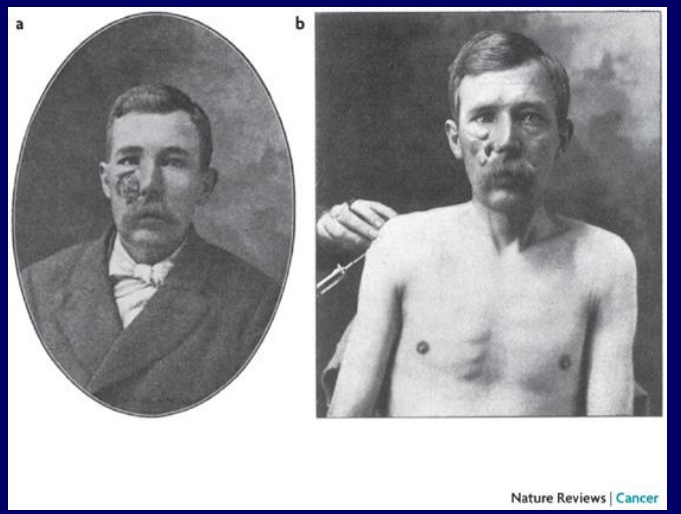
ERYSIPELAS GERMS AS CURE FOR CANCER

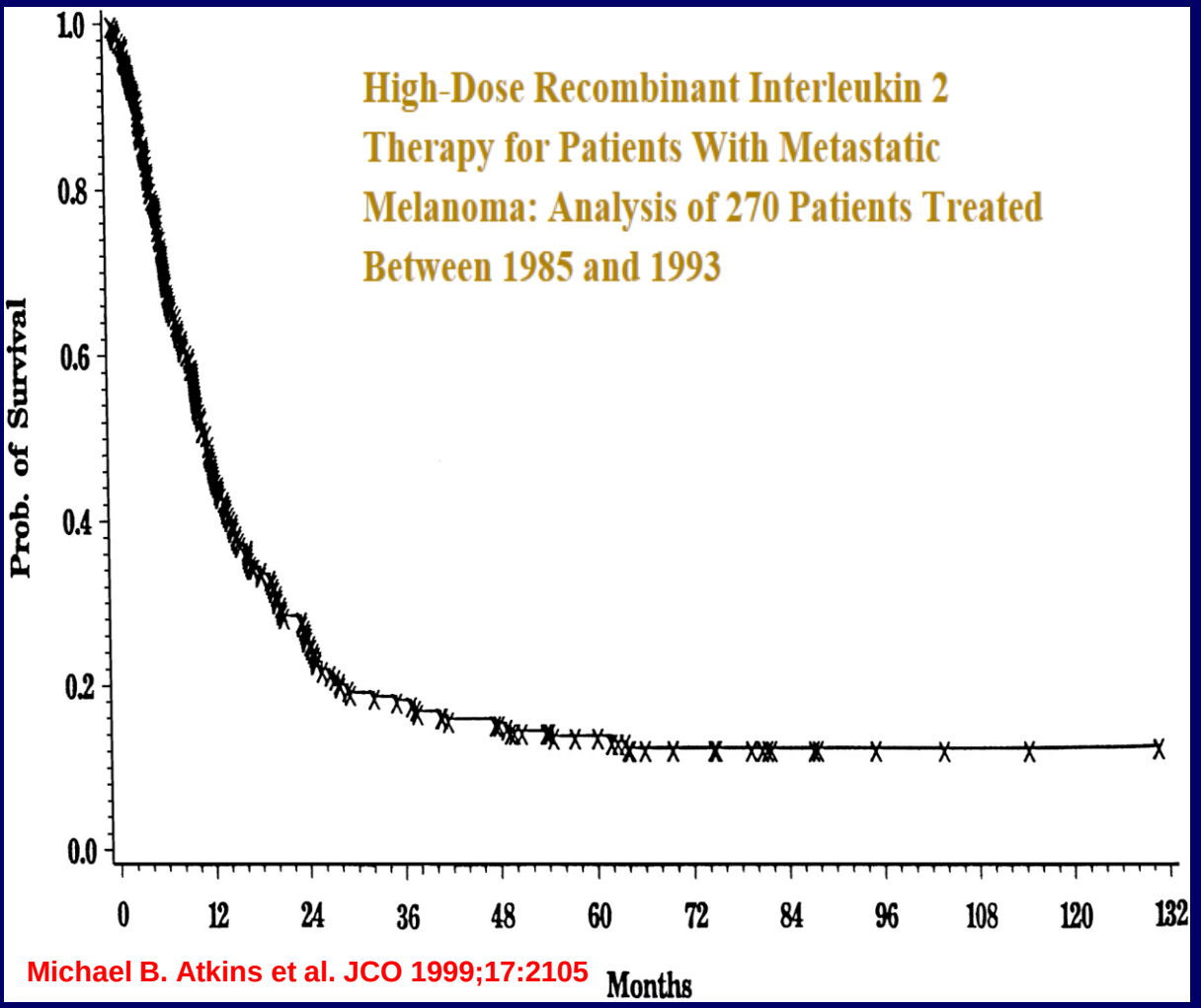
Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

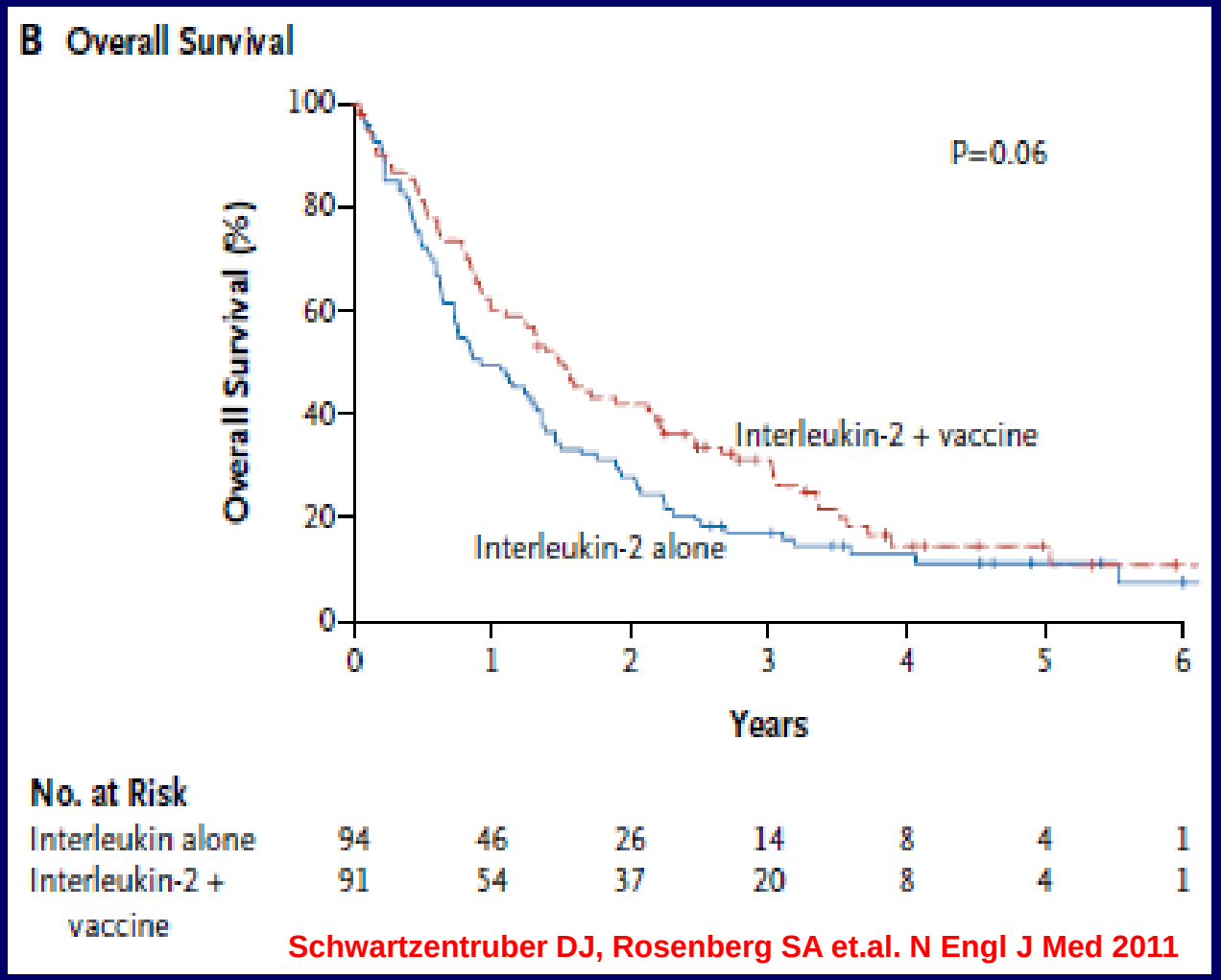
Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

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-



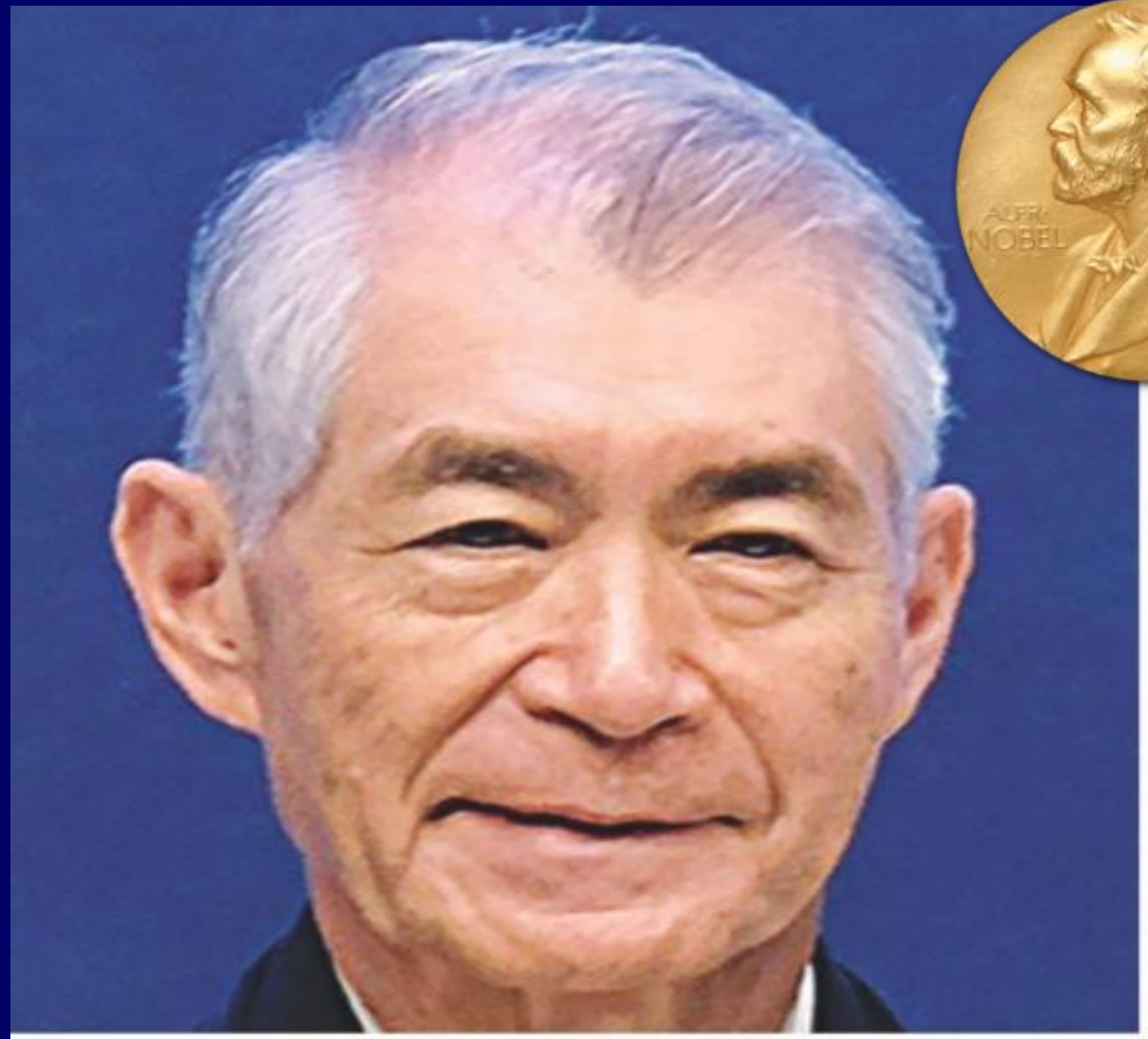


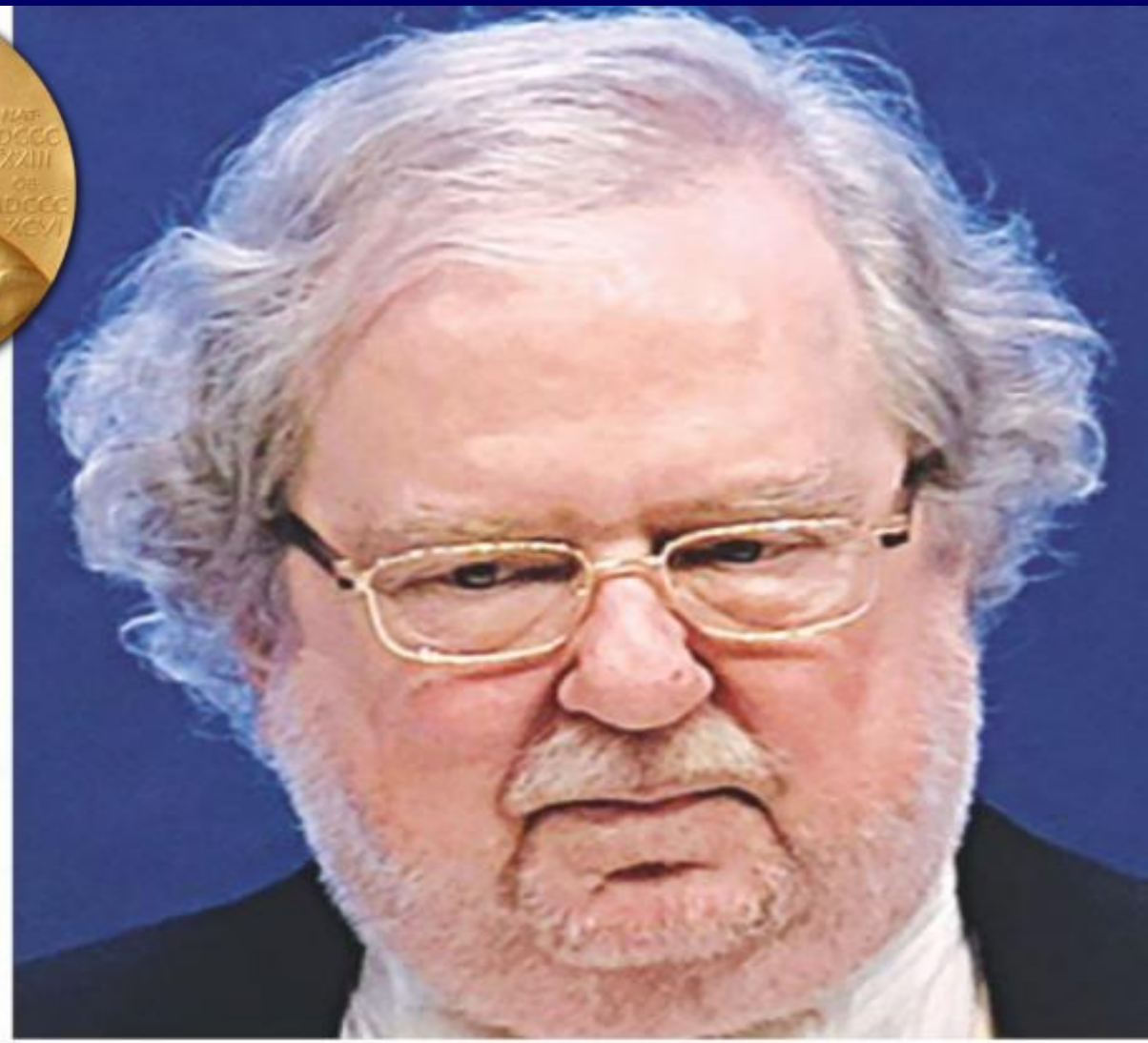
Michael B. Atkins et al. JCO 1999;17:2105



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

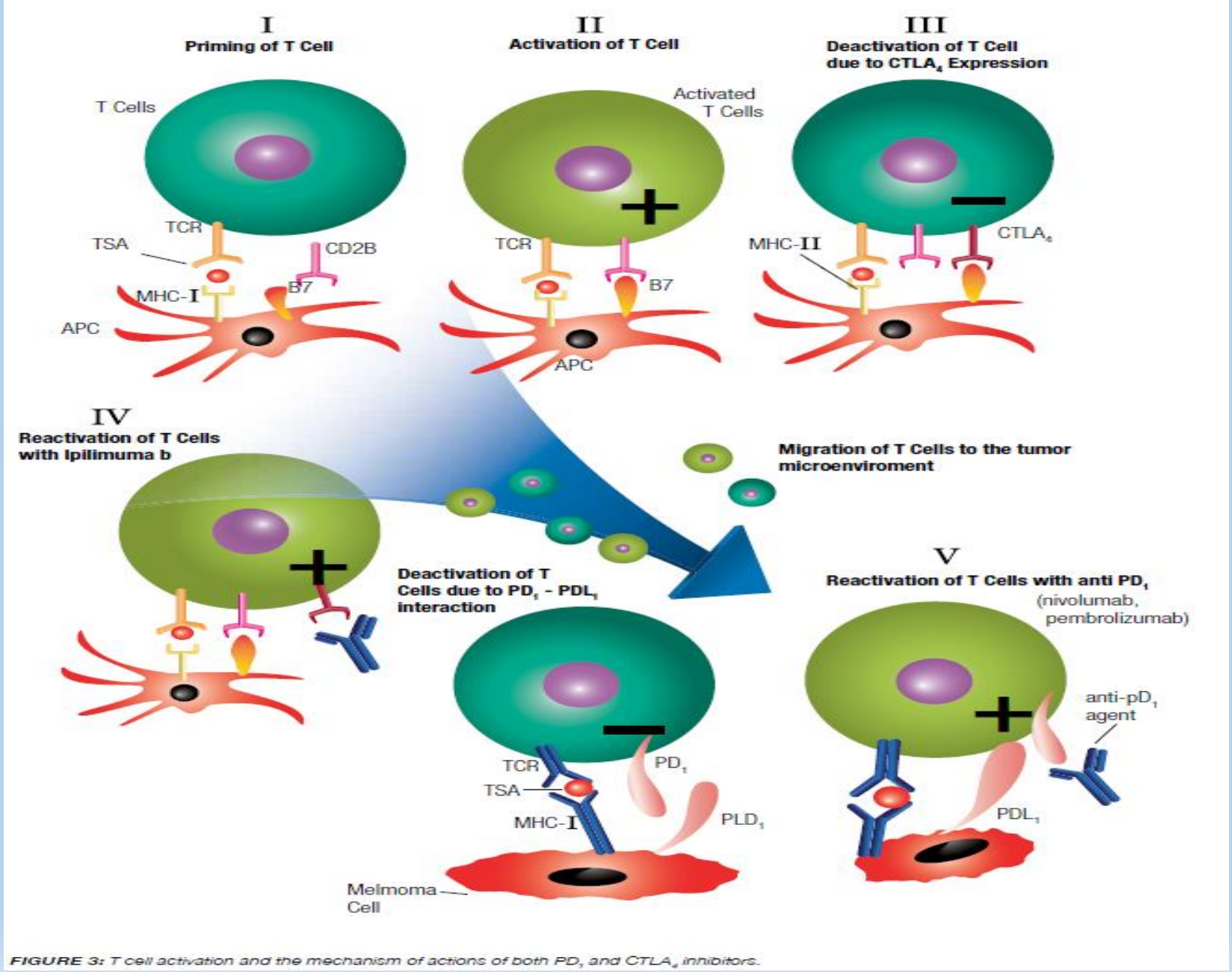
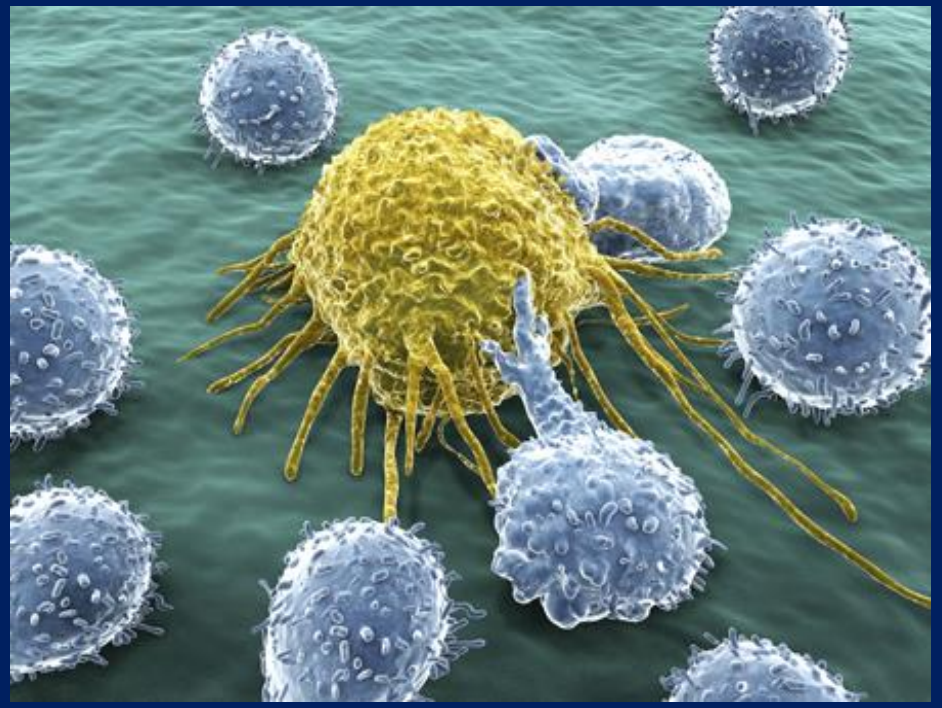


FIGURE 3: T cell activation and the mechanism of actions of both PD_1 and $CTLA_4$ inhibitors.

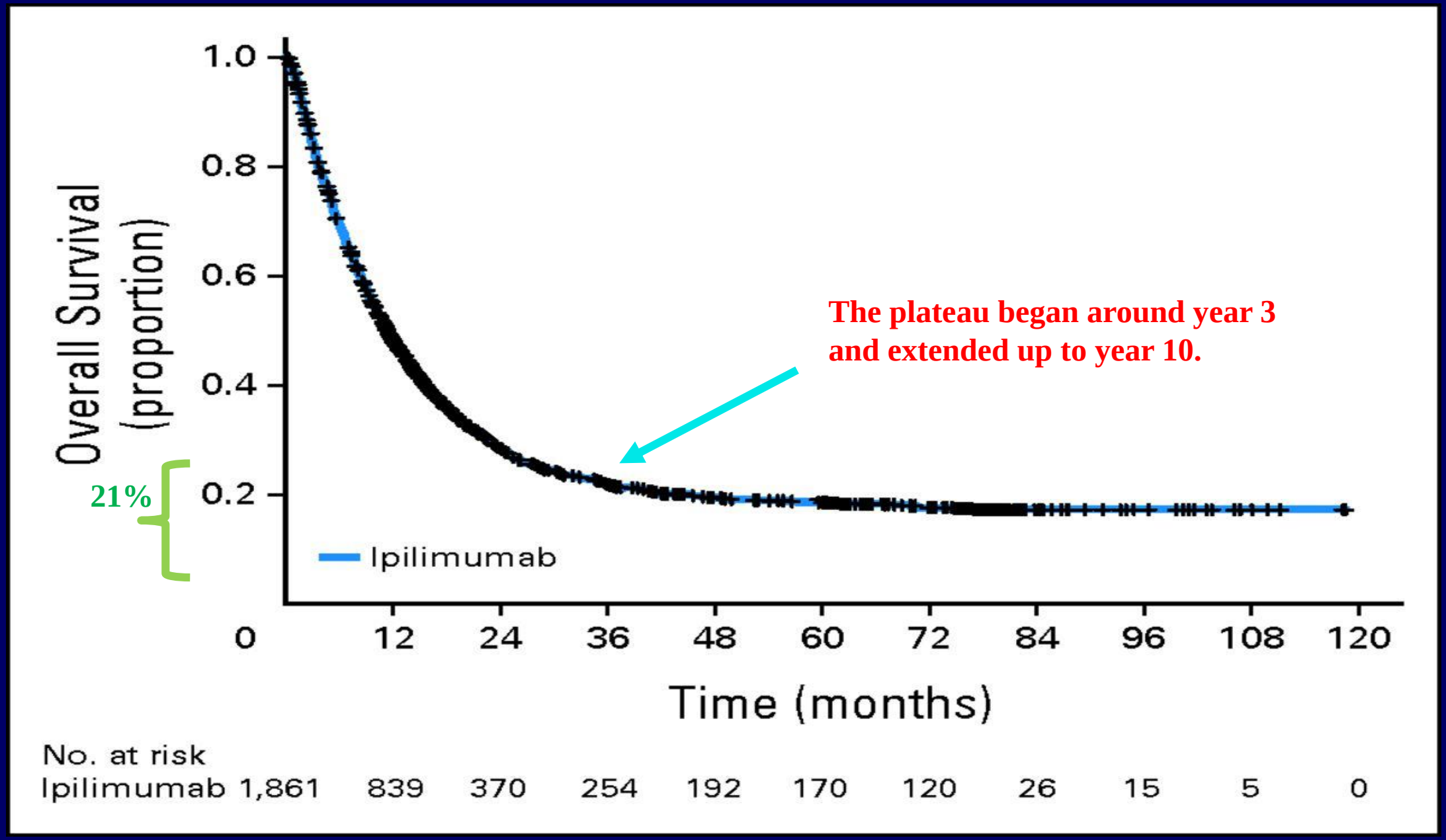
Immune Surveillance in Melanoma: *From immune attack to melanoma escape and even counterattack*.
Fade Mahmoud, Bradley Shields et.al.
Cancer Biol Ther. 2017 Jul 3;18(7):451-469.

Cytotoxic T cells attack melanoma

- Apoptosis
- The granule exocytosis pathway



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



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."

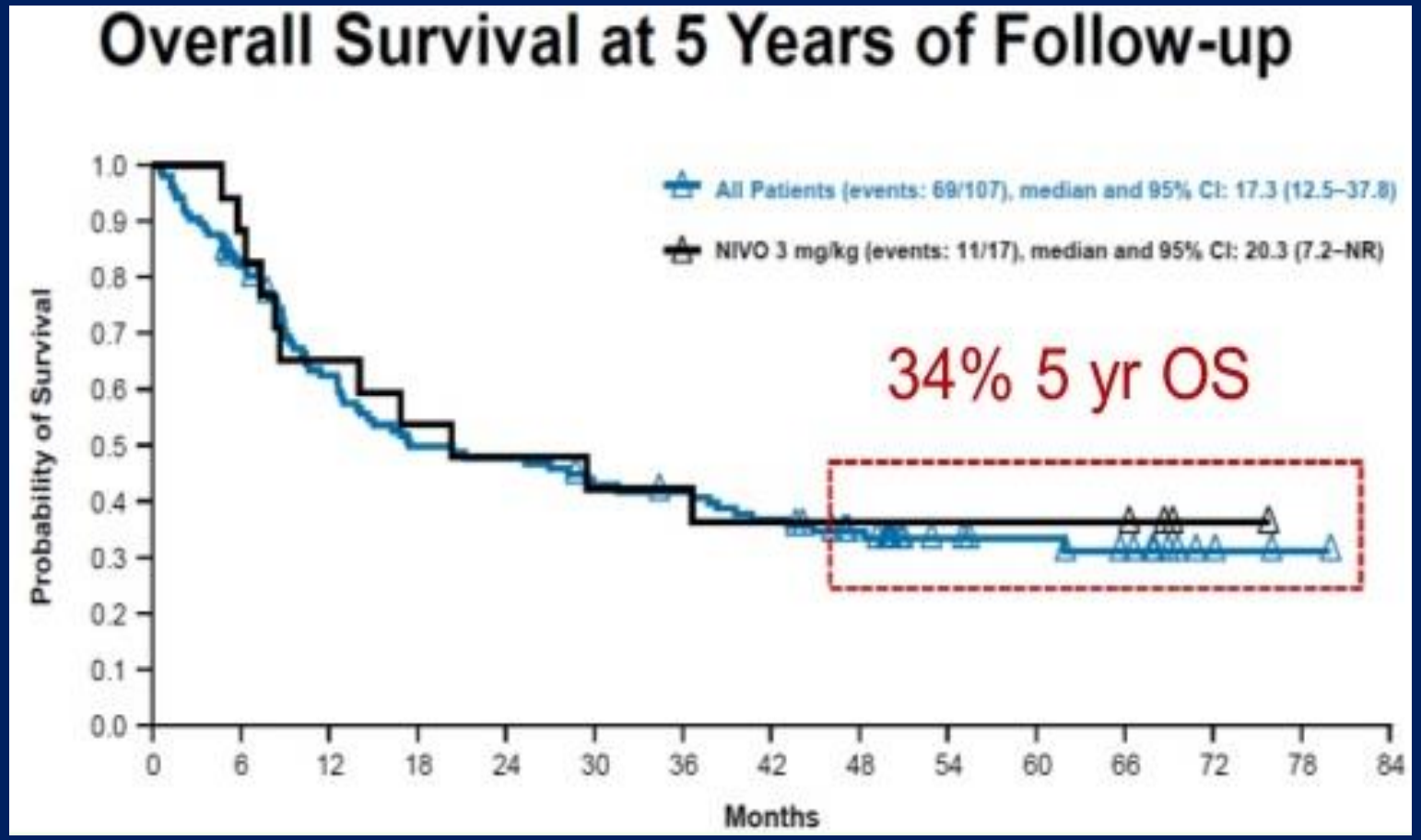
– **JIMMY CARTER**
Former U.S. President

#CIM17

CANCER RESEARCH INSTITUTE

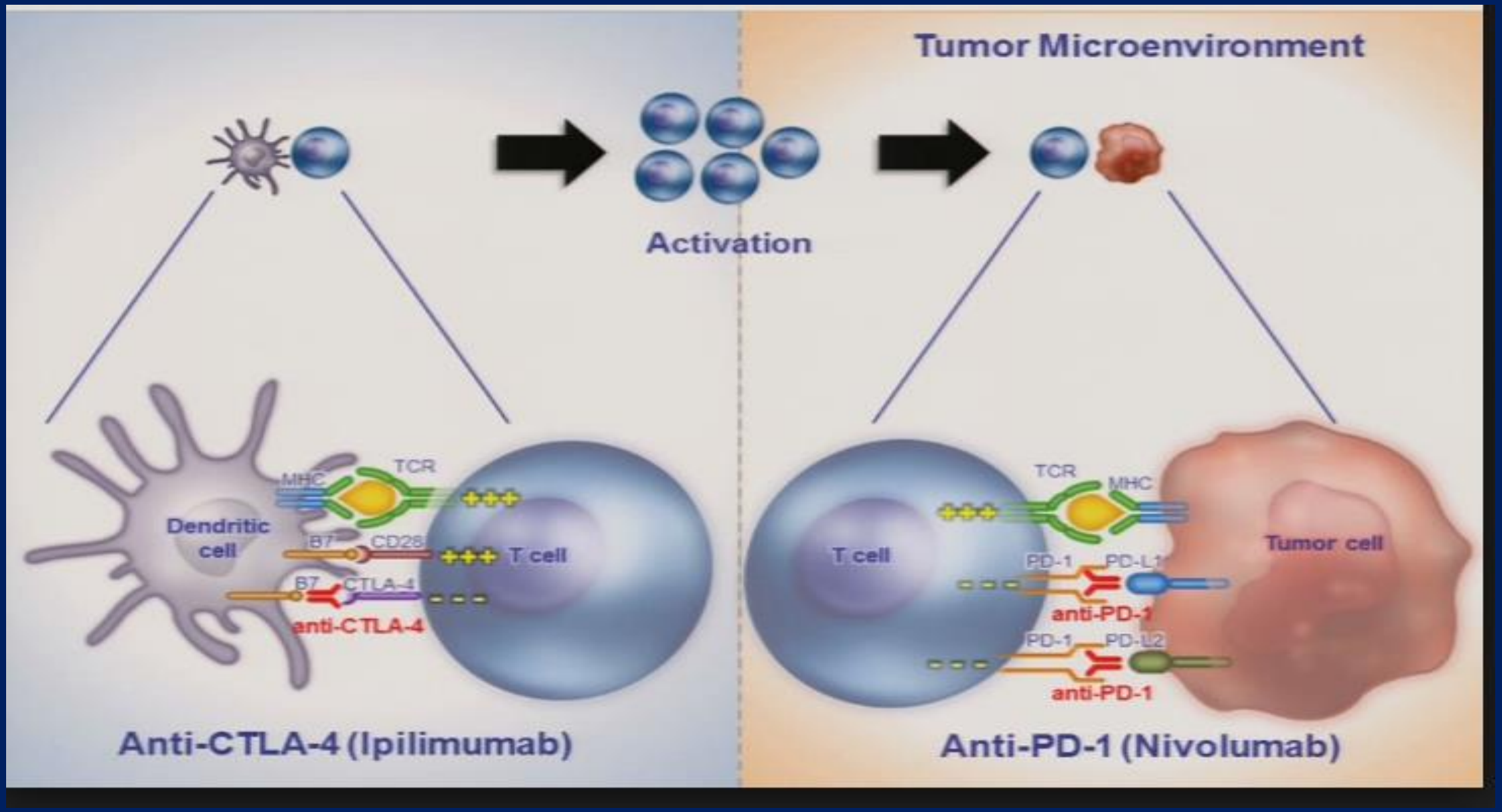
AACR 2016: 5-Year Survival Rates for Patients With Metastatic Melanoma Treated With Nivolumab Much Higher Than Historical Rates

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



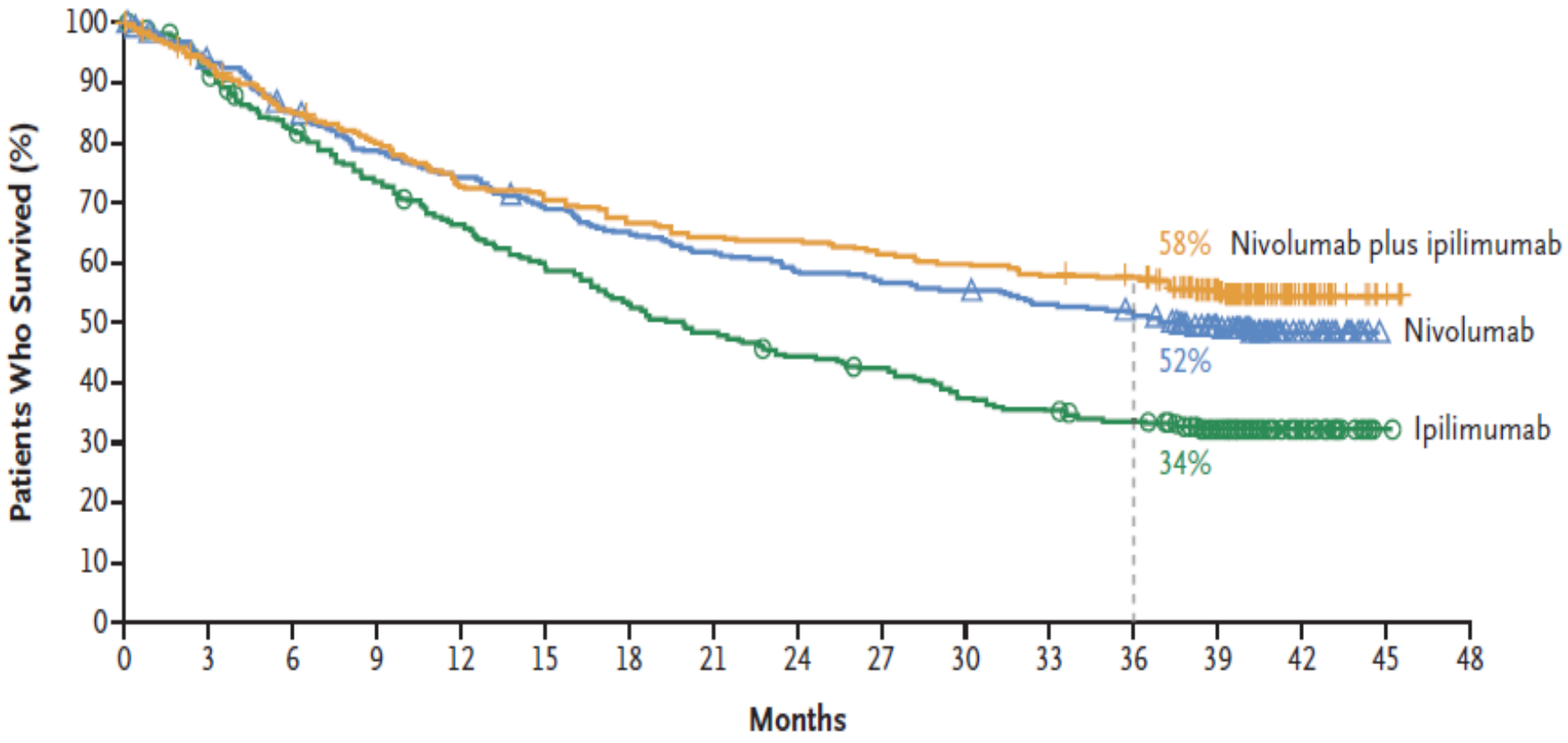
Hodi, AACR April 2016

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



CheckMate 067

B Overall Survival



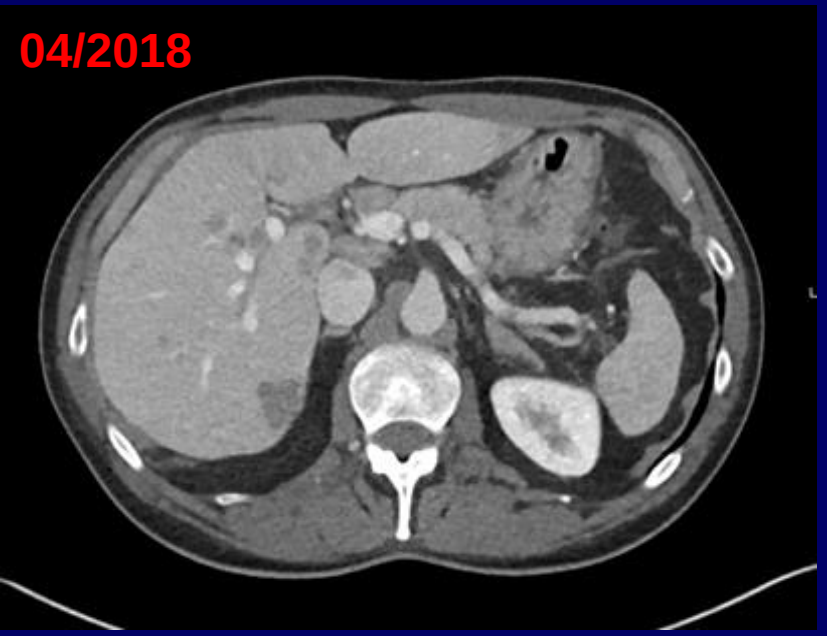
No. at Risk

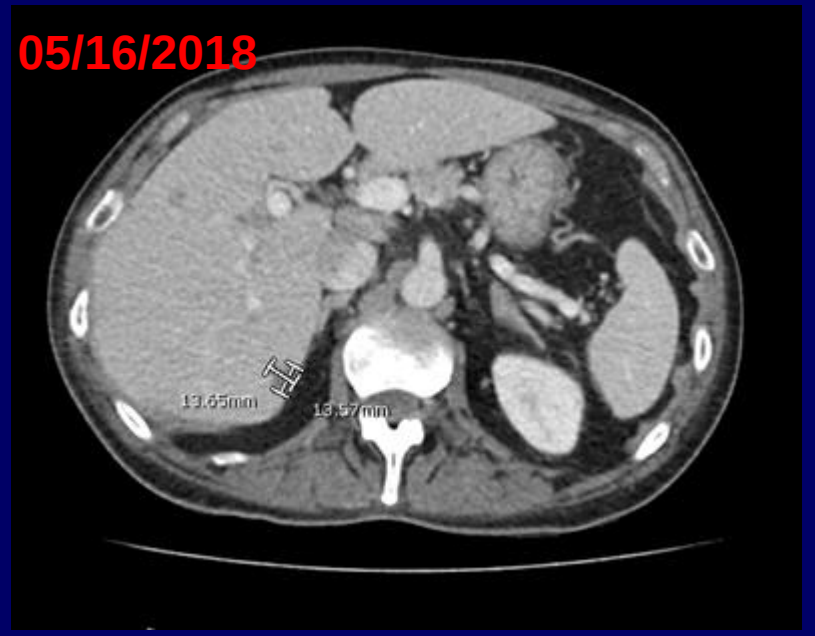
Nivolumab plus ipilimumab	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0
Nivolumab	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	117	107	100	68	20	2	0

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 high dose corticosteroids

B- Prescribe over the counter Imodium and metronidazole

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

D- Obtain a stool sample first and do not start any therapy until results of C-diff and stool culture are back.

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 mild asymptomatic skin rash chest wall and extremities.

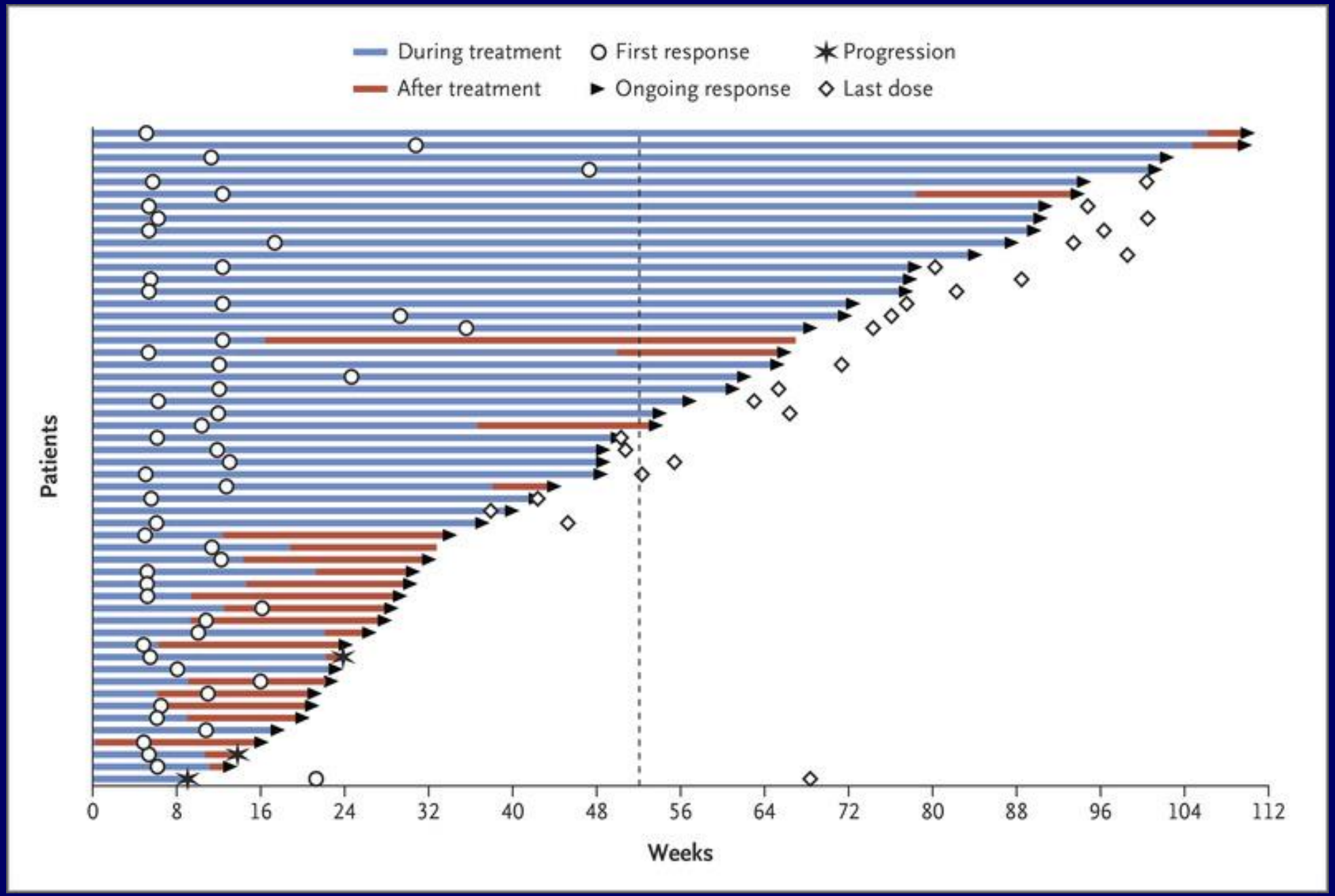
What would be your next step

A- Resume nivolumab

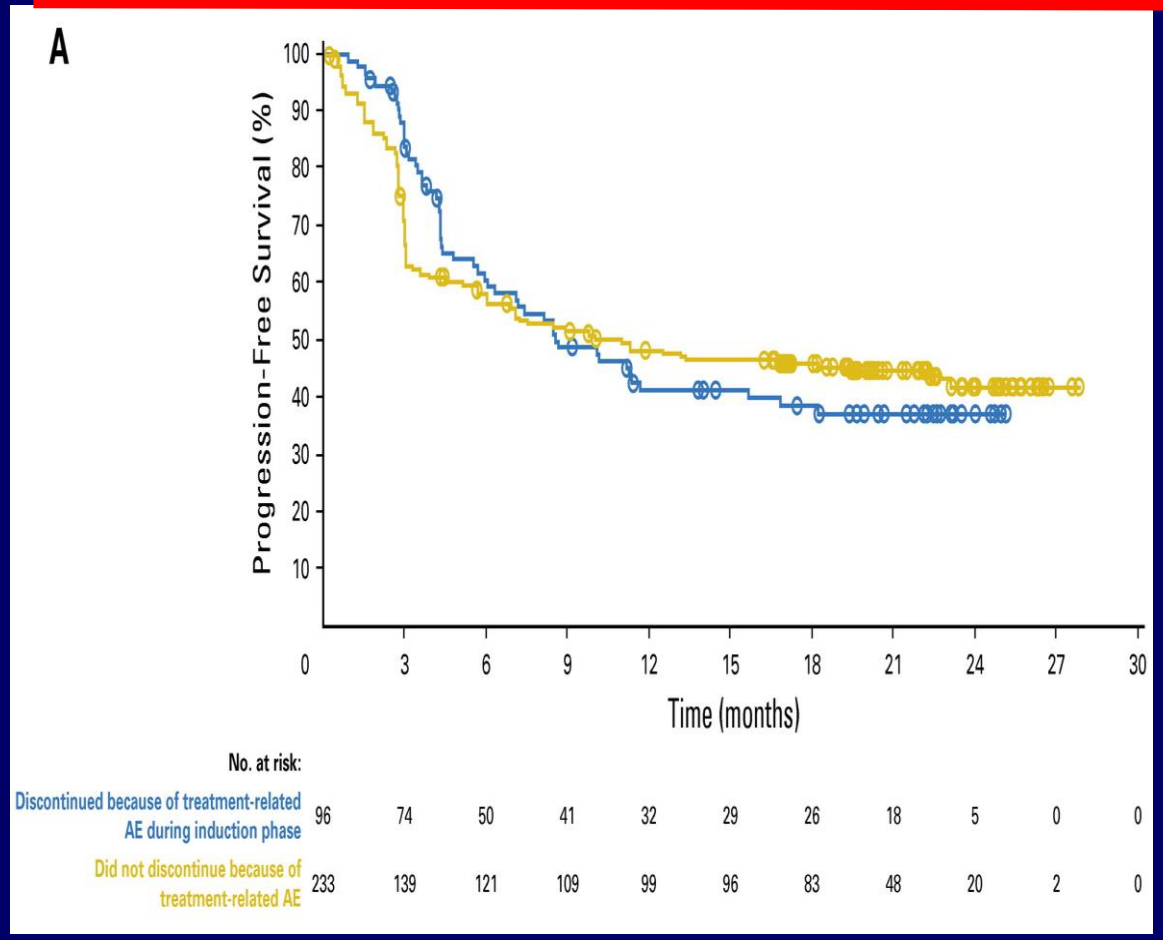
B- Stop nivolumab but initiate combination BRAFi/MEKi therapy.

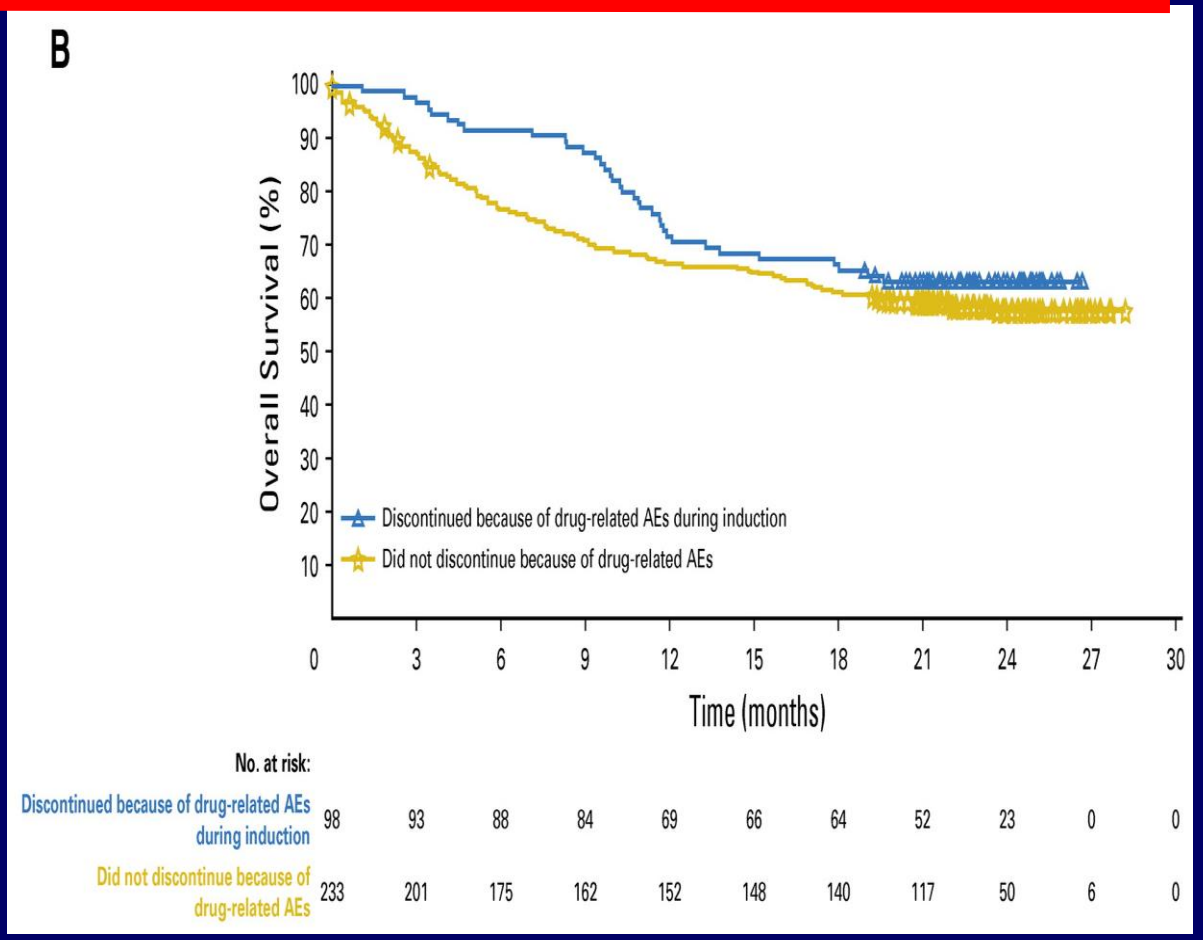
C- Obtain CT c/a/p and MRI brain; if no signs of progression continue surveillance only.

D- continue corticosteroids therapy until skin rash is resolved then resume nivolumab


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%)**

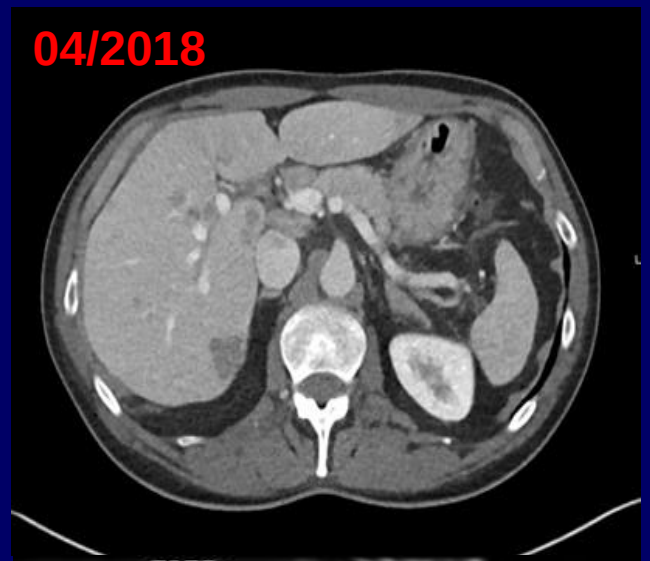


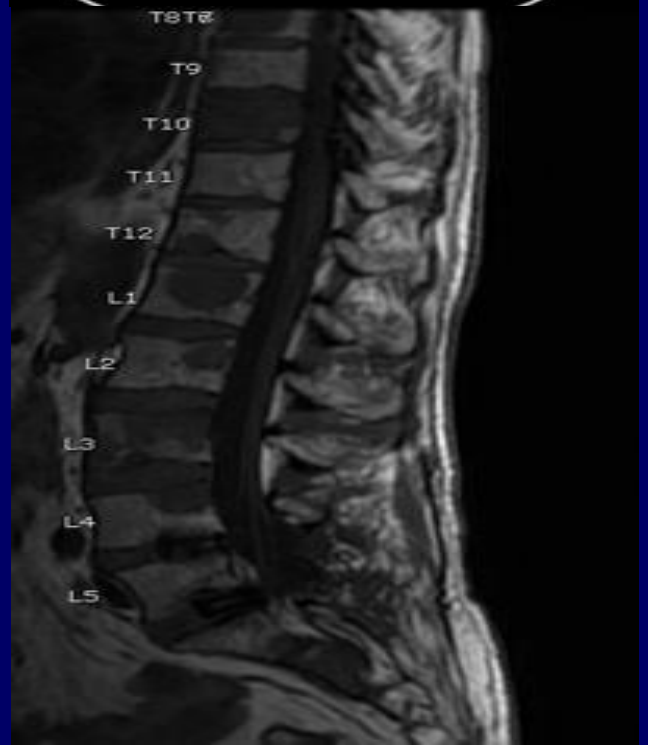


Schadendorf D, Wolchok J et.al. JCO 2017

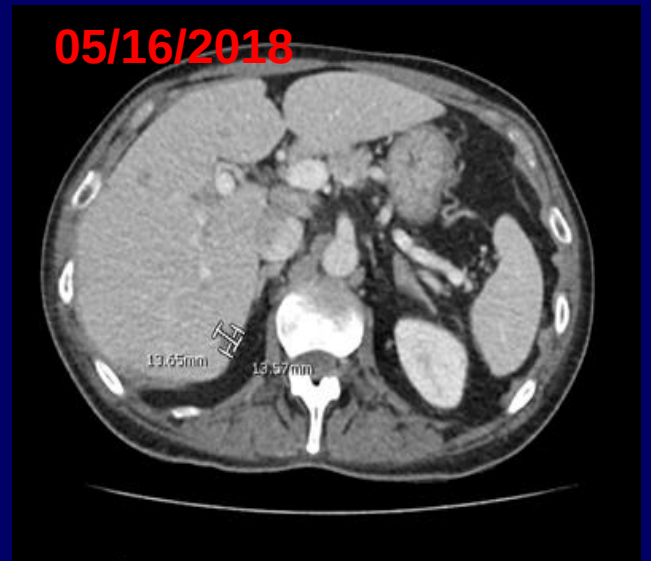
Case 1

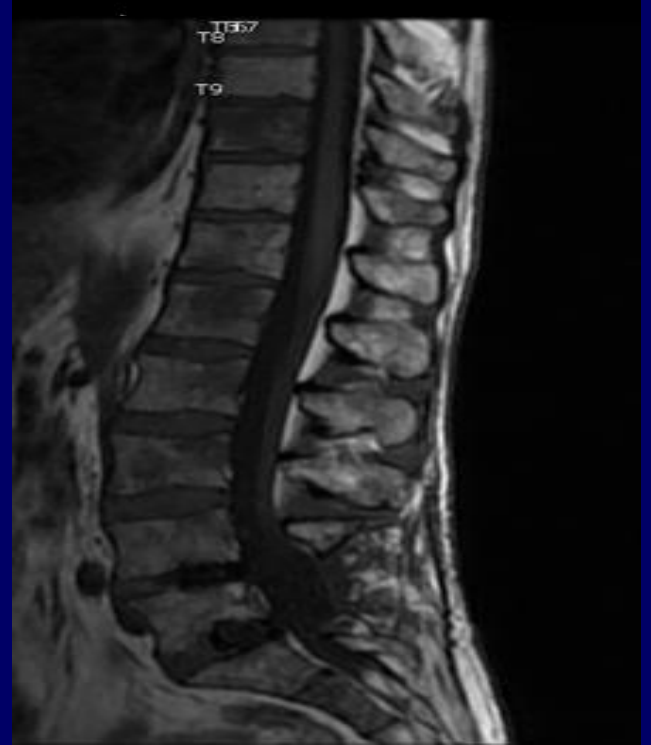
04/2018



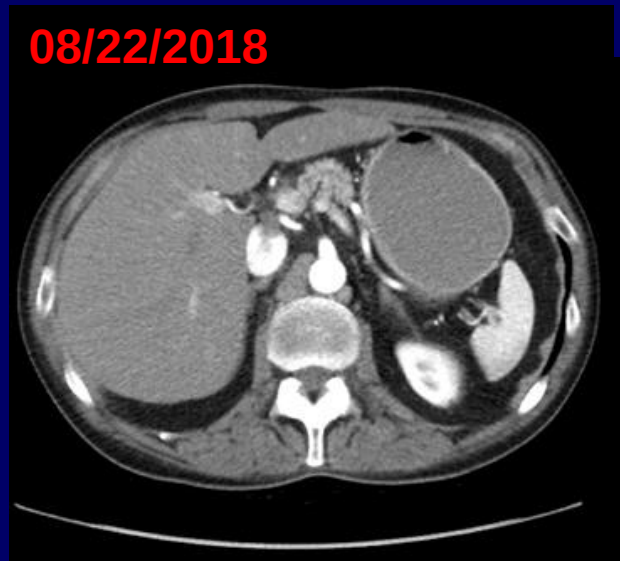


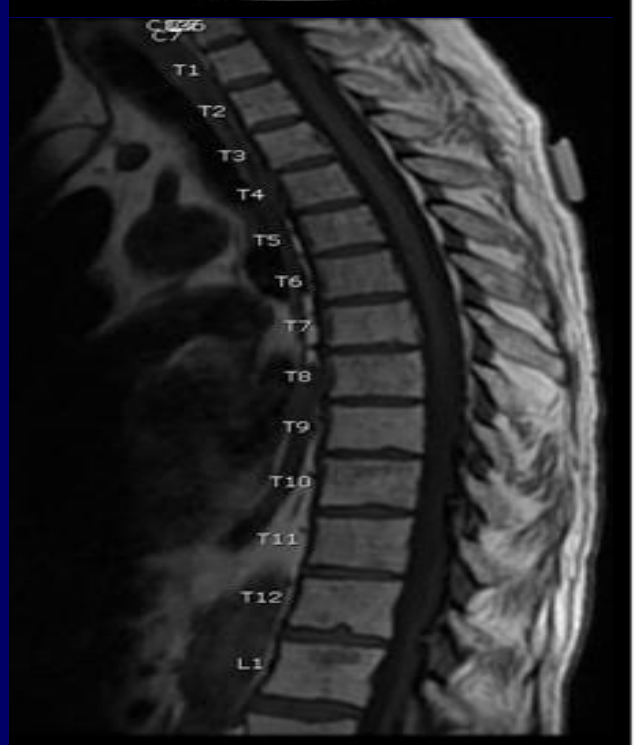
05/16/2018



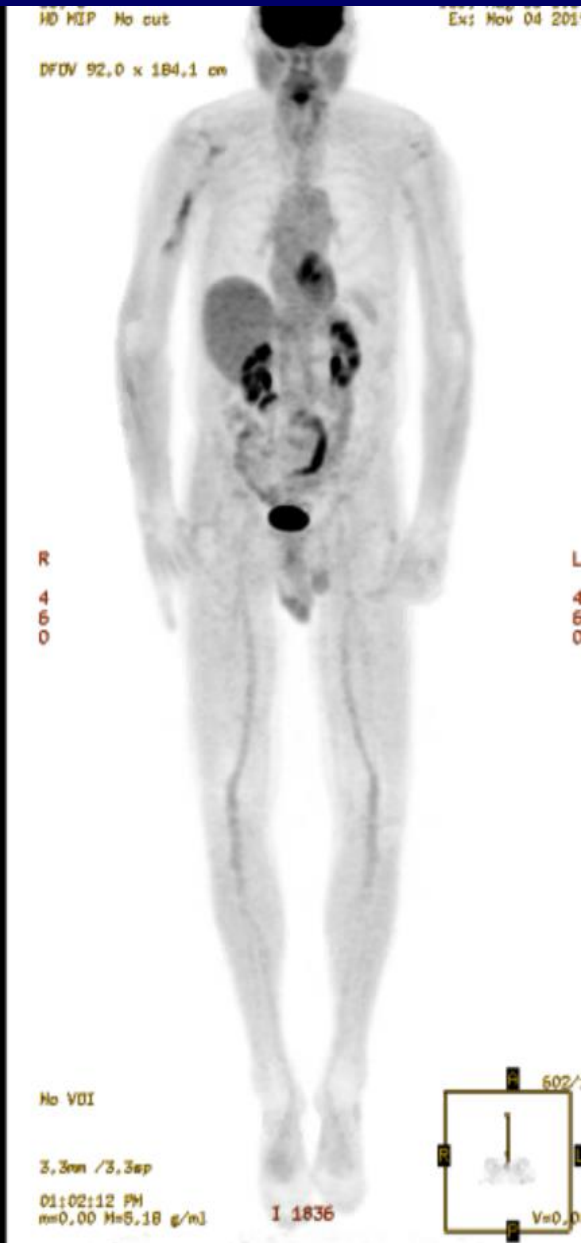


08/22/2018





11/04/2019



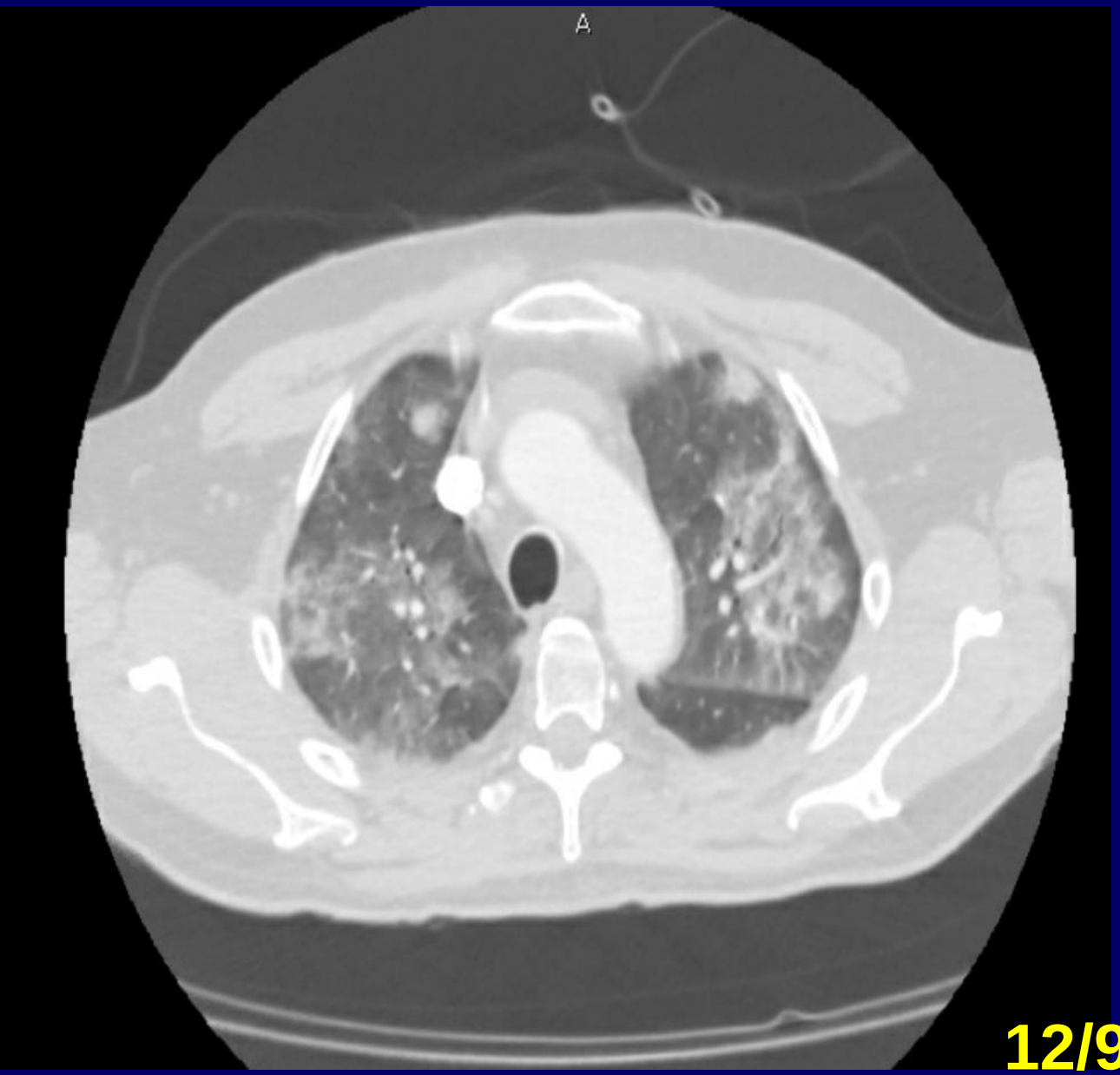
Case 2

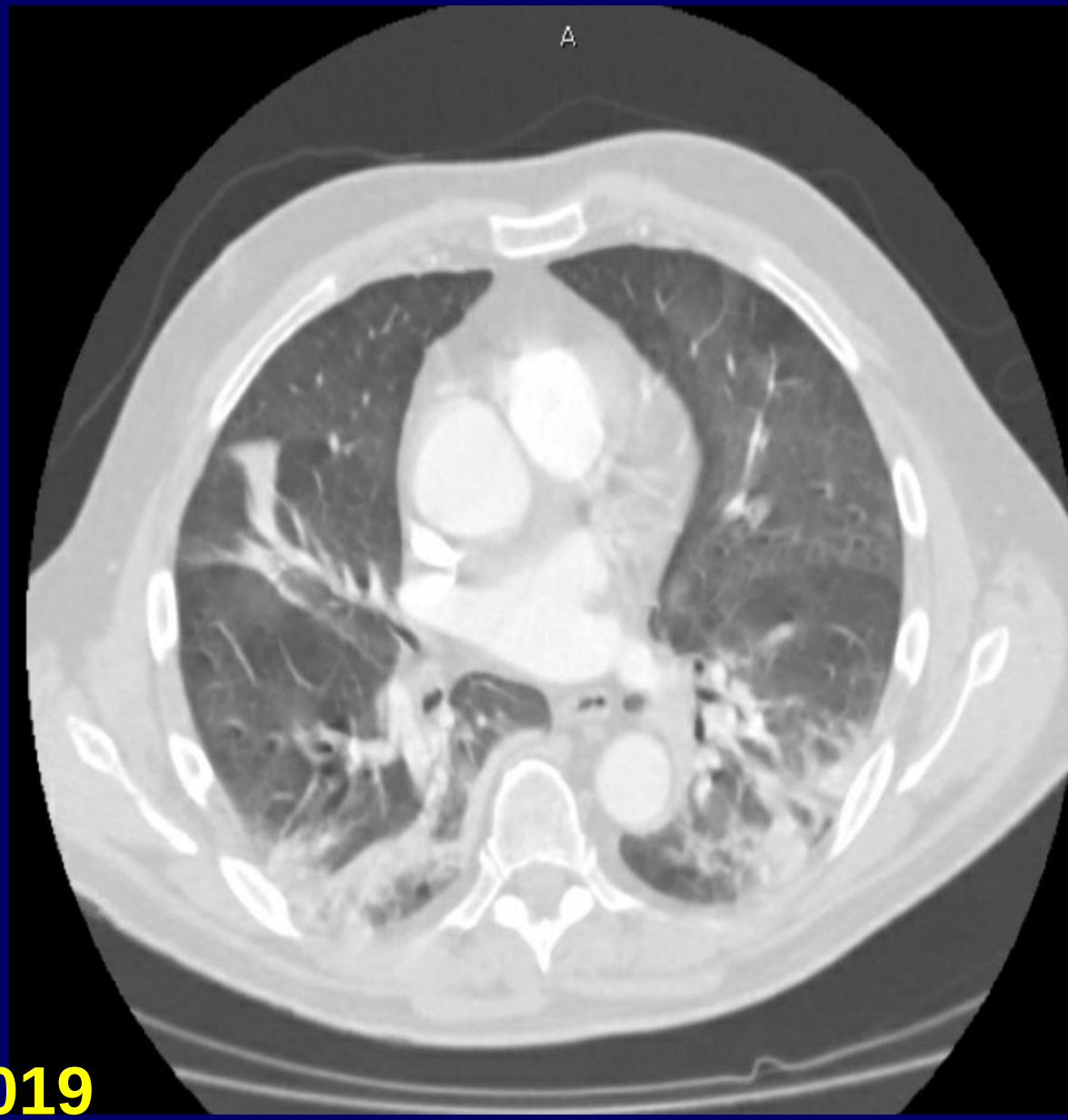
- Mr. D is a 70-year-old male diagnosed with left parietal scalp melanoma, at least 1.3 mm depth, no ulceration. He underwent WLE and SLNB on 10/28/2019; final pathology 7.1 mm depth and 1/3 LN involved. Pet CT showed no evidence of metastatic melanoma.

- He received cycle 1 of adjuvant pembrolizumab 11/22/2019.

- He was admitted to the hospital 12/9/2019 due to acute respiratory failure, and disseminated skin rash. No fever. No leukocytosis.

Case 2





12/9/2019

Case 1

The ER physician started the patient on O2, cefepime, Vancomycin, and DuoNeb. In addition to that what would be your immediate next step:

A- Consult pulmonary team for evaluation and a STAT bronchoscopy while patient still in ED.

B- Start high dose corticosteroids.

C- Skin biopsy of one of the blistering skin lesions.

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

A- Hypophysitis

B- Colitis

C- Pneumonitis

D- Skin rash

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

A phase of acute autoimmune thyroiditis with transient hyperthyroidism

Lab/POCT	02/20/2020 9:08 MST	01/30/2020 9:30 MST	01/14/2020 11:02 MST	01/02/2020 10:57 MST	12/06/2019 MST
ENDOCRINOLOGY					
T4 Free		1.03 ng/mL	1.82 ng/mL H	2.36 ng/mL H	1.72 ng/mL
TSH	1.82 uIU/mL	0.33 uIU/mL L	0.01 uIU/mL L	0.01 uIU/mL L	0.29 uIU/mL
ACTH			14 pg/mL *		
Cortisol Random			12.4 ug/dL		

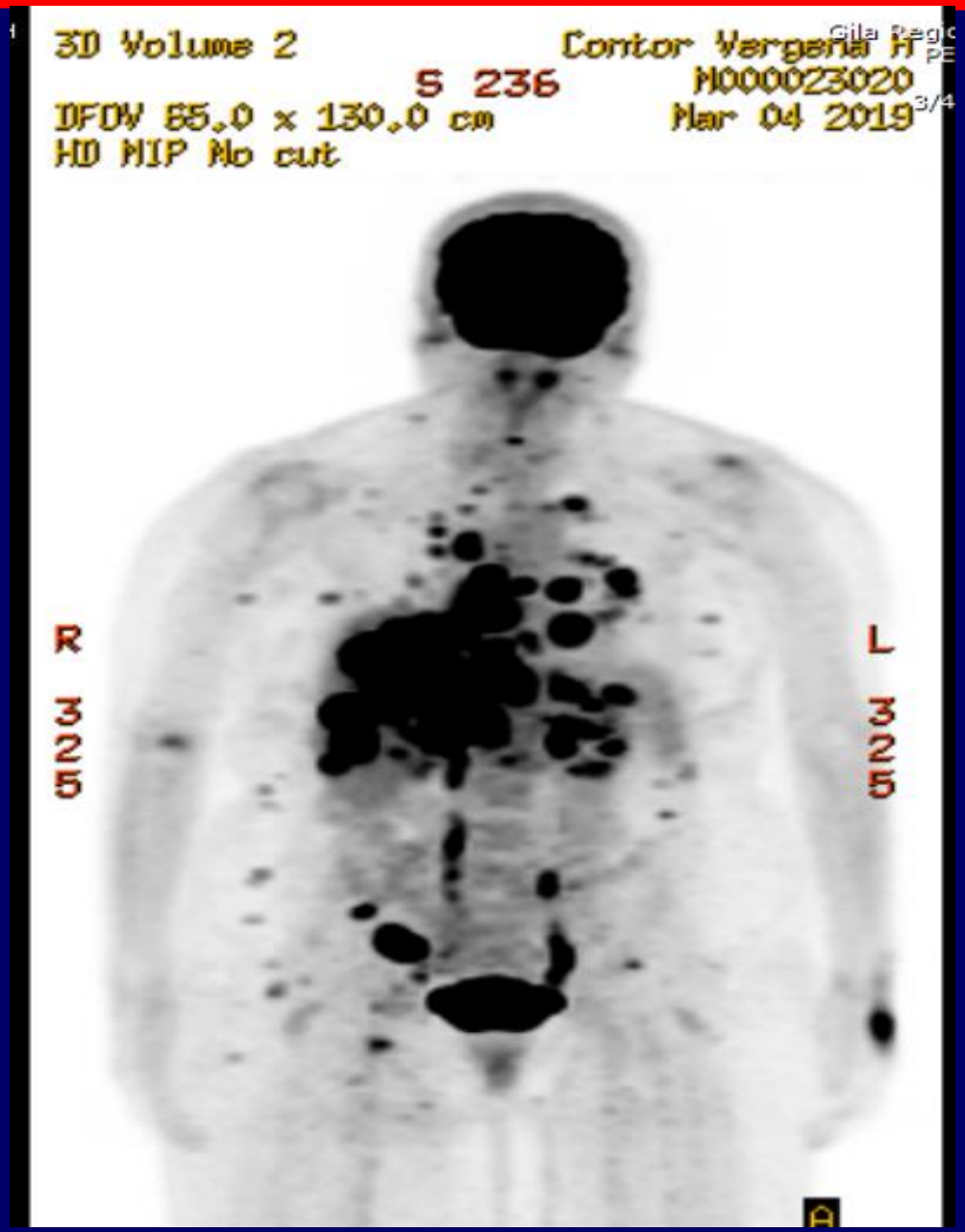
Case 3

- Mrs. C is a 55 year old female with history of stage III BRAF mutated melanoma status post WLE and SLNB, then started on targeted therapy with combination of BRAF/MEK inhibitor (Dabrafenib and Trametinib). The targeted therapy was stopped due to severe grade IV fever. Patient lost to follow up until 03/2019 when she presented with scattered skin nodules, fatigue, and 30 lbs weight loss the last 2 months. PET CT confirmed widespread metastatic disease.

- She received 3 cycles of ipilimumab and nivolumab; CT a/p 5/16/2019 revealed progression of disease. Patient was enrolled in hospice.

- She presented for second opinion, poor performance status, and her BP in clinic was 80/40.

Case


3D Volume 2
Contor Vergenia Hf
S 236
M0000023020
DFOV 65.0 x 130.0 cm
Mar 04 2019
HD MIP No cut
R
L
325
325

Case

What would you recommend now:

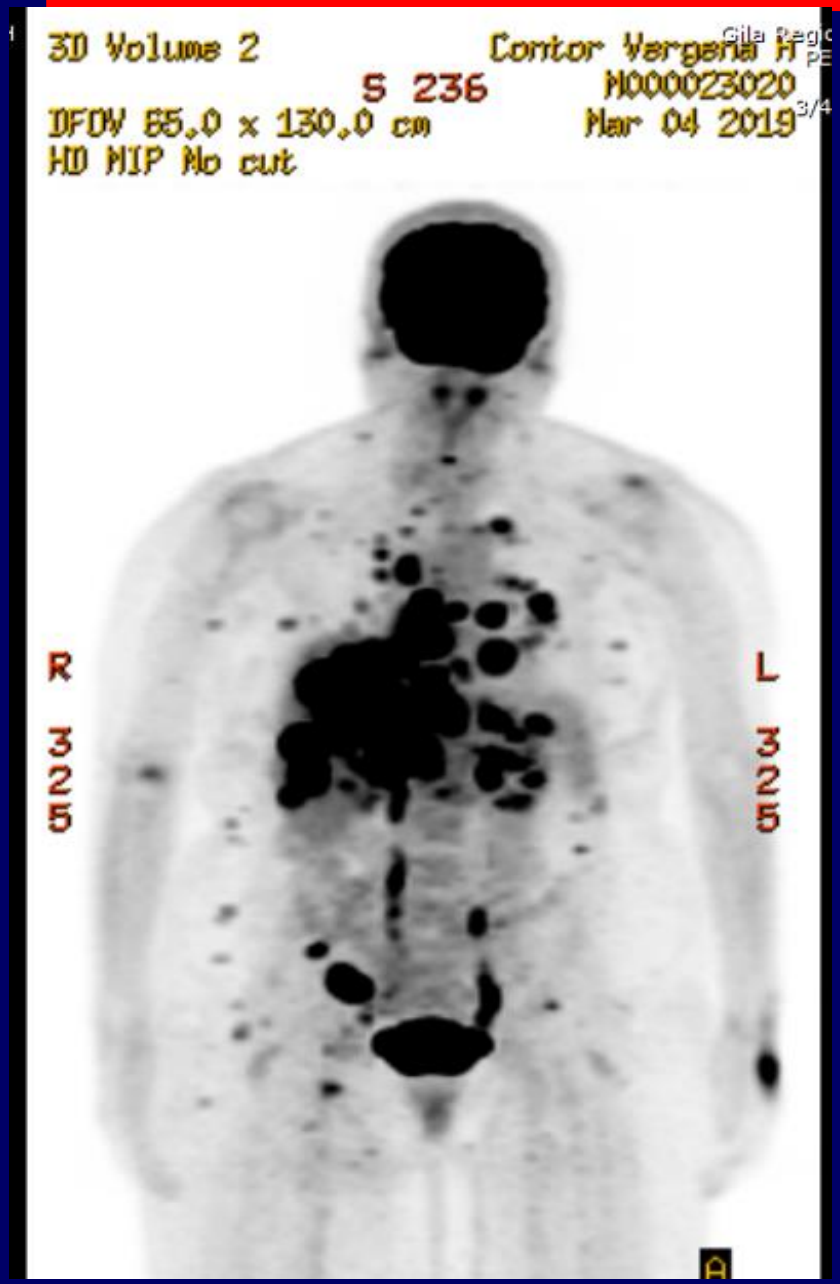
A- Keep patient in hospice care.

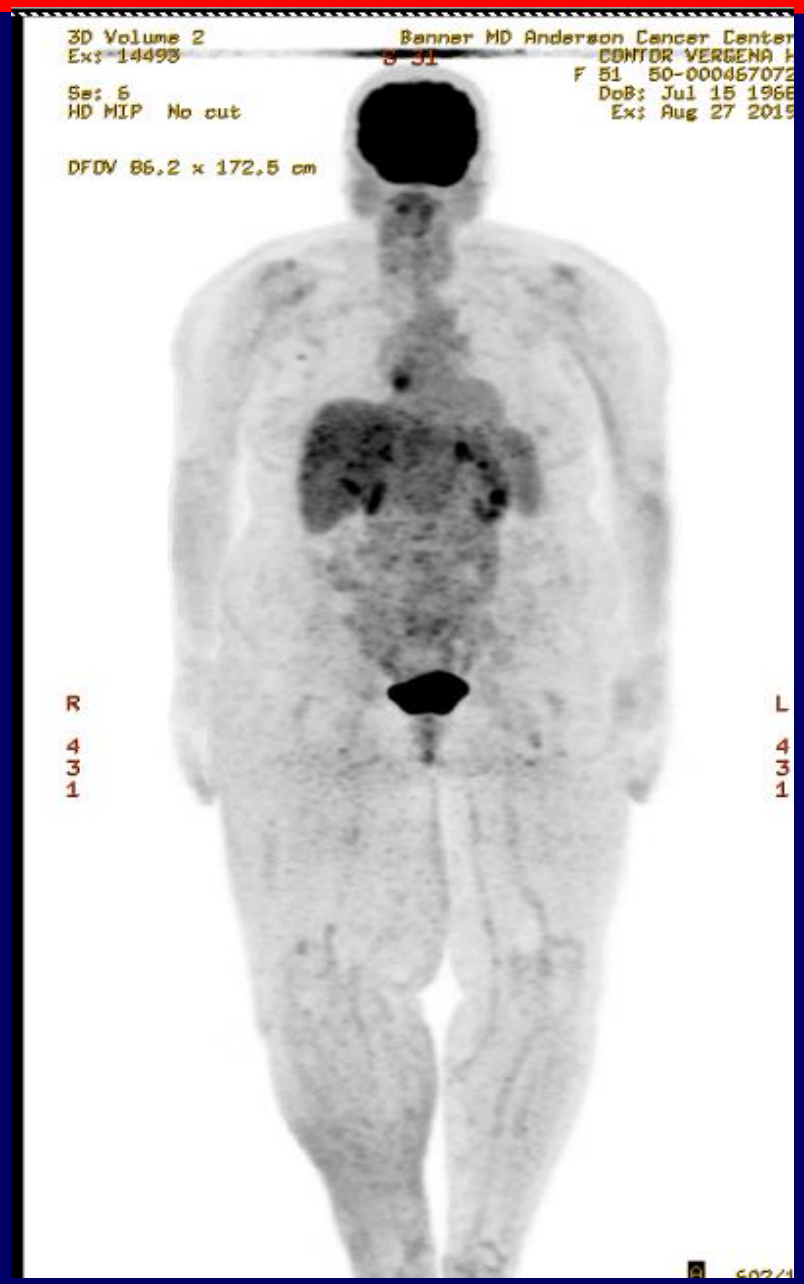
B-Admit to hospital for IV hydration.

C-Start Encorafenib and Binimetinib (another FDA approved BRAF inhibitor plus MEK inhibitor).

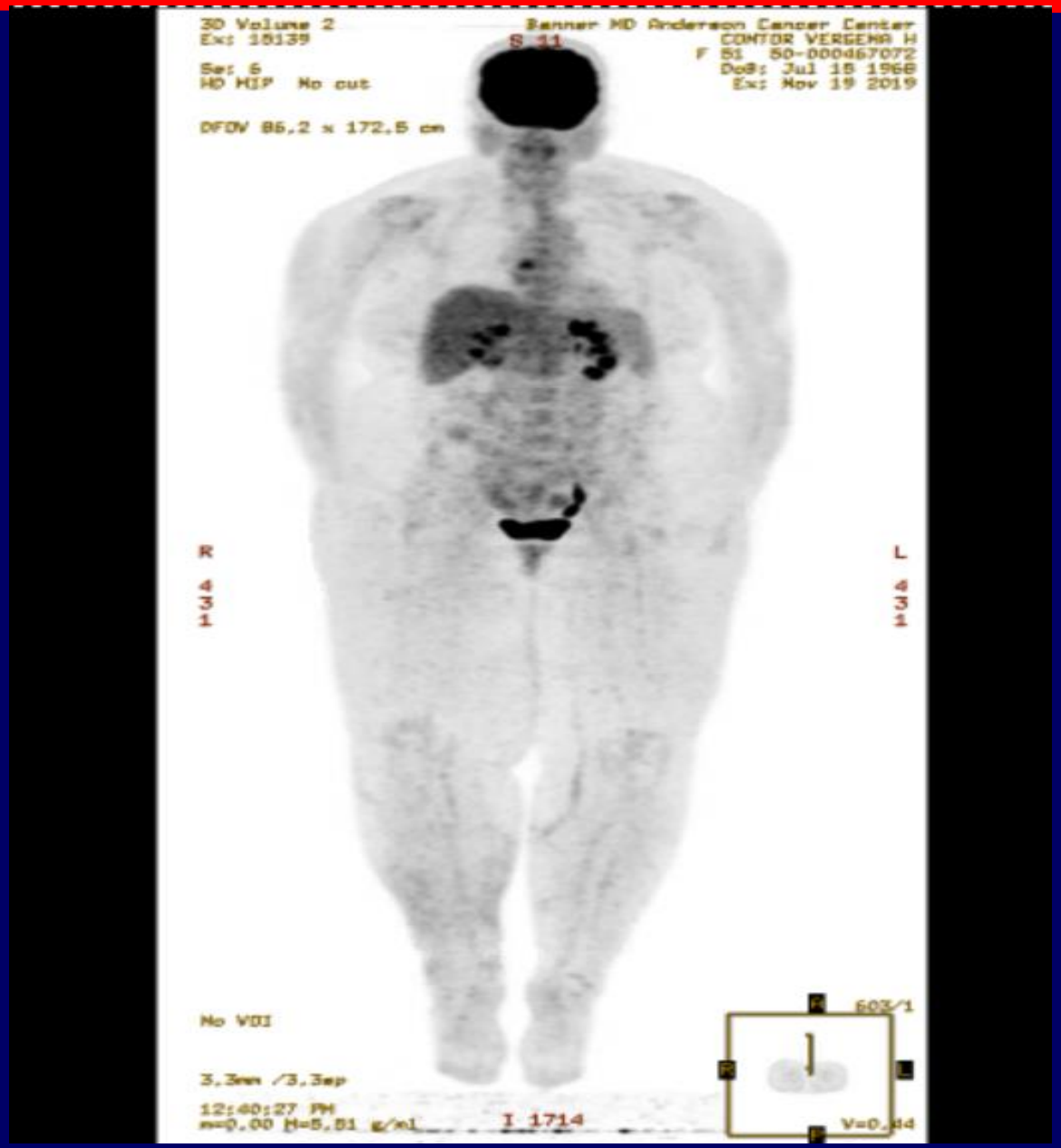
D- Enroll in clinical trial.

Follow up visit 08/27/2019

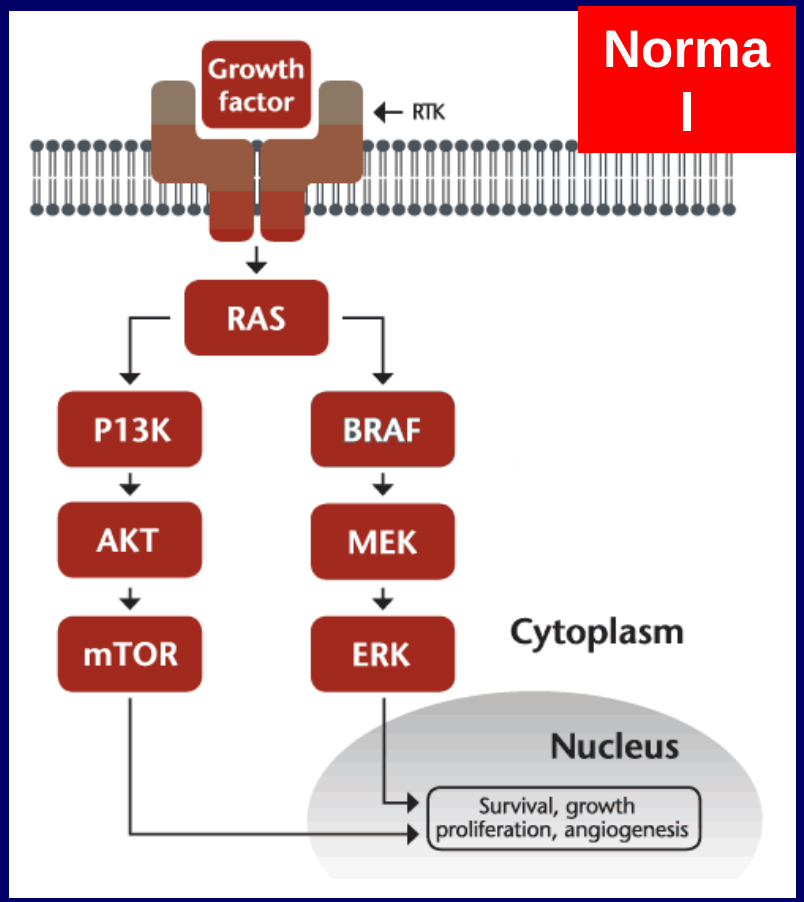


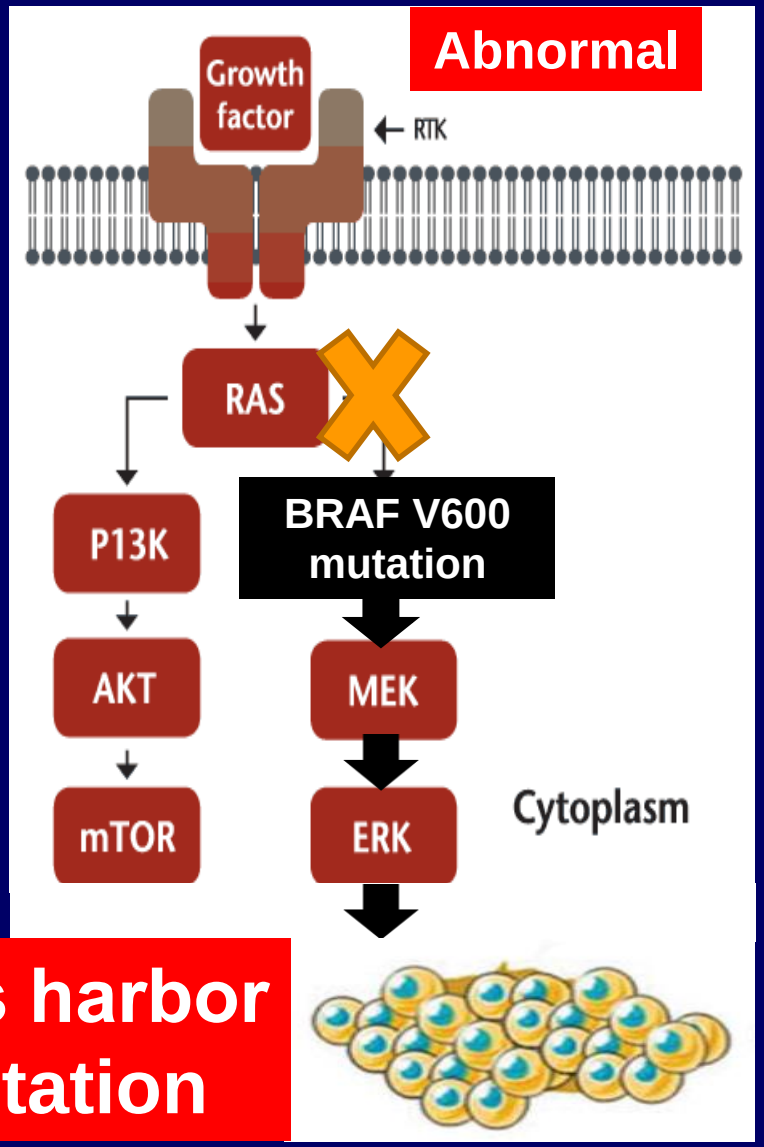


Follow up visit 11/19/2019



MAPK PATHWAY AND BRAF MUTATION

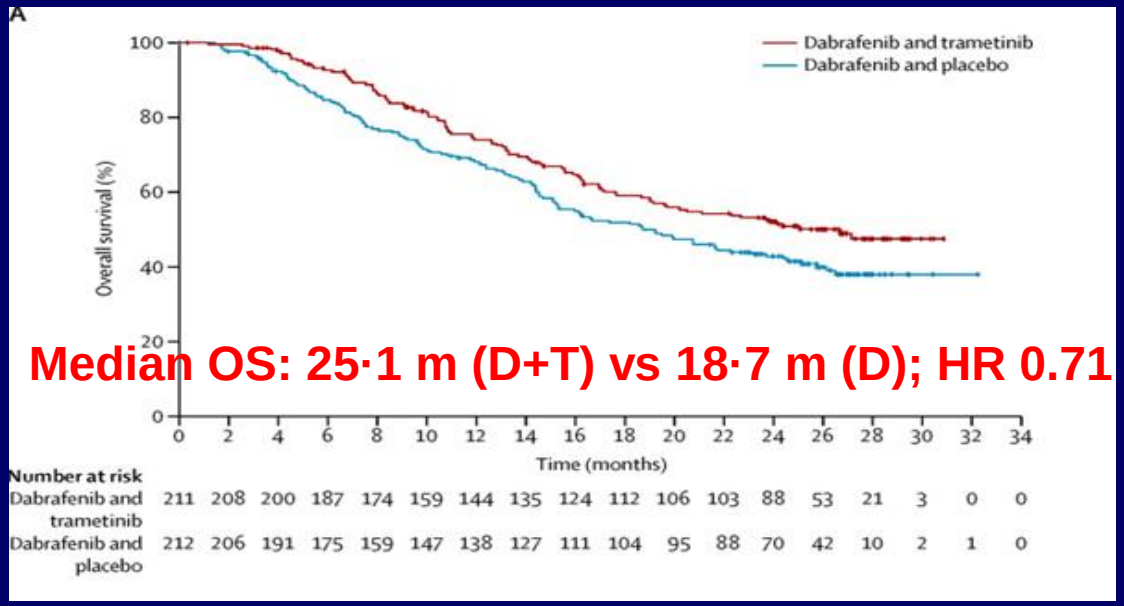




≈ 50% of melanomas harbor the BRAF V600 mutation

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

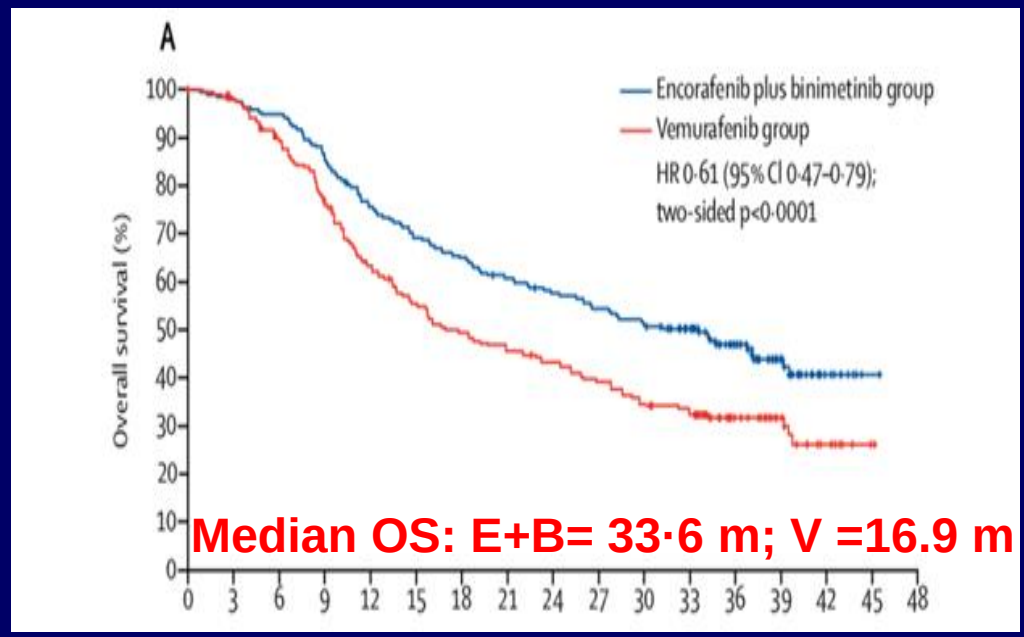
Dabrafenib+trametinib



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

Long GV et.al. Lancet. Aug 2015.

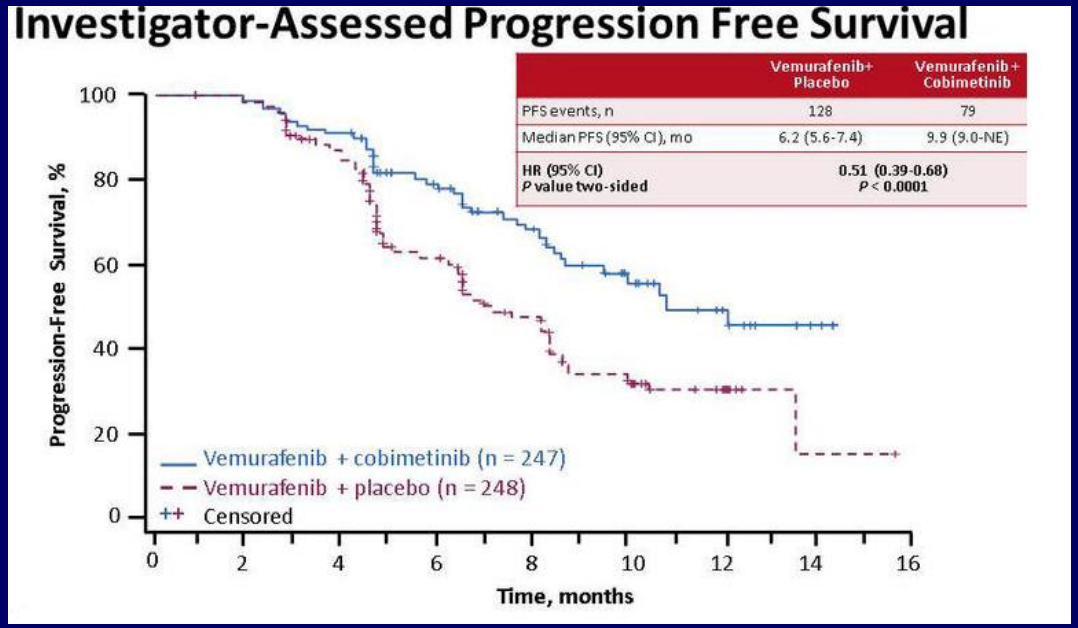
Encorafenib+Binimetinib



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

ADVERSE EVENTS

	Combi-D	Combi-V	Columbus	Co-BRIM
Toxicity % of all/>=G3	**DT**	**DT**	**EB**	**VC**
Pyrexia	**52/7**	**53/4**	18/4	26/2
Photosensitivity		4/0	5/1	**28/2**
Nausea	20/0	36/1	**41/2**	**40/1**
Elevated ALT	10/2		**13/6**	**23/11**

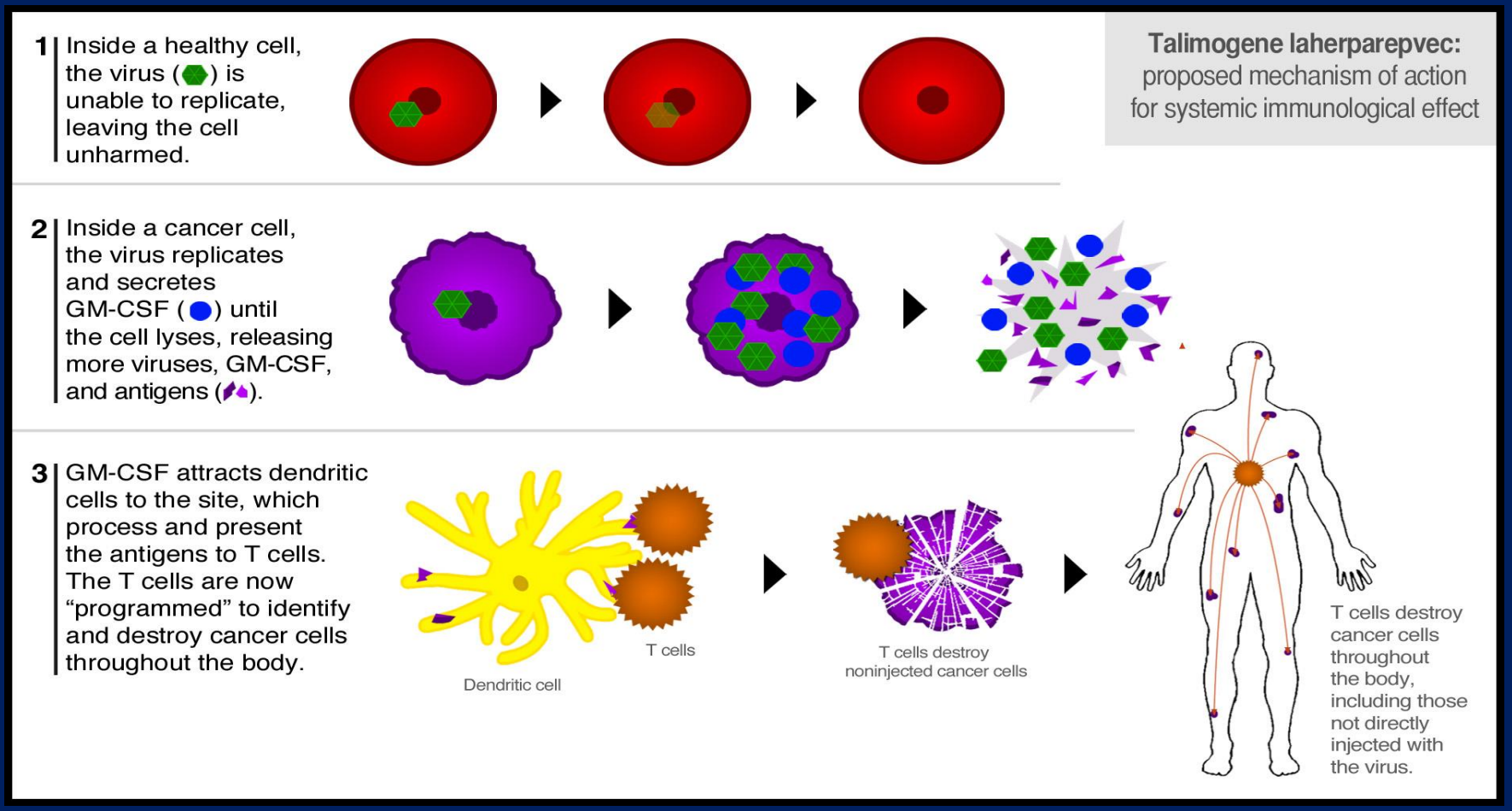
Dummeret al. Lancet Oncol May 2018

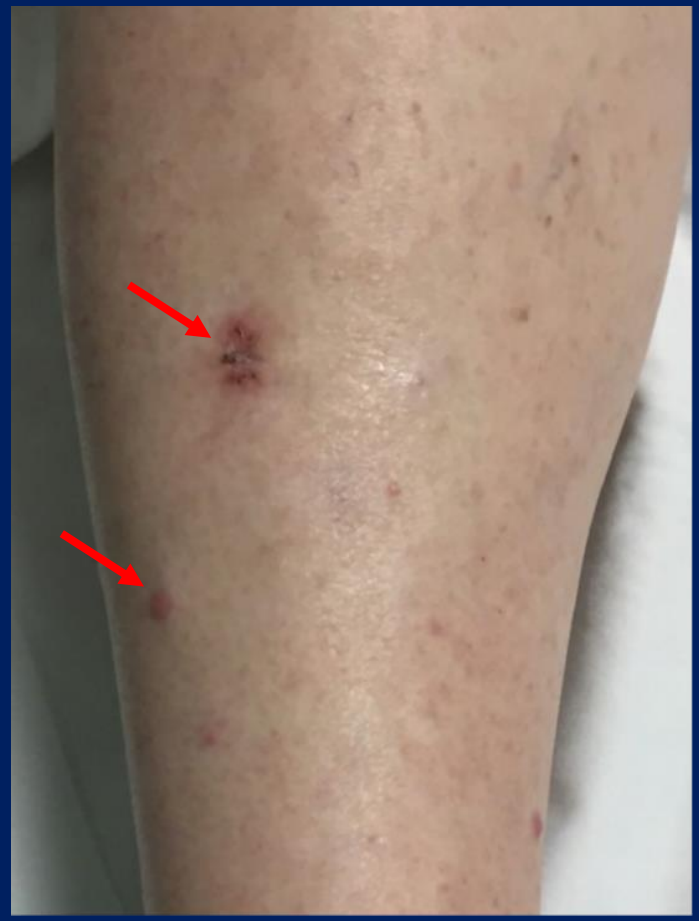
Long GV, Stroyakovskiy D, et.al. Lancet. 2015 Aug 1;386(9992):444-51.

Larkin et al. NEJM 201

Robert C, Karaszewska B, et.al. N Engl J Med. 2015 Jan 1;372(1):30-9.

Oncoloytic Immunotherapy





Metastatic Melanoma Treatment Landscape 2019