Update on Management of Melanoma

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Case presentation

- Mr. K is a 63-year-old male presented with a rapidly growing “berry-like” skin lesion on 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

QUIZ

- Which of these statements is most accurate about familial melanoma?

B- Correct:

- **Around 10% of all people with melanoma have a family history.**
- **Most melanoma is not inherited but is instead sporadic.**
- **Two genes have been primarily linked to familial melanoma: CDKN2A and CDK4. A mutation in these genes gives a person an increased risk of melanoma.**

QUIZ

- Which of these statements best reflects opinion about clinically diagnosing malignant melanoma:

A- There are no typical characteristics of melanoma

B- A combination of shape, pigmentation, and regularity of shape and size can be used to help recognize melanoma clinically

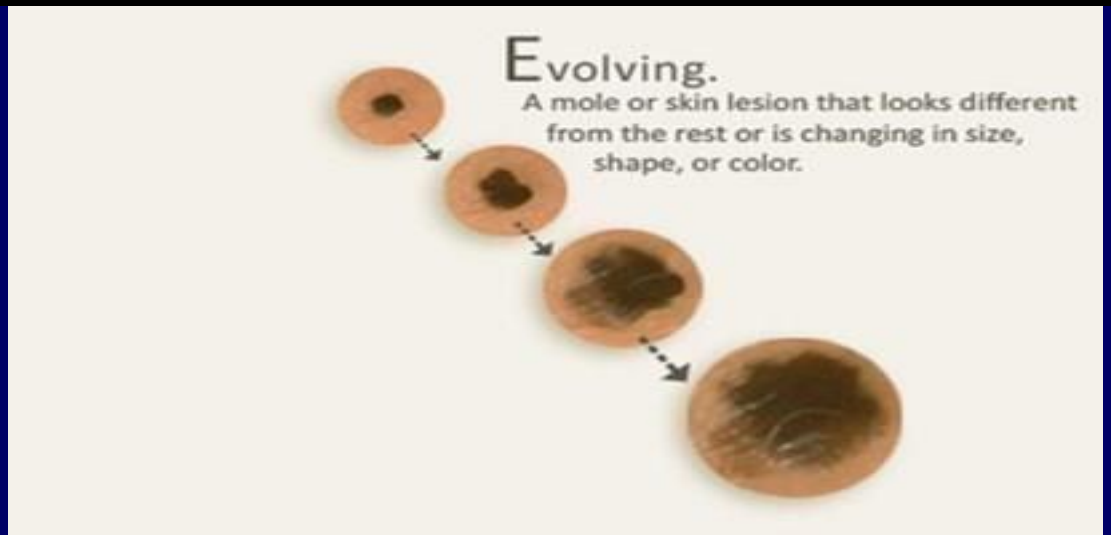
C- Melanoma are always more pigmented than the surrounding skin

The ABCDE

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

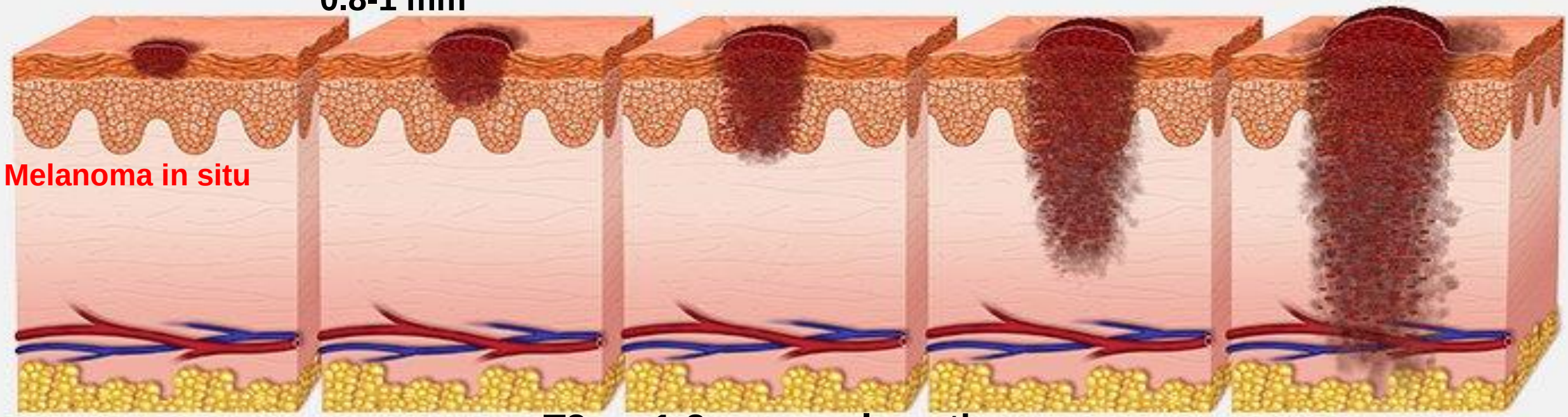


Amelanotic melanoma

Breslow depth & T stage

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

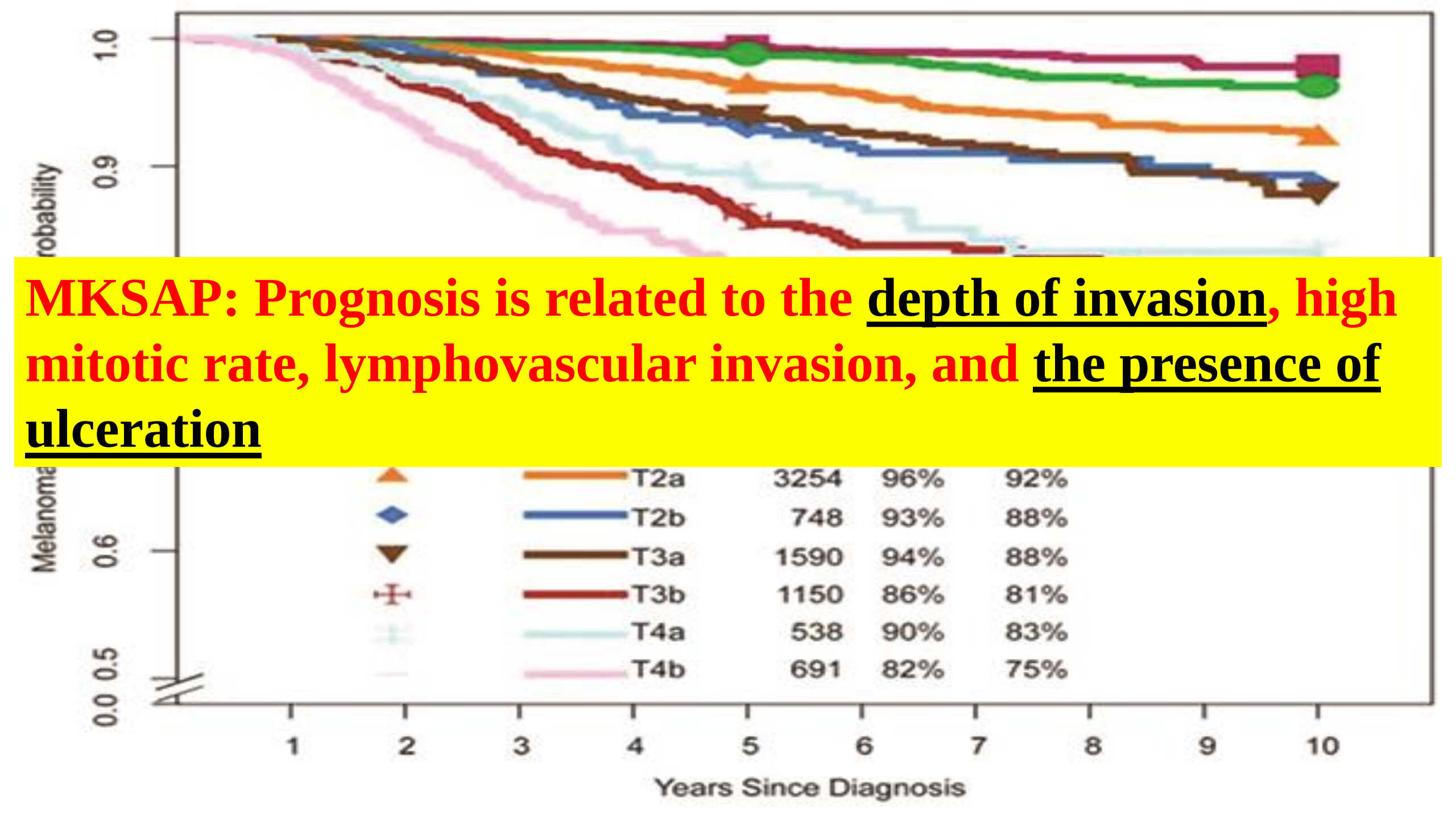
T3a: >2-4mm no ulceration
T3b: >2-4mm with ulceration



Melanoma in situ

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

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



MKSAP: Prognosis is related to the depth of invasion, high mitotic rate, lymphovascular invasion, and the presence of ulceration

Case presentation....

- An excisional biopsy was done. Pathology confirmed malignant melanoma, Breslow depth 3 mm and a close surgical margin of 0.5 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 as the lesion was excised

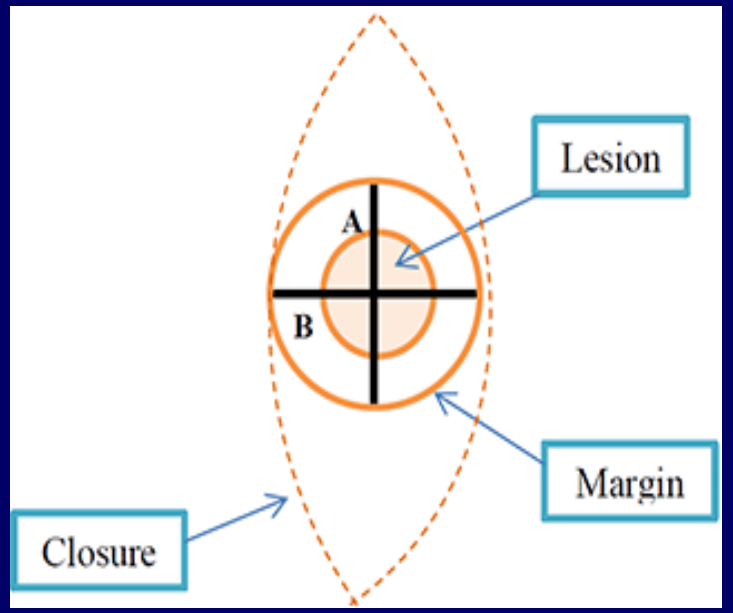
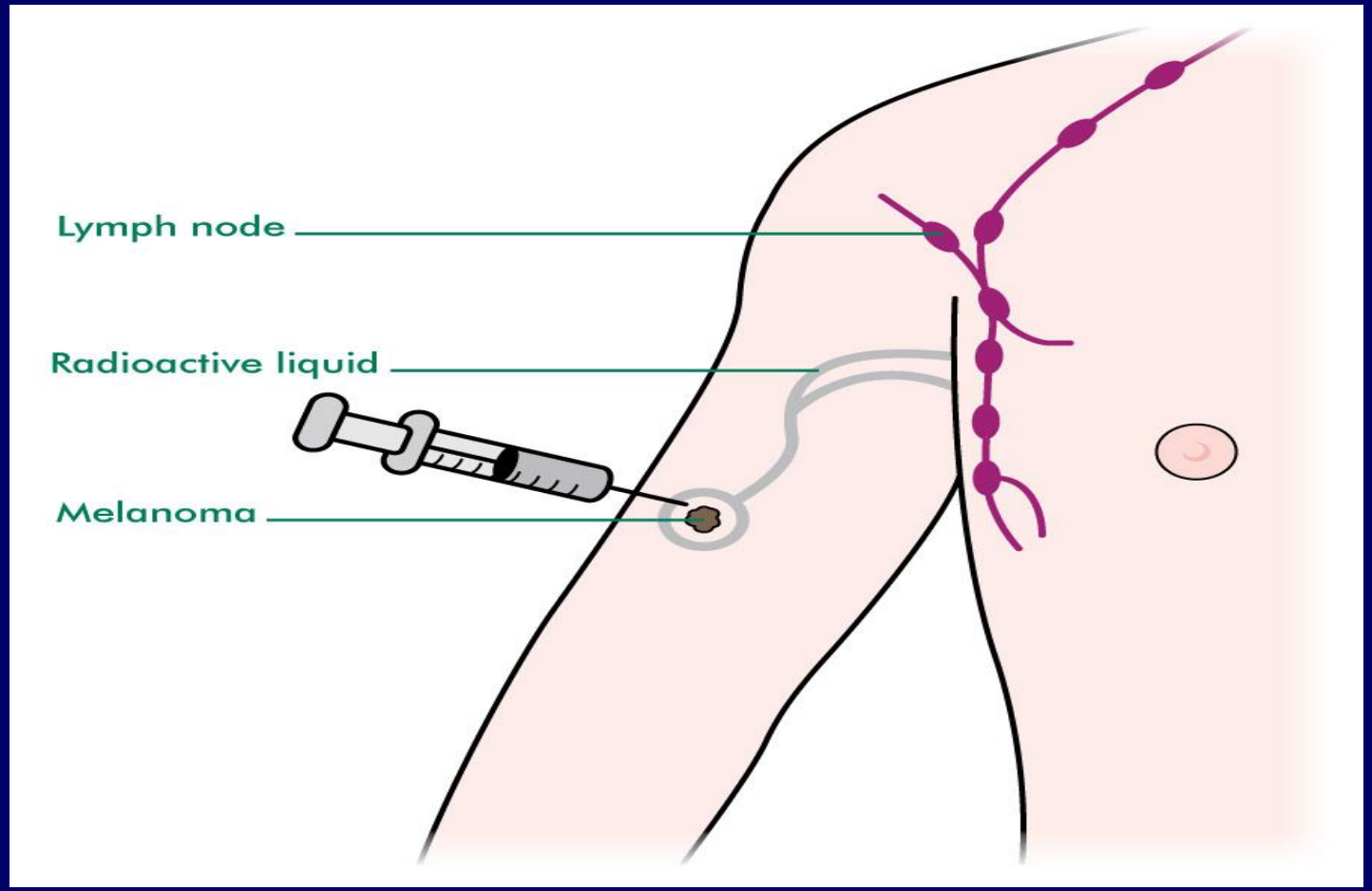


Table 4: NCCN-Recommended Surgical Margins for Melanoma

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.



SLNB should be done when depth of melanoma >=0.8 mm

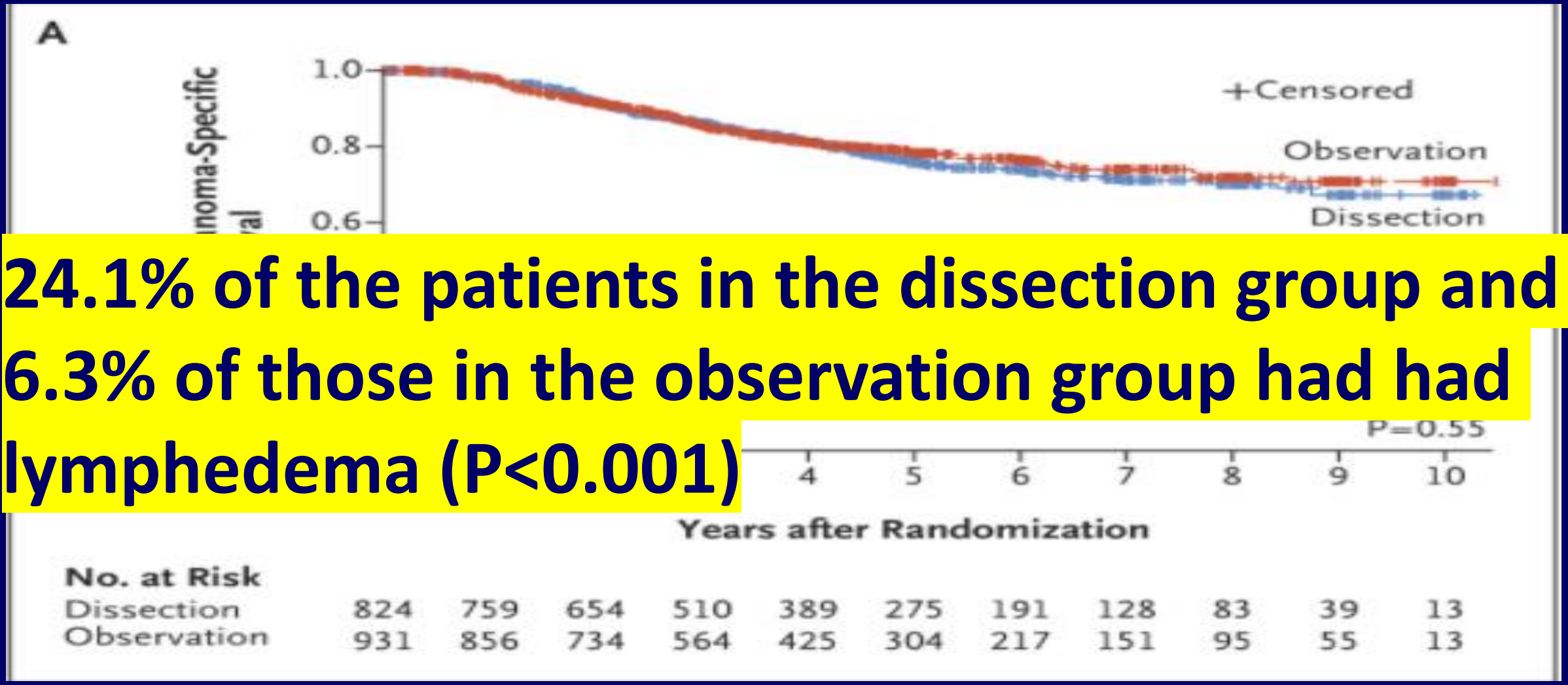
Case presentation....

C is correct.

MKSAP: Even if sentinel lymph node biopsy is positive, a completion lymph node dissection is no longer routinely performed, as there is no improvement in survival. Patients with positive SLNB (stage III) may be followed by clinical examination and serial ultrasounds of the nodal basin involved to detect nodal recurrences. These patients are also eligible for adjuvant systemic treatment.

Multicenter Selective Lymphadenectomy Trial II (MSLT-II)

1939 patients with SLNB + melanoma underwent randomization



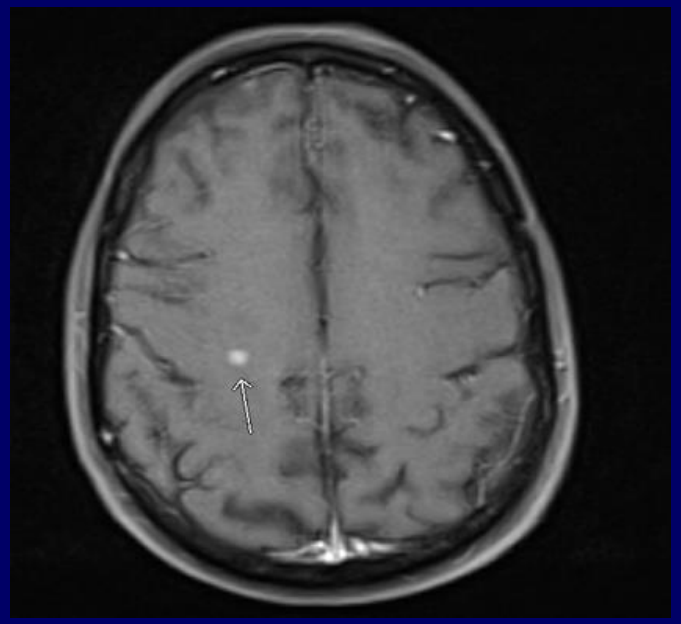
24.1% of the patients in the dissection group and 6.3% of those in the observation group had had lymphedema (P<0.001)

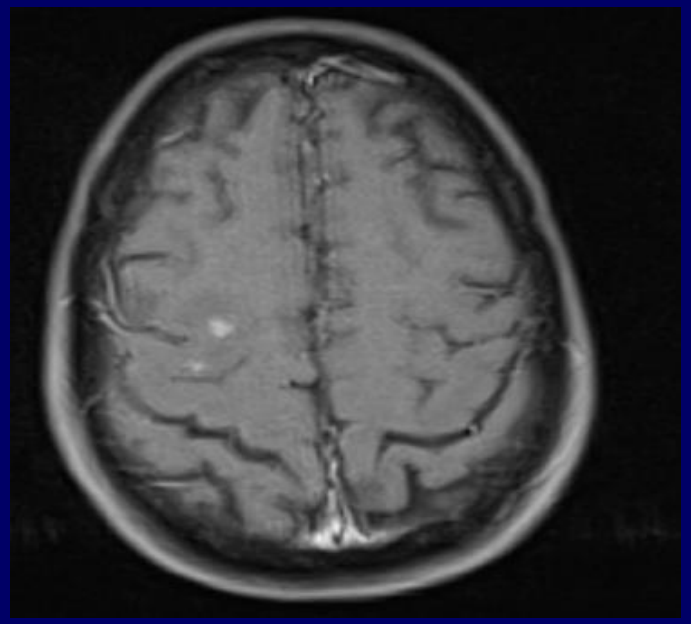
Faries M et.al. N Engl J Med 2017; 376:2211-2222

Case presentation....

- 2 years later our patient 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 revealed metastatic disease.
- US-guided liver biopsy and pathology confirmed metastatic melanoma.

Images 04/2018





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

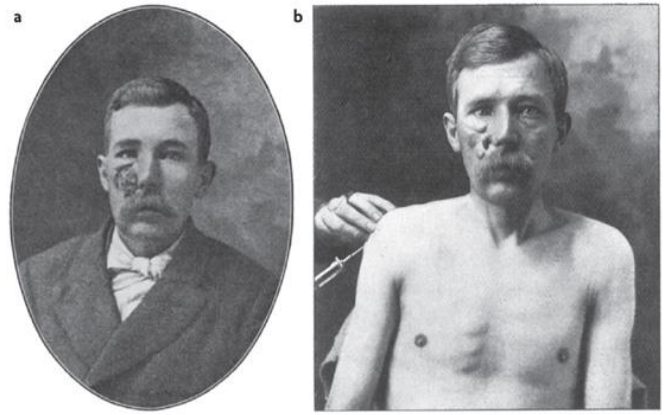
ERYSIPELAS GERMS AS CURE FOR CANCER

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

MANY CASES CURED HERE

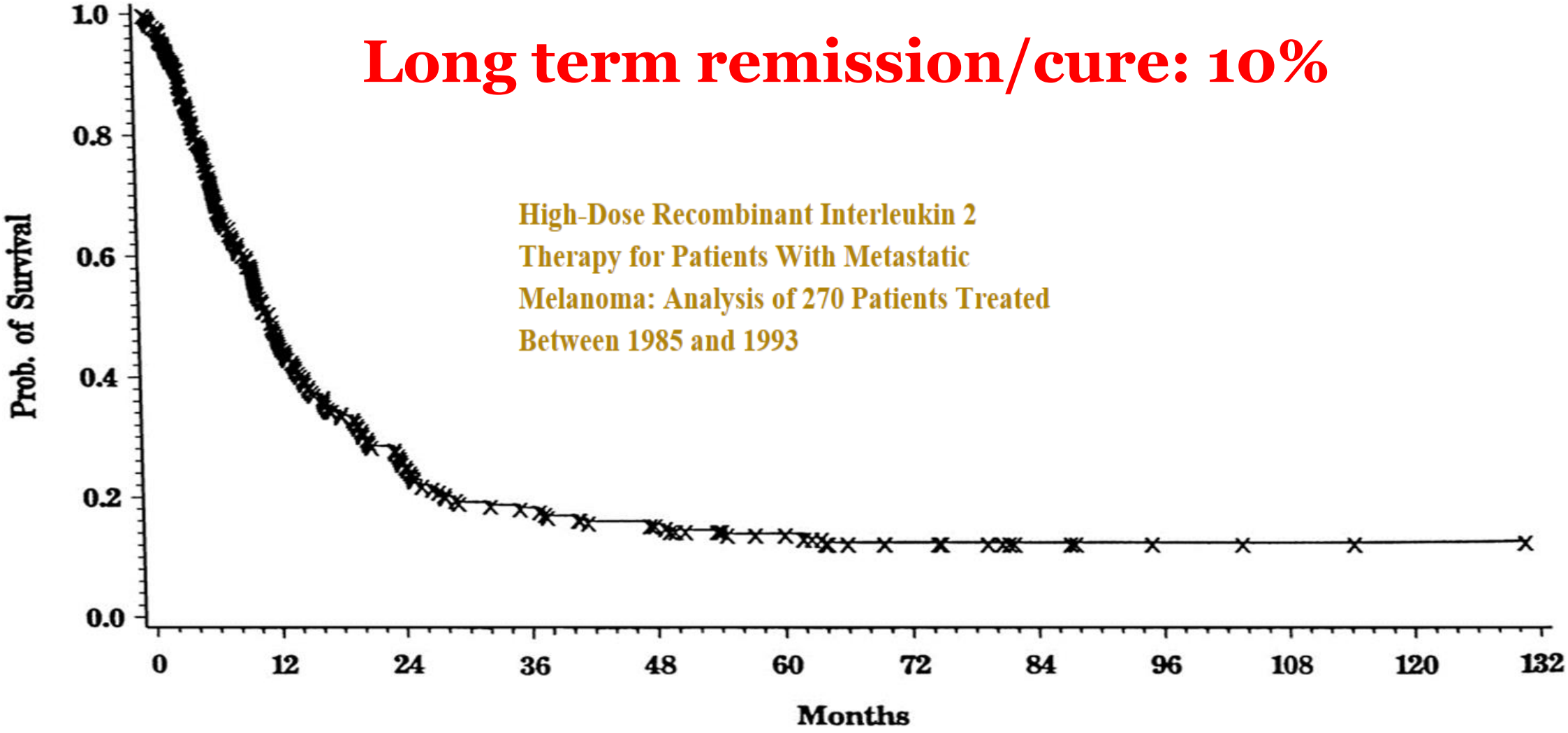
Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

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-



High Dose IL2

Long term remission/cure: 10%



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

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Quiz

Which of the following agent is a CTLA4 inhibitor:

A- Pembrolizumab

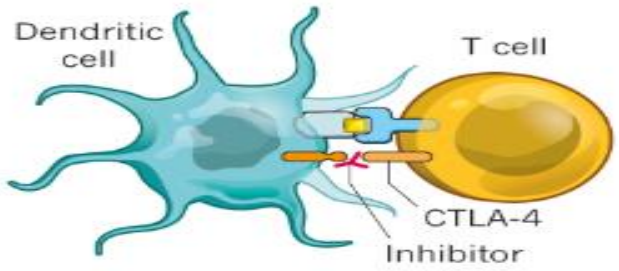
B- Nivolumab

C- Ipilimumab

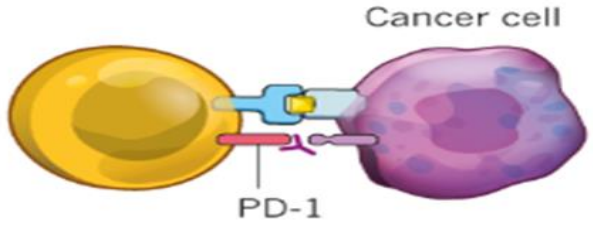
D- Relatlimab

Checkpoint Inhibitor

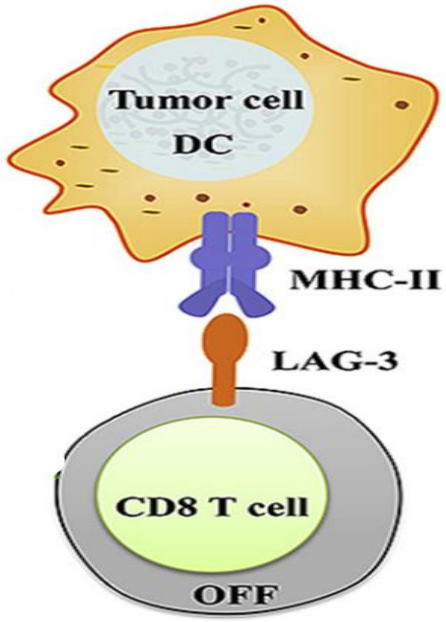
CTLA4



PD1



LAG-3



TLA4 inhibitor.

mab: PD1 inhibitors.

itor.

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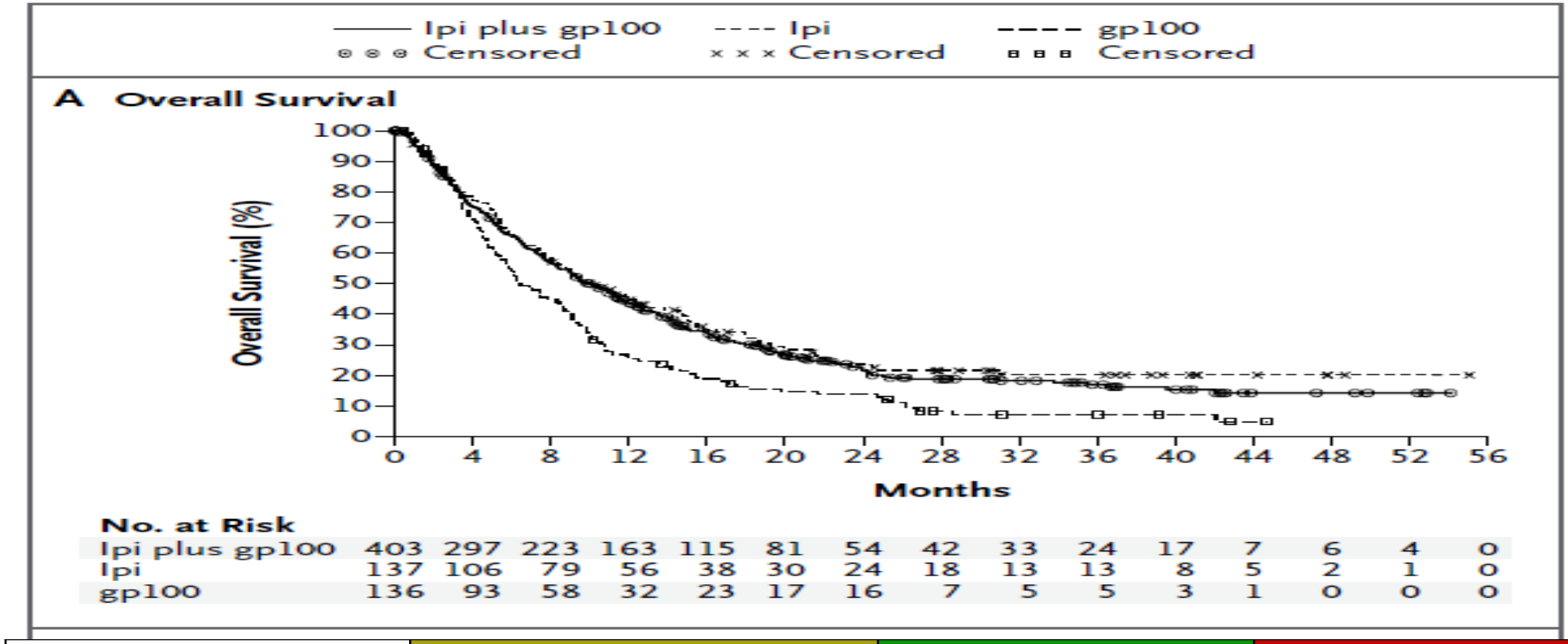
Ipilimumab Improved Survival in Patients with Metastatic Melanoma



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. N Engl J Med. 2010 Aug 19;363(8):711-23

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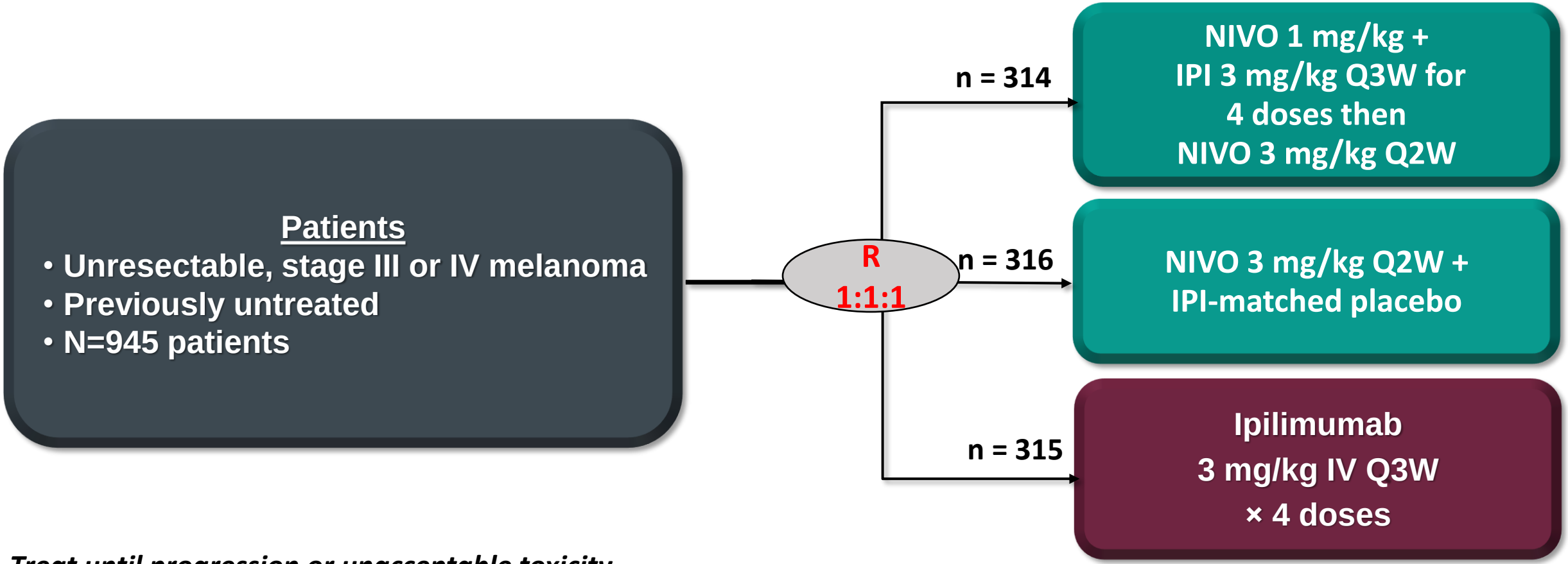
CheckMate-067

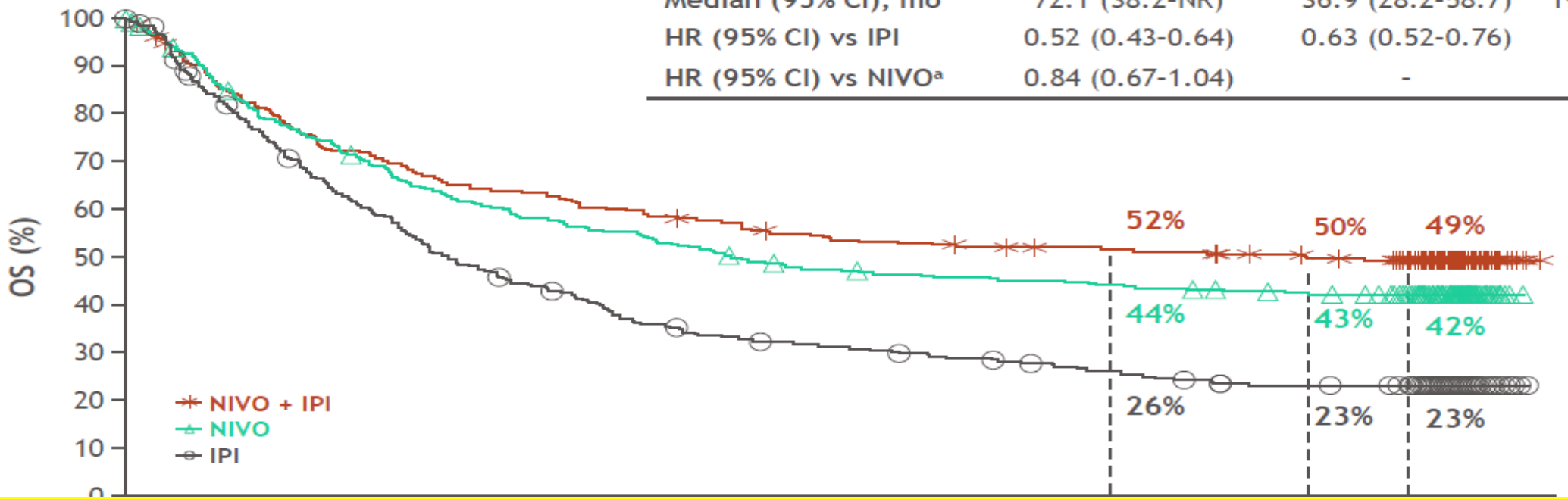


- *Treat until progression or unacceptable toxicity*
- *Coprimary endpoints: PFS, OS*
- *The study was not powered for a comparison between NIVO+IPI and NIVO*

Wolchok JD. CheckMate 067: 6.5-year outcomes in patients with advanced melanoma. Abstract ASCO 2021

CheckMate-067: 6.5-Yr Overall Survival

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	72.1 (38.2-NR)	36.9 (28.2-58.7)	19.9 (16.8-24.6)
HR (95% CI) vs IPI	0.52 (0.43-0.64)	0.63 (0.52-0.76)	-
HR (95% CI) vs NIVO[a]	0.84 (0.67-1.04)	-	-



MKSAP: Combining ipilimumab with nivolumab improves response rates compared with either ipilimumab or nivolumab alone but results in significantly more immune-related toxicities

Wolchok JD. CheckMate 067: 6.5-year outcomes in patients with advanced melanoma. Abstract ASCO 2021

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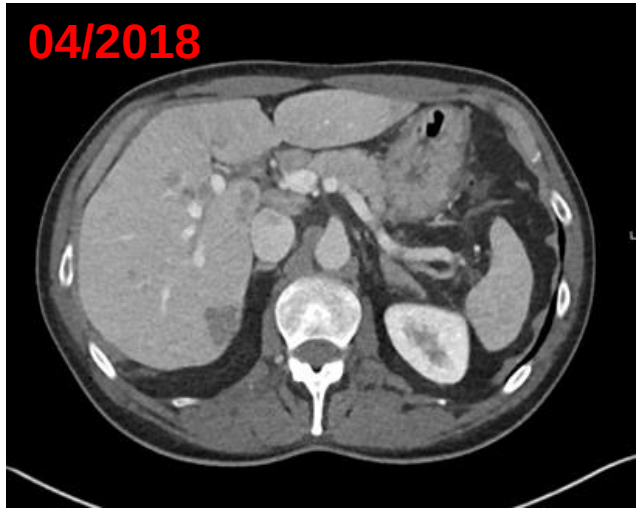
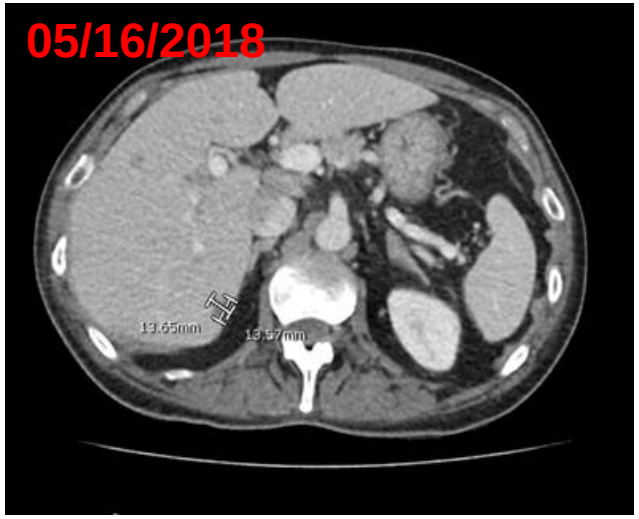
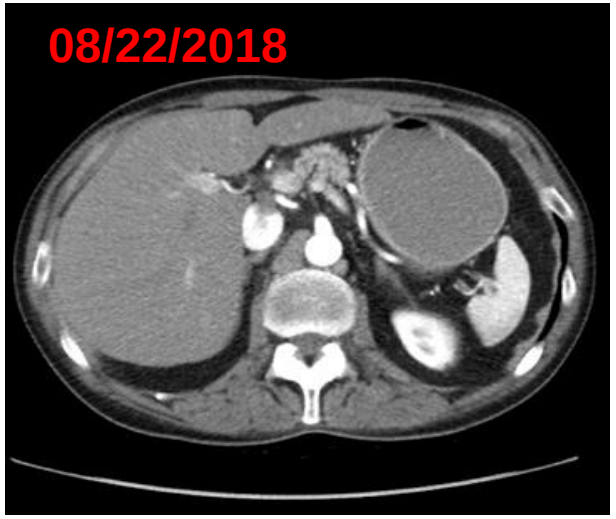
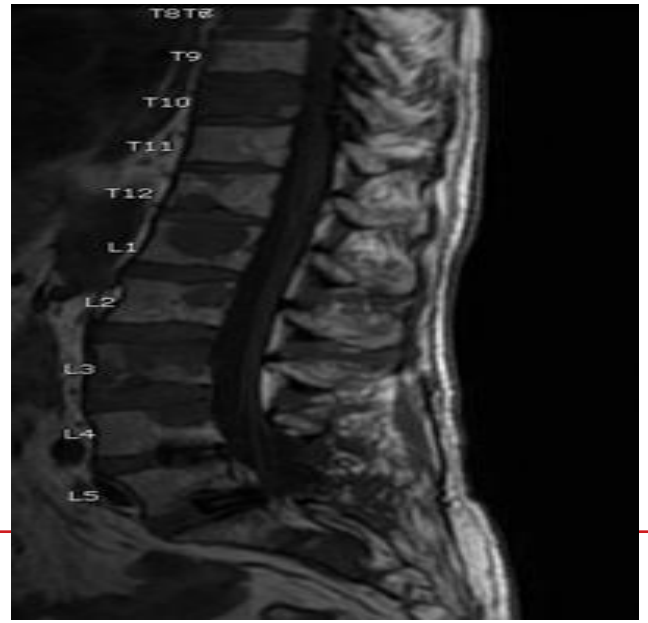
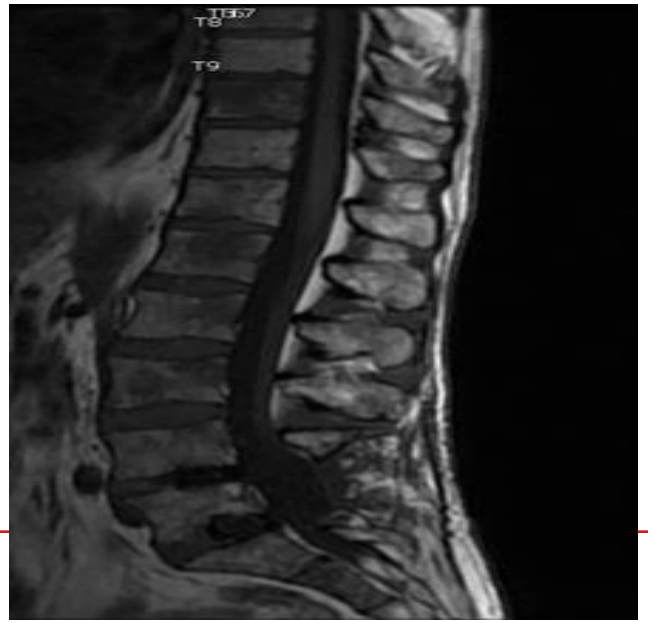
Continue Case Presentation.....

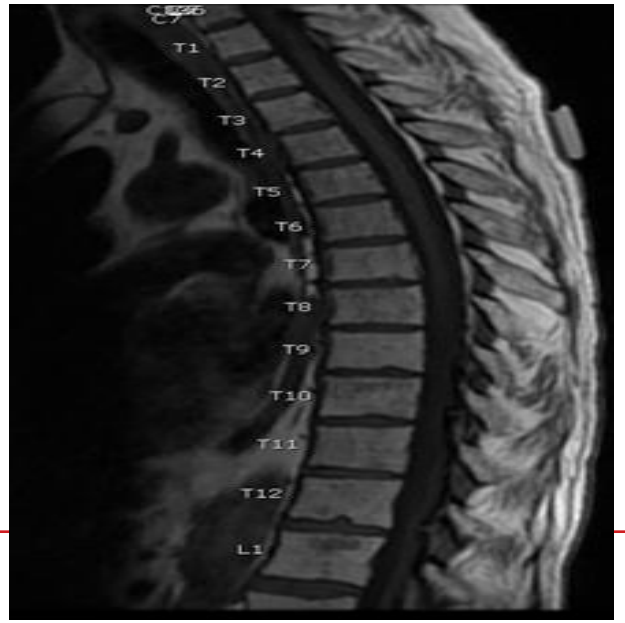












04/20/2018 C1 ipi+nivo

05/10/2018 C2 ipi+nivo

5/16/2018: grade 2 colitis, hypophysitis, and skin rash.

5/31/2018: nivolumab

6/2021: severe colitis.

Immunotherapy stopped

Patient is alive as of now (2022) with complete response.

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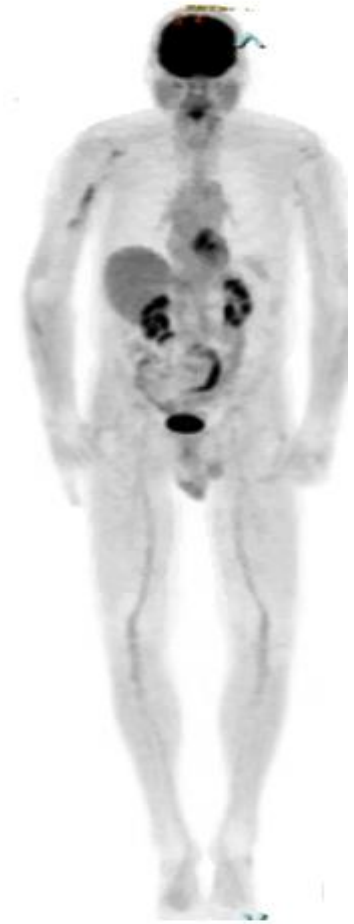
Continue Case Presentation.....

11/04/2019



02/25/2020

06/16/2020

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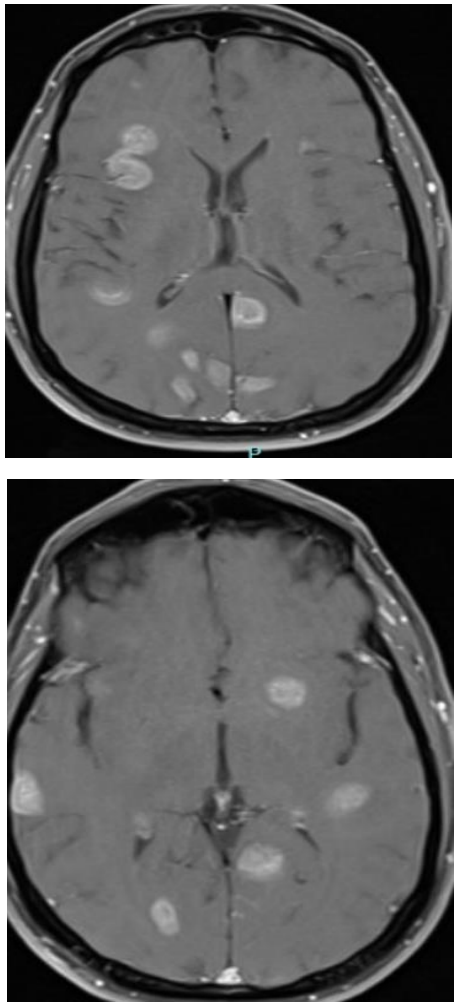
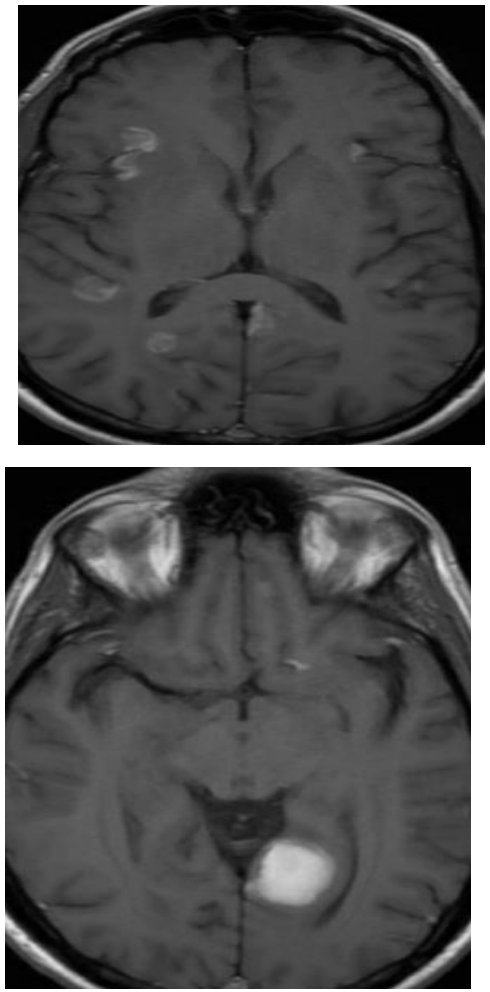
CASE 2: 48 years old male with metastatic melanoma to brain

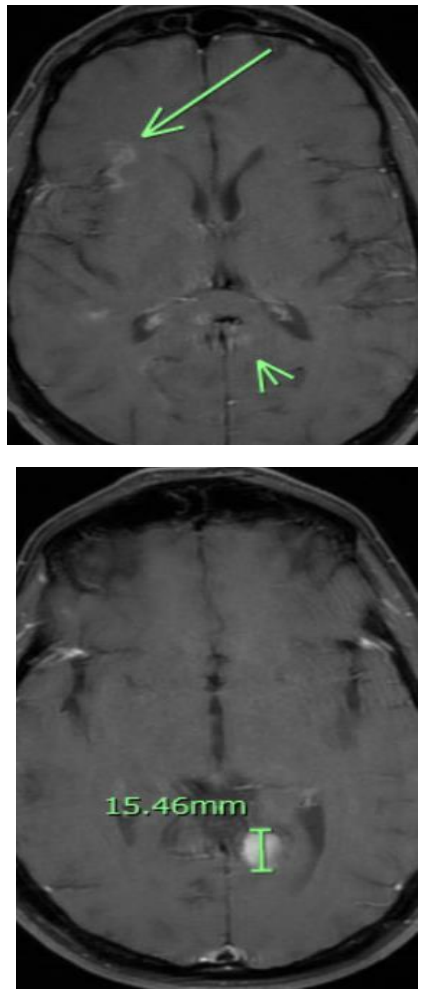
10/13/2020



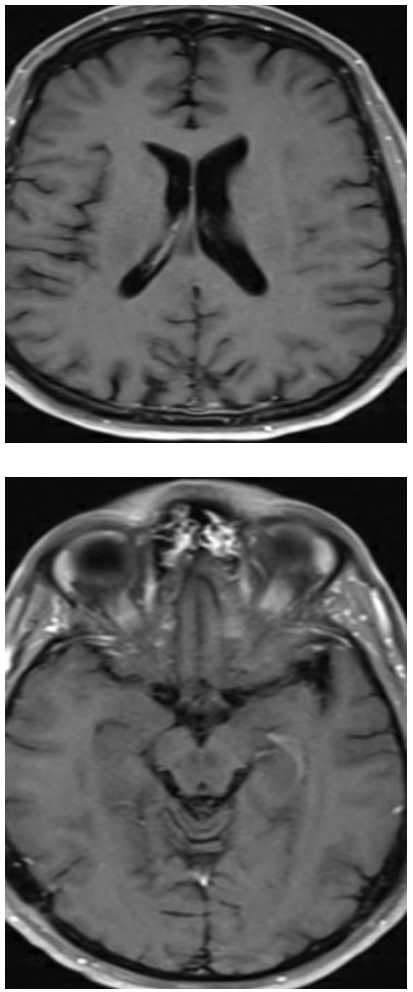
11/05/2020



12/17/2020



12/10/2021



7/2019:1.6 mm depth, left ear helix s/p WLE/SLNB 0/4

9/2020: recurrence. left neck dissection 1/18 LN.

10/13/2020: Brain mets
Asymptomatic
No steroids
No radiation

Ipi 3 mg/kg+nivo 1 mg/kg
10/15/2020 C1
11/05/2020 C2
11/25/2020 C3
12/17/2020 C4
Maintenance Nivolumab
01/05/2021- until now

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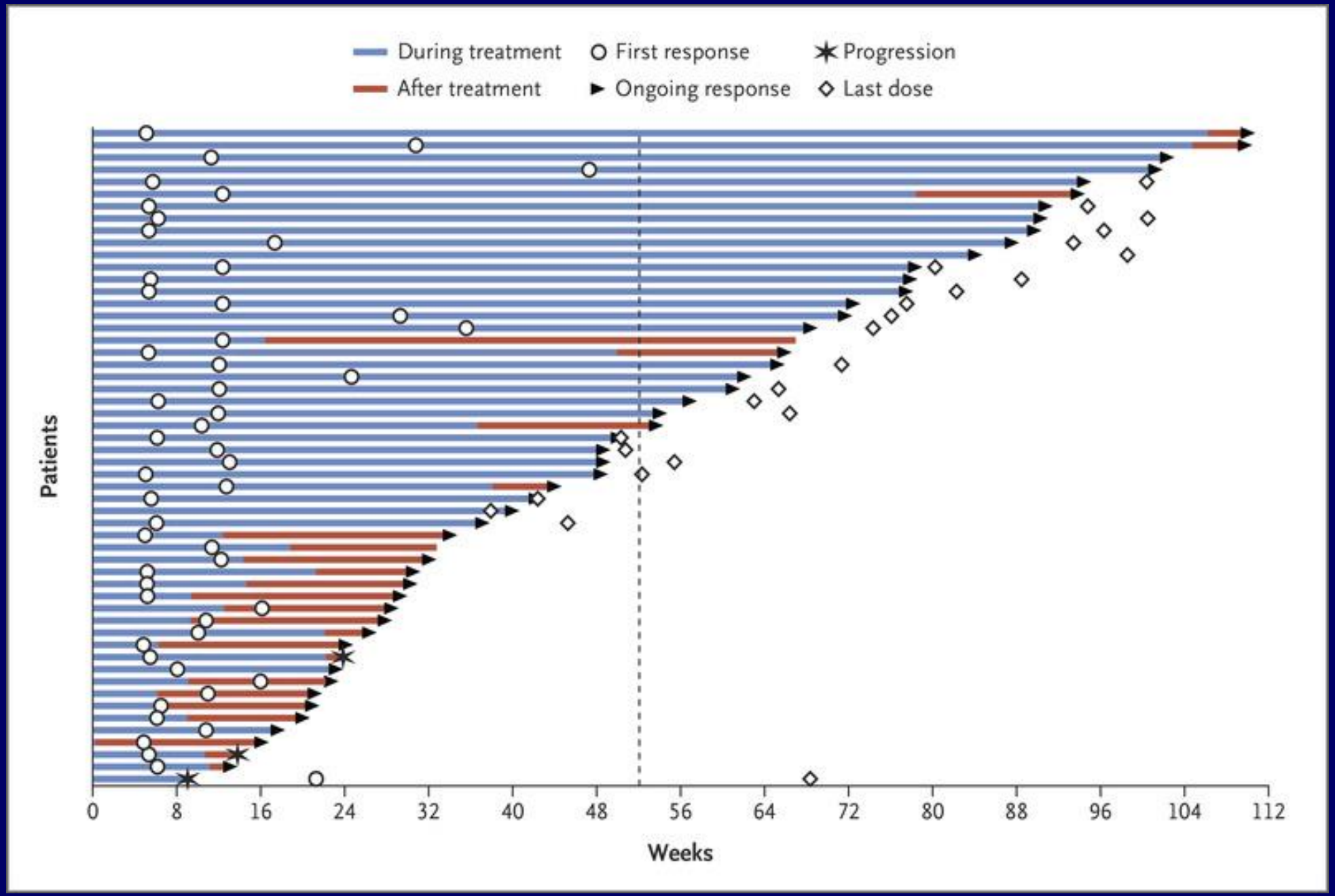
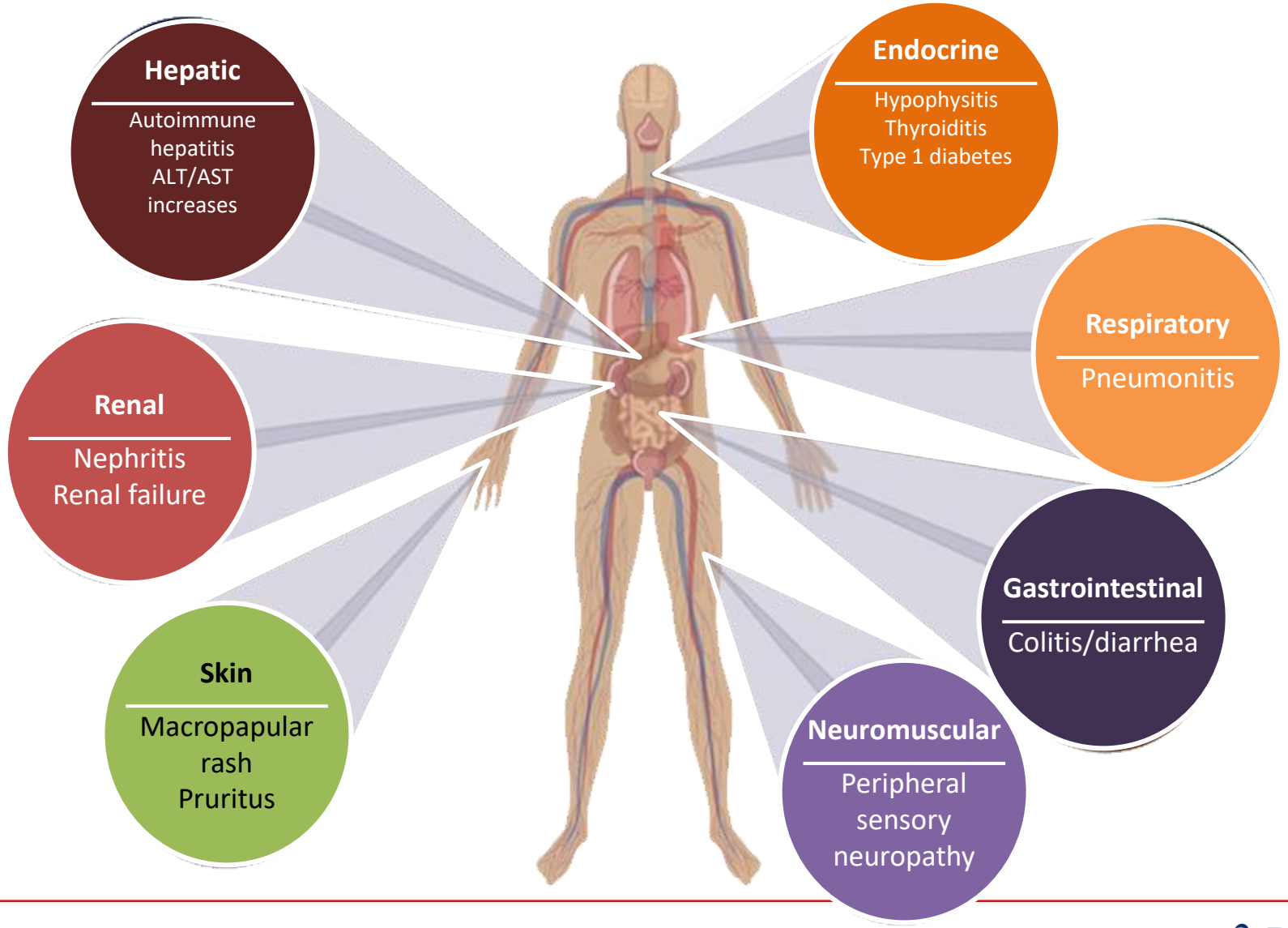

During treatment
After treatment
First response
Ongoing response
Progression
Last dose
Patients
0
8
16
24
32
40
48
56
64
72
80
88
96
104
112
Weeks

CheckMate-067: Adverse Events

	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 AE, %	96	59	87	24	86	28
Treatment-related AE leading to discontinuation, %	42	31	14	8	15	13
Treatment-related death,[a] n (%)	2 (1)		1 (< 1)		1 (< 1)	

Wolchok JD. CheckMate 067: 6.5-year outcomes in patients with advanced melanoma. Abstract ASCO 2021

Immune mediate adverse events



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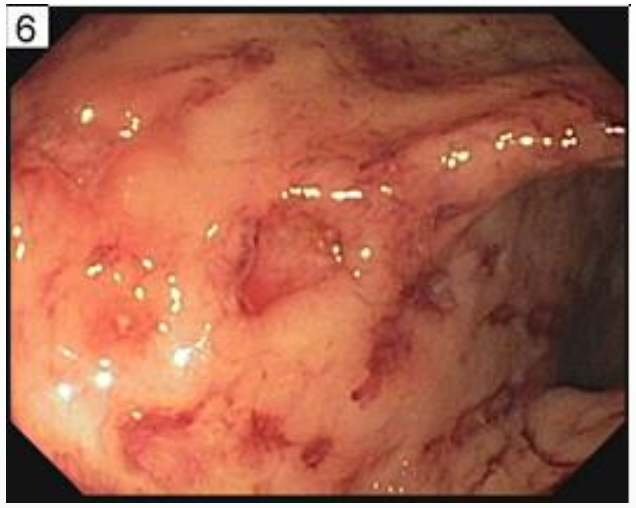
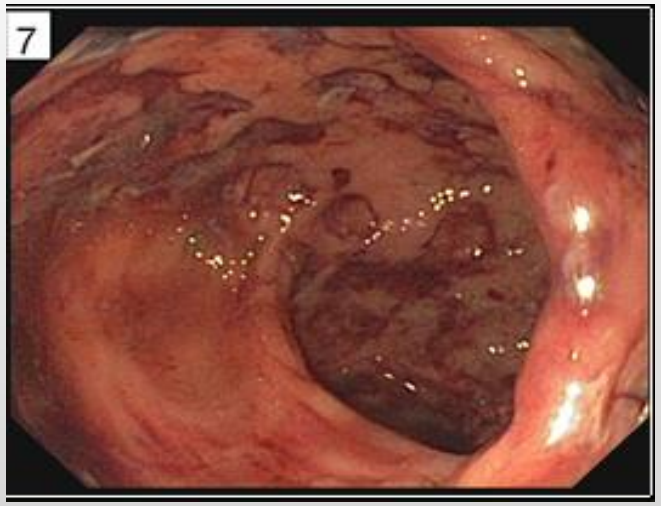
Inflammatory Colitis

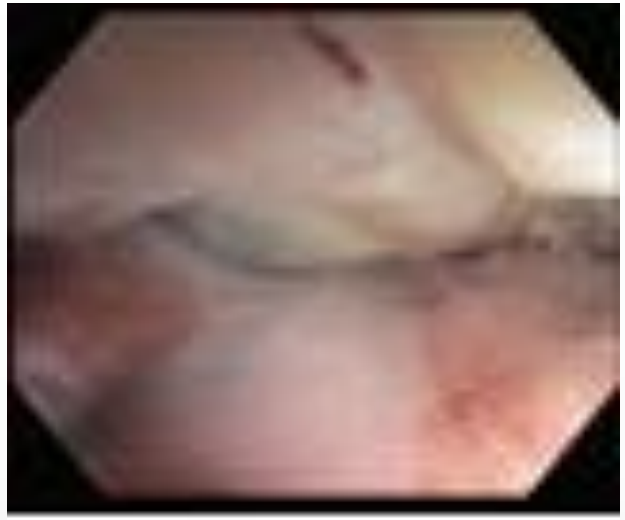




Severe inflammation and ulceration c/w Immune mediated colitis

5wks Post Treatment:

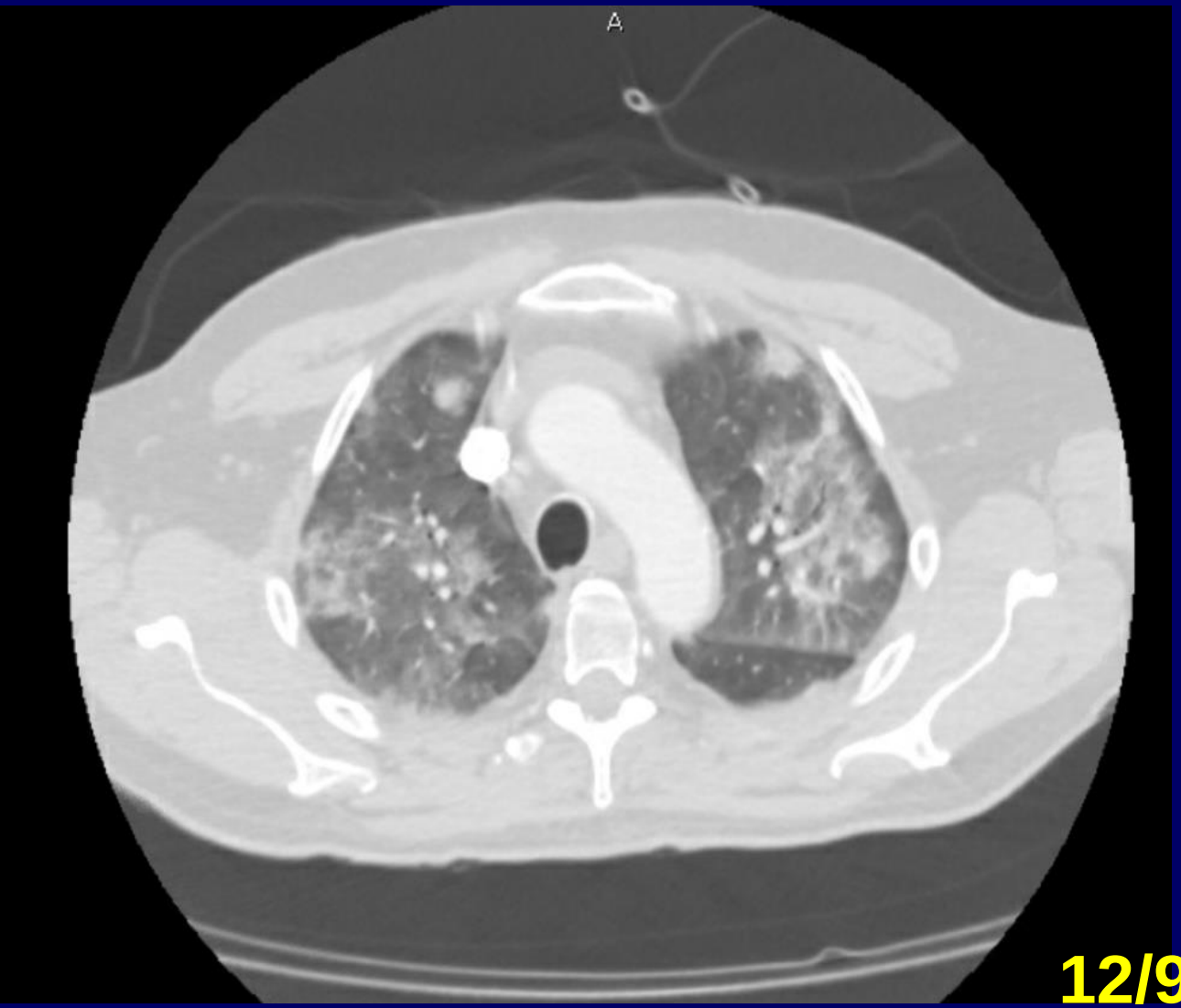
Including:
Infliximab
Short term steroids

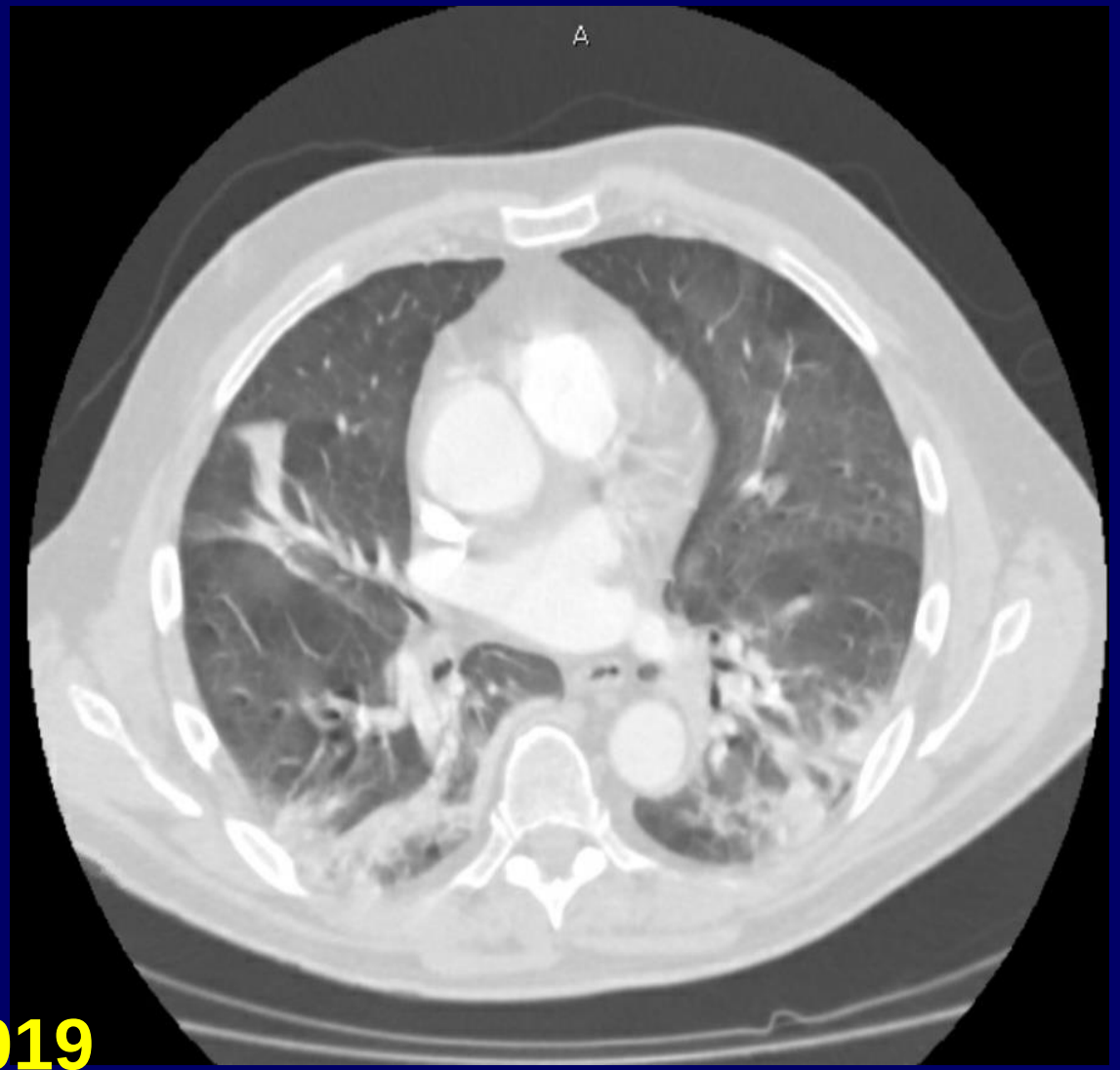


Friable mucosa, but **no signs** of active inflammation or ulceration

Managing Adverse Events With Immune Checkpoint Agents. Dadu R[1], Zobniw C, Diab A. Cancer J. 2016 Mar-Apr;

Case 2: 70 yo male presented with dyspnea and skin rash after cycle 1 of pembrolizumab





12/9/2019

Quiz

Ipilimumab is a CTLA4 inhibitor. All 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 followed by permanent hypothyroidism

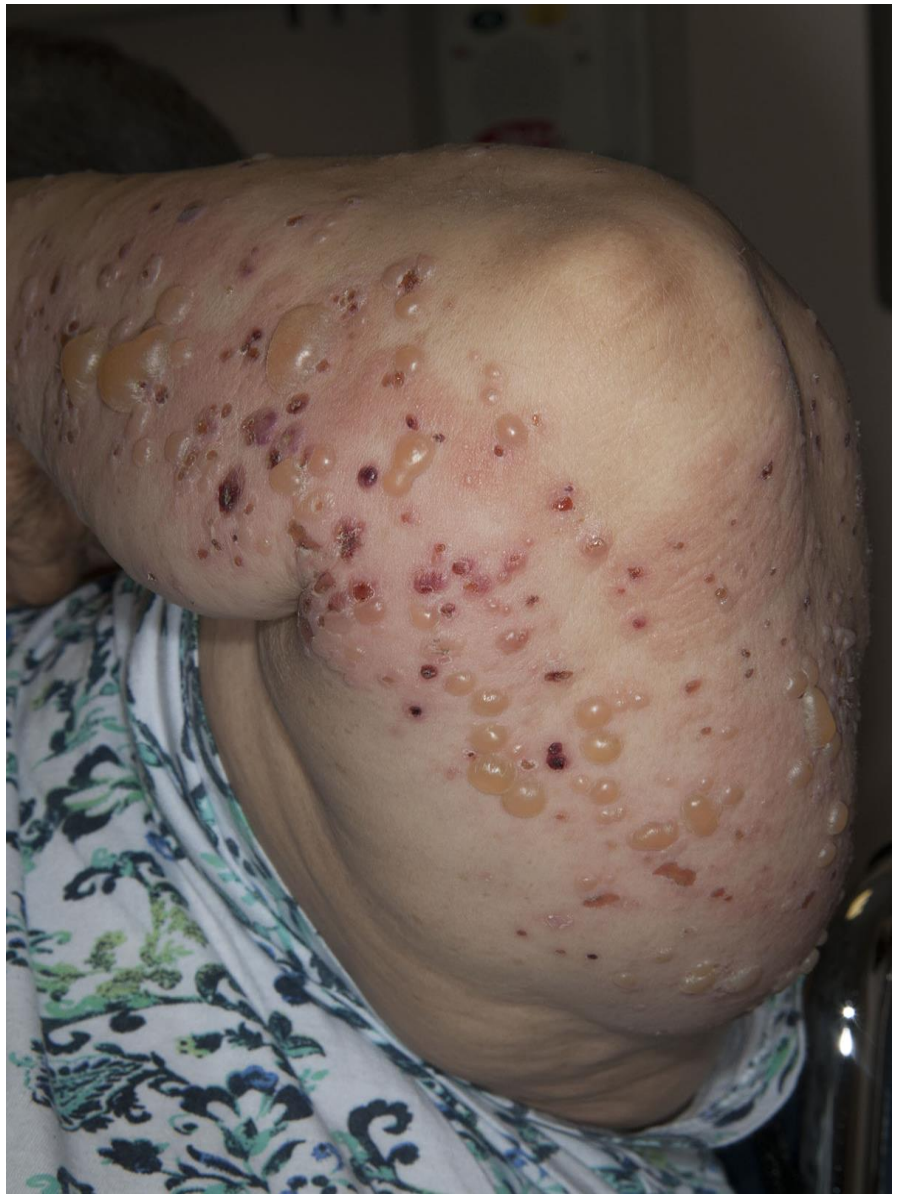
Complete Vitiligo within Weeks

Receiving first infusion
of ipi/Nivo

Weeks later

Slide courtesy of Dr. Isabella Glitza
MDA Houston

Bullous pemphigoid

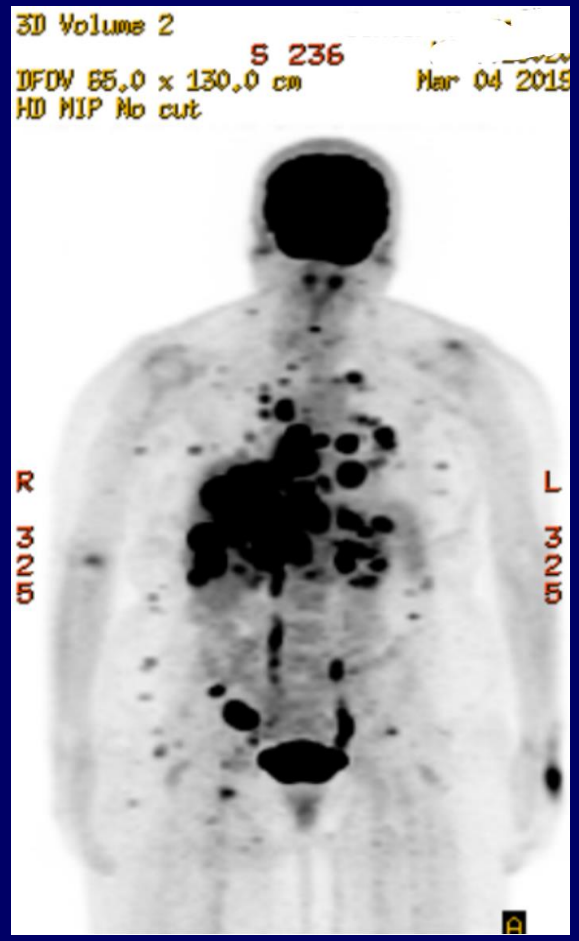


Above: Large bullae on foot. Patient was initiated on high dose steroids, and bullae decreased within few days in size and incidence

Right: Separate female patient who developed significant bullae after 9 cycles of pembrolizumab; she also initially presented with a faint rash

Case 3

- Mrs. C is a 55-year-old female with metastatic BRAF V600E mutated melanoma received 3 cycles of ipilimumab and nivolumab; CT a/p 5/16/2019 revealed progression of disease. She presented for second opinion, poor performance status, and her BP in clinic was 80/40.



Case

What would you recommend now:

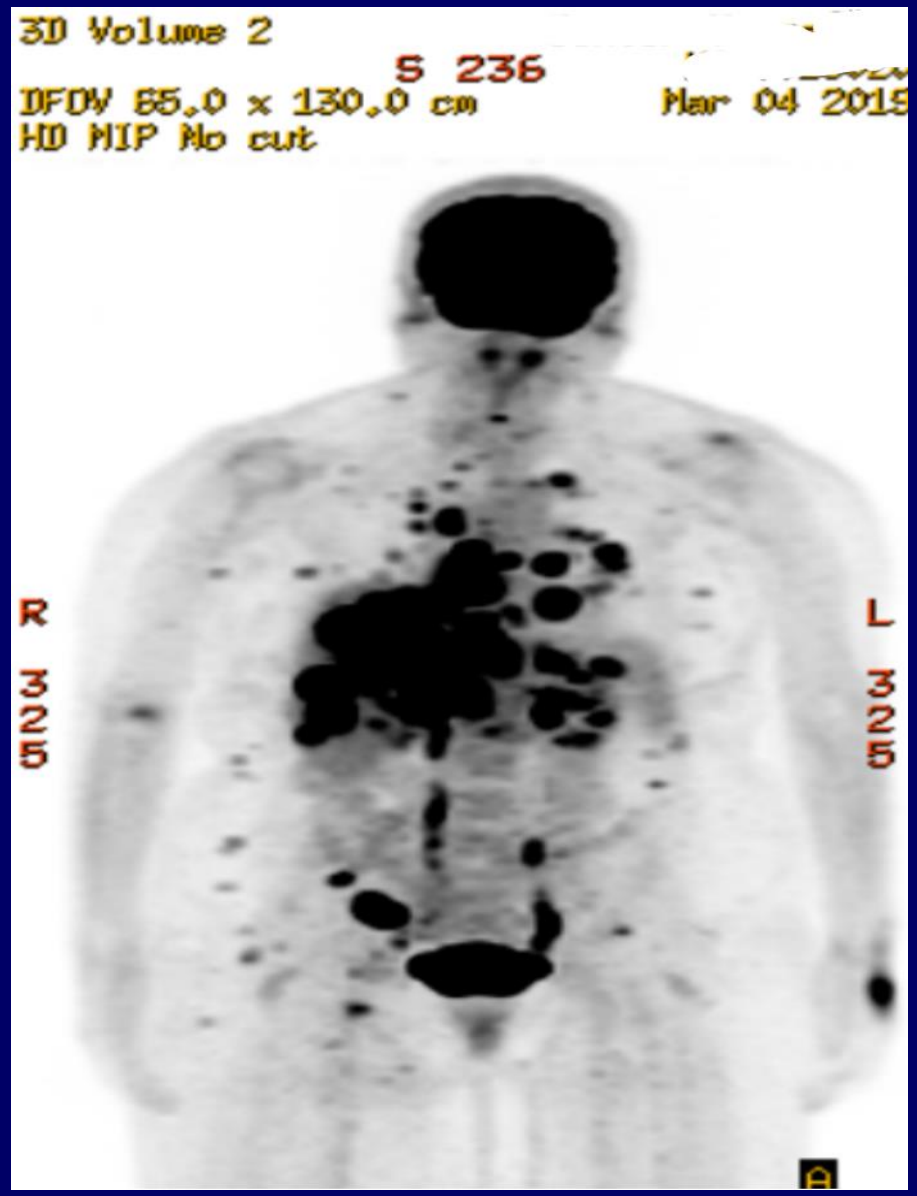
A- Refer patient to hospice care.

B-Admit to hospital for IV hydration.

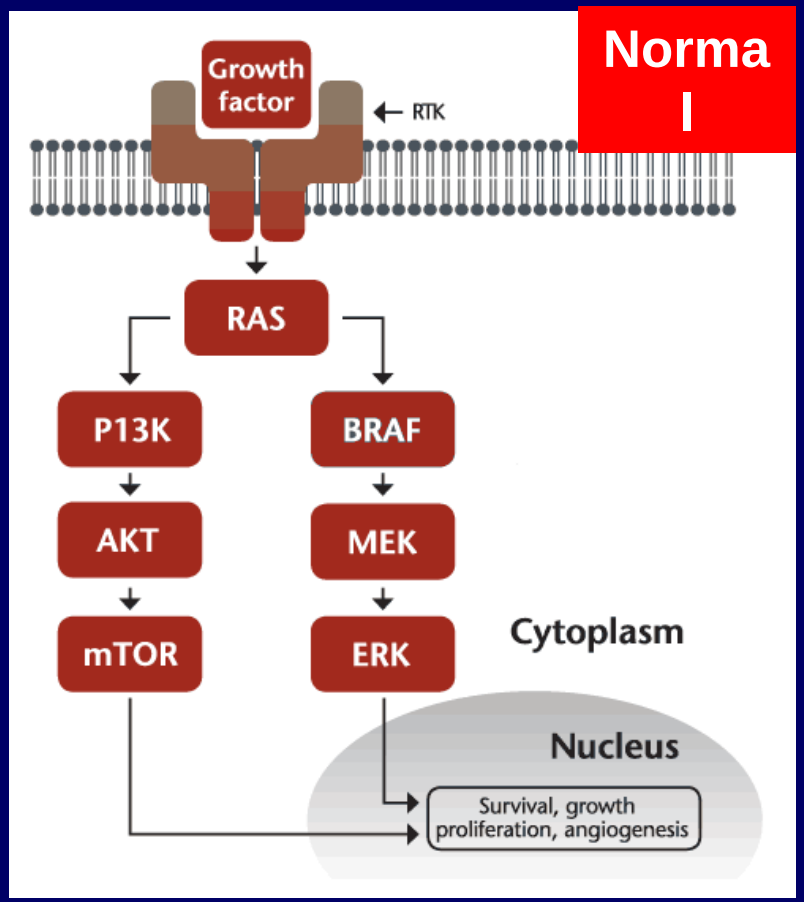
C-Start Encorafenib and Binimetinib (BRAF inhibitor plus MEK inhibitor).

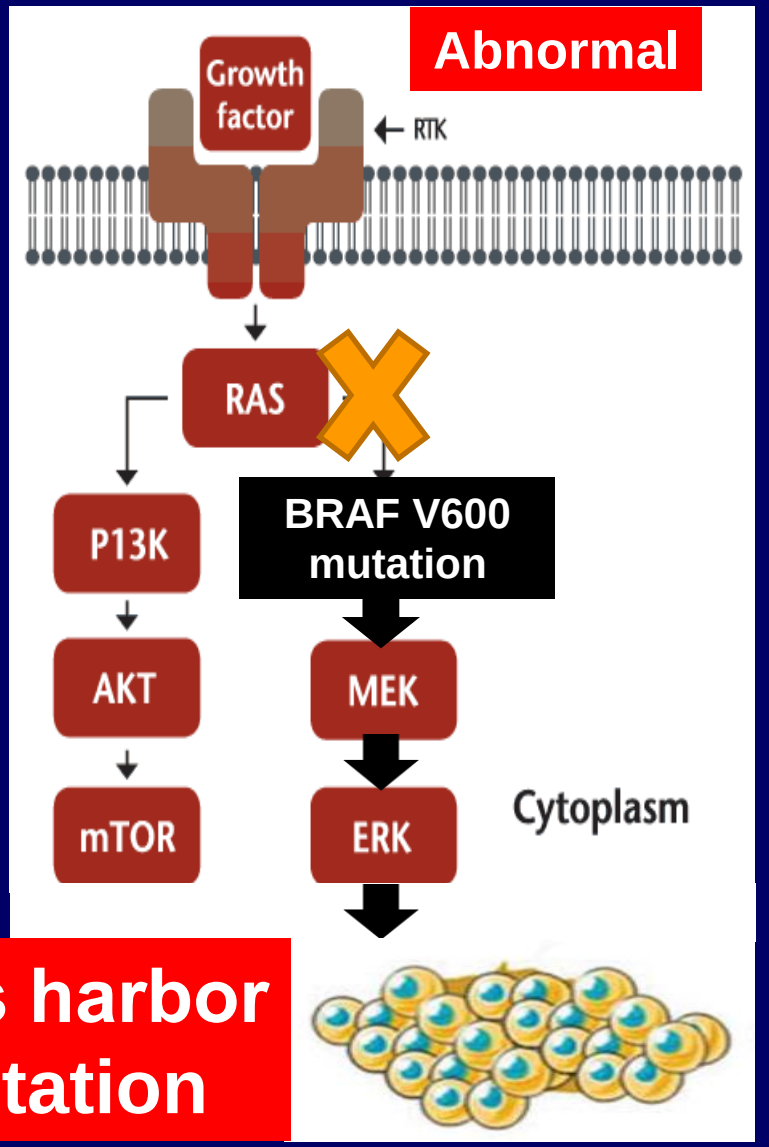
D- Enroll in clinical trial.

Follow up visit 08/27/2019



MAPK PATHWAY AND BRAF MUTATION





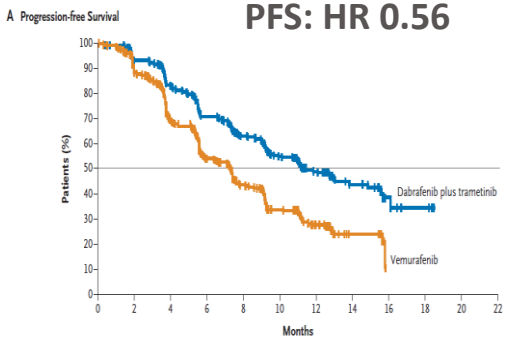
≈ 50% of melanomas harbor the BRAF V600 mutation

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

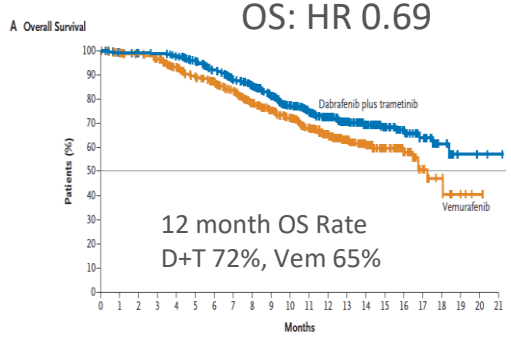
BRAFi + MEKi for *BRAF^{V600}*-Mutant Melanoma

Dabrafenib + Trametinib vs Vem

PFS: HR 0.56



OS: HR 0.69



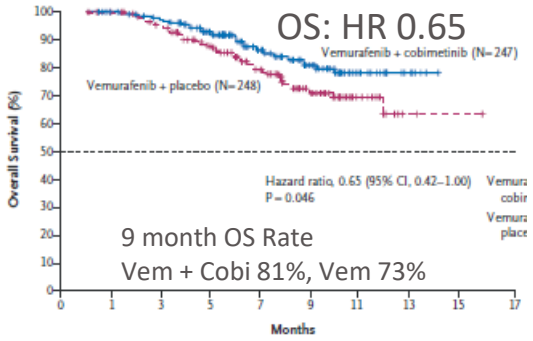
Robert, *NEJM,* 2014

FDA Approval, 2014, BRAF^{V600}-Mutant Stage IV or Unresectable Stage III Melanoma

Vemurafenib + Cobimetinib vs Vem

PFS: HR 0.51

OS: HR 0.65



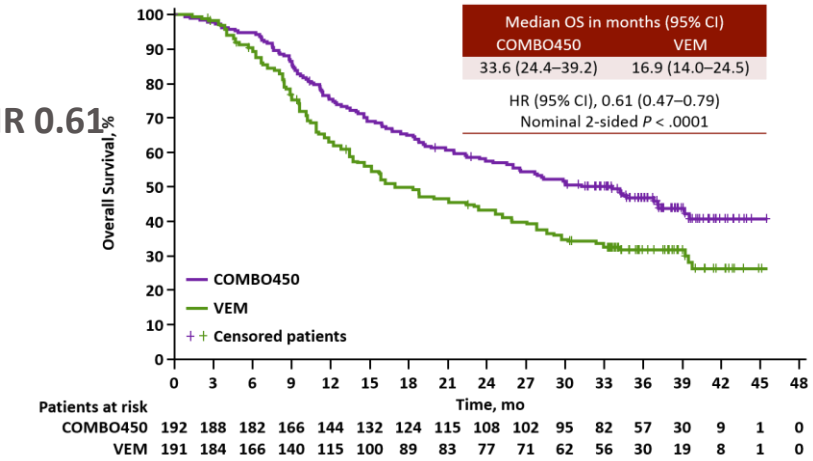
Larkin, *NEJM,* 2014

FDA Approval, 2015, BRAF^{V600}-Mutant Stage IV or Unresectable Stage III Melanoma

Encorafenib + Binimetinib vs Vem

PFS: HR 0.54

OS: HR 0.61



FDA Approval, 2018, BRAF^{V600}-Mutant Stage IV or Unresectable Stage III Melanoma

BRAFi + MEKi for *BRAF^{V600}*-Mutant Melanoma

	Dabrafenib 150 mg BID + Trametinib 2 mg QD[1]	Vemurafenib 960 mg BID (D1-28) + Cobimetinib 60 mg QD (D1-21)[2]	Encorafenib 450 mg QD + Binimetinib 45 mg BID[3]
N	563	247	192
ORR, %	68	70	76
CR	19	21	21
PR	49	49	55
SD	23	18	17
PD	6	7	7
DCR, %	91	93	93
Median PFS, mos	11.1	12.6	14.9
Median OS, mos	25.9	22.5	33.6

- Cross-trial comparison limited by differences in trial populations, i.e. % with LDH > ULN (DT: 34%; VC: 46%; EB: 29%)

1. Robert. NEJM, 2019;381:626. 2. McArthur. SMR 2019. 3. Ascierto. EJC. 2020;126:33.

Slide courtesy of Dr. Michael Davies
MDA Houston

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.

Summary

- Most melanoma is sporadic. Around 10% of all people with melanoma have a family history (mutations in CDKN2A and CDK4).
- Prognosis is related to the depth of invasion, high mitotic rate, lymphovascular invasion, and the presence of ulceration.
- Wide local excision is the standard of care procedure for cutaneous melanoma lesions. Sentinel lymph node biopsy is added for melanoma >=0.8 mm depth.
- Ipilimumab is a CTLA4 inhibitor
- Nivolumab and pembrolizumab are PD1 inhibitors.

Summary

- Immunotherapy revolutionized the management of metastatic melanoma
  - 6.5-year OS with ipilimumab and nivolumab (49%) and nivolumab (42%)
- 50% of patients with melanoma harbor the BRAF mutation.
- Targeted therapy for BRAF-mutant melanoma
  - 3 approved regimens (BRAF inhibitor + MEK inhibitor): high response rates.
- Immune mediated adverse events: Skin rash, colitis, thyroiditis, hypophysitis, hepatitis, nephritis, pneumonitis, etc

THANK YOU

Banner MD Anderson Cancer Center
Making Cancer History®