Melanoma: What a Difference A Decade Makes

University of Texas Southwestern Medical Center

This is to acknowledge that Jade Homsi, M.D. has disclosed that he does have financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Homsi will not be discussing off-label uses in his presentation.

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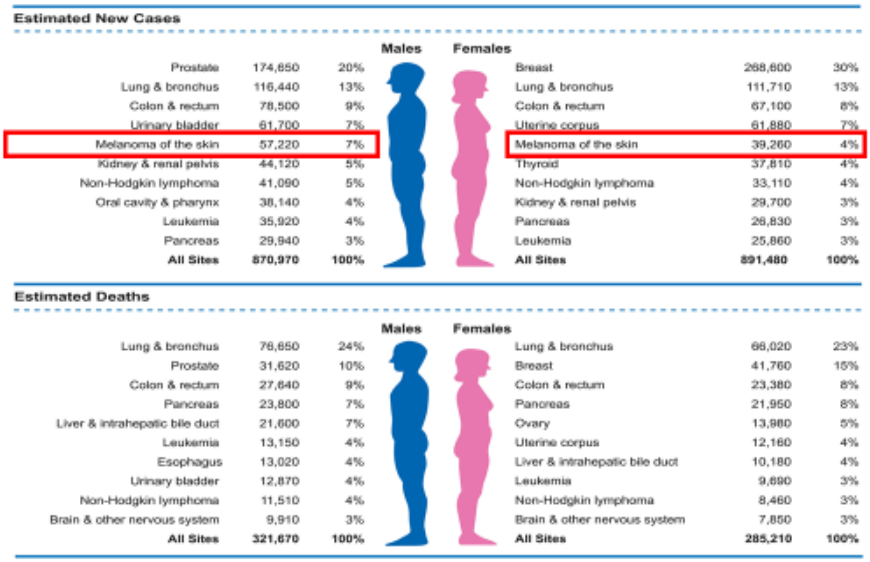
Purpose & Overview

The purpose of this program is to review the recent advances in the management of melanoma. The presentation will provide a comprehensive review of the diagnosis and treatment of melanoma. It will review the incidence of melanoma and how this compares to other cancers. It will also review the different types of melanoma and discuss some of the risk factors associated with this disease. Finally, the presentation will summarize the recent data evaluating the surgical and medical management of melanoma. Different treatment options will be presented including details on the efficacy and side effects of these therapies.

Educational Objectives

1. Understanding the clinical presentation of melanoma
2. Learning about the genetic abnormalities associated with melanoma and how these are used to treat melanoma
3. Learning the mechanism of action, efficacy and side effects of immunotherapy in melanoma

Melanoma estimated new cases 2019 (1)



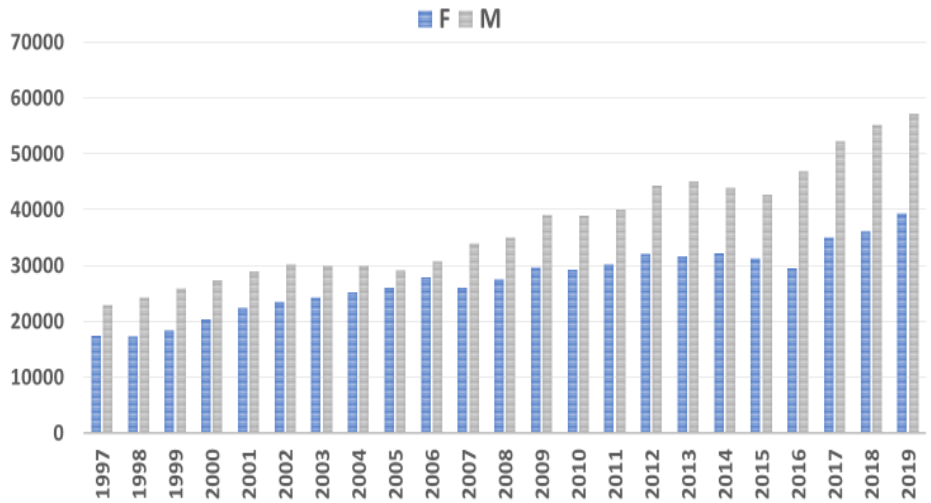
Estimated New Cases

	Males			Females		
Prostate	174,650	20%		Breast	268,600	30%
Lung & bronchus	116,440	13%		Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%		Colon & rectum	67,100	8%
Urinary bladder	61,700	7%		Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%		Melanoma of the skin	39,260	4%
Kidney & renal pelvis	44,120	5%		Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%		Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%		Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%		Pancreas	26,830	3%
Pancreas	29,940	3%		Leukemia	25,860	3%
All Sites	**870,970**	**100%**		**All Sites**	**891,480**	**100%**

Estimated Deaths

	Males			Females		
Lung & bronchus	76,850	24%		Lung & bronchus	66,020	23%
Prostate	31,620	10%		Breast	41,760	15%
Colon & rectum	27,640	9%		Colon & rectum	23,380	8%
Pancreas	23,800	7%		Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%		Ovary	13,980	5%
Leukemia	13,150	4%		Uterine corpus	12,160	4%
Esophagus	13,020	4%		Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%		Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%		Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%		Brain & other nervous system	7,850	3%
All Sites	**321,670**	**100%**		**All Sites**	**285,210**	**100%**

Melanoma number of new cases over 22 years



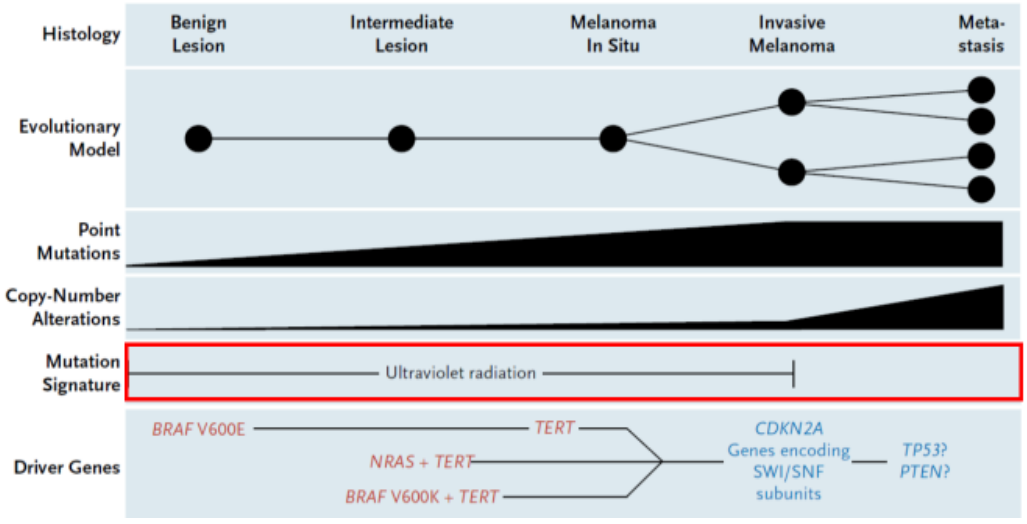
Life Time Probability for Developing Melanoma (1)

	All Sites	Melanoma 1990s	Melanoma 2019
Female	1 in 3	1 in 82	1 in 40
Male	1 in 3	1 in 58	1 in 27

Melanoma New Risk Factors: Tanning Beds & Occupation (2,3)

- The UV output of a tanning bed compared to the noon sunlight during the summer
  - UVA: four times higher
  - UVB: two times higher
- Adults using indoor tanning at least once/yr
  - Overall: 5%
  - White women 18-21 yrs old: 32%
  - White women 18-21 yrs old in the Midwest: 44%
- More than 450,000 NMSC and more than 10,000 melanoma each year attributable to indoor tanning
- Pilots flying 57 min at 30,000 feet receive the same amount of UV-A radiation as that from a 20 minute tanning bed session
- Pilots and cabin crew compared with the general population: twice the incidence of melanoma
- Military members have an increased risk of skin cancer, including melanoma

The role of UV radiation in the initiation and progression of melanoma (4)



Unusual melanomas

Acral Lentiginous

- 1-3%
- Palms, soles, nails
- People with darker skin

Mucosal

- 1%
- Oral/nasal mucosa, sinuses, vaginal, anorectal
- Surgery
- Lower response to therapy. Worse prognosis.

Uveal/Choroidal

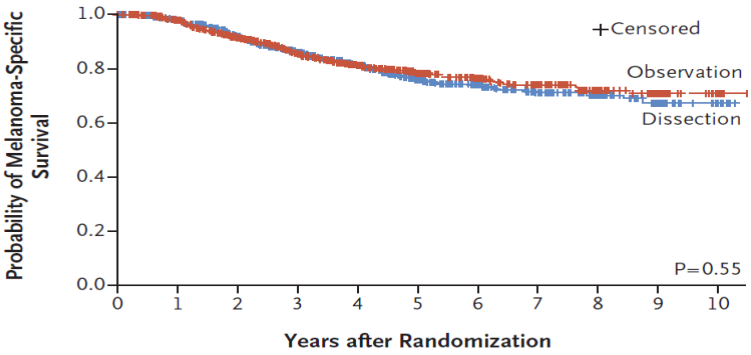
- 5%
- RT plaques brachytherapy or Enucleation
- Mets disease: liver-directed therapy
- Systemic therapy limited activity

What happened in Melanoma in the Last Decade?

1. Less extensive surgery
2. Targeted therapy (Braf mutation)
3. Better immunotherapy
4. Better response in brain metastases
5. Patients no longer treated indefinitely
6. Maintaining a response for many years after discontinuing therapy “Cure”

Melanoma Surgery (5)

Immediate completion lymph-node dissection increases the rate of regional disease control and provides prognostic information but does not increase melanoma-specific survival among patients with melanoma and sentinel-node metastases**.** In an international trial, patients with sentinel-node metastases detected by means of standard pathological assessment or a multi-marker molecular assay were assigned to immediate completion lymph-node dissection (dissection group) or nodal observation with ultrasonography (observation group). The primary end point was melanoma-specific survival. Secondary end points included disease-free survival and the cumulative rate of nonsentinel-node metastasis. Immediate completion lymph-node dissection was not associated with increased melanoma-specific survival among 1934 patients with data that could be evaluated in an intention-to-treat analysis or among 1755 patients in the per-protocol analysis. In the per-protocol analysis, the mean (±SE) 3-year rate of melanoma-specific survival was similar in the dissection group and the observation group (86±1.3% and 86±1.2%, respectively; P=0.42 by the log-rank test) at a median follow-up of 43 months. The rate of disease-free survival was slightly higher in the dissection group than in the observation group (68±1.7% and 63±1.7%, respectively; P=0.05 by the log-rank test) at 3 years, based on an increased rate of disease control in the regional nodes at 3 years (92±1.0% vs. 77±1.5%; P<0.001 by the log-rank test); these results must be interpreted with caution. Nonsentinel-node metastases, identified in 11.5% of the patients in the dissection group, were a strong, independent prognostic factor for recurrence (hazard ratio, 1.78; P=0.005). Lymphedema was observed in 24.1% of the patients in the dissection group and in 6.3% of those in the observation group.

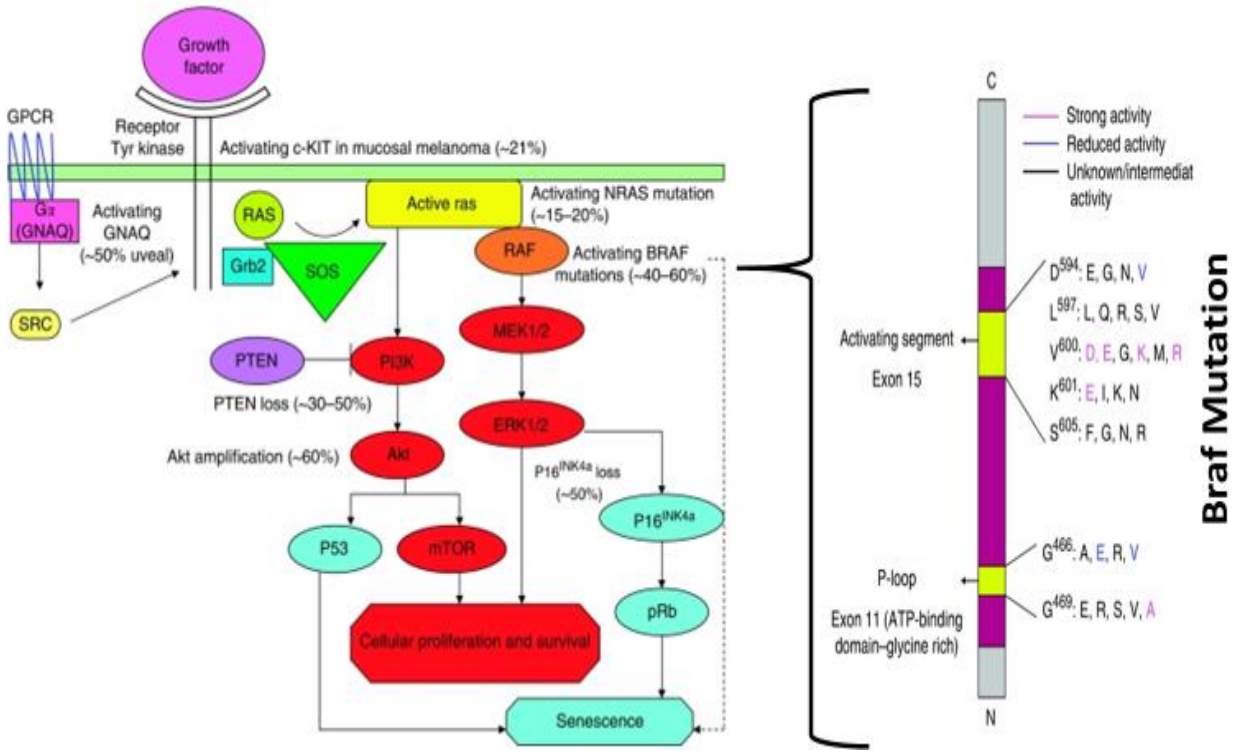


No. at Risk

Dissection	824	759	654	510	389	275	191	128	83	39	13
Observation	931	856	734	564	425	304	217	151	95	55	13

Targeted Therapy for Melanoma (BRAF/MEK) (6)

Initially introduced as monotherapy treatment for patients with *BRAF*V600-mutant melanoma, showed improved efficacy compared with standard therapy, including improved response rates and progression-free and overall survival. However, response durations were short and BRAF inhibitor treatment was associated with the development of squamous cell skin cancer and other skin toxicities related to paradoxical MAPK pathway activation. BRAF–MEK inhibitor combinations have a central role in the targeted treatment of *BRAF* V600-mutant melanoma. BRAF–MEK inhibitor combinations have improved progression free and overall survival in patients with *BRAF*-mutant melanoma but with treatment-limiting and dose-limiting toxicities



<u>FDA approved Braf targeted therapy (7,8)</u>

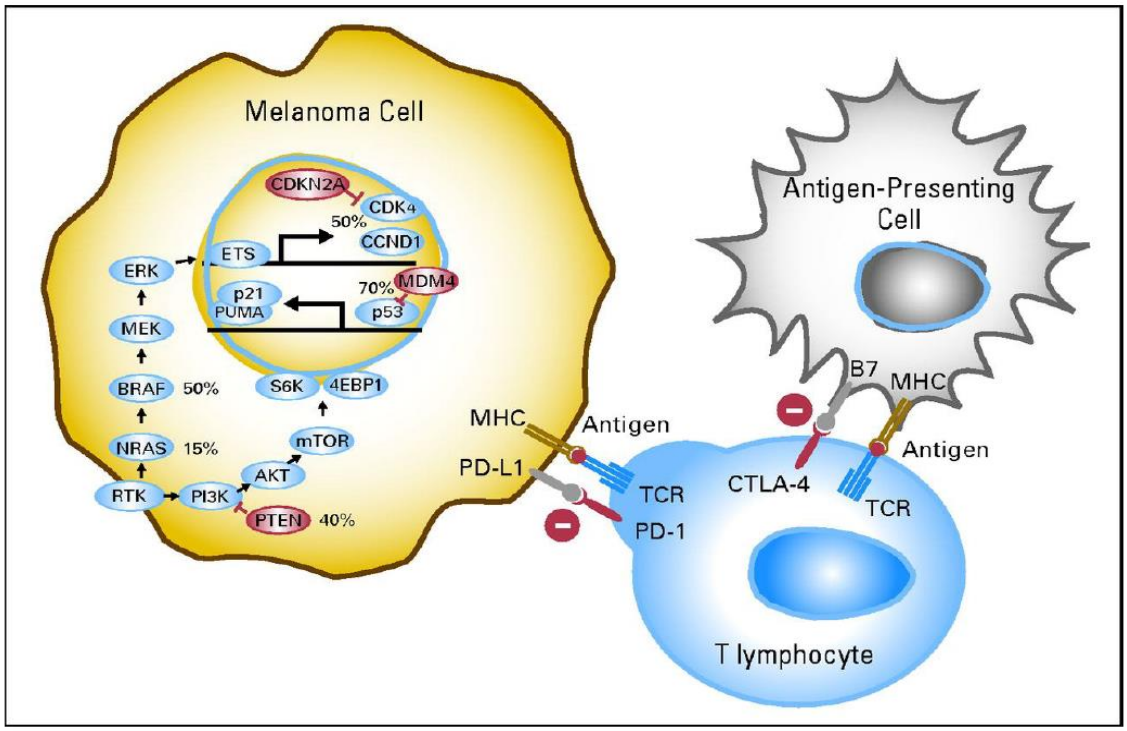
<u>Adjuvant setting</u>

Dabrafenib + Trametinib (2018)

<u>Uresectable/Metastatic setting</u>

Vemurafinib (2011)
Dabrafenib (2013)
Trametinib (2013)
Dabrafenib + Trametinib (2014)
Vemurafenib + Cobimetinib (2015)
Encorafenib and Binimetinib (2018)

Mechanism of action of immunotherapy in Cancer (9)

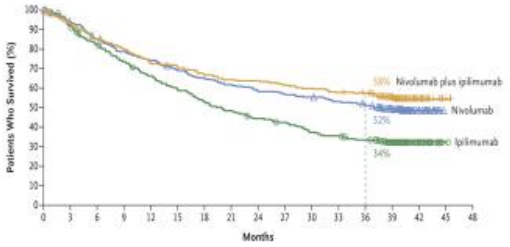


FDA Approved Immune check point inhibitors in cancer

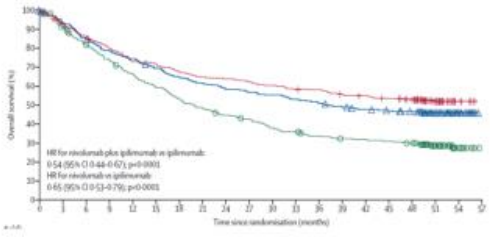
Drug	Target	Year	Cancer			
Ipilimumab	CTLA-4	2011	Melanoma Kidney MSI-H Colon			
Pembrolizumab	PD-1	2014	Melanoma NSC+SC lung H&N	Hodgkin lymphoma Large cell lymphoma Urothelial	MSI-H cancer Gastric Cervical	Hepatocellular Merkel cell Kidney
Nivolumab	PD-1	2014	Melanoma NSC lung Small cell lung	Kidney Hodgkin lymphoma MSI-H colorectal	Urothelial Hepatocellular H&N	
Atezolizumab	PD-L1	2016	Urothelial NSC lung	Small cell lung Breast		
Avelumab	PD-L1	2017	Merkel Cell Urothelial	Kidney		
Durvalumab	PD-L1	2017	Urothelial NSC lung			
Cemiplimab	PD-1	2018	cutaneous squamous cell			

Combination Immunotherapy in metastatic melanoma (10,11)

Among patients with advanced melanoma, significantly longer overall survival occurs with combination therapy with nivolumab plus ipilimumab or with nivolumab alone than with ipilimumab alone. Patients were randomly assigned, in a 1:1:1 ratio, patients with previously untreated advanced melanoma to receive nivolumab at a dose of 1 mg per kilogram of body weight plus ipilimumab at a dose of 3 mg per kilogram every 3 weeks for four doses, followed by nivolumab at a dose of 3 mg per kilogram every 2 weeks; nivolumab at a dose of 3 mg per kilogram every 2 weeks plus placebo; or ipilimumab at a dose of 3 mg per kilogram every 3 weeks for four doses plus placebo, until progression, the occurrence of unacceptable toxic effects, or withdrawal of consent. Randomization was stratified according to programmed death ligand 1 (PD-L1) status, *BRAF* mutation status, and metastasis stage. The two primary end points were progression free survival and overall survival in the nivolumab-plus-ipilimumab group and in the nivolumab group versus the ipilimumab group. At a minimum follow-up of 36 months, the median overall survival had not been reached in the nivolumab-plus-ipilimumab group and was 37.6 months in the nivolumab group, as compared with 19.9 months in the ipilimumab group (hazardratio for death with nivolumab plus ipilimumab vs. ipilimumab, 0.55 [P<0.001]; hazard ratio for death with nivolumab vs. ipilimumab, 0.65 [P<0.001]). The overall survival rate at 3 years was 58% in the nivolumab-plus-ipilimumab group and 52% in the nivolumab group, as compared with 34% in the ipilimumab group. The safety profile was unchanged from the initial report. Treatment-related adverse events of grade 3 or 4 occurred in 59% of the patients in the nivolumab-plus-ipilimumab group, in 21% of those in the nivolumab group, and in 28% of those in the ipilimumab group.



3-Year Survival: 58%, 52%, 34%



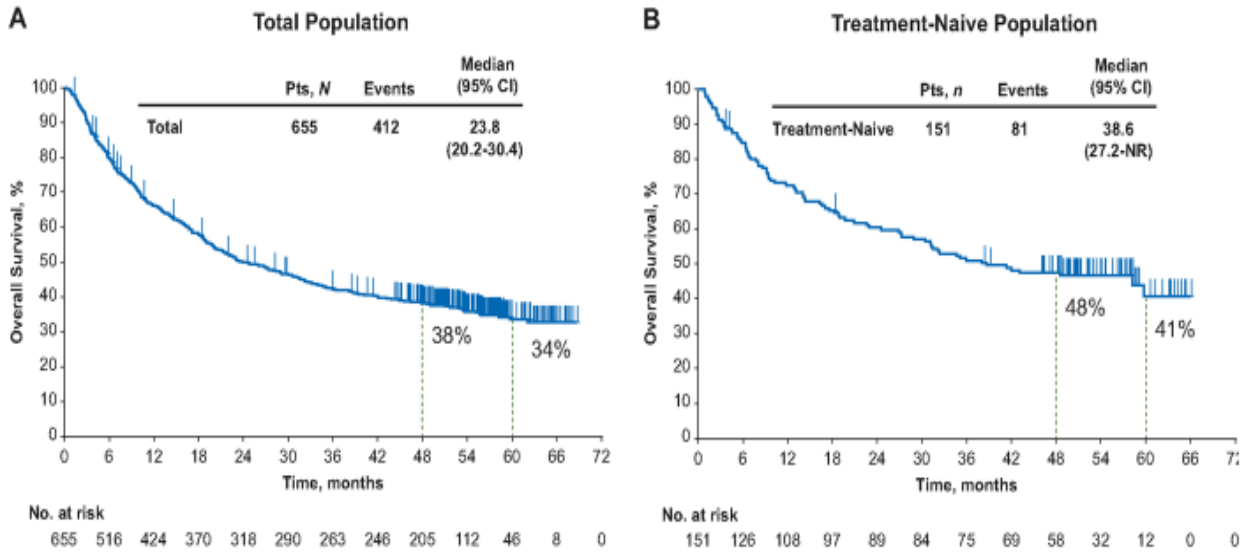
4-Year Survival: 53%, 46%, 30%

	Nivolumab plus ipilimumab group (n=313)			Nivolumab group (n=313)			Ipilimumab group (n=311)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any treatment-related adverse event	115 (37%)	151 (48%)	34 (11%)	200 (64%)	54 (17%)	16 (5%)	181 (58%)	74 (24%)	12 (4%)
Diarrhoea	112 (36%)	29 (9%)	1 (<1%)	60 (19%)	9 (3%)	0	87 (28%)	18 (6%)	0
Fatigue	107 (34%)	13 (4%)	0	111 (36%)	3 (1%)	0	86 (28%)	3 (1%)	0
Pruritus	106 (34%)	6 (2%)	0	68 (22%)	1 (<1%)	0	112 (36%)	1 (<1%)	0
Rash	83 (27%)	10 (3%)	0	73 (23%)	1 (<1%)	0	64 (21%)	5 (2%)	0
Nausea	81 (26%)	7 (2%)	0	41 (13%)	0	0	49 (16%)	2 (1%)	0

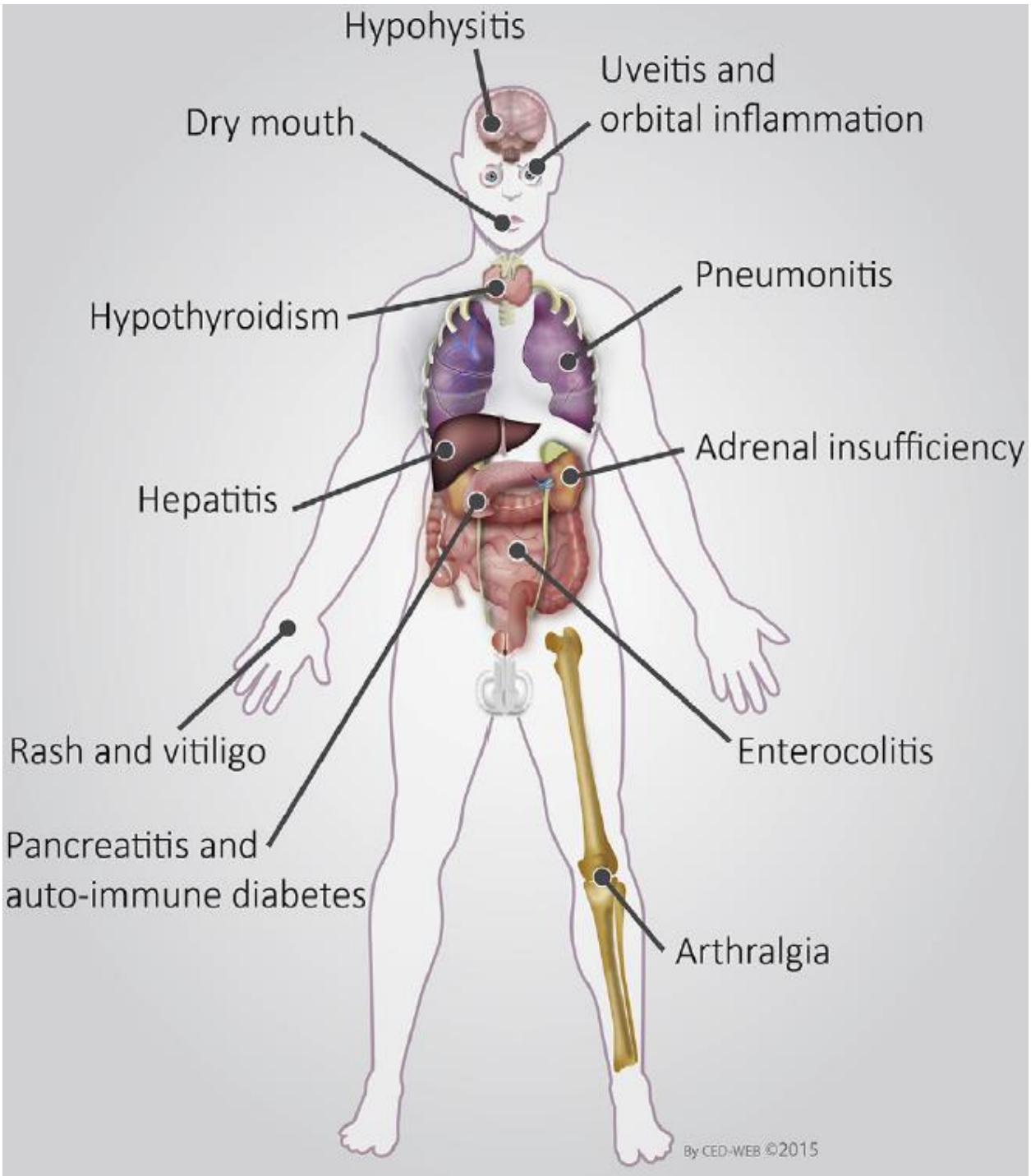
Immunotherapy in melanoma brain metastases (12)

Nivolumab combined with ipilimumab has a clinically meaningful intracranial efficacy, concordant with extracranial activity, in patients with melanoma who have untreated brain metastases. In this open-label, multicenter, phase 2 study, patients with metastatic melanoma and at least one measurable, nonirradiated brain metastasis (tumor diameter, 0.5 to 3 cm) and no neurologic symptoms received nivolumab (1 mg per kilogram of body weight) plus ipilimumab (3 mg per kilogram) every 3 weeks for up to four doses, followed by nivolumab (3 mg per kilogram) every 2 weeks until progression or unacceptable toxic effects. The primary end point was the rate of intracranial clinical benefit, defined as the percentage of patients who had stable disease for at least 6 months, complete response, or partial response. Among 94 patients with a median follow-up of 14.0 months, the rate of intracranial clinical benefit was 57% (95% confidence interval [CI], 47 to 68); the rate of complete response was 26%, the rate of partial response was 30%, and the rate of stable disease for at least 6 months was 2%. The rate of extracranial clinical benefit was 56% (95% CI, 46 to 67). Treatment-related grade 3 or 4 adverse events were reported in 55% of patients, including events involving the central nervous system in 7%. One patient died from immune-related myocarditis. The safety profile of the regimen was similar to that reported in patients with melanoma who do not have brain metastases.

5-year survival in melanoma patients who received pembrolizumab (13)



Immunotherapy mediated side effects (14)



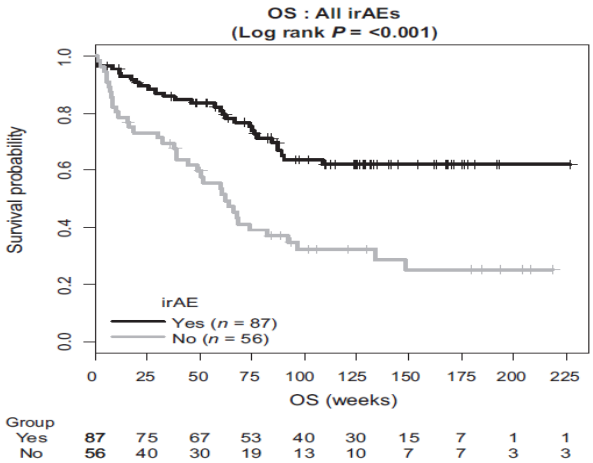
The management of Immunotherapy Side Effects (15)

The American society of Clinical Oncology Recommendations regarding the management of immune checkpoint inhibitors (ICPis)

• Patient and family caregivers should receive timely and up-to-date education about immunotherapies, their mechanism of action, and the clinical profile of possible irAEs prior to initiating therapy and throughout treatment and survivorship.
• There should be a high level of suspicion that new symptoms are treatment related.
• In general, ICPi therapy should be continued with close monitoring for grade 1 toxicities, with the exception of some neurologic, hematologic, and cardiac toxicities.
• Hold ICPis for most grade 2 toxicities and consider resuming when symptoms and/or laboratory values revert to grade 1or less. Corticosteroids (initial dose of 0.5 to 1 mg/kg/d of prednisone or equivalent) may be administered.
• Hold ICPis for grade 3 toxicities and initiate high-dose corticosteroids (prednisone 1 to 2 mg/kg/d or methylprednisolone IV 1 to 2 mg/kg/d). Corticosteroids should be tapered over the course of at least 4 to 6 weeks. If symptoms do not improve with 48 to 72 hours of high-dose corticosteroid, infliximab may be offered for some toxicities.
• When symptoms and/or laboratory values revert to grade 1 or less, rechallenging with ICPis may be offered; however, caution is advised, especially in those patients with early-onset irAEs. Dose adjustments are not recommended.
• In general, grade 4 toxicities warrant permanent discontinuation of ICPis, with the exception of endocrinopathies that have been controlled by hormone replacement.

All recommendations in this guideline are based on expert consensus, benefits outweigh harms, moderate strength of recommendation.

Significant Survival advantage in Melanoma Patients with Immune-Related Adverse Events (16)



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