Malignant Melanoma

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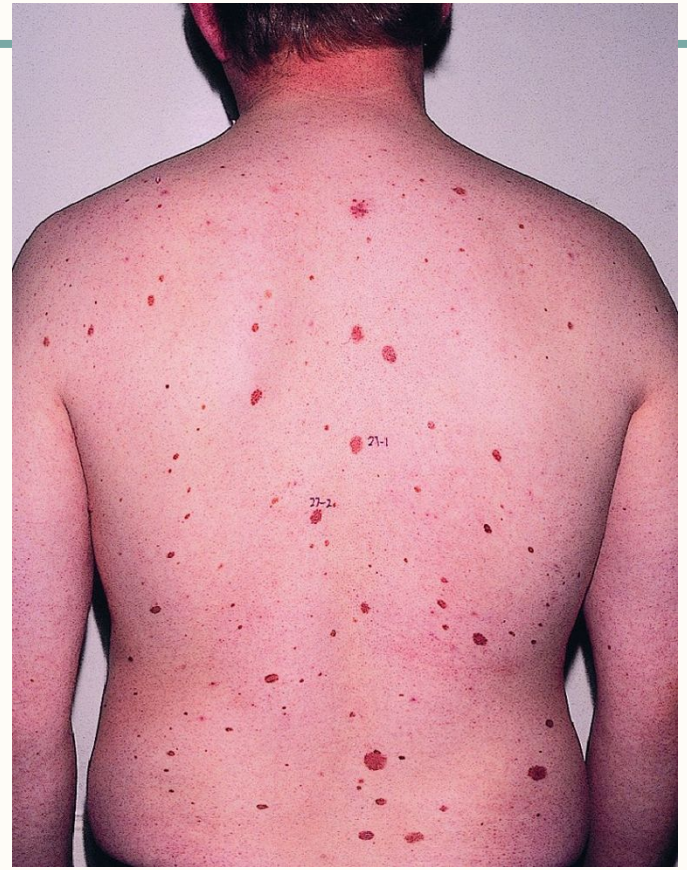
RISK FACTORS

- Fair skinned.
- Hair color other than black.
- Excessive sun exposure .
- Melanoma in first-degree relative(s) .
- Prior ***nonmelanoma*** skin cancer (basal cell and squamous cell carcinoma).
- Presence of ***xeroderma pigmentosum*** or ***familial atypical mole melanoma syndrome***.

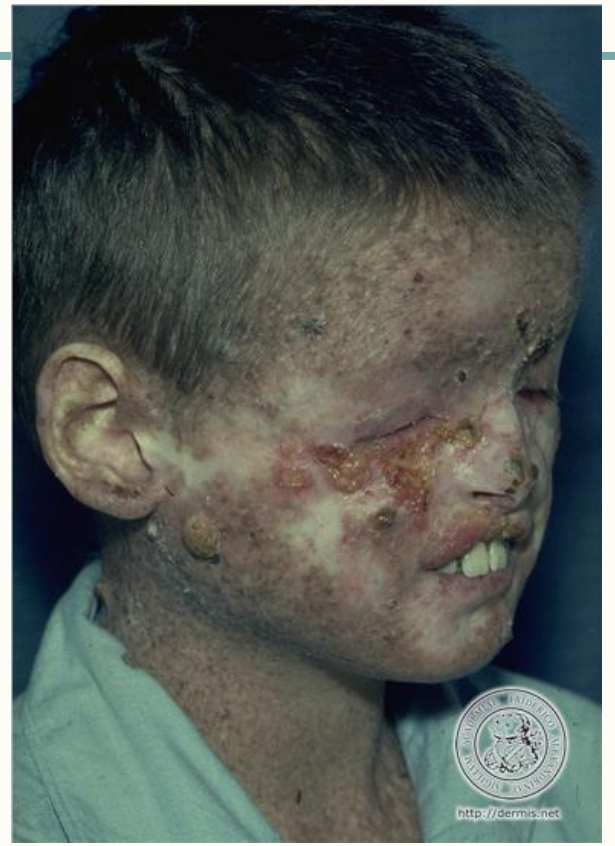
Familial Atypical Mole Melanoma Syndrome

- Autosomal dominant
- Neoplastic risk
- "atypical melanocytic nevus“
- 25-40% with CDKN2A mutation

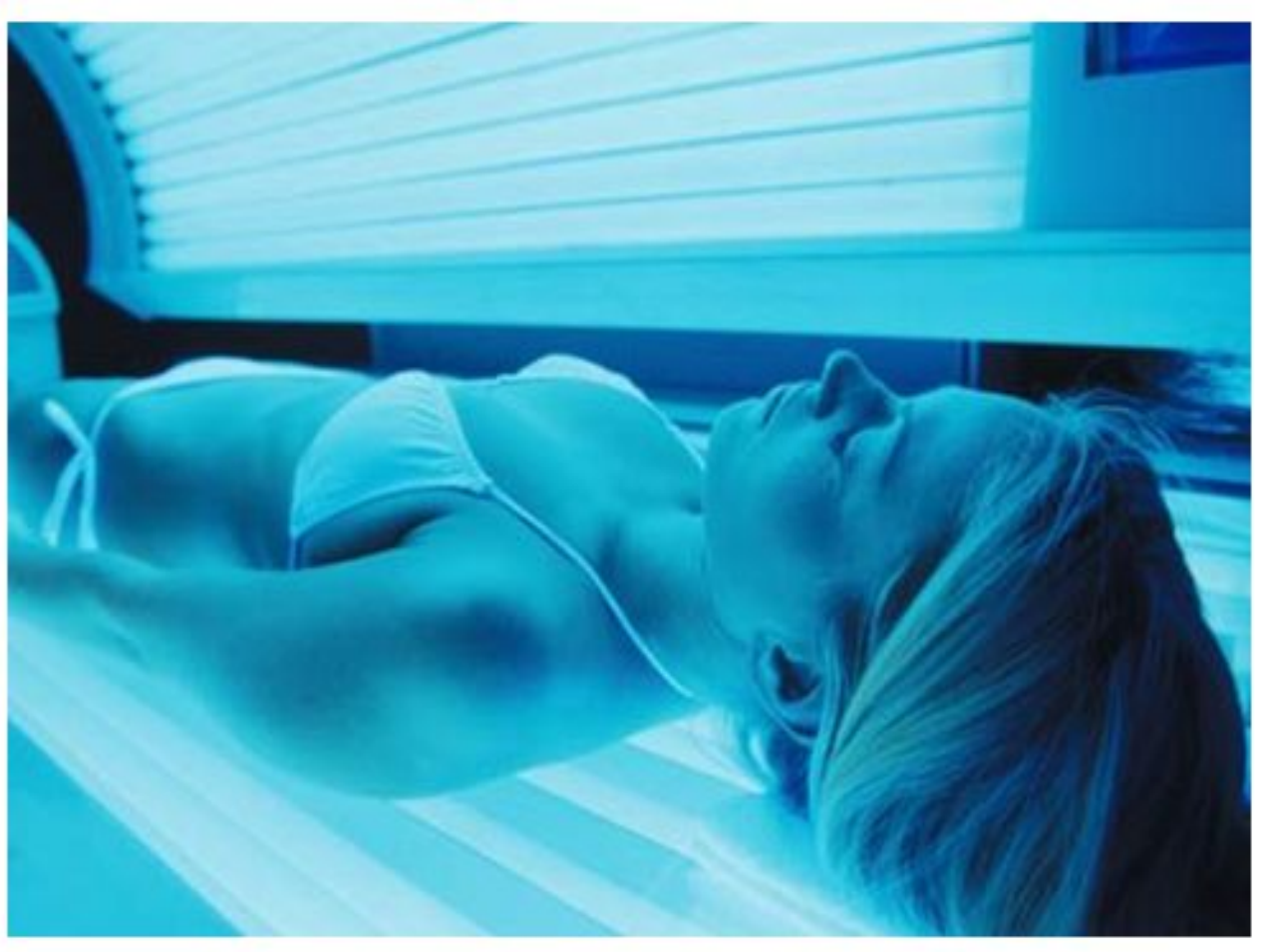


Xeroderma Pigmentosum

- Rare Autosomal recessive disease
- DNA repair enzyme defect
- Photosensitivity
- Photodamage
- Cutaneous malignancies
- Severe ophthalmological abnormalities
- Early death from malignancy



Ultraviolet light



UVC (< 290 nm)

Completely absorbed by the atmosphere and is non-relevant for UV induced skin carcinogenesis.

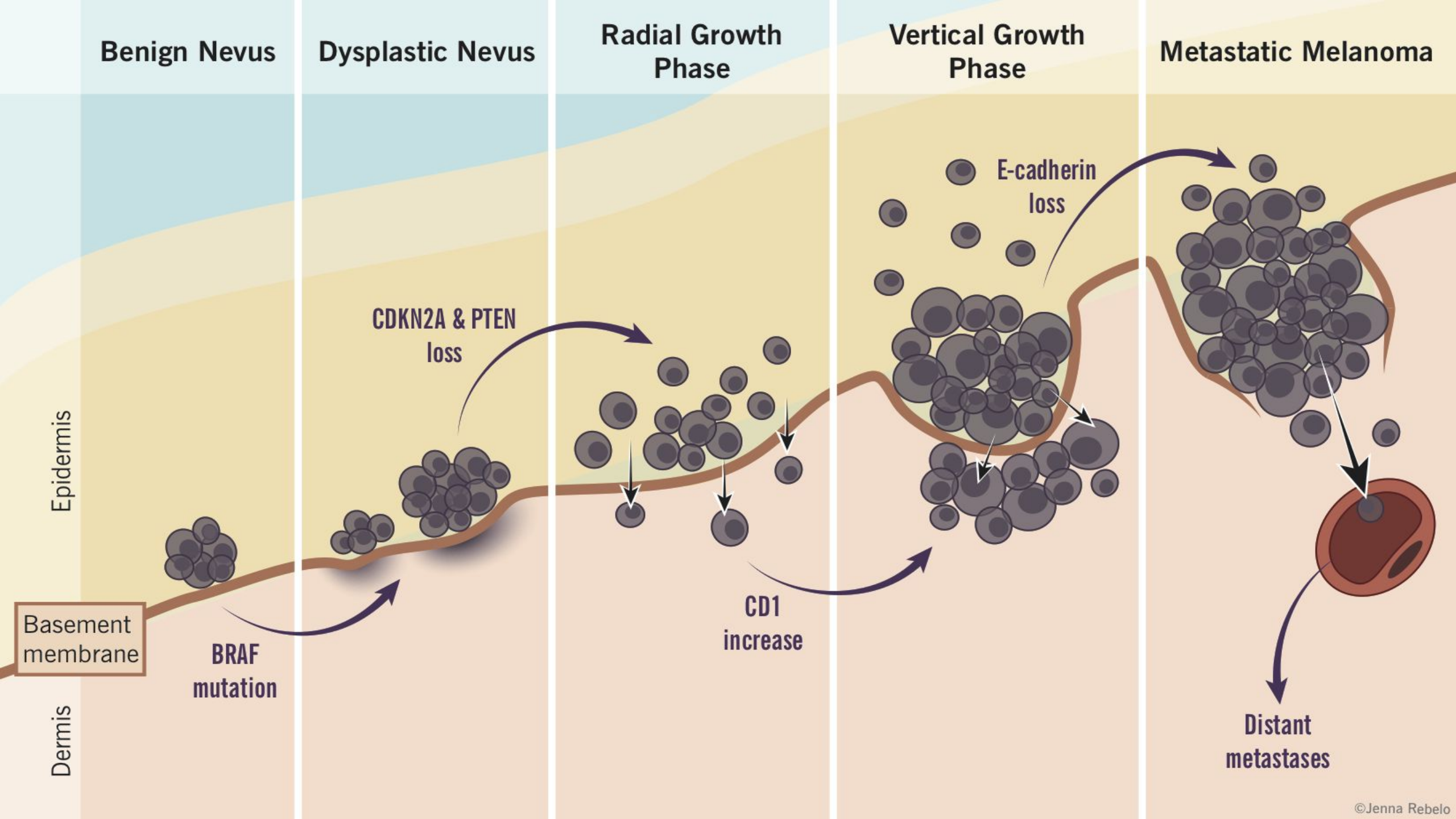
UVB (290-390 nm)

Absorbed by ozone, but 5-10% of it reaches the earth surface.

The exposure to the high penetrating UVB radiation leads to DNA damage .

UVA (520-400 nm)

Genotoxicity seems to be induced by indirect mechanisms mediated by reactive oxygen radicals and associated with chronic sun damage changes.


Benign Nevus
Dysplastic Nevus
Radial Growth Phase
Vertical Growth Phase
Metastatic Melanoma
Epidermis
Dermis
Basement membrane
BRAF mutation
CDKN2A & PTEN loss
CD1 increase
E-cadherin loss
Distant metastases
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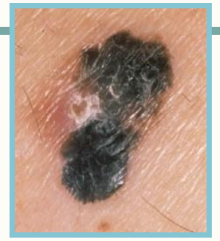
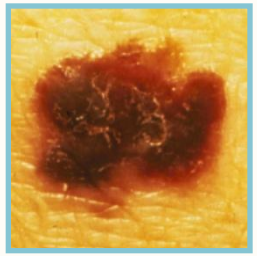
The ABCDEs of Melanoma Diagnosis

Asymmetry



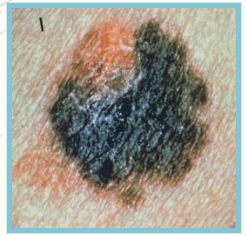
One half of the lesion is shaped differently than the other

Border



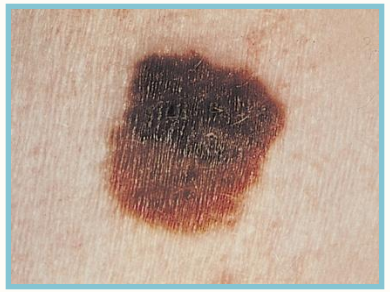
The border of the lesion is irregular, blurred, or ragged

Color



Inconsistent pigmentation, with varying shades of brown and black

Diameter



mm, or a 6< progressive change in size

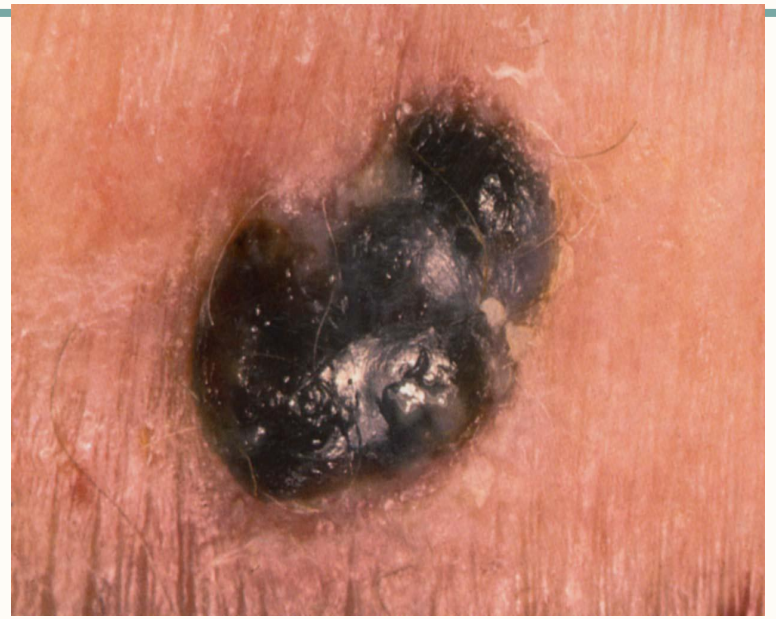
Evolution

History of change in the lesion

TYPES OF MELANOMA

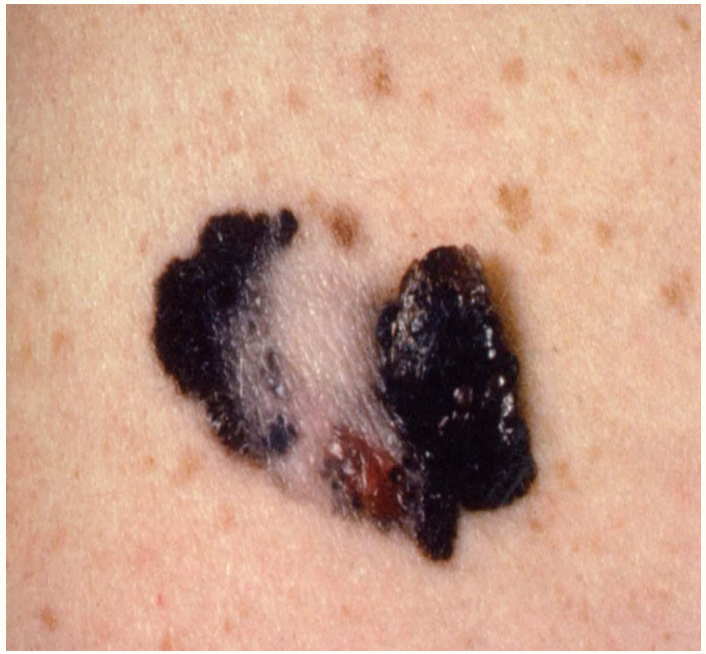
NODULAR

- Commoner in males
- Trunk is a common site
- Poor prognosis
- Black/brown nodule
- Ulceration and bleeding are common



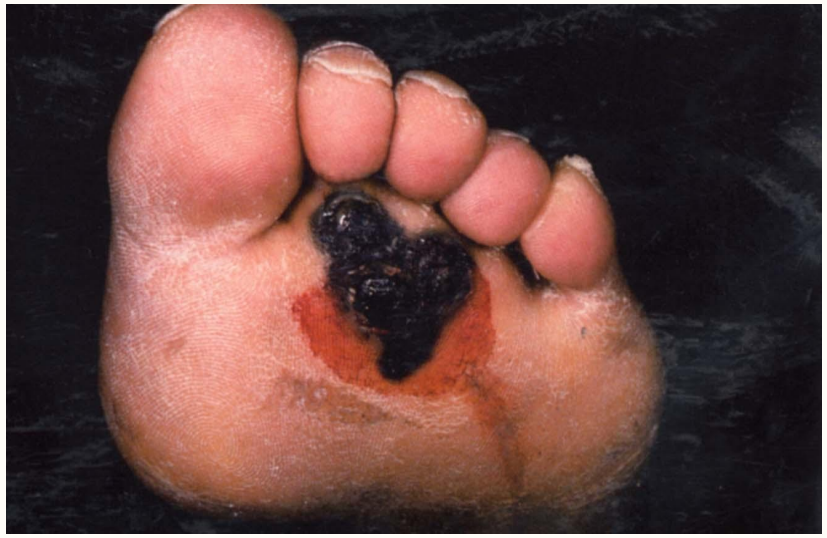
SUPERFICIAL SPREADING

- The most common type of MM in the white-skinned population – 70% of cases
- Commonest sites – lower leg in females and back in males
- In early stages may be small, then growth becomes irregular



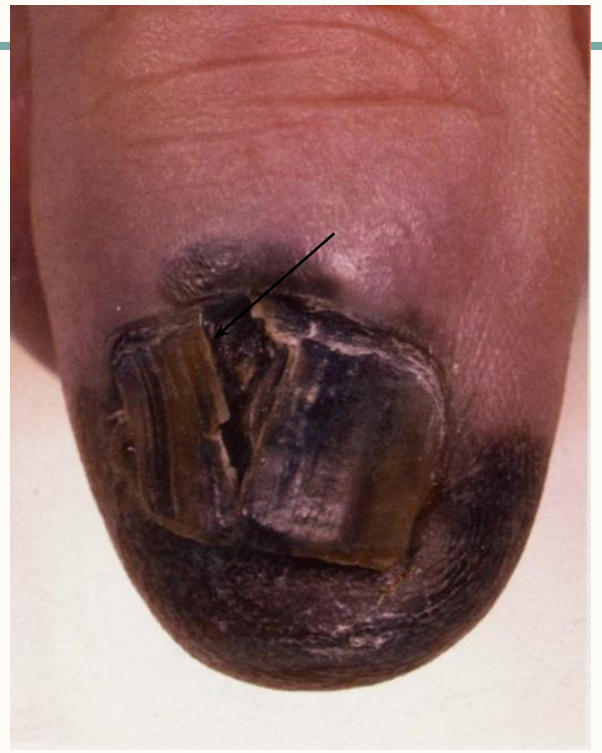
ACRAL LENTIGINOUS MELANOMA

- Commonest MM in nonwhite-skinned nations
- Usually comprises a flat lentiginous area with an invasive nodular component.
- Poorer prognosis.



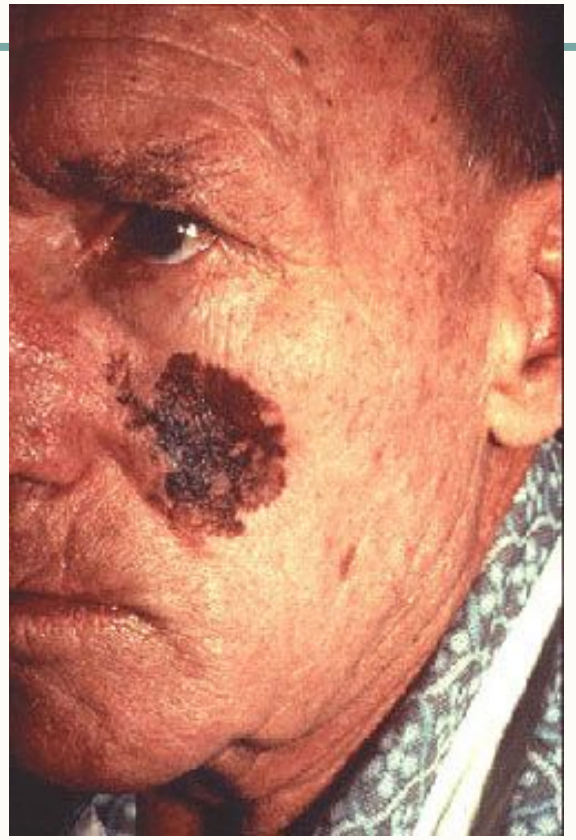
SUBUNGAL MELANOMA

- Rare
- Often diagnosed late – confusion with benign subungal naevus, paronychial infections, trauma.
- Hutchinson's sign – spillage of pigment onto the surrounding nailfold



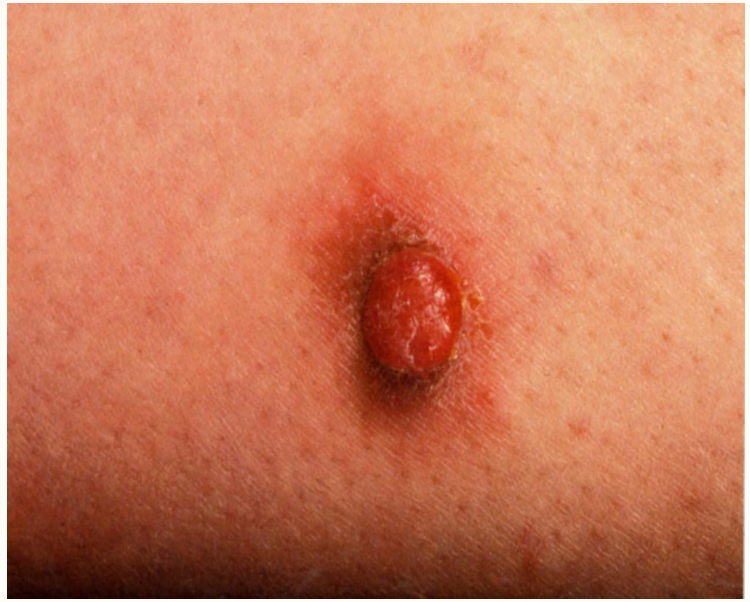
LENTIGO MALIGNA MELANOMA

- Occurs as a late development in a lentigo maligna.
- Mainly on the face in elderly patients .
- May be many years before an invasive nodule develops.



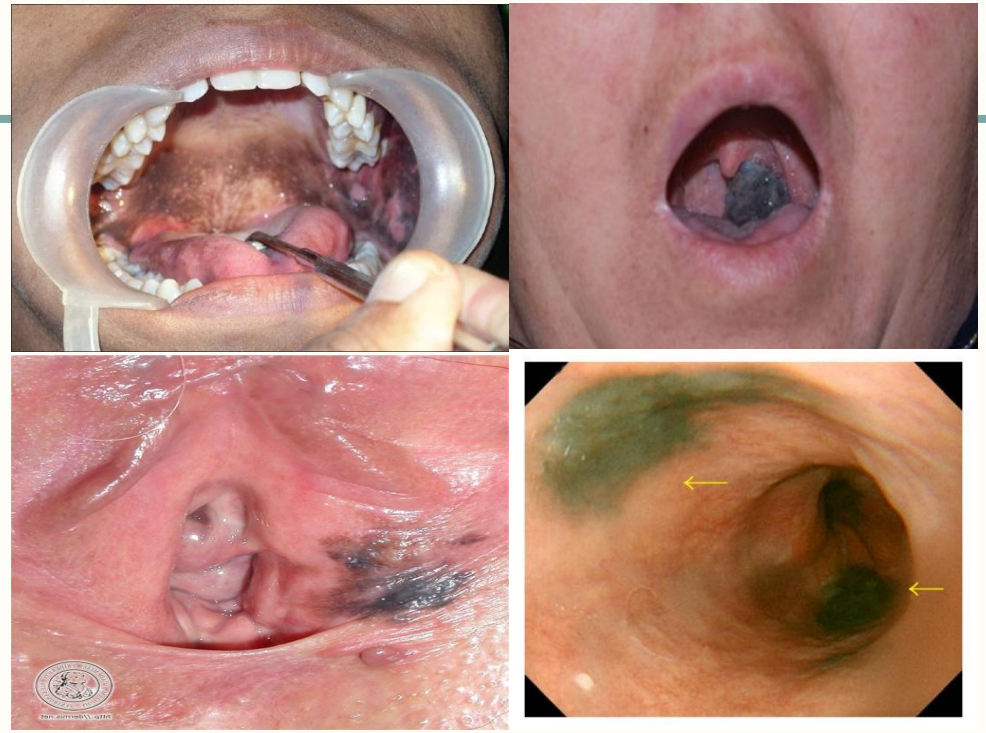
AMELANOTIC MELANOMA

- Diagnosis is often missed clinically.
- The lack of pigmentation is due to the rapid growth of the tumour and the differentiation of the malignant melanocytes.



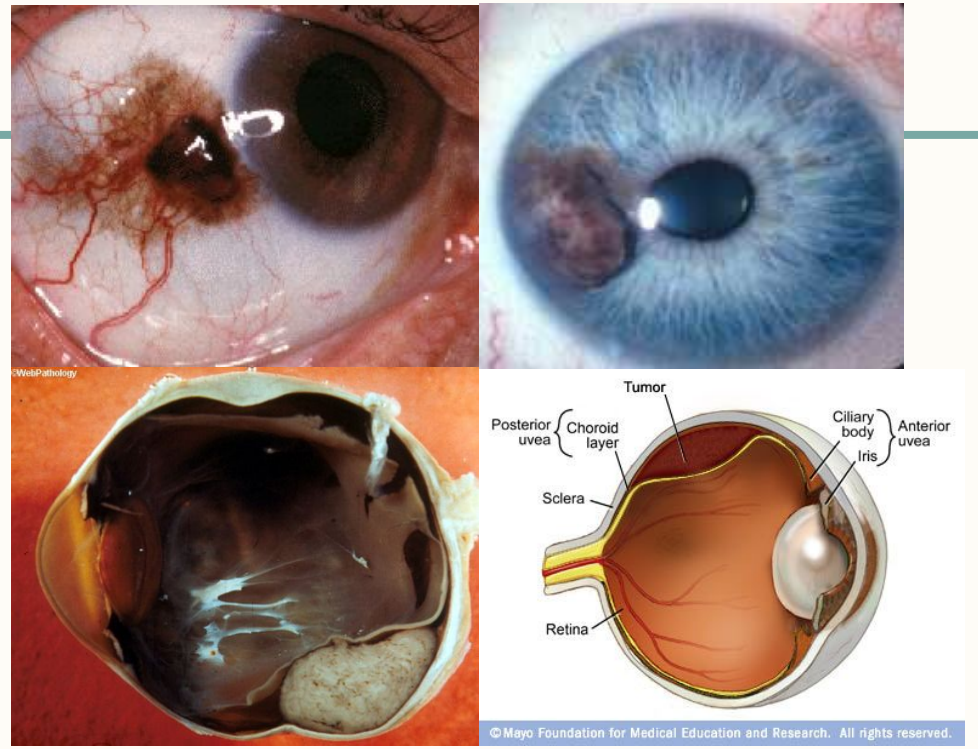
Mucosal melanoma

- Muc M approximately 1 % of all melanomas .
- Arise primarily in the head and neck, anorectal, and vulvovaginal regions (55, 24, and 18 percent of cases, respectively).
- Rarer sites of origin include the urinary tract, gall bladder, and small intestine.
- Worse prognosis



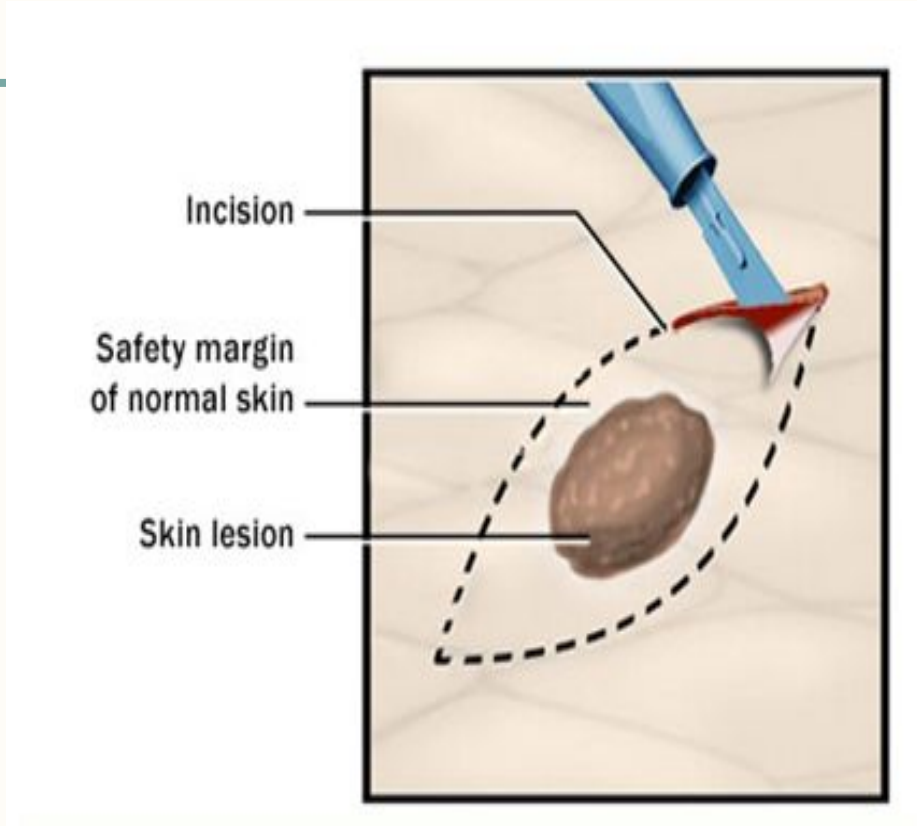
Ocular melanoma

- OM is the most common type of cancer to affect the eye, although it's still quite rare.
- Incidence: 5.3 to 10.9 cases per million
- The incidence of ocular melanoma increases with age, and most cases are diagnosed in people in their 50s.
- OM may be more common in people who have atypical mole syndrome .



Skin biopsy

- ✔ Excisional Bx.
- ✔ Location
- ✔ Breslow thickness
- ✔ Ulceration
- ✔ Peripheral and deep margins.



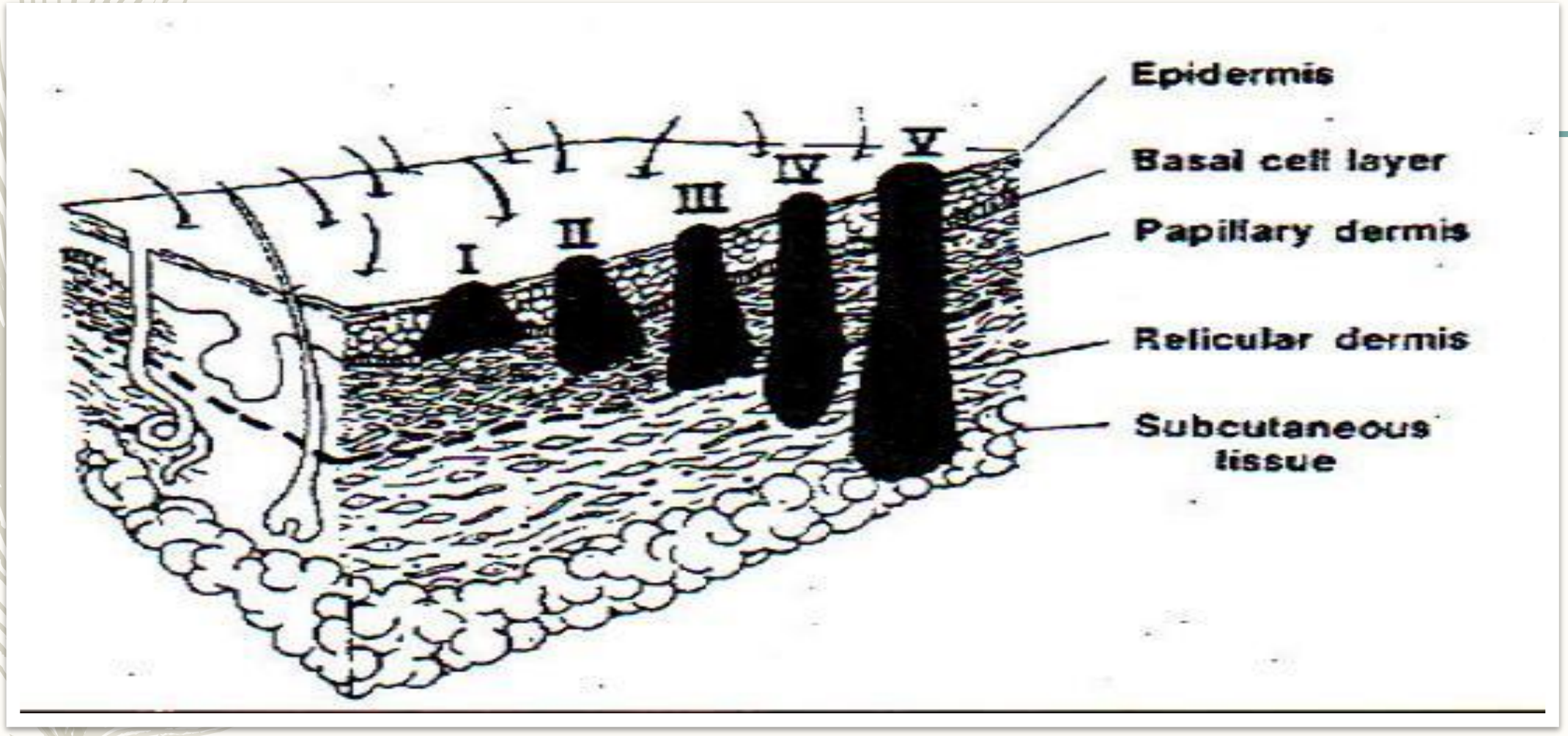
Breslow Thickness:

- **< 1 mm (T1) thin**
- **1-2 mm (T2)**
- **2-4 mm (T3)**

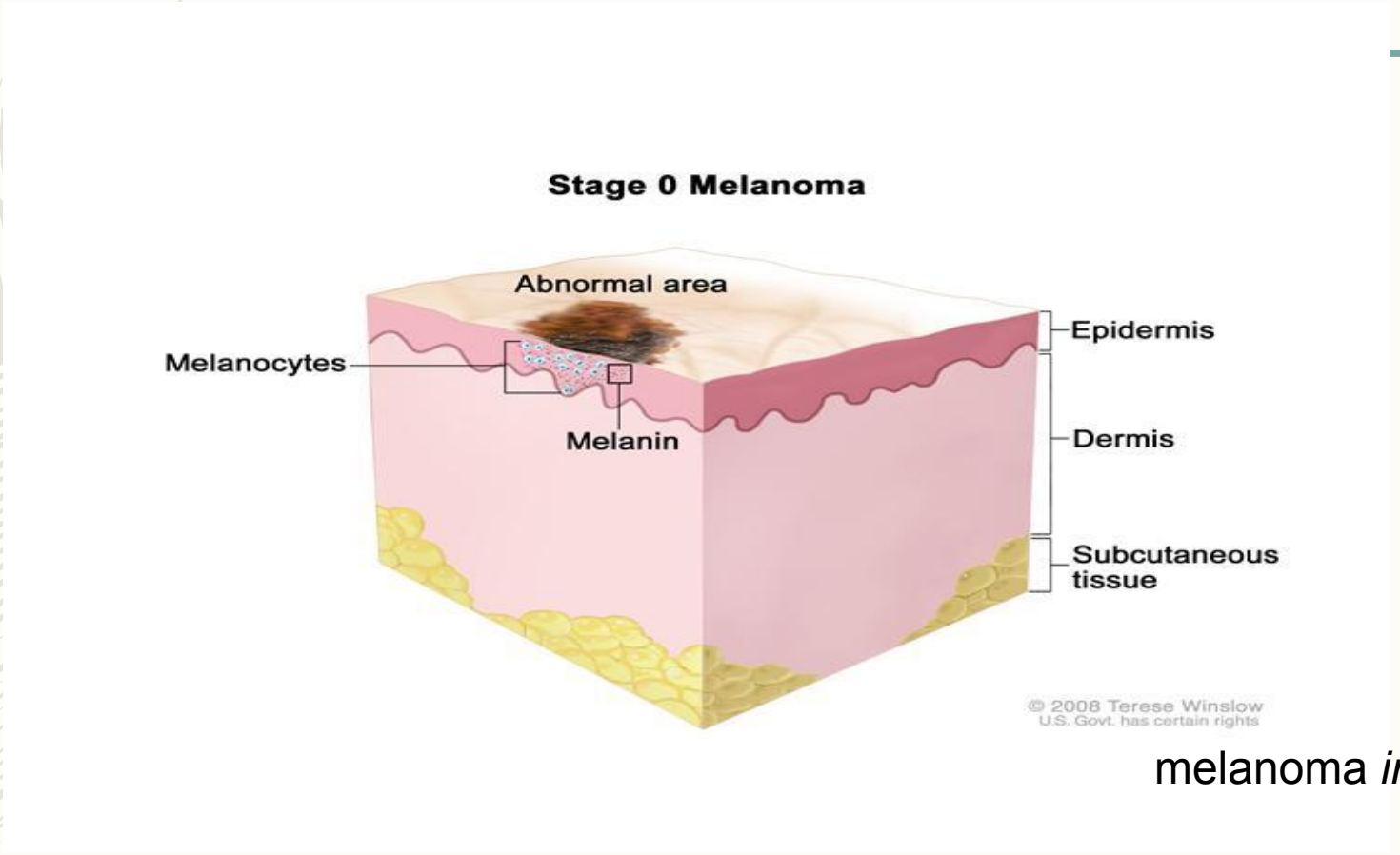
Intermediate

- **> 4.0 mm (T4) thick**

Clark Level

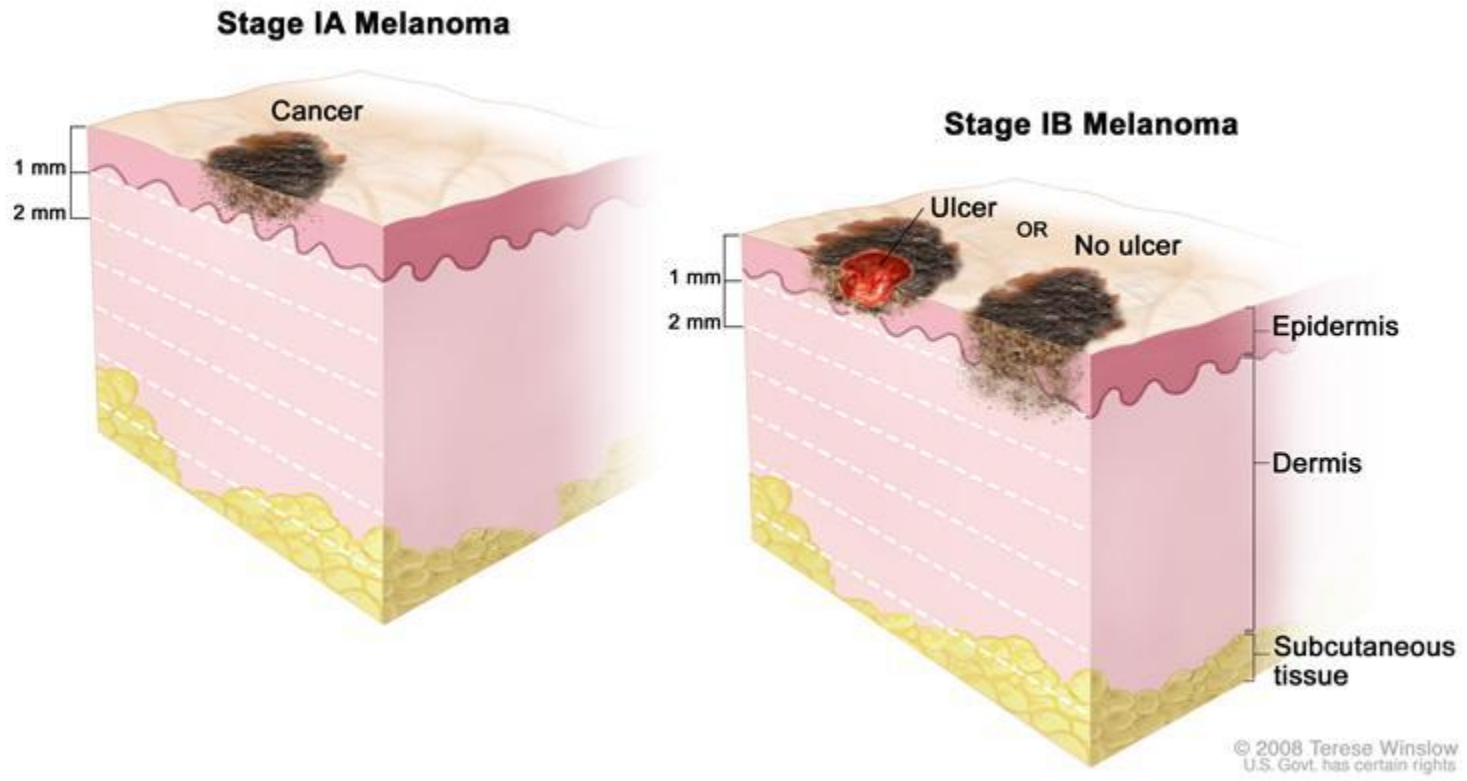

I
II
III
IV
V
Epidermis
Basal cell layer
Papillary dermis
Relicular dermis
Subcutaneous tissue

Stage 0: (TisN0M0).

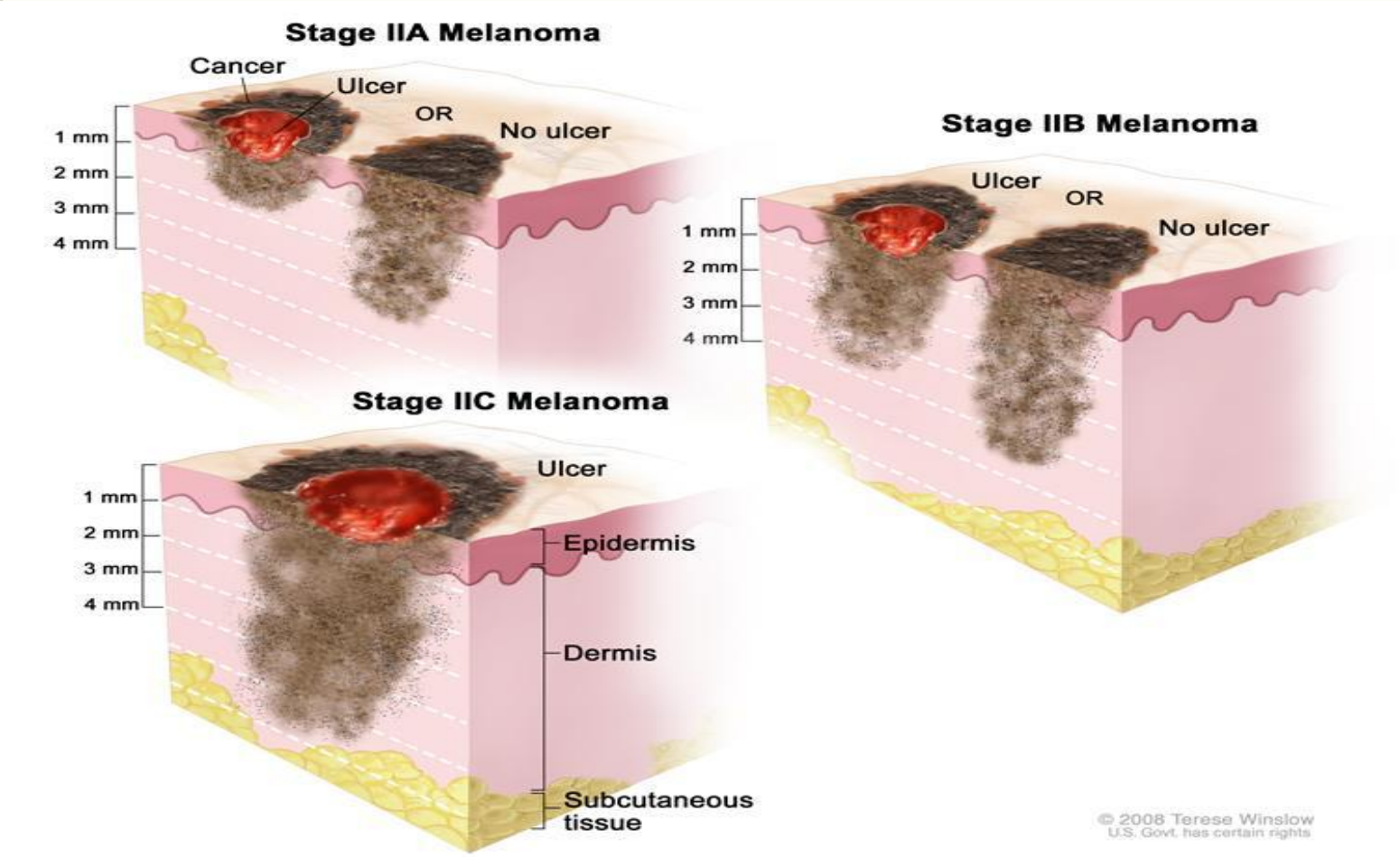


melanoma *in situ*

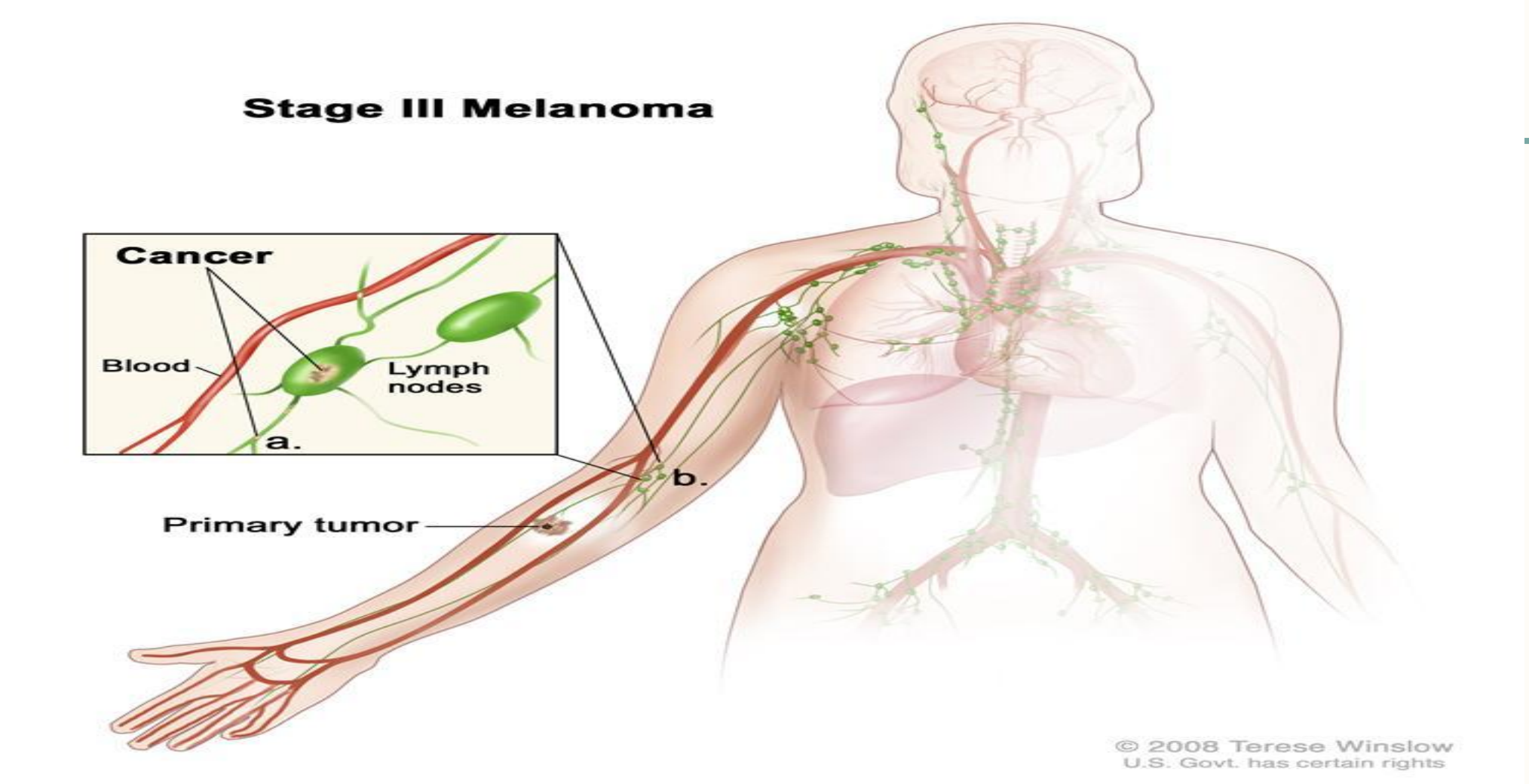
Stage I: Local disease - superficial



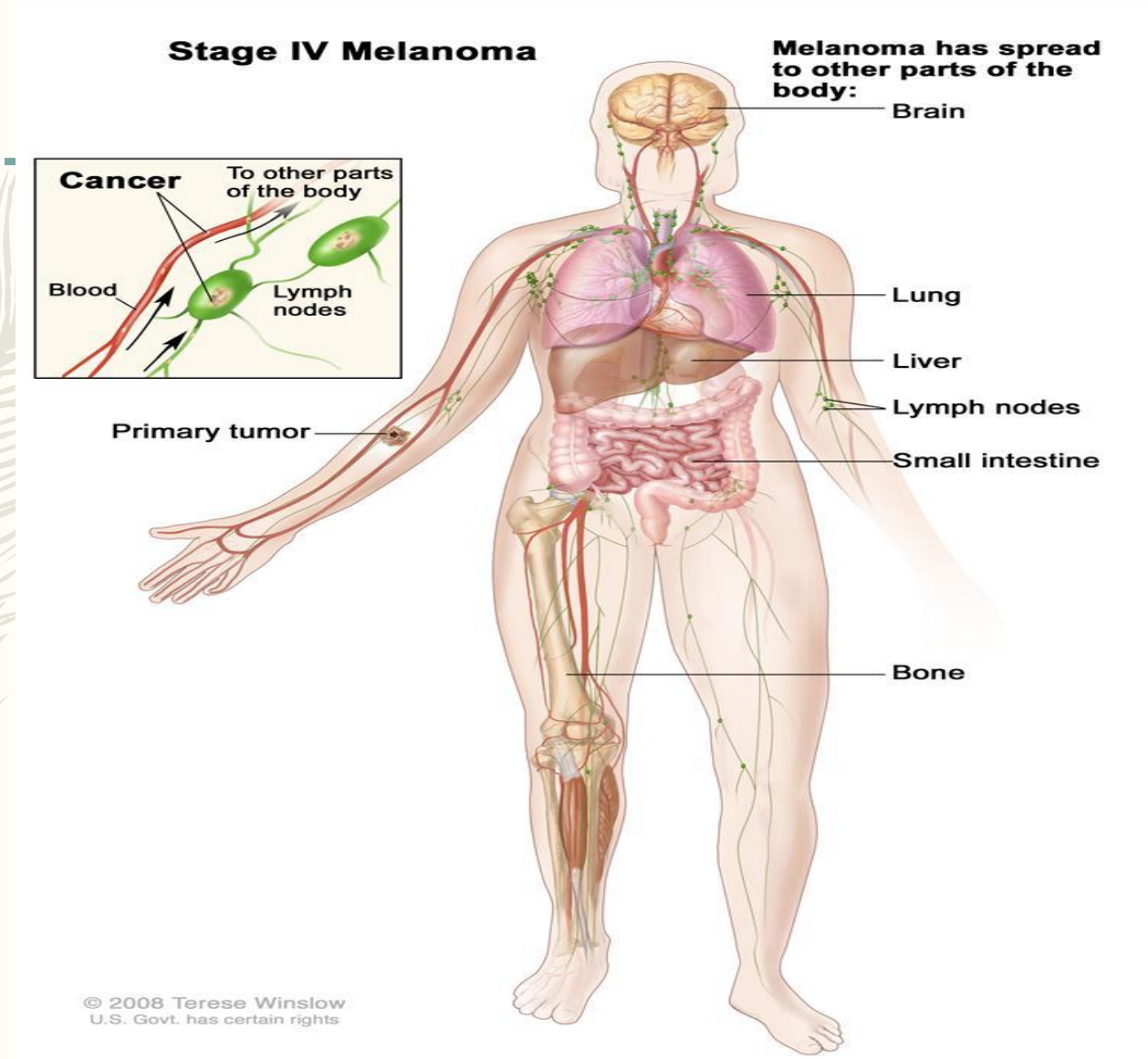
Stage II: Local disease - deep invasion.



Stage III: Regional disease

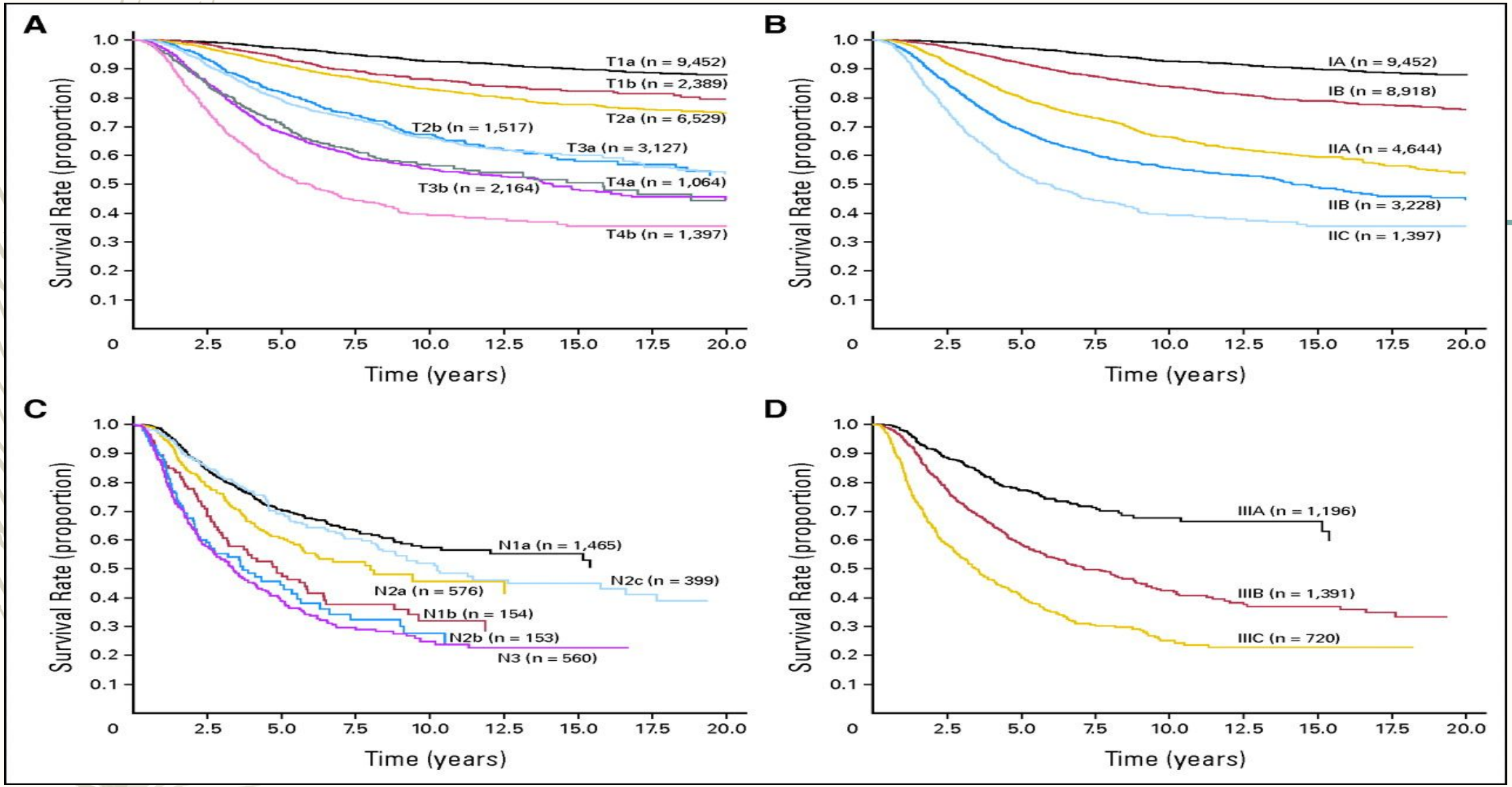


Stage IV: Metastatic disease



Prognostic factors

- Depth of Invasion
- Ulceration
- Lymph Node
- *Mitotic Rate (TNM staging system 2010)*
- *LDH level*
- Patient Gender : women better than men
- Anatomic site:
  - head and neck- scalp worse
  - extremity better than trunk


A
Survival Rate (proportion)
Time (years)
T1a (n = 9,452)
T1b (n = 2,389)
T2a (n = 6,529)
T2b (n = 1,517)
T3a (n = 3,127)
T3b (n = 2,164)
T4a (n = 1,064)
T4b (n = 1,397)
B
Survival Rate (proportion)
Time (years)
IA (n = 9,452)
IB (n = 8,918)
IIA (n = 4,644)
IIB (n = 3,228)
IIC (n = 1,397)
C
Survival Rate (proportion)
Time (years)
N1a (n = 1,465)
N2c (n = 399)
N2a (n = 576)
N1b (n = 154)
N2b (n = 153)
N3 (n = 560)
D
Survival Rate (proportion)
Time (years)
IIIA (n = 1,196)
IIIB (n = 1,391)
IIIC (n = 720)

PRINCIPLES OF SURGICAL MARGINS FOR WIDE EXCISION OF PRIMARY MELANOMA

Tumor Thickness	Recommended Clinical Margins[2]
In situ[1]	0.5 cm
≤ 1.0 mm	1.0 cm (category 1)
1.01 - 2 mm	1-2 cm (category 1)
2.01 - 4 mm	2.0 cm (category 1)
> 4 mm	2.0 cm

NCCN Guidelines Version 1.2017 Staging Melanoma

NCCN Guidelines Index
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Discussion

Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging System for Melanoma (7th ed., 2010)

Primary Tumor (T)

TX	Primary tumor cannot be assessed (eg, curettaged or severely regressed melanoma)
T0	No evidence of primary tumor
Tis	Melanoma *in situ*
T1	Melanomas 1.0 mm or less in thickness
T2	Melanomas 1.01–2.0 mm
T3	Melanomas 2.01–4.0 mm
T4	Melanomas more than 4.0 mm

Note: a and b sub categories of T are assigned based on ulceration and number of mitoses per mm^2 as shown below:

T classification	*Thickness (mm)*	*Ulceration Status/Mitoses*
T1	≤1.0	a: w/o ulceration and mitosis $<1/mm^2$ b: with ulceration or mitoses $\geq 1/mm^2$
T2	1.01–2.0	a: w/o ulceration b: with ulceration
T3	2.01–4.0	a: w/o ulceration b: with ulceration
T4	>4.0	a: w/o ulceration b: with ulceration

Regional Lymph Nodes (N)

NX	Patients in whom the regional lymph nodes cannot be assessed (eg, previously removed for another reason)
N0	No regional metastases detected
N1-3	Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (in transit or satellite metastases)

Note: N1-3 and a-c sub categories are assigned as shown below:

N Classification	*No. of Metastatic Nodes*	*Nodal Metastatic Mass*
N1	1 node	a: micrometastasis* b: macrometastasis**
N2	2–3 nodes	a: micrometastasis* b: macrometastasis** c: in transit met(s)/ satellite(s) *without* metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) *with* metastatic node(s)	

*Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).

**Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

Distant Metastasis (M)

M0	No detectable evidence of distant metastases
M1a	Metastases to skin, subcutaneous, or distant lymph nodes
M1b	Metastases to lung
M1c	Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH

Note: Serum LDH is incorporated into the M category as shown below:

M Classification	*Site*	*Serum LDH*
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Anatomic Stage/Prognostic Groups

Clinical Staging*

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	AnyT	≥N1	M0
Stage IV	Any T	Any N	M1

*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

Pathologic Staging**

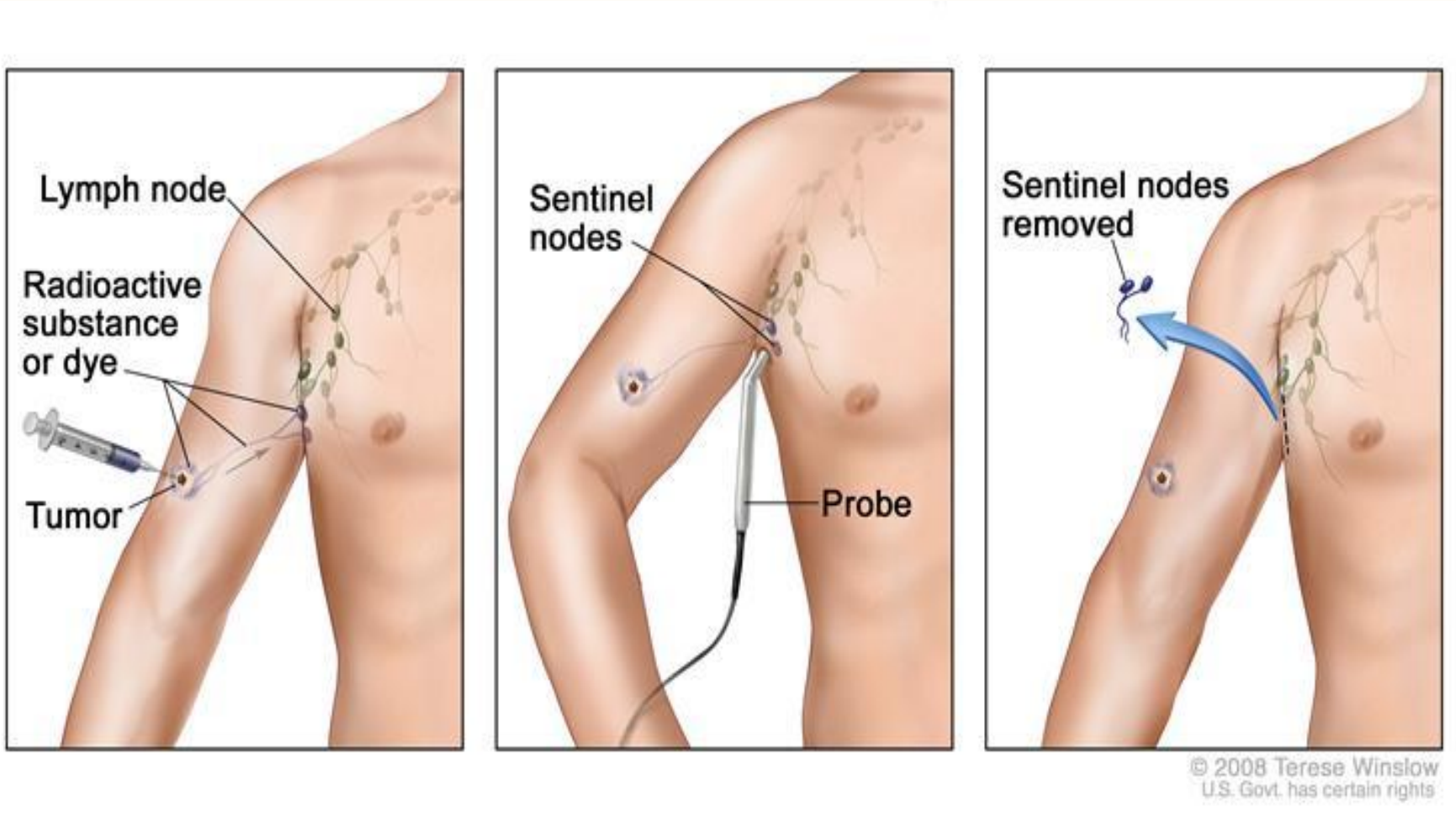
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T(1–4)a	N1a	M0
	T(1–4)a	N2a	M0
Stage IIIB	T(1–4)b	N1a	M0
	T(1–4)b	N2a	M0
	T(1–4)a	N1b	M0
	T(1–4)a	N2b	M0
	T(1–4)a	N2c	M0
Stage IIIC	T(1–4)b	N1b	M0
	T(1–4)b	N2b	M0
	T(1–4)b	N2c	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

**Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

Sentinel lymph node biopsy

- SLN = **First node(s) draining the area of primary lesion**.
- Sentinel node biopsy is generally **recommended for patients with melanomas at least 1 mm thick or more then 0.75 mm with 1 or more mitoses**
- Prognostic factor - data for patient.
- Applying adjuvant therapy.
- **Survival benefit.**

Sentinel lymph node mapping and biopsy



Adjuvant Therapy of Melanoma: History

- Microbial/chemical immunomodulators (BCG, levamisole)
- Chemotherapy, chemobiotherapy, BMT
- Vaccines
  - Whole cell and cell-derived antigen
  - Peptide and protein antigen (T cell)
  - Ganglioside antigen (B cell)
- Passive (antibody) and adoptive (cellular) transfer
- IFN
- Radiation

Adjuvant therapy

- Potential candidates
  - Stage IIB
  - Stage III

(recurrence rate 50%-/+)

- Chemotherapy - not effective (DTIC).
- Immunotherapy - IFN α and Ipillimumab
- Vaccination – not effective.
- Clinical trails (anti BRAF , anti PD1, anti PD1+anti CTLA4- ongoing)

CLINICAL/ PATHOLOGIC STAGE	WORKUP[q]	PRIMARY TREATMENT	ADJUVANT TREATMENT
Stage III (sentinel node positive)	• Consider imaging[i] for baseline staging (category 2B) • Imaging[i] to evaluate specific signs or symptoms	Discuss and offer complete lymph node dissection[r]	Clinical trial or Observation or Interferon alfa[s] or High-dose ipilimumab for SLN metastasis >1 mm[t,u]
Stage III (clinically positive node[s])	• FNA preferred, if feasible, or core, incisional, or excisional biopsy • Imaging[i] for baseline staging and to evaluate specific signs or symptoms	Wide excision of primary tumor[m] (category 1) + complete therapeutic lymph node dissection	Locoregional option: • Consider RT to nodal basin in selected high-risk patients based on location, size, and number of involved nodes, and/or macroscopic extranodal extension[v,w] (category 2B)
			Systemic options: • Clinical trial • Observation • Interferon alfa[s] • High-dose ipilimumab[t] (category 1) • Biochemotherapy (category 2B)[x]

See Follow-up (ME-9)

[i] See Principles of Imaging--Workup (ME-C).

[m] See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-D).

[q] Mutational analysis is recommended if patients are being considered for either routine treatment or clinical trials, but is not recommended for patients with cutaneous melanoma who are otherwise NED.

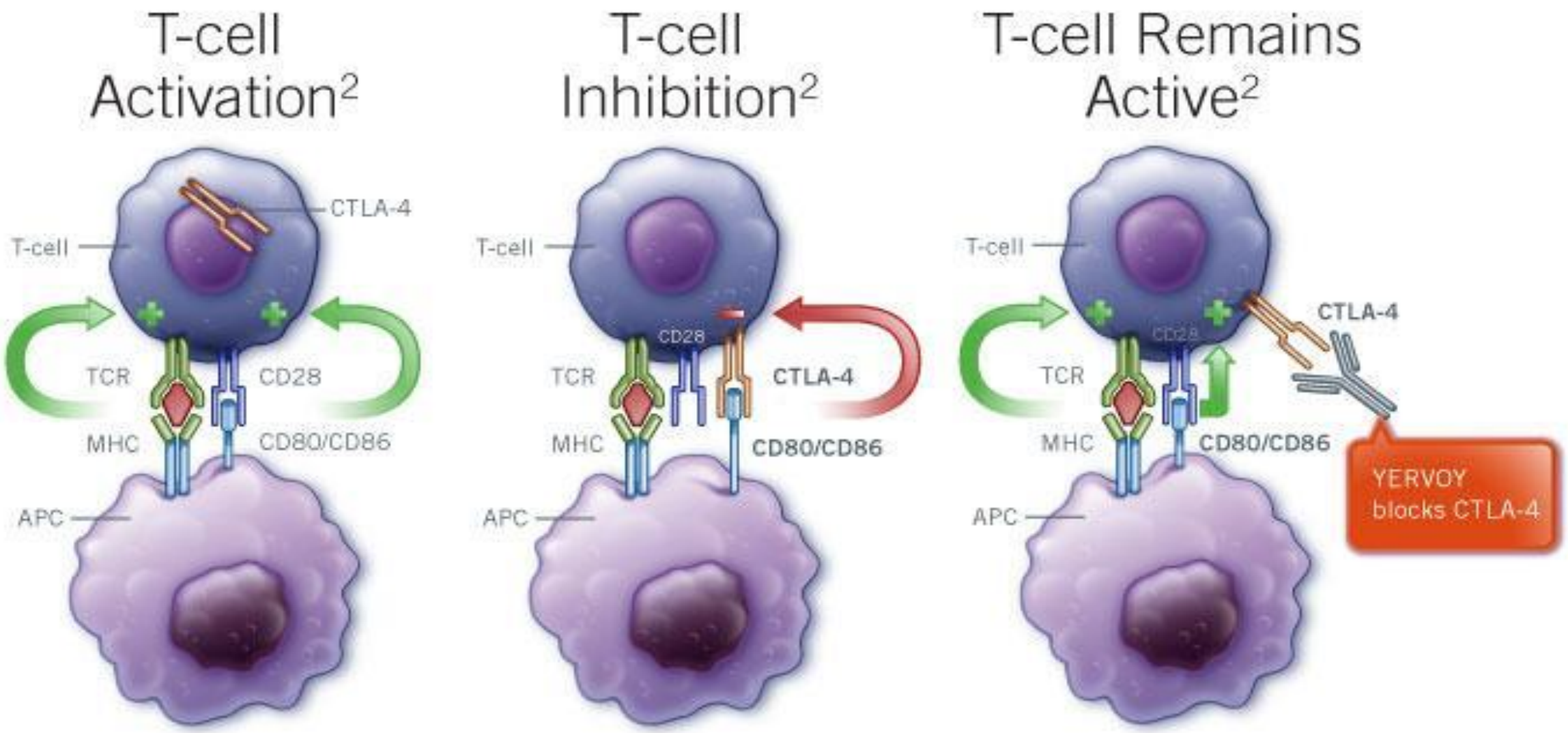
[r] CLND contributes to staging. Its impact on regional disease control and overall survival is the focus of ongoing clinical trials. Factors that predict non-sentinel lymph node positivity include sentinel node tumor burden, number of positive nodes, and thickness/ulceration of the primary tumor. See Principles of Complete Lymph Node Dissection (ME-E).

[s] Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been shown to improve DFS (category 1); but there is no

IPILIMUMAB

Yervoy

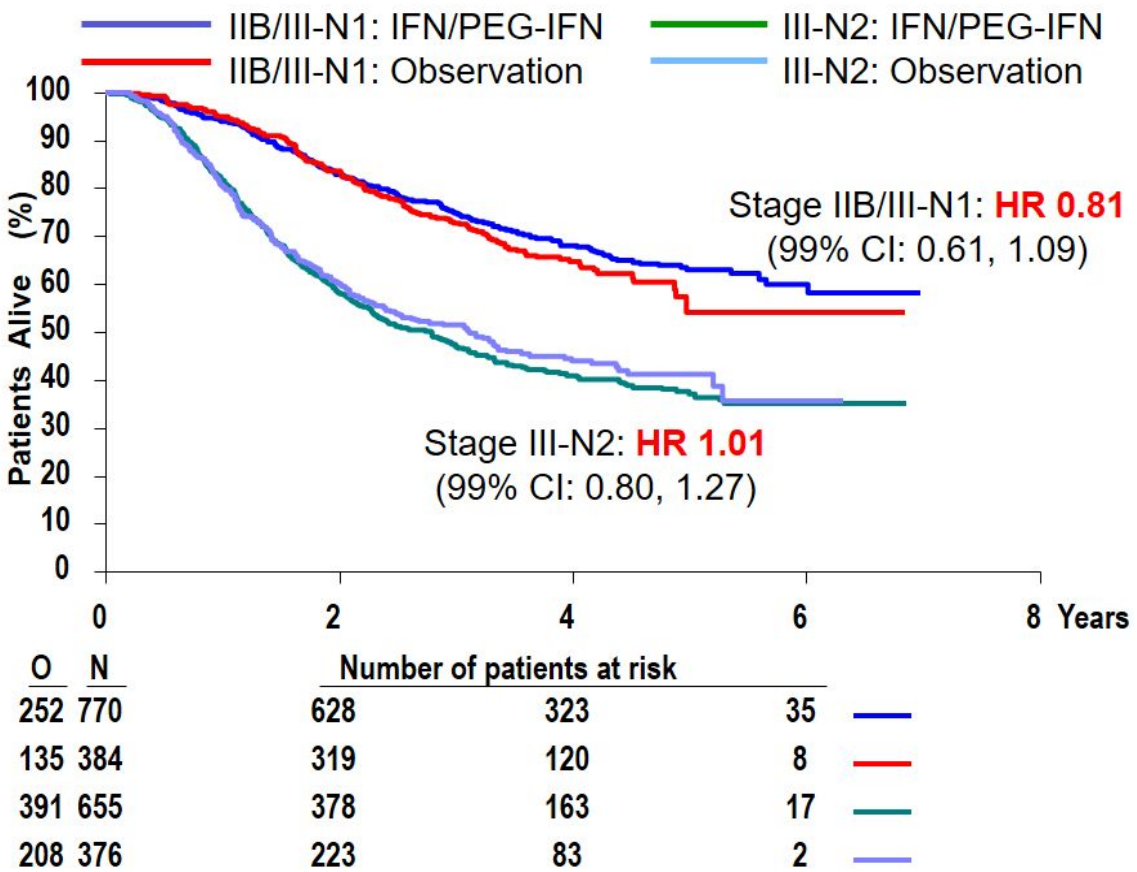
Anti CTLA4 Antibody



APC: antigen presenting cell; CTLA-4: cytotoxic T-lymphocyte antigen 4; MHC: major histocompatibility complex; TCR: T-cell receptor.

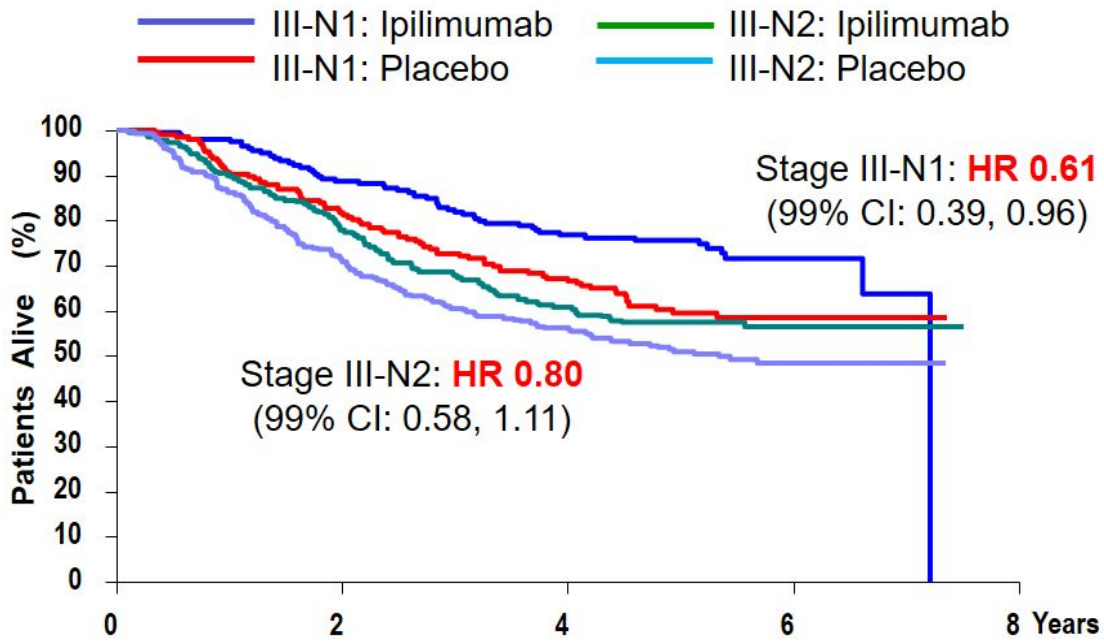
Comparison of Impact on OS:
EORTC IFN vs Ipilimumab Experience

IFN/PEG-IFN
EORTC 18952/EORTC 18991[1]



O	N	Number of patients at risk			
252	770	628	323	35	
135	384	319	120	8	
391	655	378	163	17	
208	376	223	83	2	

Ipilimumab
EORTC 18071



O	N	Number of patients at risk			
54	210	175	145	34	
76	193	154	122	23	
108	265	194	145	28	
138	283	194	151	35	

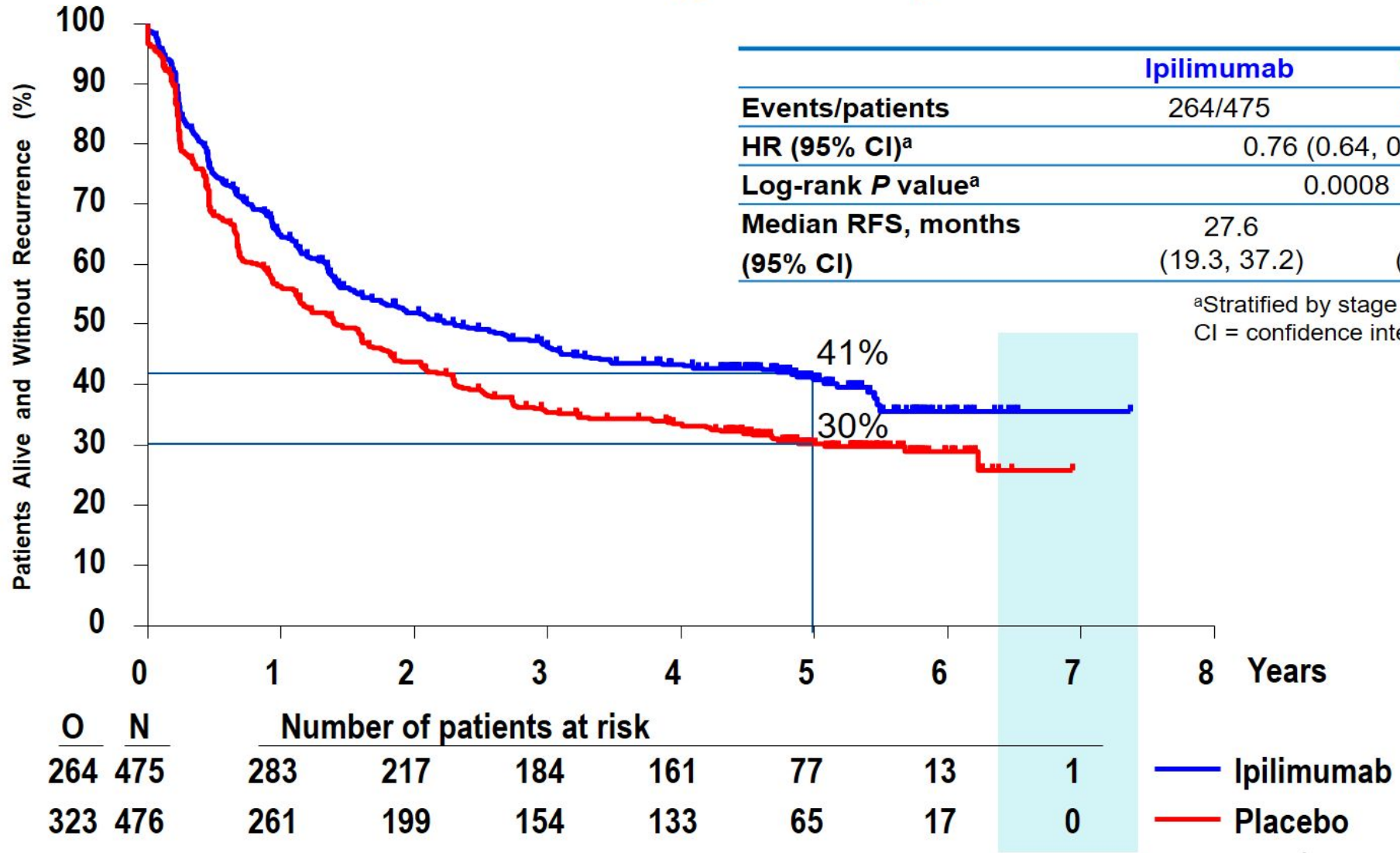
EORTC

1. Eggermont AM, et al. *Eur J Cancer*. 2012;48:218-225.

RFS (per IRC)

	Ipilimumab	Placebo
Events/patients	264/475	323/476
HR (95% CI)[a]	0.76 (0.64, 0.89)	
Log-rank *P* value[a]	0.0008	
Median RFS, months (95% CI)	27.6 (19.3, 37.2)	17.1 (13.6, 21.6)

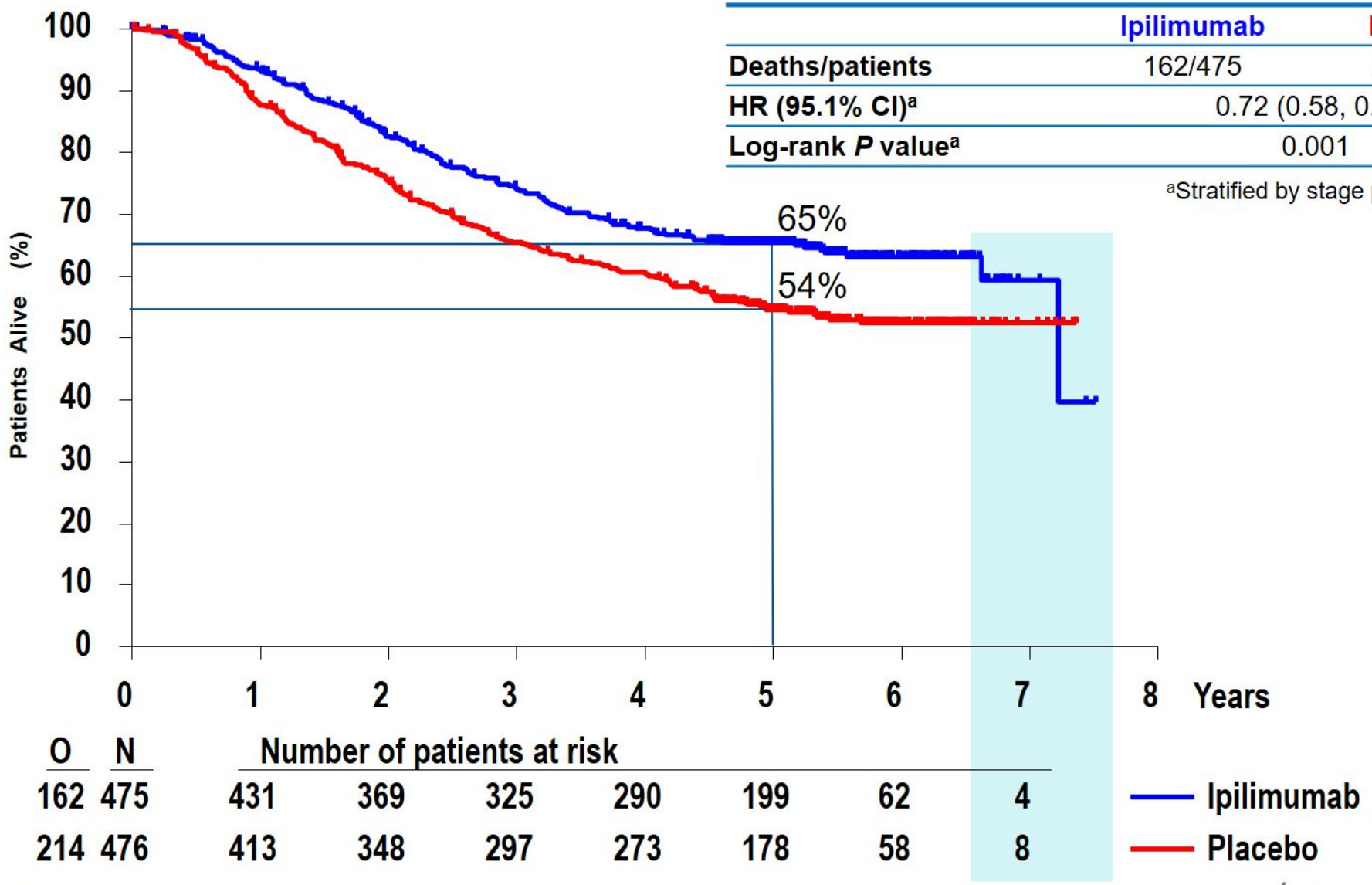
[a]Stratified by stage provided at randomization.
CI = confidence interval.



OS

	Ipilimumab	Placebo
Deaths/patients	162/475	214/476
HR (95.1% CI)[a]	0.72 (0.58, 0.88)	
Log-rank *P* value[a]	0.001	

[a]Stratified by stage provided at randomization.



Safety Summary

	Ipilimumab (n = 471)		Placebo (n = 474)	
	Any Grade	Grade 3/4	Any grade	Grade 3/4
Any AE, %	98.7	54.1	91.1	26.2
Treatment-related AE, %	94.1	45.4	59.9	4.0
Treatment-related AE leading to discontinuation, %	48.0	32.9	1.5	0.6
Any immune-related AE, %	90.4	41.6	39.7	2.7

- No new deaths due to drug-related AEs compared with the primary analysis
  - 5 patients (1.1%) in the ipilimumab group
    - 3 patients with colitis (2 with gastrointestinal perforations)
    - 1 patient with myocarditis
    - 1 patient had multiorgan failure with Guillain-Barré syndrome
  - No deaths related to study drug in the placebo group

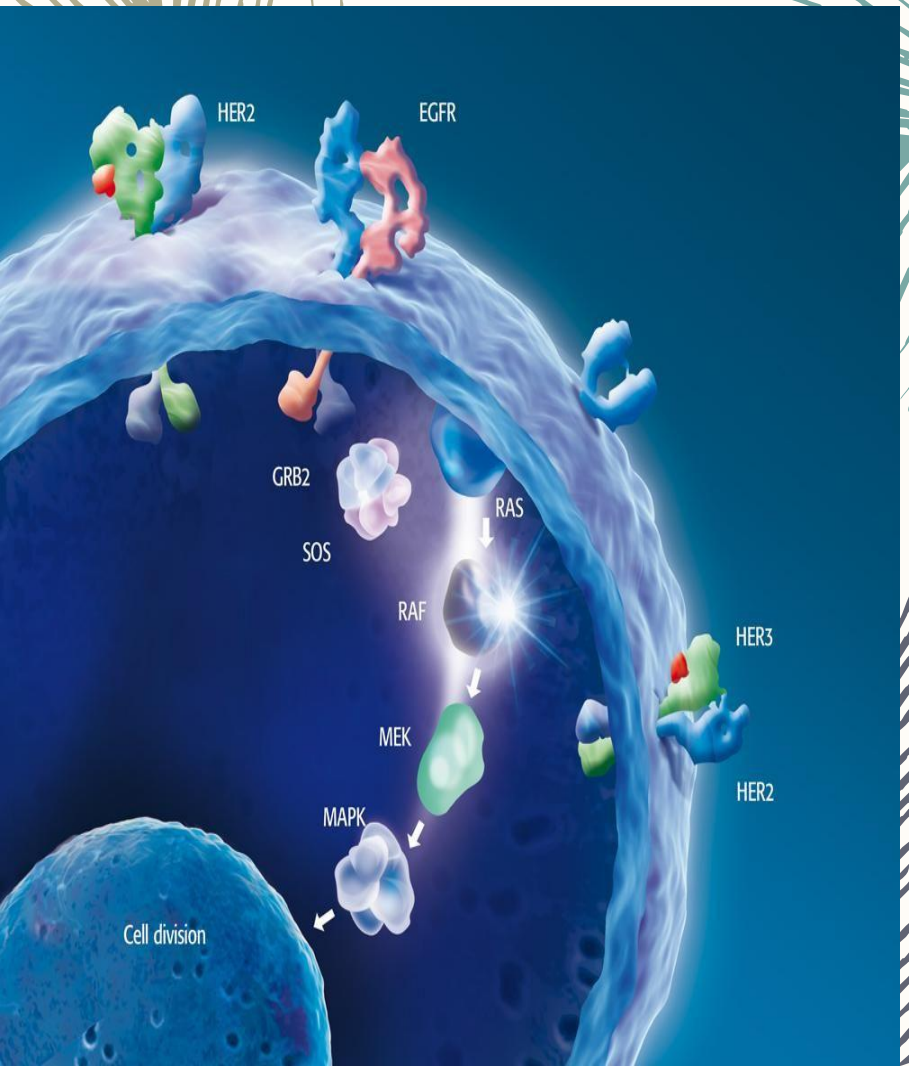
IFN α - Side effects

- **Acute toxicity :**

  (Due to PGE2 synthesis and/or other cytokines)
  - Flue like syndrome
  - malaise
  - Arthralgia
  - DLT - hepatotoxicity
- **Chronic constitutional effects:**

  (Due to hypothalamic, endocrine and/or neurotransmitter dysfunction)
  - fatigue
  - anorexia
  - weight loss
  - depression
  - impaired cognitive function
  - diminished libido and potency
  - myelosuppression
  - Hepatic toxicity

Treatment Options for advanced Melanoma

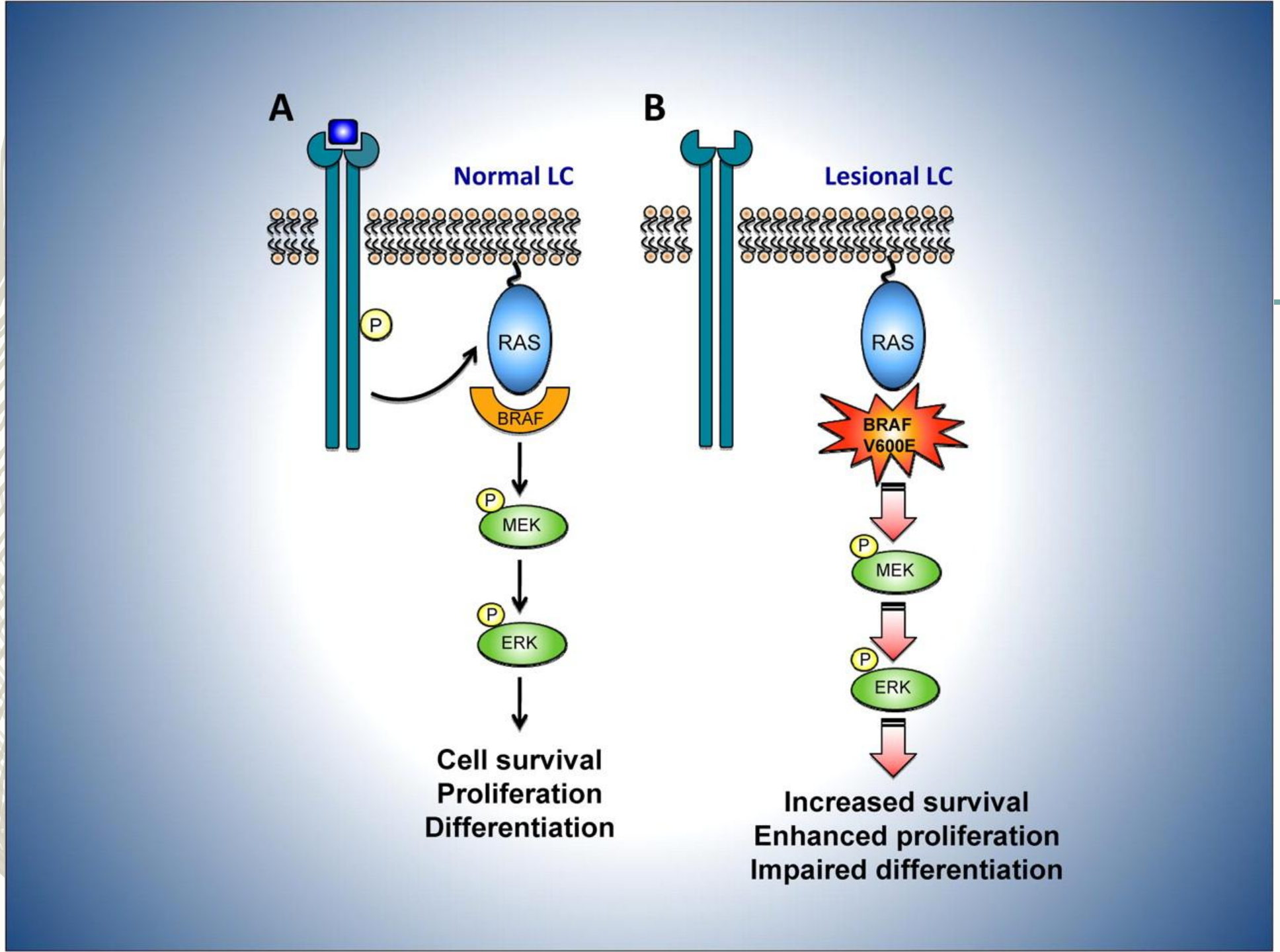


BRAF\MEK Inhibitors

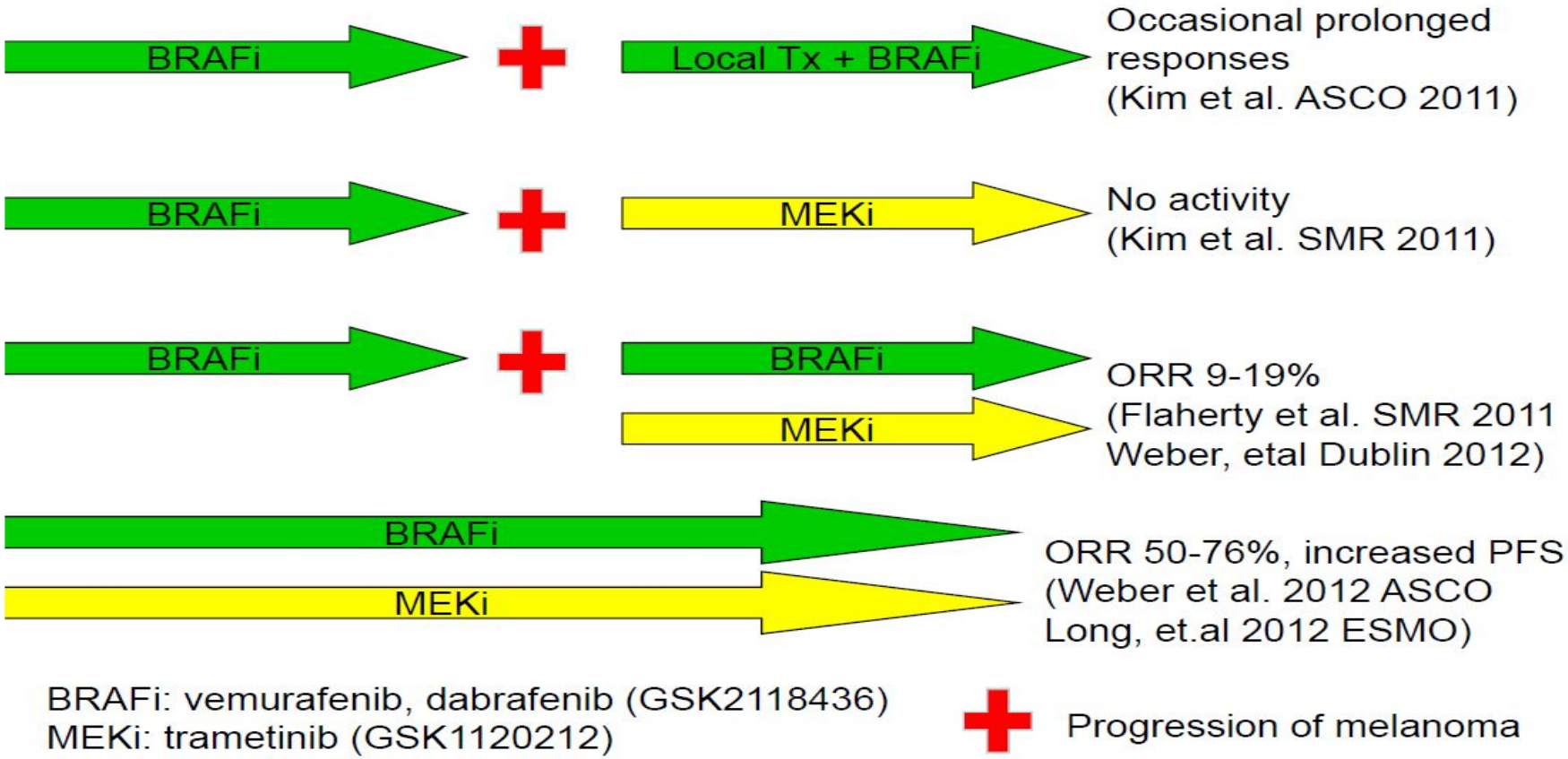
Dabrafenib (TAFINLAR) Trametinib (MEKINIST)

Vemurafenib (ZELBORAF)

Cobimetinib (COTELIC)

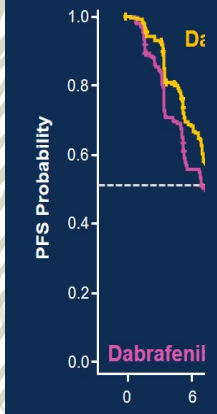

A
Normal LC
P
RAS
BRAF
P
MEK
P
ERK
Cell survival
Proliferation
Differentiation
B
Lesional LC
RAS
BRAF
V600E
P
MEK
P
ERK
Increased survival
Enhanced proliferation
Impaired differentiation

Treating resistance to BRAFi



COMBI-d: PFS and OS[a]

Progression-Free Survival

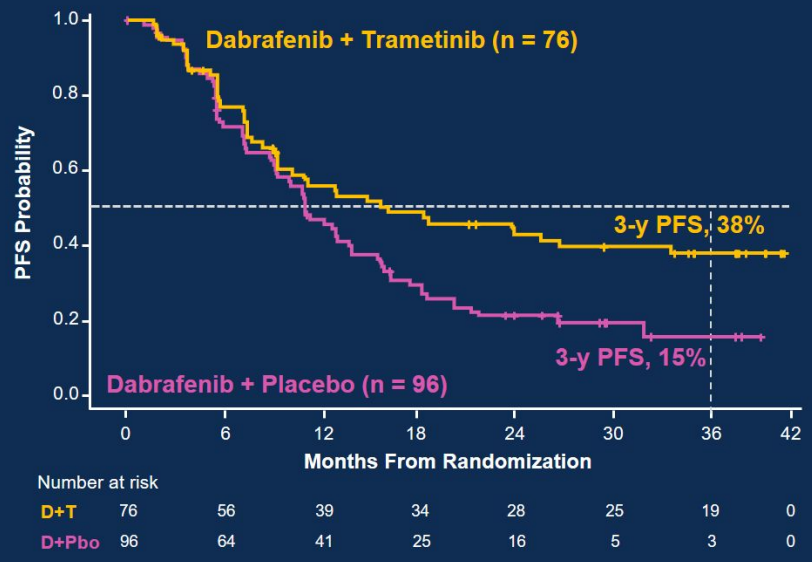


[a] Intent-to-treat popu

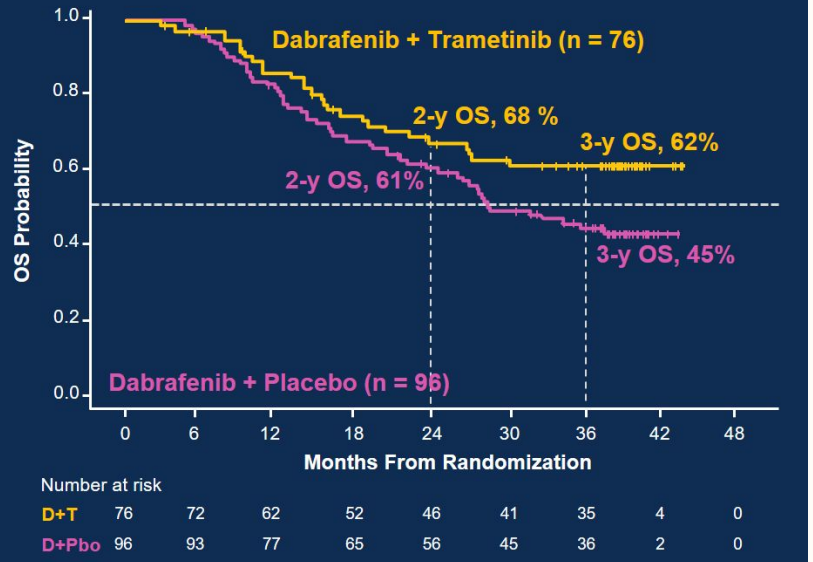
Overall Survival

COMBI-d: Normal LDH[a] and < 3 Disease Sites[b]

PFS



OS



[a] Baseline LDH ≤ ULN; [b] Any organ at baseline with ≥ 1 metastasis could be counted as a single disease site; +, censored.

COMBI-d: Treatment-Related AEs (≥ 20% of Patients)

Preferred Term, %	Dabrafenib + Trametinib (n = 211)		Dabrafenib + Placebo (n = 212)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any AE	97	41 / 7	97	45 / 5
Pyrexia	59	7 / 0	33	2 / 0
Fatigue	39	2 / 0	37	1 / 0
Nausea	36	< 1 / 0	27	1 / 0
Headache	34	< 1 / 0	29	1 / 0
Chills	32	< 1 / 0	17	< 1 / 0
Diarrhea	31	0 / 0	17	< 1 / 0
Rash	27	< 1 / 0	22	< 1 / 0
Vomiting	26	< 1 / 0	15	< 1 / 0
Arthralgia	26	6 / 0	32	0 / 0
Hypertension	25	0 / 0	16	6 / 0
Cough	22	< 1 / 0	22	0 / 0
Edema peripheral	22	< 1 / 0	9	< 1 / 0
Hyperkeratosis	7	0 / 0	35	< 1 / 0
Alopecia	9	< 1 / 0	28	0 / 0
Skin papilloma	2	0 / 0	22	0 / 0

- Cutaneous squamous cell carcinoma/keratoacanthoma: D+T, n = 8 (4%); D+Pbo, n = 25 (12%)
- Grade 5 AEs: D+T, n = 5; D+Pbo, n = 1; no new grade 5 AEs with additional follow-up

Adverse Event Incidence Rates With Cobimetinib Combined With Vemurafenib Treatment: Extended Follow-up of the Phase 3 coBRIM Study

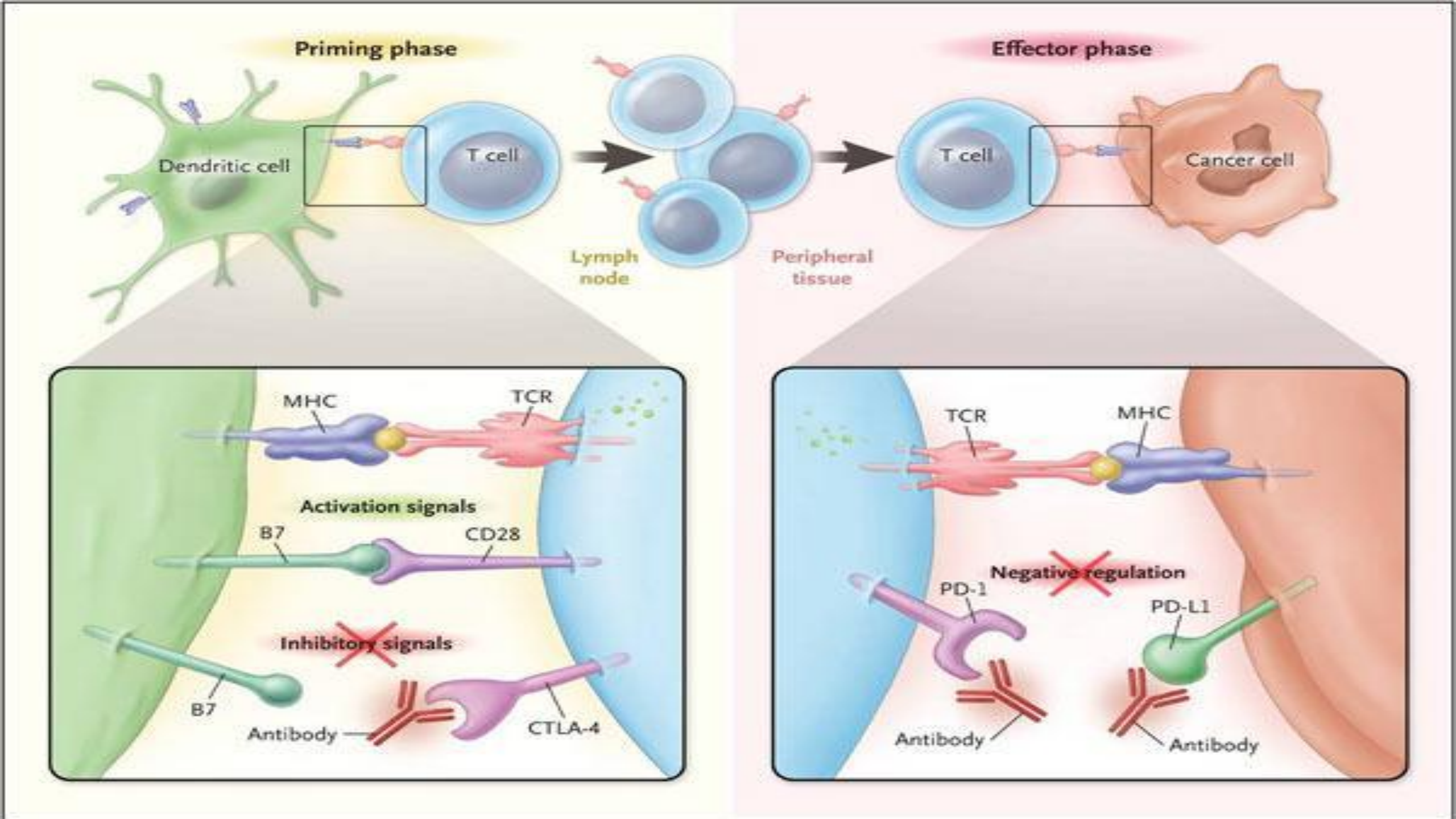
Incidence rates (events/patient-years) of select AEs at the time of the initial and updated data cuts

Although **incidences** of diarrhea, serous retinopathy, photosensitivity, and liver laboratory value abnormalities were higher in the cobimetinib combined with vemurafenib arm, they **decreased over time**, suggesting that fewer new AEs of these types are reported later in treatment.

Events/patient-year (95% CI)	Cobimetinib + vemurafenib n = 247		Placebo + vemurafenib n = 246	
	Initial (May 9, 2014)	Updated (September 30, 2015)	Initial (May 9, 2014)	Updated (September 30, 2015)
Diarrhea	1.59 (1.39-1.80)	1.09 (0.96-1.22)	0.71 (0.57-0.86)	0.69 (0.57-0.80)
Serous retinopathy	0.54 (0.42-0.66)	0.36 (0.29-0.44)	0.04 (<0.01-0.08)	0.05 (0.02-0.08)
Photosensitivity	0.93 (0.77-1.09)	0.76 (0.65-0.86)	0.87 (0.70-1.03)	0.73 (0.61-0.85)
Liver laboratory value abnormalities	1.64 (1.42-1.84)	1.10 (0.97-1.23)	1.23 (1.03-1.42)	0.85 (0.72-0.98)
Left ventricular dysfunction	0.13 (0.07-0.19)	0.15 (0.10-0.20)	0.06 (0.02-0.11)	0.08 (0.04-0.11)

AEs, adverse events; CI, confidence interval.

Imunotherapy


Priming phase
Effector phase
Dendritic cell
T cell
Lymph node
Peripheral tissue
T cell
Cancer cell
MHC
TCR
Activation signals
B7
CD28
Inhibitory signals
B7
Antibody
CTLA-4
TCR
MHC
Negative regulation
PD-1
PD-L1
Antibody
Antibody

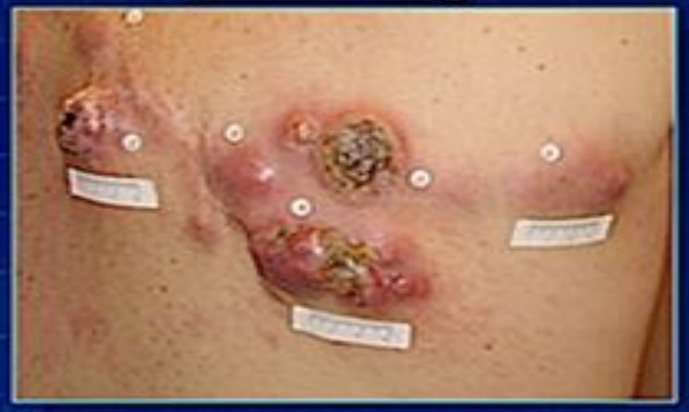
Ipillimumab (Yervoy)

In pooled analysis of 12 studies, a plateau in the survival curve begins at approximately three years, with some patients followed for up to ten years

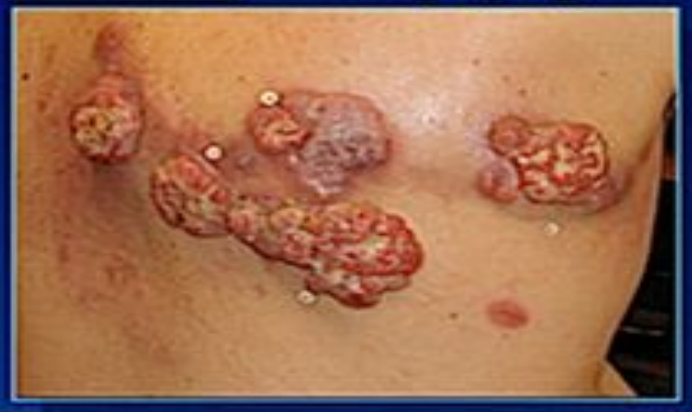
Three-year and five-year estimated survival rate of 22% and 18% respectively observed in patients treated with Yervoy

Ipilimumab: Efficacy at > 2 Yrs

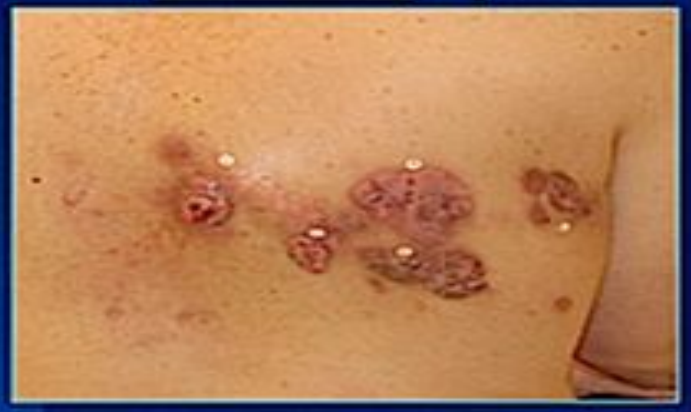
Screening



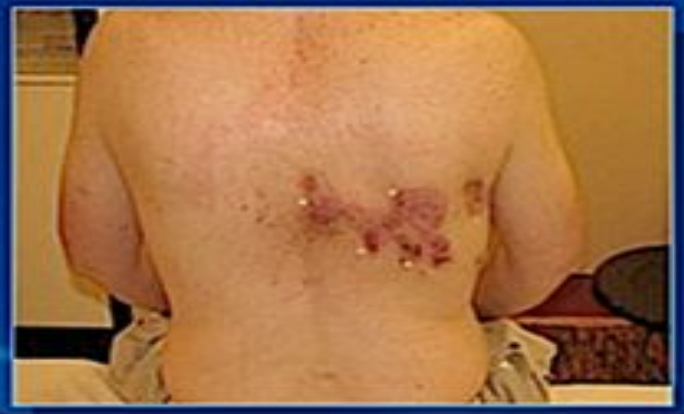
Week 12: swelling & progression



Week 14: improved

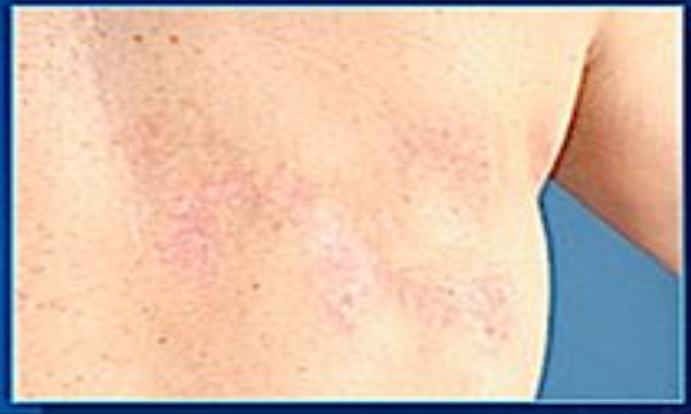


Week 16: continued improvement



Week 72: complete remission

Week 108: complete remissior



Anti PD1 therapy :

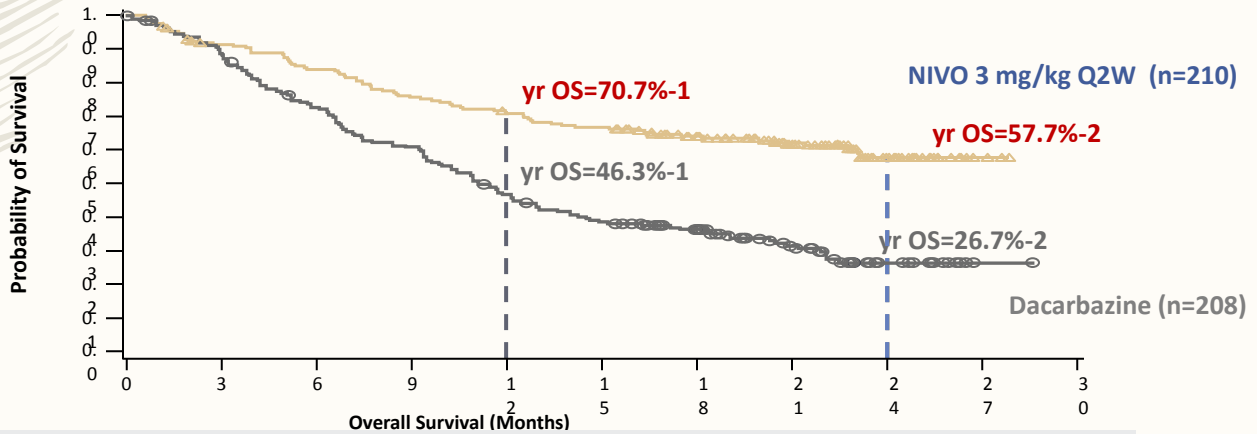
Opdivo
(Nivolumab)

Keytruda
(Pembrolizumab)

Opdivo Monotherapy Phase 3 Trial: Improved OS Versus Dacarbazine in BRAF Wild-type, *Untreated* Patients

	NIVO	DTIC
Median OS, mo (95% CI)	NR (23.1, NR)	11.2 (9.6, 13.0)
HR (95% CI)	0.43 (0.33, 0.57); P <0.001	

Phase III CheckMate 066



Patients at Risk											
Nivolumab	210	186	171	154	143	135	111	81	30	4	0
Dacarbazine	208	179	146	122	92	76	60	38	16	1	0

.Atkinson V et al. Presented at SMR 2015. 2. Robert C, et al. *N Engl J Med.* 2015;372:320-323 .1

Best Overall Response

	Nivolumab (N = 210)	Dacarbazine (N = 208)
ORR, % (95% CI)	**40% (33–47%)**	**14% (10–19%)**
Best overall response		
Complete response	**8%**	**1%**
Partial response	**32%**	**13%**
Stable disease	17%	22%
Progressive disease	33%	49%
Unable to determine	11%	15%

.Based on 5 August 2014 database lock

Pembrolizumab Versus Ipilimumab For Advanced Melanoma: Final Overall Survival Analysis of KEYNOTE-006

Jacob Schachter,[1] Antoni Ribas,[2] Georgina V. Long,[3] Ana Arance,[4] Jean-Jacques Grob,[5] Laurent Mortier,[6] Adil Daud,[7] Matteo S. Carlino,[8] Catriona McNeil,[9] Michal Lotem,[10] James Larkin,[11] Paul Lorigan,[12] Bart Neyns,[13] Christian Blank,[14] Teresa M. Petrella,[15] Omid Hamid,[16] Honghong Zhou,[17] Scot Ebbinghaus,[17] Nageatte Ibrahim,[17] Caroline Robert[18]

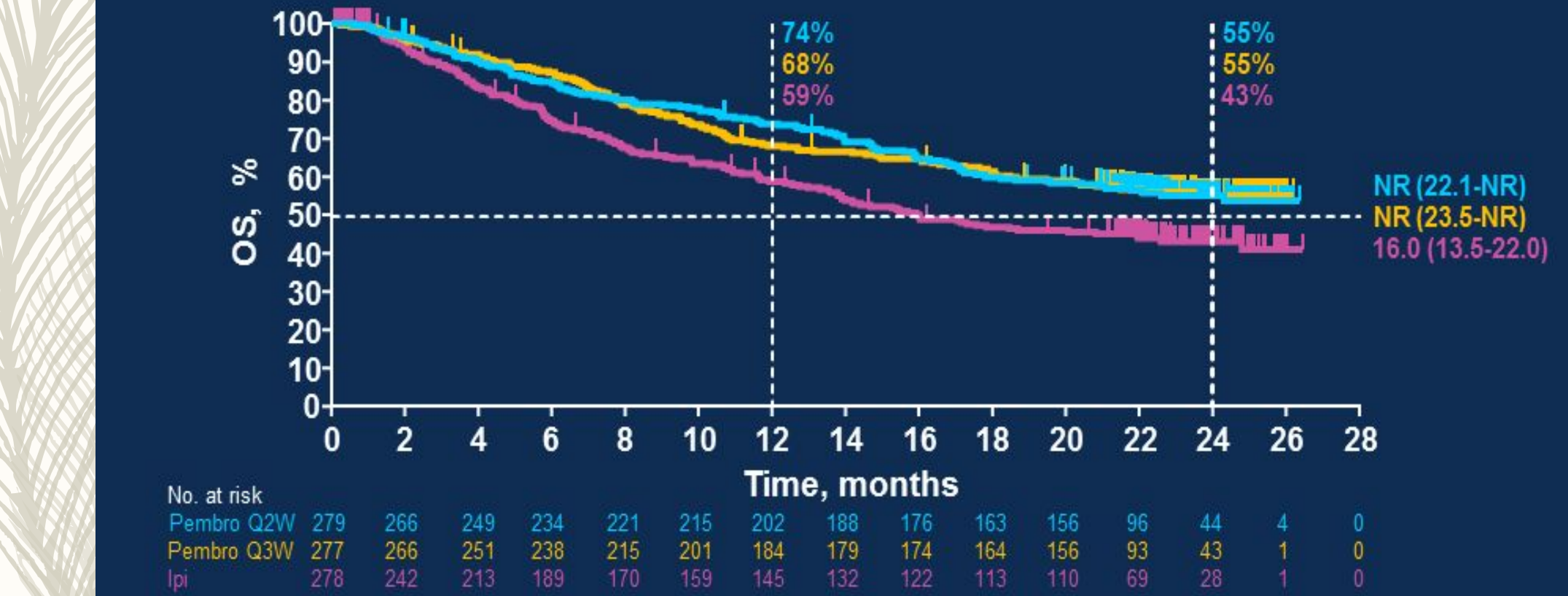
[1]Ella Lemelbaum Institute for Melanoma, Sheba Medical Center, Tel Hashomer, Israel; [2]University of California, Los Angeles, Los Angeles, CA; [3]Melanoma Institute Australia, The University of Sydney, Mater Hospital, and Royal North Shore Hospital, Sydney, Australia; [4]Hospital Clinic de Barcelona, Barcelona, Spain; [5]Aix Marseille University, Hôpital de la Timone, Marseille, France; [6]Université Lille, Centre Hospitalier Régional Universitaire de Lille, Lille, France; [7]University of California, San Francisco, San Francisco, CA; [8]Westmead and Blacktown Hospitals, Melanoma Institute Australia, and The University of Sydney, Sydney, Australia; [9]Chris O'Brien Lifehouse, Royal Prince Alfred Hospital, and Melanoma Institute Australia, Camperdown, Australia; [10]Sharett Institute of Oncology, Hadassah Hebrew Medical Center, Jerusalem, Israel; [11]Royal Marsden Hospital, London, UK; [12]University of Manchester and the Christie NHS Foundation Trust, Manchester, UK; [13]Universitair Ziekenhuis Brussel, Brussels, Belgium; [14]Netherlands Cancer Institute, Amsterdam, Netherlands; [15]Sunnybrook Health Sciences Center, Toronto, ON; [16]The Angeles Clinic and Research Institute, Los Angeles, CA; [17]Merck & Co., Inc., Kenilworth, NJ; [18]Gustave Roussy and Paris-Sud University, Villejuif, France

PRESENTED AT: ASCO ANNUAL MEETING '16

J Schachter. ASCO 2016.

Overall Survival

Arm	Events, n	HR (95% CI)	*P*
Pembro Q2W	122	0.68 (0.53-0.87)	0.00085
Pembro Q3W	119	0.68 (0.53-0.86)	0.00083
Ipi	142	—	—



Final analysis data cutoff date: Dec 3, 2015.

Updated Results From a Phase III Trial of Nivolumab Combined With Ipilimumab in Treatment-naïve Patients With Advanced Melanoma (Checkmate 067)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

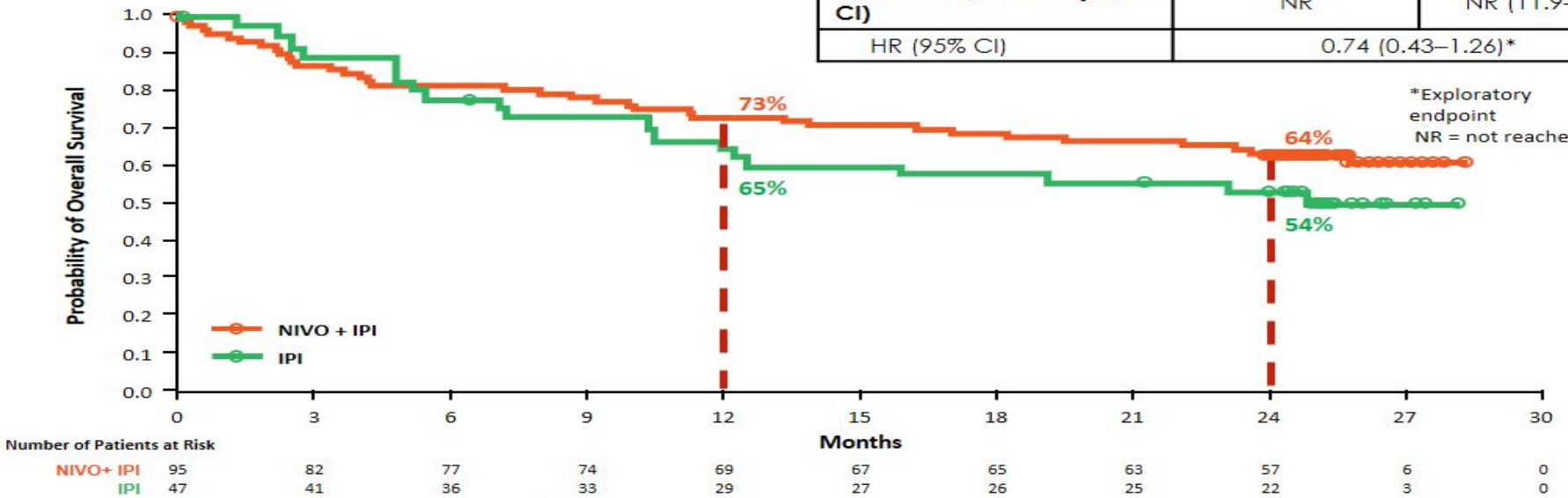
Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, and J.D. Wolchok

OS AT 2 YEARS OF FOLLOW-UP (ALL RANDOMIZED PATIENTS)

CHECKMATE 069

	NIVO + IPI (N = 95)	IPI (N = 47)
Median OS, months (95% CI)	NR	NR (11.9–NR)
HR (95% CI)	0.74 (0.43–1.26)*	



- 30/47 (64%) of patients randomized to IPI crossed over to receive any systemic therapy at progression

AACR 2016

Table 1. Summary of Updated PFS and ORR

	NIVO + IPI (N = 314)	NIVO (N = 316)	IPI (N = 315)
Median PFS, months (95% CI)	11.5 (8.7, 19.3)	6.9 (5.1, 9.7)	2.9 (2.8, 3.2)
HR vs IPI	0.43 (0.35, 0.52)	0.55 (0.45, 0.66)	-
HR vs NIVO	0.78 (0.64, 0.96)		-
ORR, % (95% CI)[a]	58.3 (52.6, 63.8)	44.3 (38.7, 50.0)	18.7 (14.6, 23.5)
Best overall response, %			
Complete response	19.4	16.5	5.1
Partial response	38.9	27.8	13.7
Median DOR, months (95% CI)	NR	NR (36.3, NR)	19.3 (8.3, NR)

[a]By RECIST v1.1

CI = confidence interval; NR = not reached

Database lock: May 24, 2017. Median follow-up of approximately 36 months in both NIVO-containing arms

Safety Summary

– **Updated safety information with 9 additional months of follow-up were consistent with the initial report**

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	**56.5**	84.0	19.8	85.9	27.0
Treatment-related AE leading to discontinuation	38.7	**30.7**	10.5	7.3	15.4	13.5
Treatment-related death*	0		0.3		0.3	

– **68.8%** of patients who discontinued NIVO+IPI due to treatment-related AEs achieved a response

One reported in the NIVO group (neutropenia) and one in the IPI group (colon perforation)*

Database lock Nov 2015

Table 2. Safety Summary

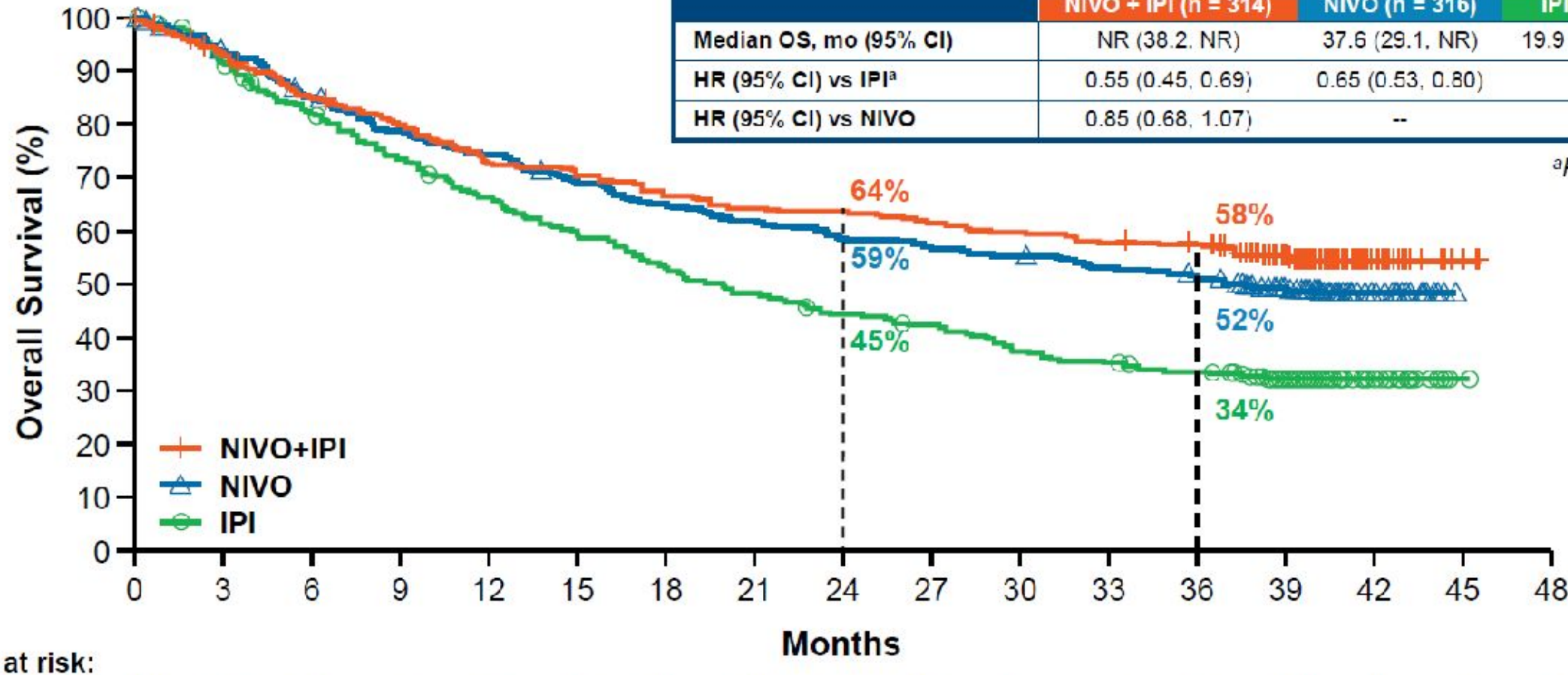
	NIVO + IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
Patients reporting event, %	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Treatment-related AE	95.8	58.8	86.3	21.4	86.2	27.7
Treatment-related AE leading to discontinuation	39.3	30.4	11.8	7.7	15.8	13.8
Treatment-related death, n (%)	2 (0.6)[a]		1 (0.3)[b]		1 (0.3)[c]	

[a]Cardiomyopathy (NIVO+IPI, n = 1); liver necrosis (NIVO+IPI, n = 1). Both deaths occurred >100 days after the last treatment
[b]Neutropenia (NIVO, n = 1)
[c]Colon perforation (IPI, n = 1)

Figure 1. OS (Intent-to-Treat)[1]

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2, NR)	37.6 (29.1, NR)	19.9 (16.9, 24.6)
HR (95% CI) vs IPI[a]	0.55 (0.45, 0.69)	0.65 (0.53, 0.80)	--
HR (95% CI) vs NIVO	0.85 (0.68, 1.07)	--	--

[a]$P < 0.0001$

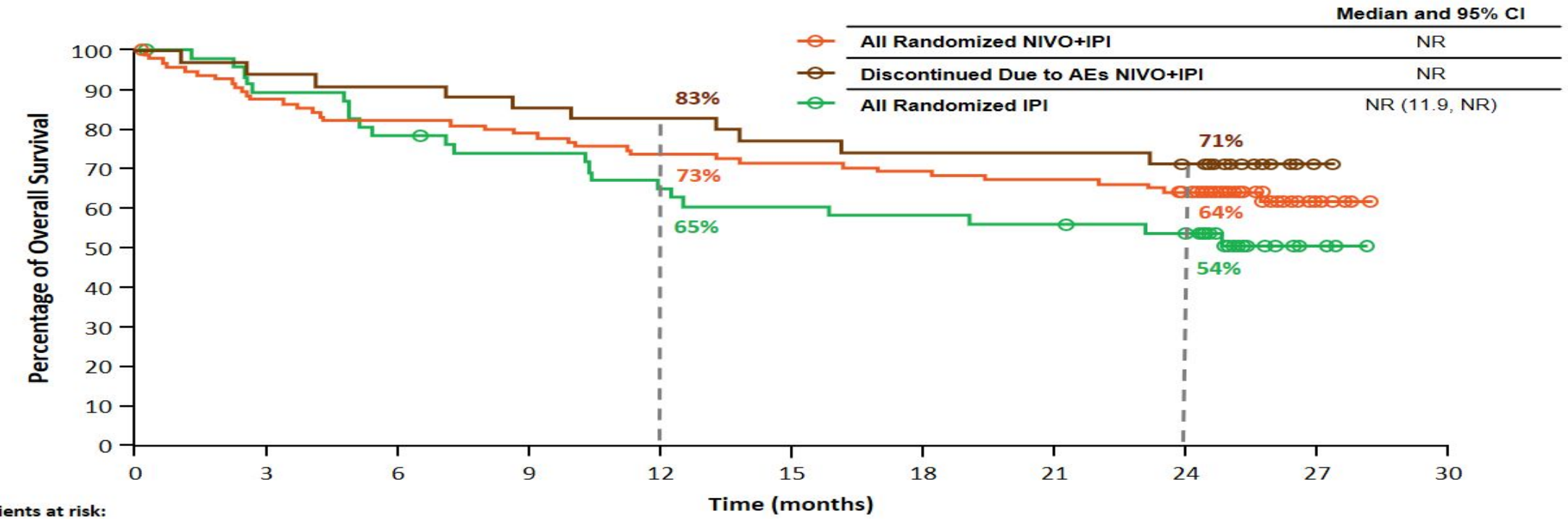


Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0
NIVO	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0
IPI	315	285	253	227	203	181	163	148	135	126	117	107	100	68	20	2	0

1. Wolchok JD et al. *N Engl J Med*. In press.

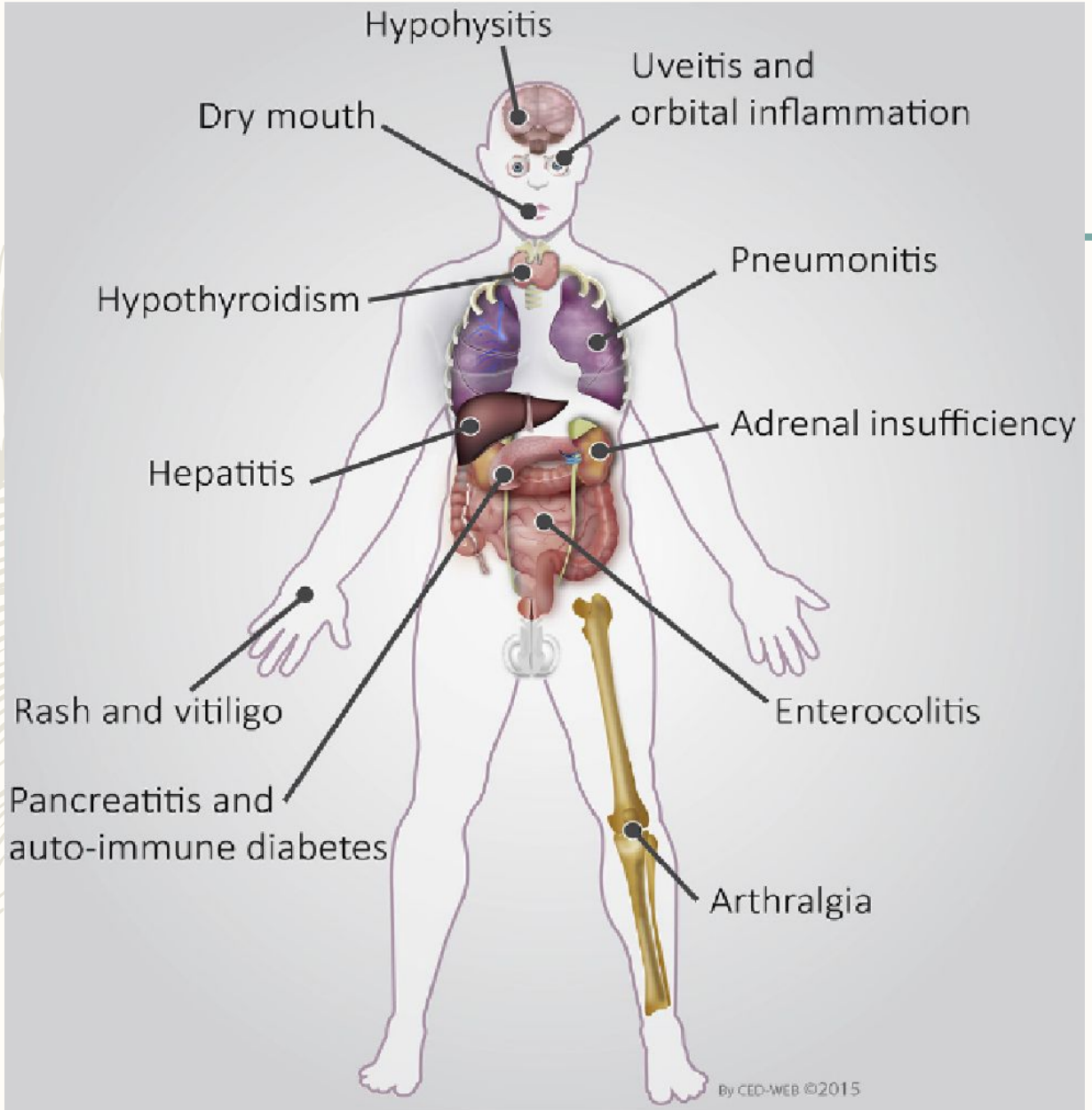
OVERALL SURVIVAL AT 2 YEARS OF FOLLOW-UP



Number of patients at risk:

NIVO + IPI	95	82	77	74	69	67	65	63	57	6	0
NIVO + IPI	35	33	32	30	29	27	26	26	24	1	0
IPI	47	41	36	33	29	27	26	25	22	3	0

Database lock February 2016



J.M. Michot et al. European Journal of Cancer 54 (2016)

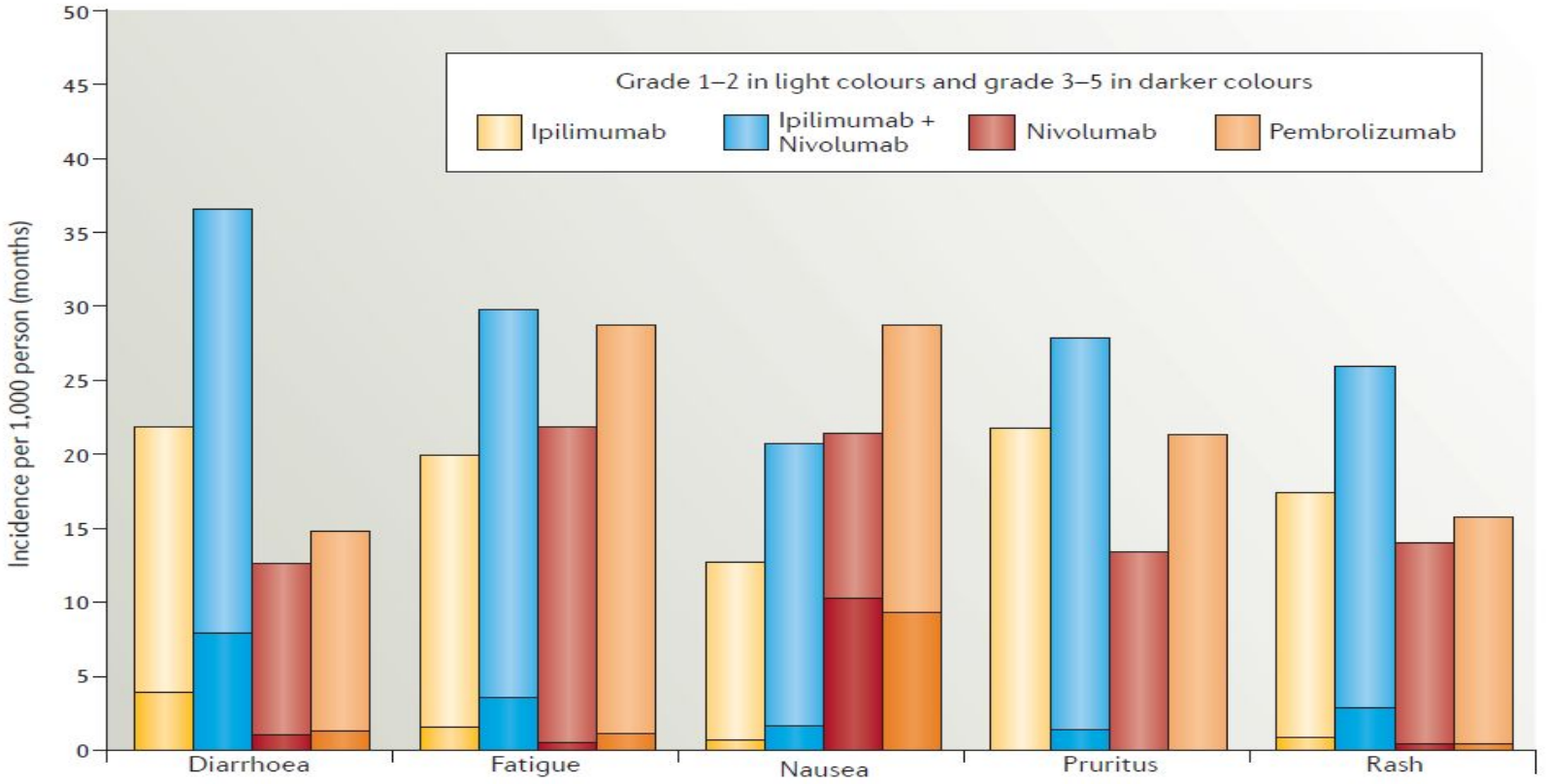


Figure 2 | **The most common adverse events in patients treated with ipilimumab, pembrolizumab, nivolumab, or ipilimumab plus nivolumab.** Incidence per 1,000 person-months. These incidences include data from the following studies: CA-184-002 (REF. 16), KEYNOTE-001 (REF. 30), KEYNOTE-001 (randomized cohorts[31]), KEYNOTE-002 (REF. 32), KEYNOTE-006 (REF. 33), CheckMate-037 (REF. 100), CheckMate-066 (REF. 29), CheckMate-067 (REF. 45), and CheckMate-069 (REF. 44).

Boutros et al. Nature Reviews Clinical Oncology Volume: 13, Pages:473–486 Year published:(2016)

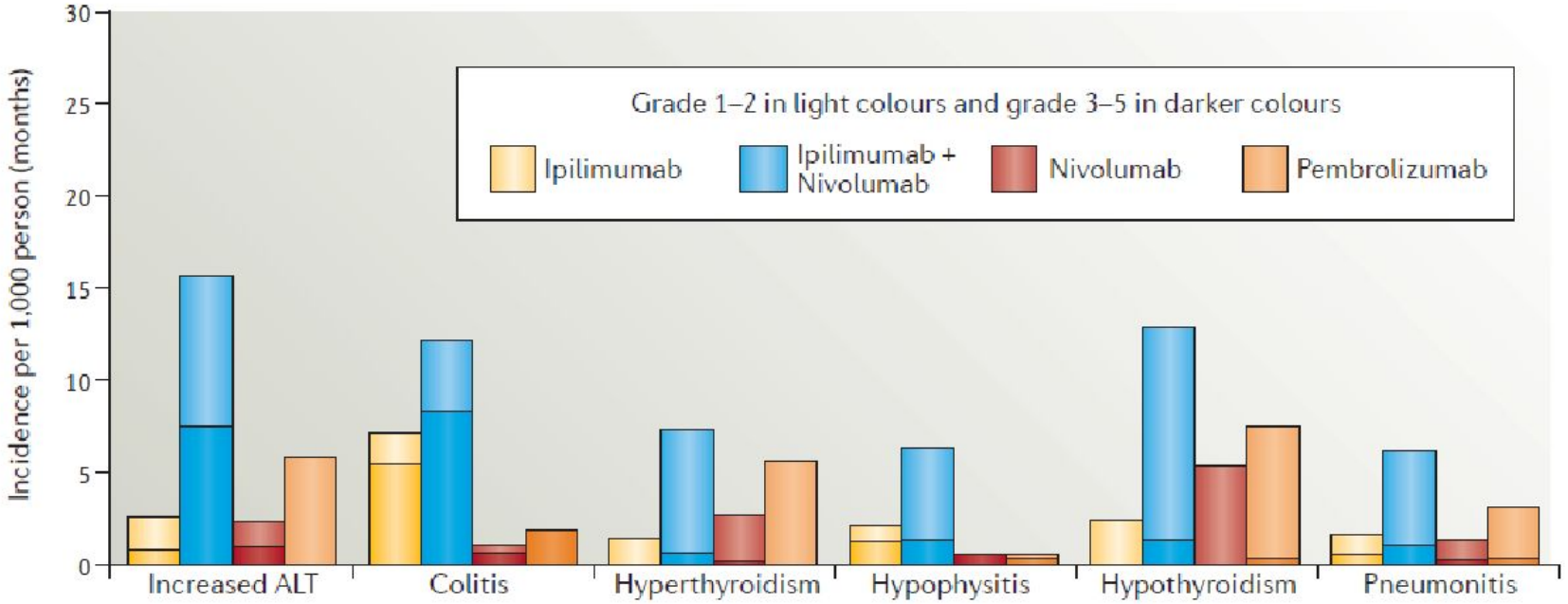
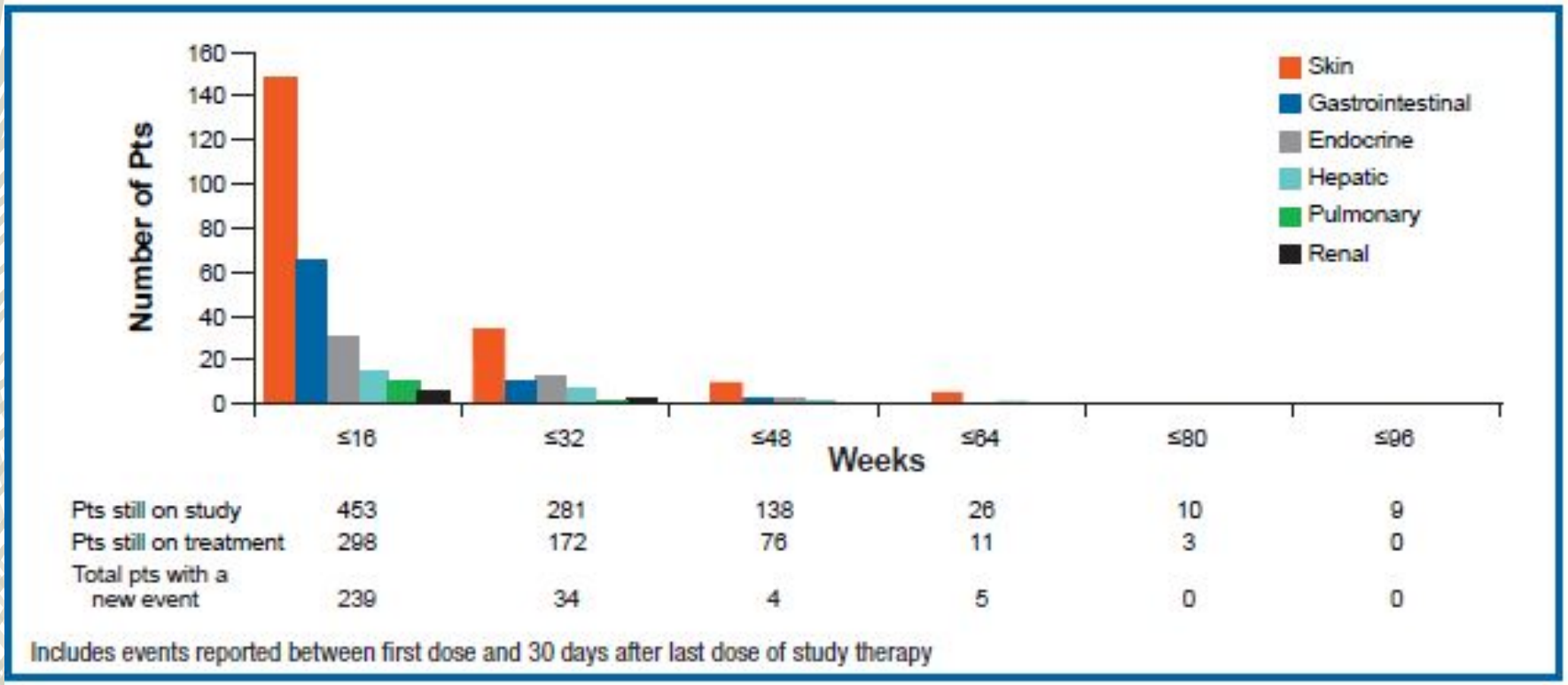


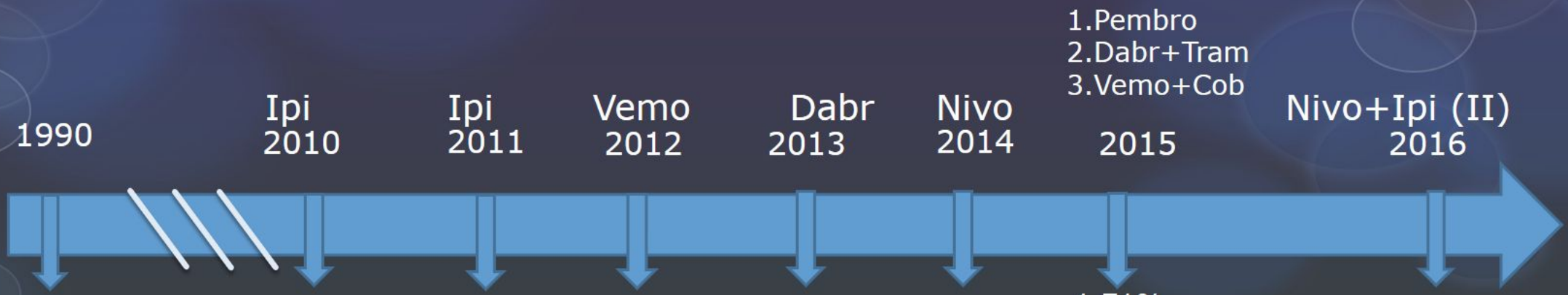
Figure 3 | **Adverse events of special interest noted with immune-checkpoint inhibitors.** These adverse events are a direct result of activation of the immune system, as reported in patients treated with ipilimumab, pembrolizumab, nivolumab or ipilimumab plus nivolumab. Incidence per 1,000 person-months; these incidences include data from the following studies: CA-184-002 (REF. 16), KEYNOTE-001 (REF. 30), KEYNOTE-001 (randomized cohorts[31]), KEYNOTE-002 (REF. 32), KEYNOTE-006 (REF. 33), CheckMate-037 (REF. 100), CheckMate-066 (REF. 29), CheckMate-067 (REF. 45), and CheckMate-069 (REF. 44).

Boutros et al. Nature Reviews Clinical Oncology 13, 473–486 (2016)



Webber JS , Safety profile of nivolumab in patients with advanced melanoma, Pooled Analysis. ASCO 2016 (Poster).

OS in metastatic Melanoma Phase I-III studies



	1990	Ipi 2010	Ipi 2011	Vemo 2012	Dabr 2013	Nivo 2014	2015	Nivo+Ipi (II) 2016
1y	25-35%	46%	47%	56%	70%	71%	1.71% 2.74% 3.75%	73%
2y	15%	24%	29%		45%	58%	1.55% 2.53% 3.48%	64%
3y		22%				42%	1.40% (ph I) 2. 38 % (ph II)	
5y			18%			34% (ph I Nivo)		

Georgina V. Long , ASCO 2016


Thank
you!