Modern therapy in oncology
Metastatic melanoma

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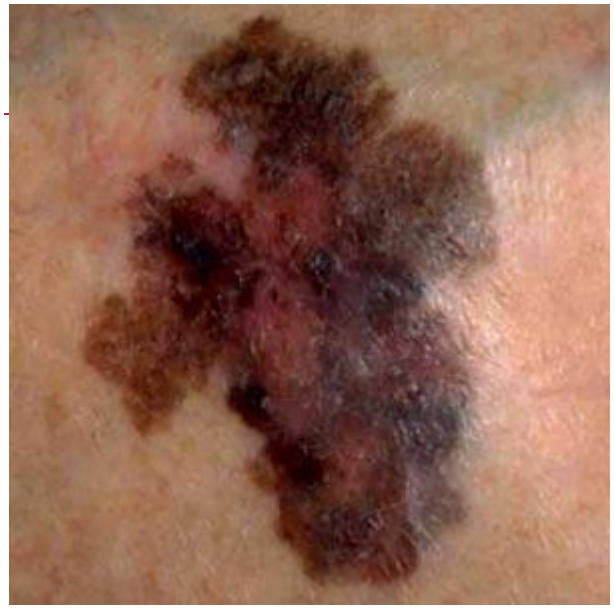
Melanoma

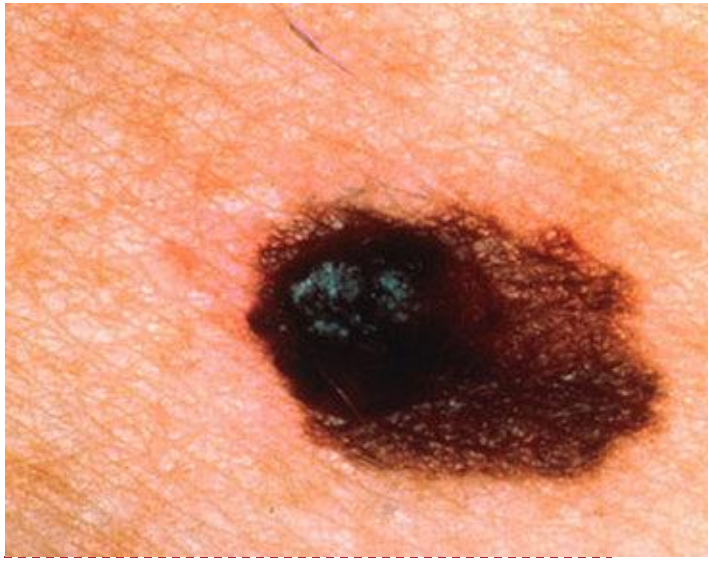
- *Malignant skin neoplasm derived from neuroectodermal melanomatous cells.*
- The incidence:
  - 2-5/100,000 per year (Mediterranean countries)
  - 12-25/100,000 per year (Nordic countries)
  - 19.7/100,000 per year (USA)
  - 48.8/100,000 per year (Australia)
  - In most developed countries, the incidence of malignant melanoma has risen faster than any other type of cancer since the mid-1950s
  - The highest incidence – Australia, New Zealand, Norway, Sweden, United States of America.

- Major carcinogen in melanoma genesis is UV irradiation
  - recreational exposure to the sun and a history of sunburn
- The incidence rate is highest in lighter skinned patients and is much rarer in darker skinned individuals

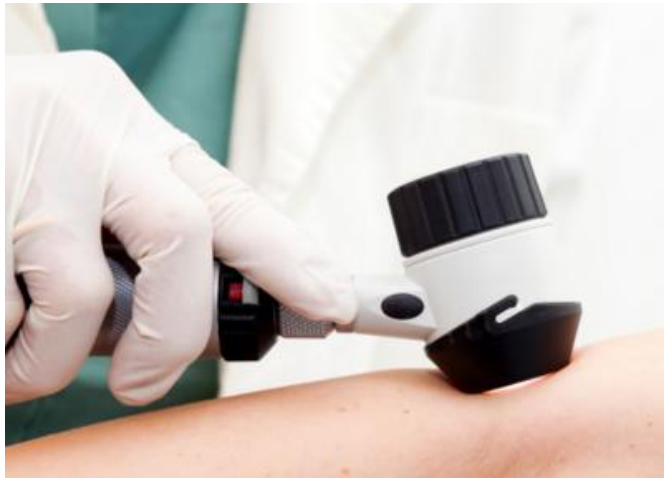
Diagnosis – ABCDE rule

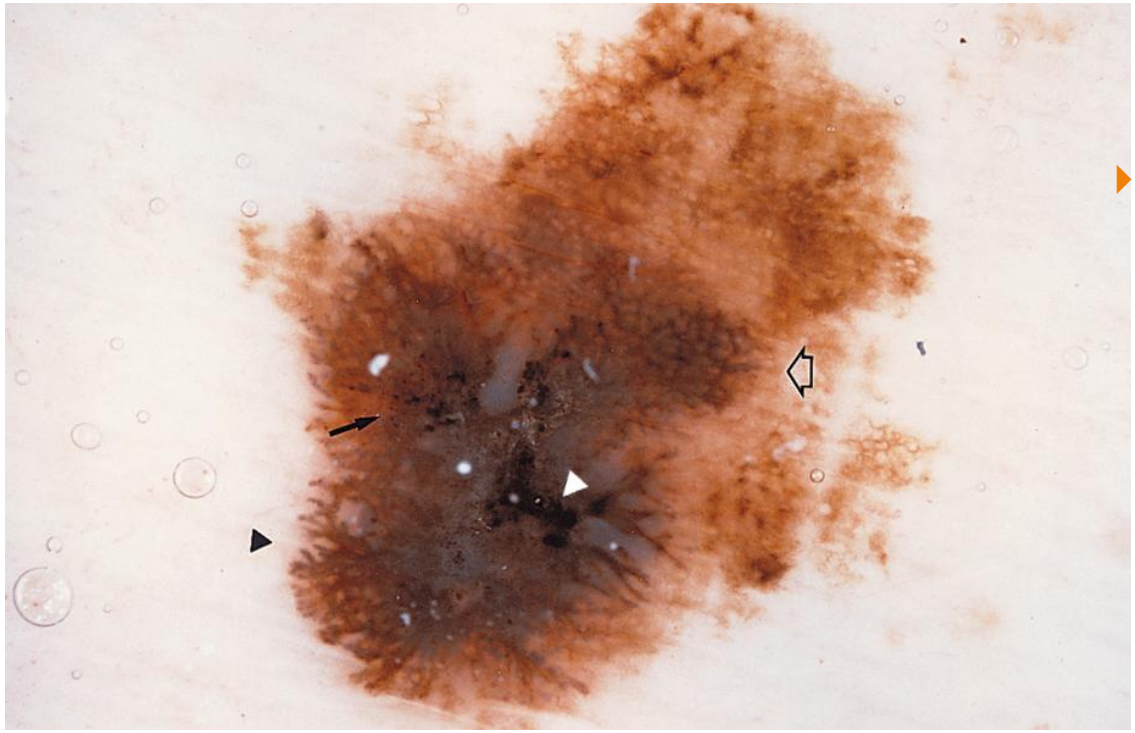
A	• Asymmetry
B	• Border
C	• Colour heterogeneity
D	• Diameter (>5mm or dynamics in morphological changes)
E	• Elevation/evolution





Diagnosis -dermatoscopy





- **Cutaneous melanoma**

(0.45 mm thick) with:

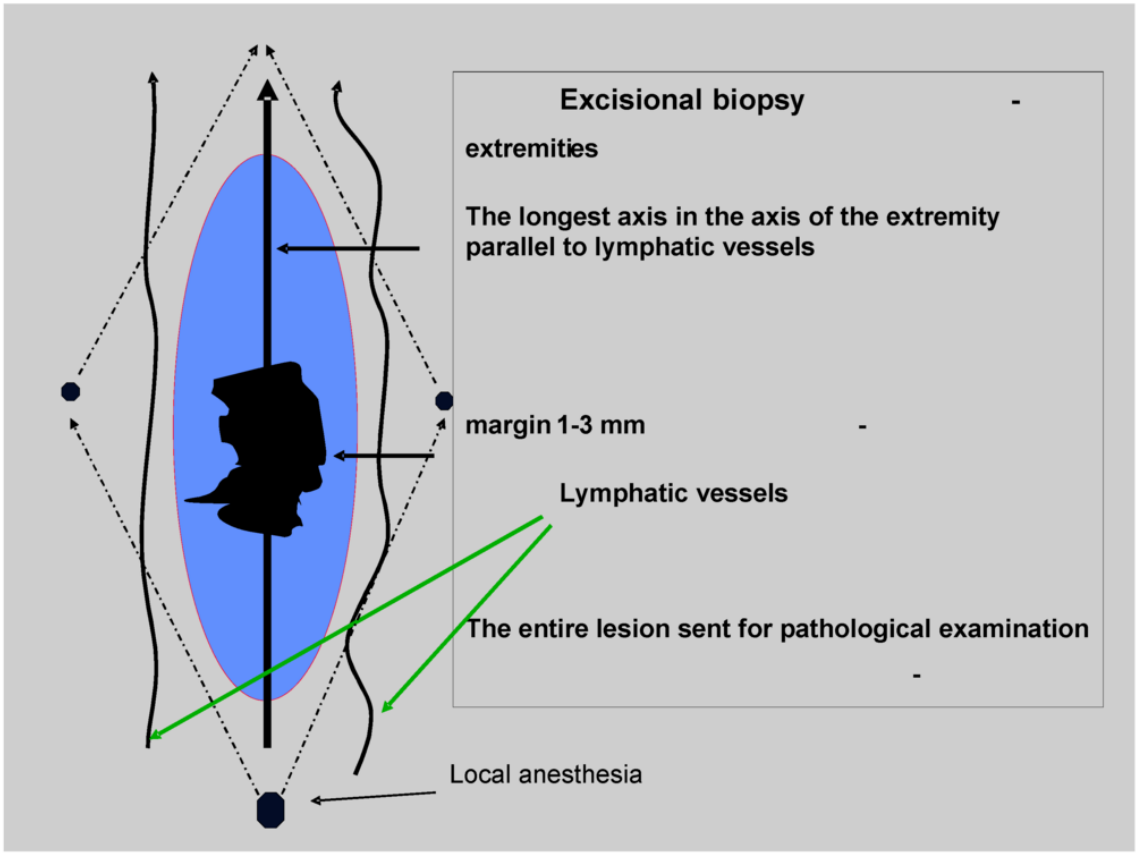
- an irregular and prominent (atypical) pigment network (white arrow),
- streaks (black arrowhead),
- blotches (white arrowhead),
- irregular dots and globules (black arrow),

(original magnification ×10).

http://archderm.jamanetwork.com/article.aspx?articleid=189703

Diagnosis -suspected lesion

- Full thickness excisional biopsy
  - minimal margin of normal skin 1–3 mm wide and with 2 mm margin of subcutaneous tissue



The pathology report

- Maximum thickness (Breslow scale)
- Mitotic rate
- Presence of ulceration
- Presence and extent of regresion
- Clearance of surgical margins
- Anatomical site
- Melanoma type

- Experienced pathology institute

Diagnosis confirmed -melanoma

- Radical surgery of the primary tumor
  - Wide excision with safety margins

Melanoma thickness (Breslow)	Safety margins*
In situ (pTis)	0,5 cm
≤ 2,0 mm (pT1, pT2)	1 cm
≥ 2,0 mm (pT3, pT4)	2 cm

* Modifications are acceptable in acral or facial melanomas for preservation of function

Prognostic factors –localised melanoma

- **Maximum thickness**
  - **Breslow –millimiters**
  - *Clark scale
- **Ulceration of primary lesion**
- **Mitotic rate** (mitoses/mm2)

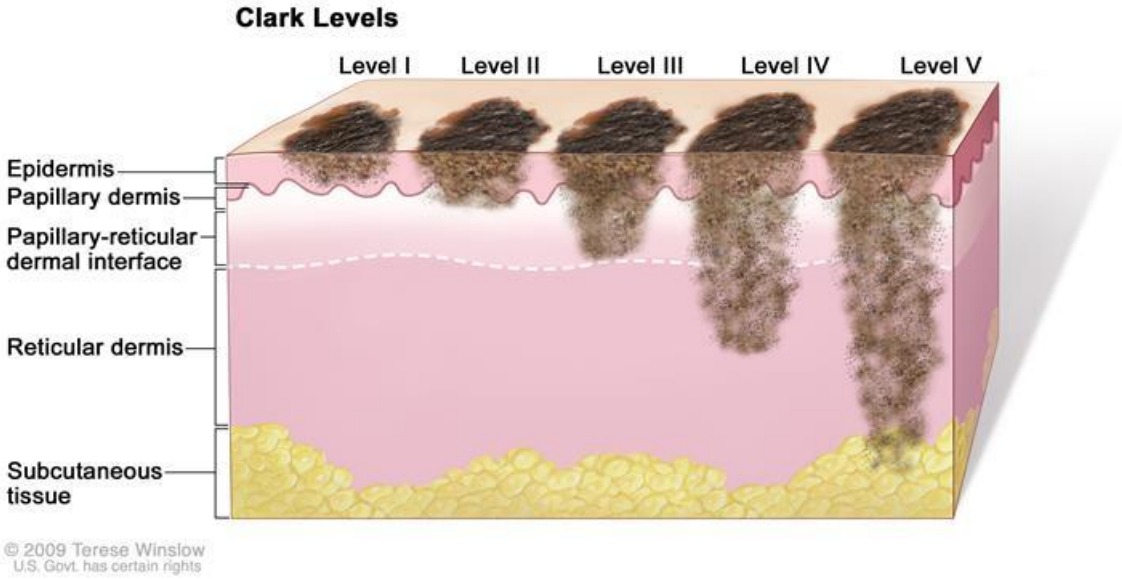
Mitotic rate -A measure of how fast cancer cells are dividing and growing. To find the mitotic rate, the number of cells dividing in a certain amount of cancer tissue is counted. Higher mitotic rates - lower survival rates.

- Localisation:
  - upper **B**ack/thorax
  - upper **A**rm
  - **N**eck
  - **S**calp
- Gender
  - men –worse prognosis

Clark scale

OUT-OF-DATE

- Level I – melanoma in situ – the melanoma cells are only in the outer layer of the skin (the epidermis)
- Level 2 – presence of melanoma cells in the layer directly under the epidermis (the papillary dermis)
- Level 3 – presence of melanoma cells are throughout the papillary dermis and touching on the next layer down (the reticular dermis)
- Level 4 – the melanoma has spread into the reticular or deep dermis
- Level 5 – the melanoma has grown into the layer of fat under the skin (subcutaneous fat)



Tumor (Breslow scale)

- Tis – melanoma cells are present only in the most superficial layer of skin
- T1 – the melanoma is less than 1 mm thick
- T2 – the melanoma is between 1,01 mm and 2,0 mm thick
- T3 – the melanoma is between 2,01 mm and 4,0 mm thick
- T4 – the melanoma is more than 4,0 mm thick

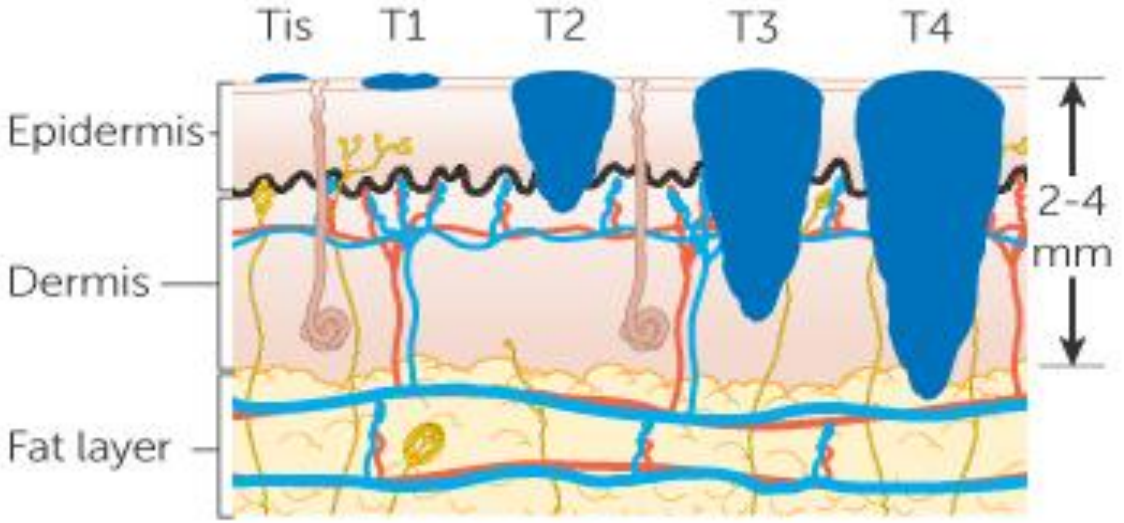


Table 1. AJCC staging system of melanoma

T classification	Thickness (mm)	Ulceration status/mitosis
T1	≤1.0	a: without ulceration and mitosis <1/mm²
		b: with ulceration or mitoses ≥1/mm²
T2	1.01–2.0	a: without ulceration
		b: with ulceration
T3	2.01–4.0	a: without ulceration
		b: with ulceration
T4	>4.0	a: without ulceration
		b: with ulceration
N classification	**No. of metastatic nodes**	**Nodal metastatic mass**
N0	0	N/A
N1	1 node	a: micrometastasis[a]
		b: macrometastasis[b]
N2	2–3 nodes	a: micrometastasis[a]
		b: macrometastasis[b]
		c: in transit metastases/satellites 'without' metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit metastases/satellites 'with' metastatic nodes	
M classification	**Site**	**Serum LDH**
M0	No distant metastasis	N/A
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

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[a]Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if carried out).

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

AJCC, American Joint Committee on Cancer; N/A, not applicable; LDH, lactate dehydrogenase.

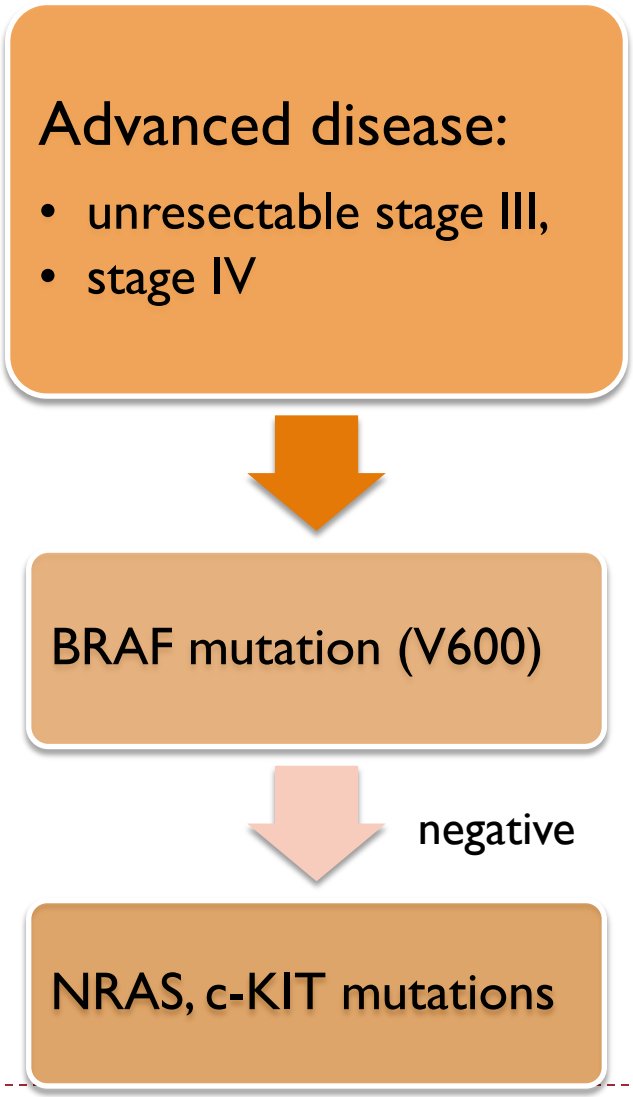
Staging

- Low risk melanoma (pT1a)
  - no investigation
- pT1b-pT3a
  - ultrasound for locoregional lymph nodes
- >pT3a
  - CT or PET scans before surgical treatment or sentinel node biopsy

Melanoma -staging

ANATOMIC STAGE/PROGNOSTIC GROUPS							
Clinical Staging[3]				Pathologic Staging[4]			
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
Stage IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
Stage IIC	T4b	N0	M0	IIC	T4b	N0	M0
Stage III	Any T	≥ N1	M0	IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
Stage IV	Any T	Any N	M1	IV	Any T	Any N	M1

Advanced disease –mutation testing



DRUGS

DRUGS

- Cytotoxic drugs:
  - dacarbazine, temozolomide, taxanes
- Immunotherapy:
  - interferon α2b,
  - interleukin-2,
  - CTLA4 inhibitor – ipilimumab
  - Anti-PD-1 antibodies: nivolumab, pembrolizumab
- Molecular therapy:
  - BRAF-inhibitors: vemurafenib,encorafenib, dabrafenib
  - MEK inhibitors: binimetinib, cobimetinib, trametinib
  - KIT inhibitor: imatinib

Dacarbazine

- Alkylating and antimetabolic agent
- „gold standard since '70 ”
- Trials results:
  - Response rate: 15,3%
    - Partial response: 11,2 %
    - Complete response: 4,2%
    - Duration of response: 5-6 months
- Side effects:
  - nausea, vomiting, leukopenia, trombocytopenia, anemia, flu-like symtoms,

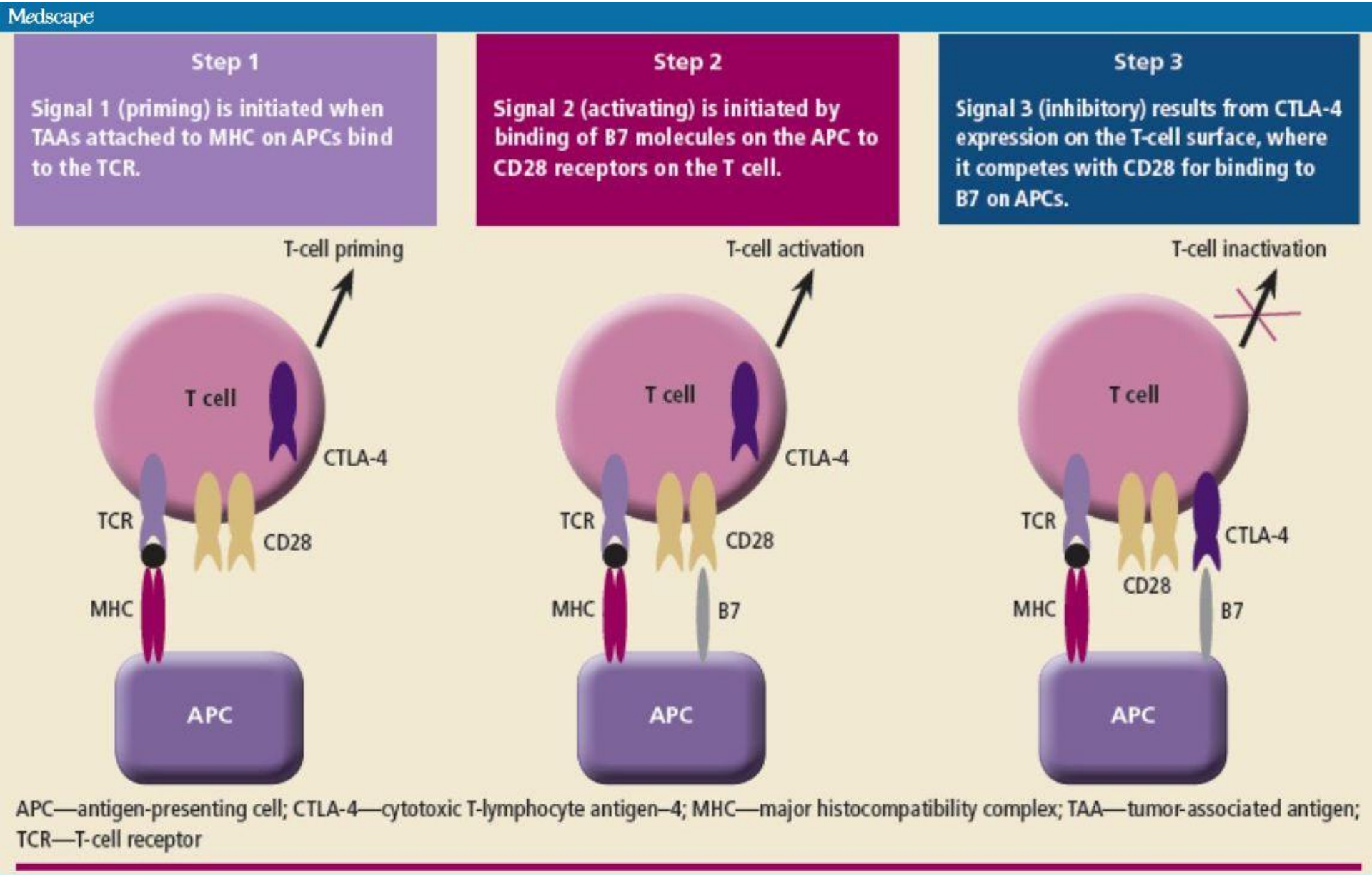
Drugs in modern therapy

- Ipilimumab
  - CTLA 4-inhibitor
- Nivolumab/pembrolizumab
  - PD1-antibodies
- Vemurafenib/dabrafenib
  - BRAF-inhibitors
- Trametinib/binimetinib/cobimetinib
  - MEK-inhibitors
- Imatinib
  - KIT inhibitor

Ipilimumab

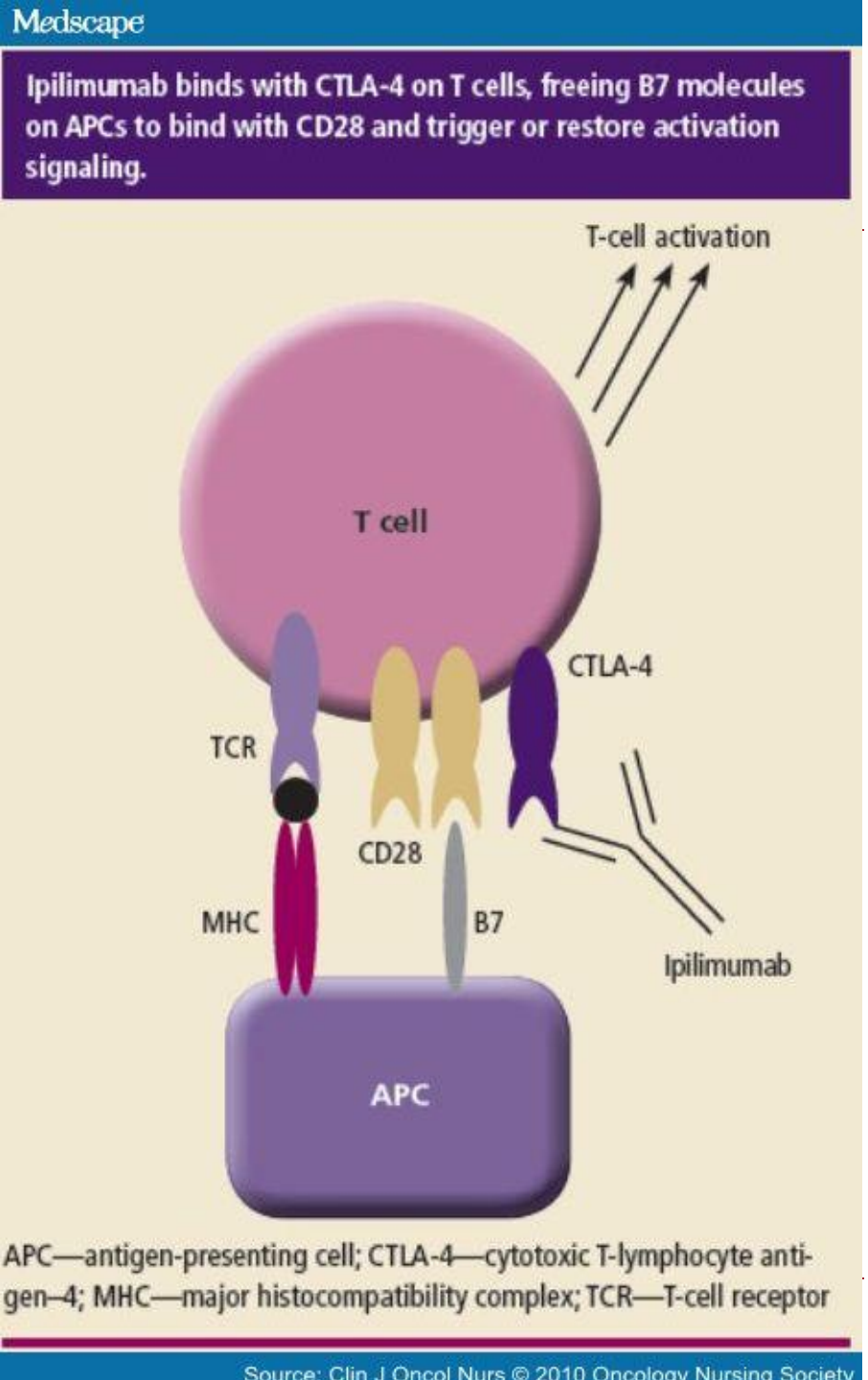
- CTLA 4-inhibitor

Priming, Activation, and Subsequent Inactivation of T Cells (by CTLA-4)



APC—antigen-presenting cell; CTLA-4—cytotoxic T-lymphocyte antigen–4; MHC—major histocompatibility complex; TAA—tumor-associated antigen; TCR—T-cell receptor

Source: Clin J Oncol Nurs © 2010 Oncology Nursing Society

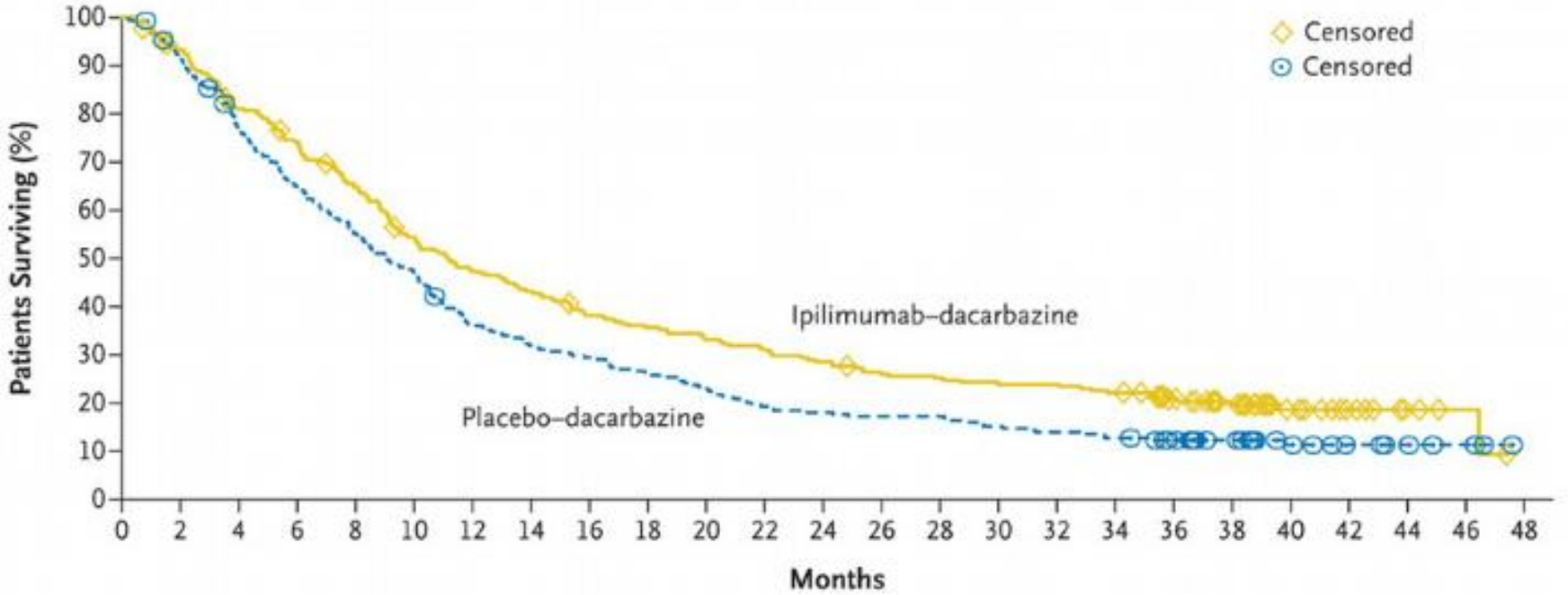


Ipilimumab

- monoclonal IgG1 antibody
- inhibits CTLA-4 antigen (cytotoxic T-lymphocyte-associated antigen 4) on the surface of lymphocyte T
- activates T-cell driven immune response

- indicated for the treatment of unresectable or metastatic melanoma
- response after 12-16 weeks of therapy

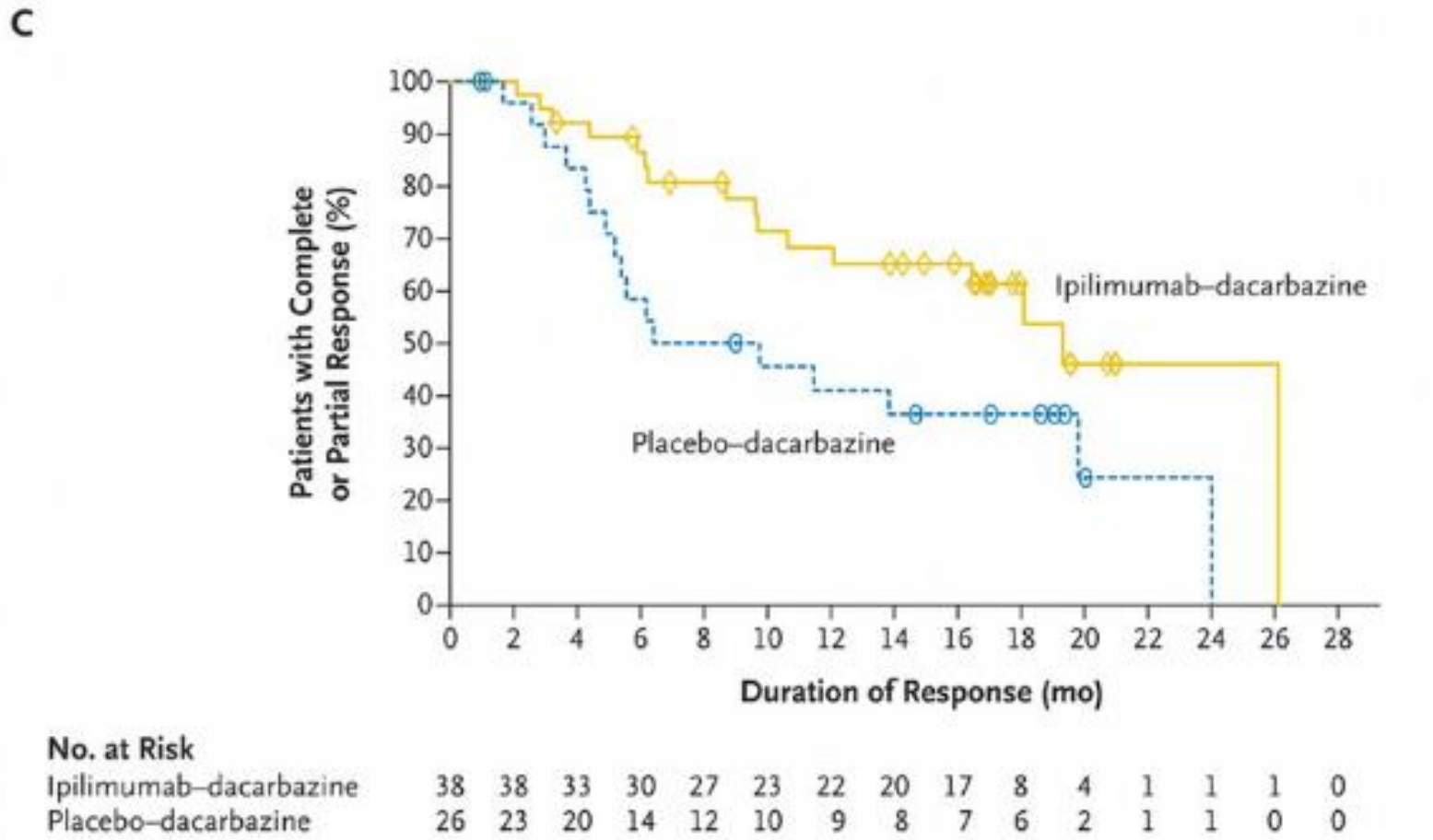
Ipilimumab with dacarbazine vs dacarbazine alone



No. at Risk																									
Ipilimumab–dacarbazine	250	230	199	181	157	131	114	104	91	85	79	74	68	61	59	56	56	52	41	31	17	10	4	2	0
Placebo–dacarbazine	252	229	190	160	136	116	89	78	72	64	56	47	44	42	42	37	34	31	26	19	11	7	5	3	0

Overall survival was significantly longer in the group receiving ipilimumab plus dacarbazine than in the group receiving dacarbazine plus placebo (11.2 months vs. 9.1 months

Ipilimumab with dacarbazine vs dacarbazine alone



The median duration of response among all randomly assigned patients with a complete or partial response was 19.3 months (95% CI, 12.1 to 26.1) in the ipilimumab–dacarbazine group and 8.1 months (95% CI, 5.19 to 19.8) in the dacarbazine group (P=0.03).

Ipilimumab –side effects

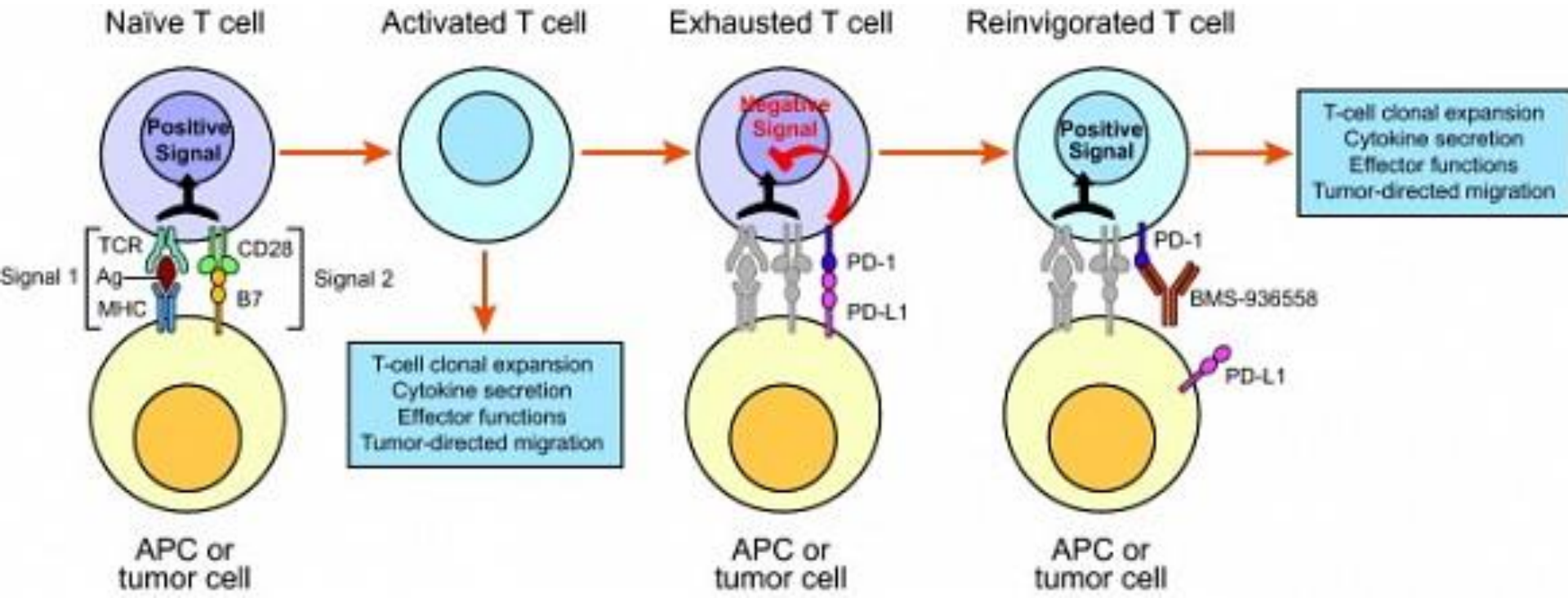
- Most common adverse reactions (≥5%):
  - fatigue, diarrhea, pruritus, rash and colitis.

- Severe immune-mediated adverse reactions*:
  - enterocolitis (gastrointestinal hemorrhage, perforation)
  - hepatitis,
  - dermatitis (including toxic epidermal necrolysis),
  - neuropathy, Guillain-Barré syndrome, myasthenia gravis
  - endocrinopathy
  - ocular disease (uveitis, iritis, episcleritis)

* Permanently discontinue the drug and administer systemic high-dose corticosteroids for severe, persistent, or recurring immune-mediated reactions.

- Nivolumab/pembrolizumab
  - PD1-antibodies

PD1-antibodies: mechanism of action



PD1-antibody blocks interaction between PD-1 and PD-L1, which reverse exhaustion of previously activated T-cells in peripheral tissue.

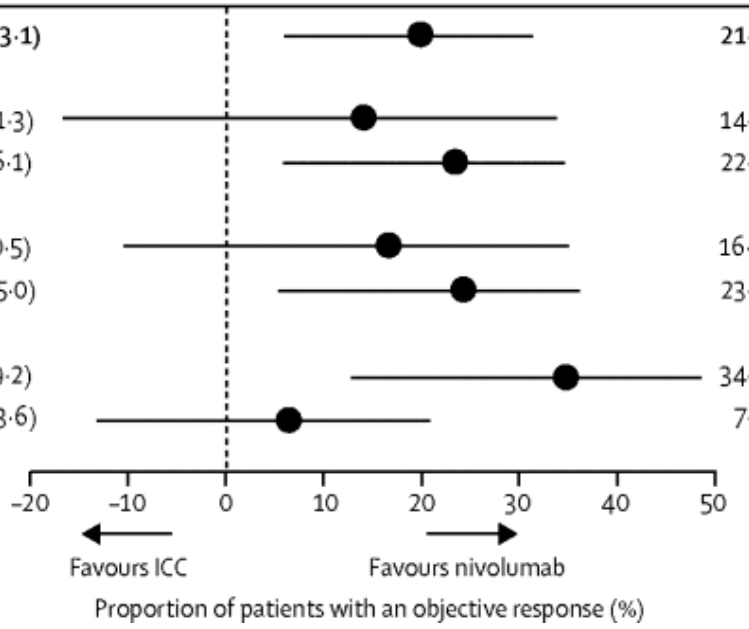
Nivolumab /pembrolizumab

- a programmed death receptor-1 (PD-1) blocking antibody

- indicated for the treatment of unresectable or metastatic melanoma:
  - as a single agent in patients with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor (nivolumab)
  - in combination with ipilimumab in patients with BRAF V600 wild-type melanoma (nivolumab)
- In patients with metastatic NSCLC whose tumors express PD-L1 (pembrolizumab)

Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment

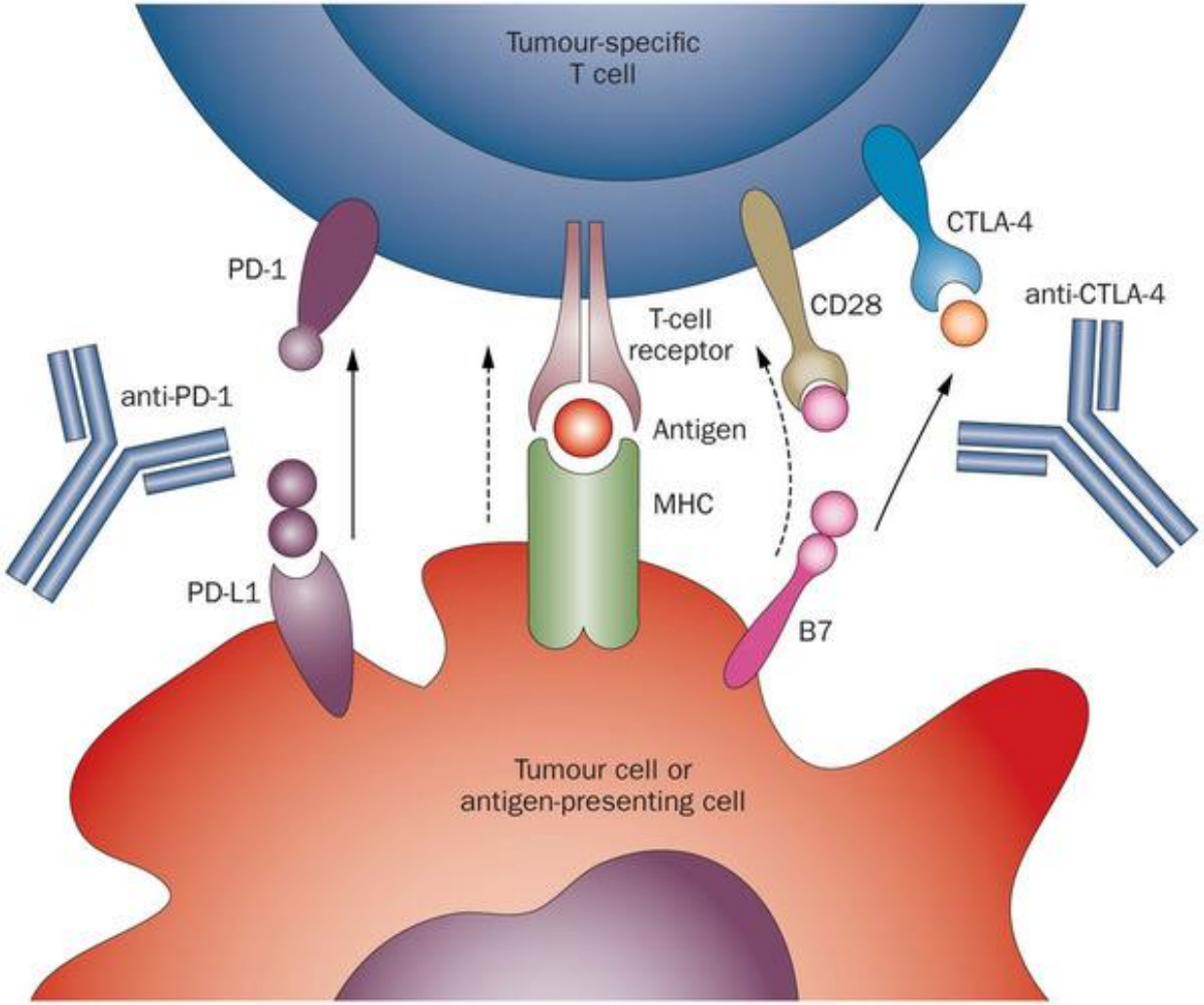
	n	Objective response % (95% CI)		Proportion of patients with an objective response % (95% CI)
		Nivolumab	ICC	
Overall	167	31·7 (23·5 to 40·8)	10·6 (3·5 to 23·1)	21·0 (6·8 to 31·7)
***BRAF* status**				
Mutant	37	23·1 (9·0 to 43·6)	9·1 (0·2 to 41·3)	14·0 (−17·1 to 34·4)
Wild-type	130	34·0 (24·6 to 44·5)	11·1 (3·1 to 26·1)	22·9 (6·2 to 35·0)
Previous ipilimumab benefit				
Yes	55	30·0 (16·6 to 46·5)	13·3 (1·7 to 40·5)	16·7 (−10·6 to 34·8)
No	112	32·5 (22·4 to 43·9)	9·4 (2·0 to 25·0)	23·1 (5·6 to 35·6)
PD-L1 status				
Positive	77	43·6 (30·3 to 57·7)	9·1 (1·1 to 29·2)	34·5 (12·2 to 49·2)
Negative	87	20·3 (11·3 to32·2)	13·0 (2·8 to 33·6)	7·3 (−13·4 to 21·5)



PD-1 antibodies side effects

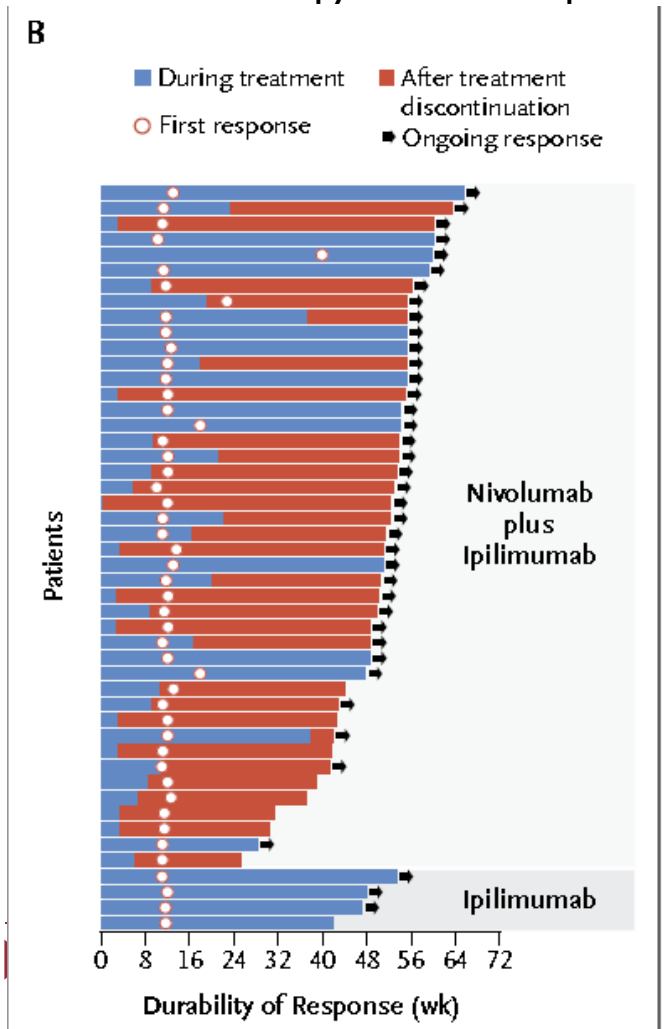
- Rash (>20% -nivolumab)
- fatigue, pruritus, constipation, diarrhea, nausea, and decreased appetite (>20% -pembrolizumab)
- Immune-mediated pneumonitis or interstitial lung disease
- Immune-mediated colitis
- Immune-related endocrinopathies:
  - Hipophysitis
  - Hiper- or hipothyroidism
  - Adrenal insufficiency
- Nephritis and Renal Dysfunction

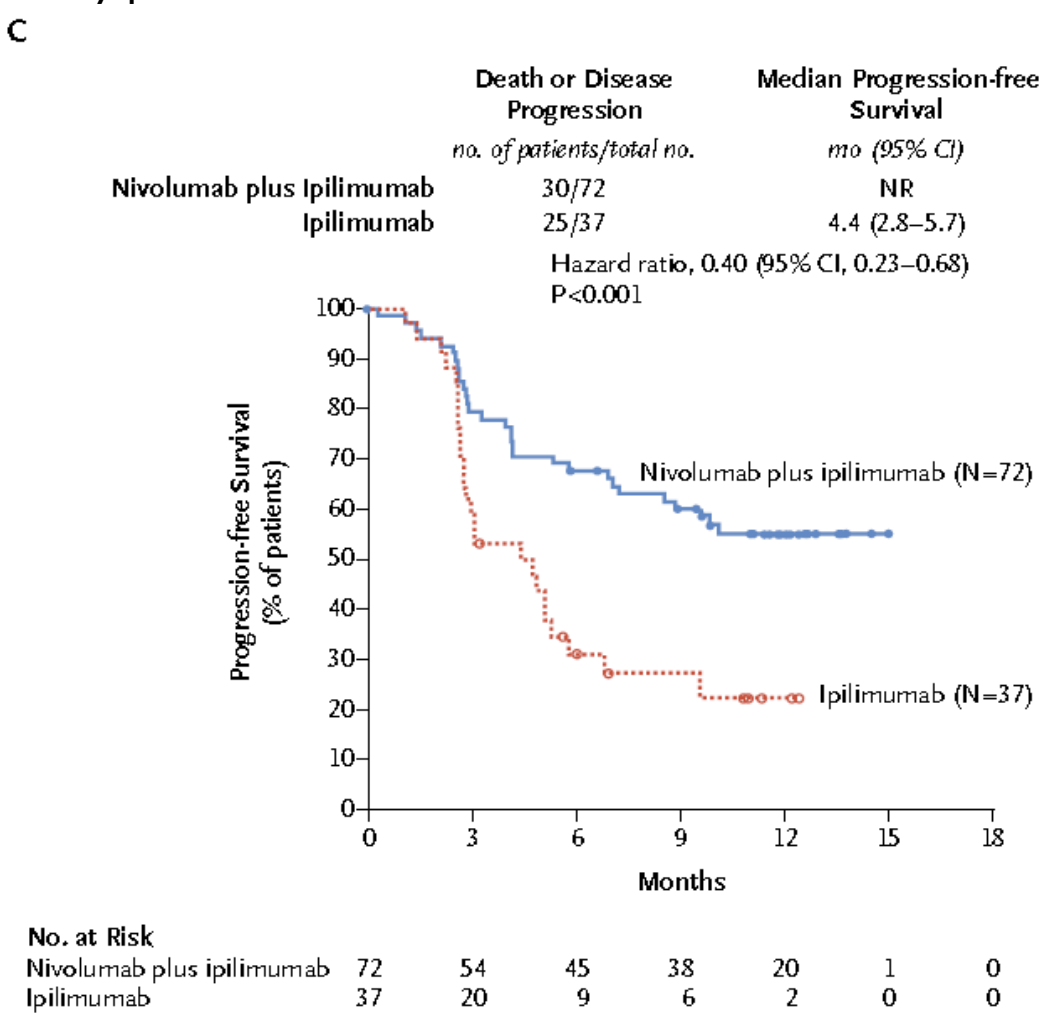
CTLA4-inhibitor with PD1-inhibitor



Nivolumab+ipilimumab vs ipilimumab alone

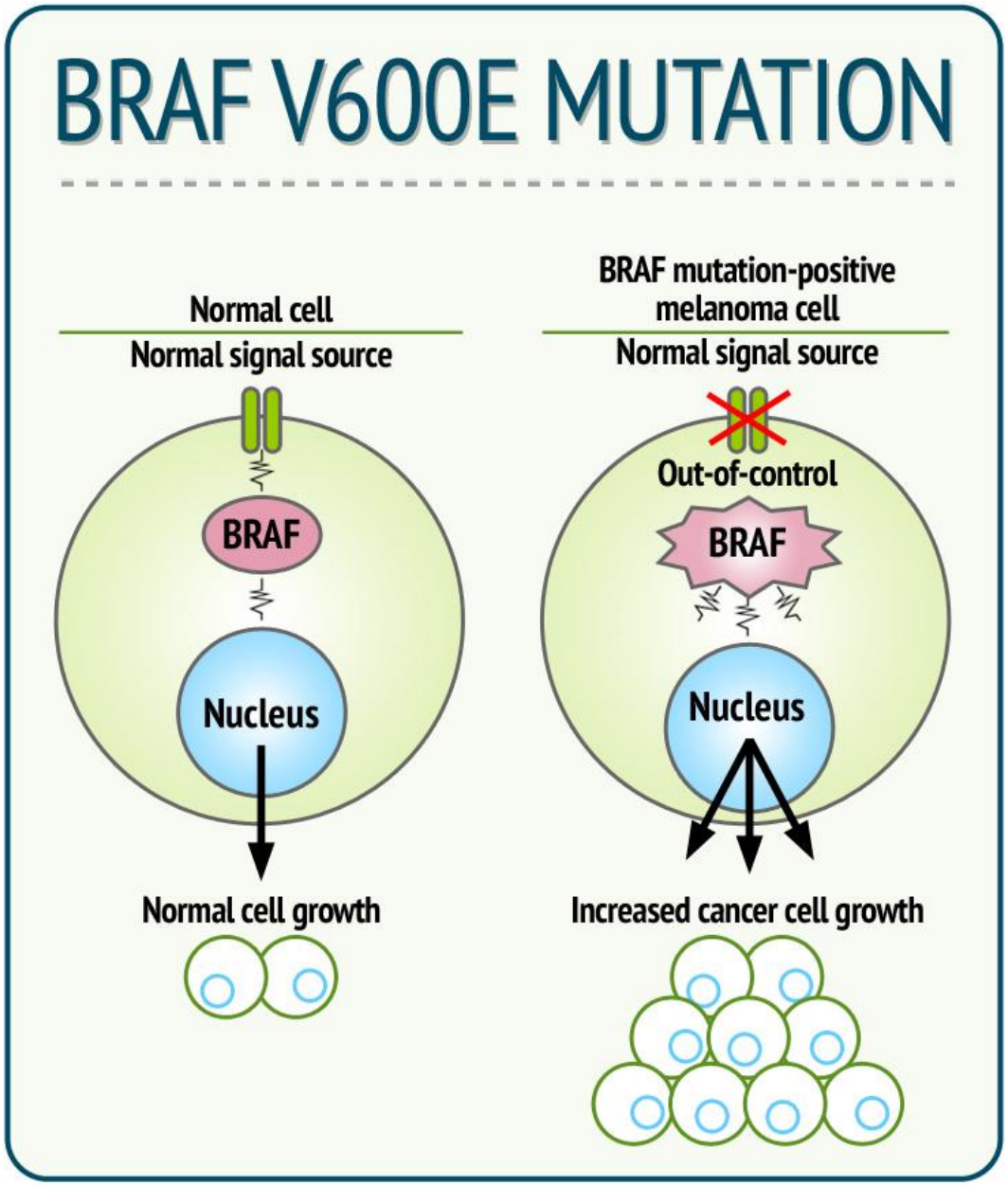
- ORR and PFS among patients with advanced melanoma who had not previously received treatment were significantly greater with nivolumab combined with ipilimumab than with ipilimumab monotherapy.
- Combination therapy had an acceptable safety profile.





Vemurafenib/dabrafenib

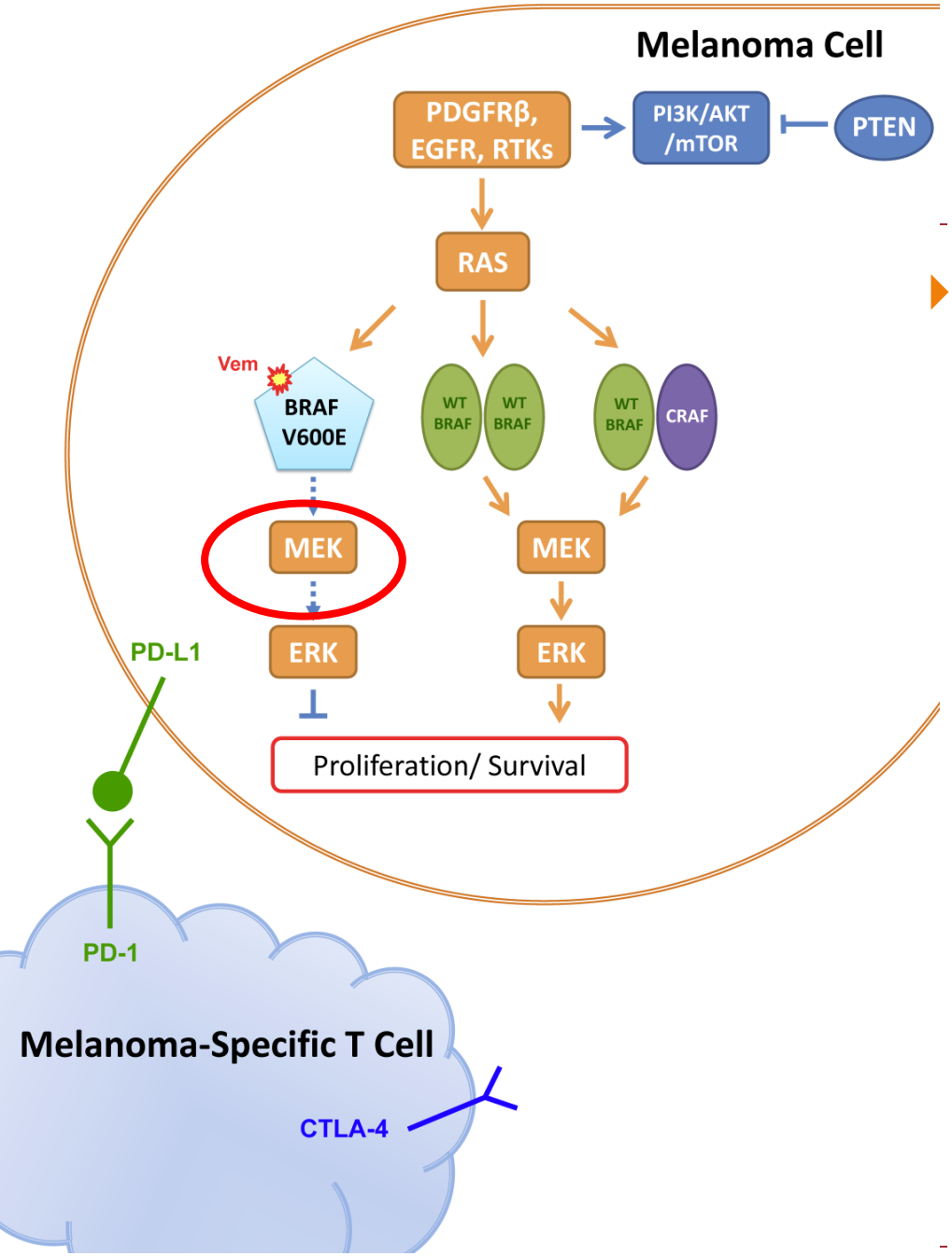
- BRAF-inhibitors



BRAF is a serine/threonine growth signal transduction protein kinase which plays an important role in the RAS/RAF/MEK/ERK pathway and directs cell division, proliferation and secretion

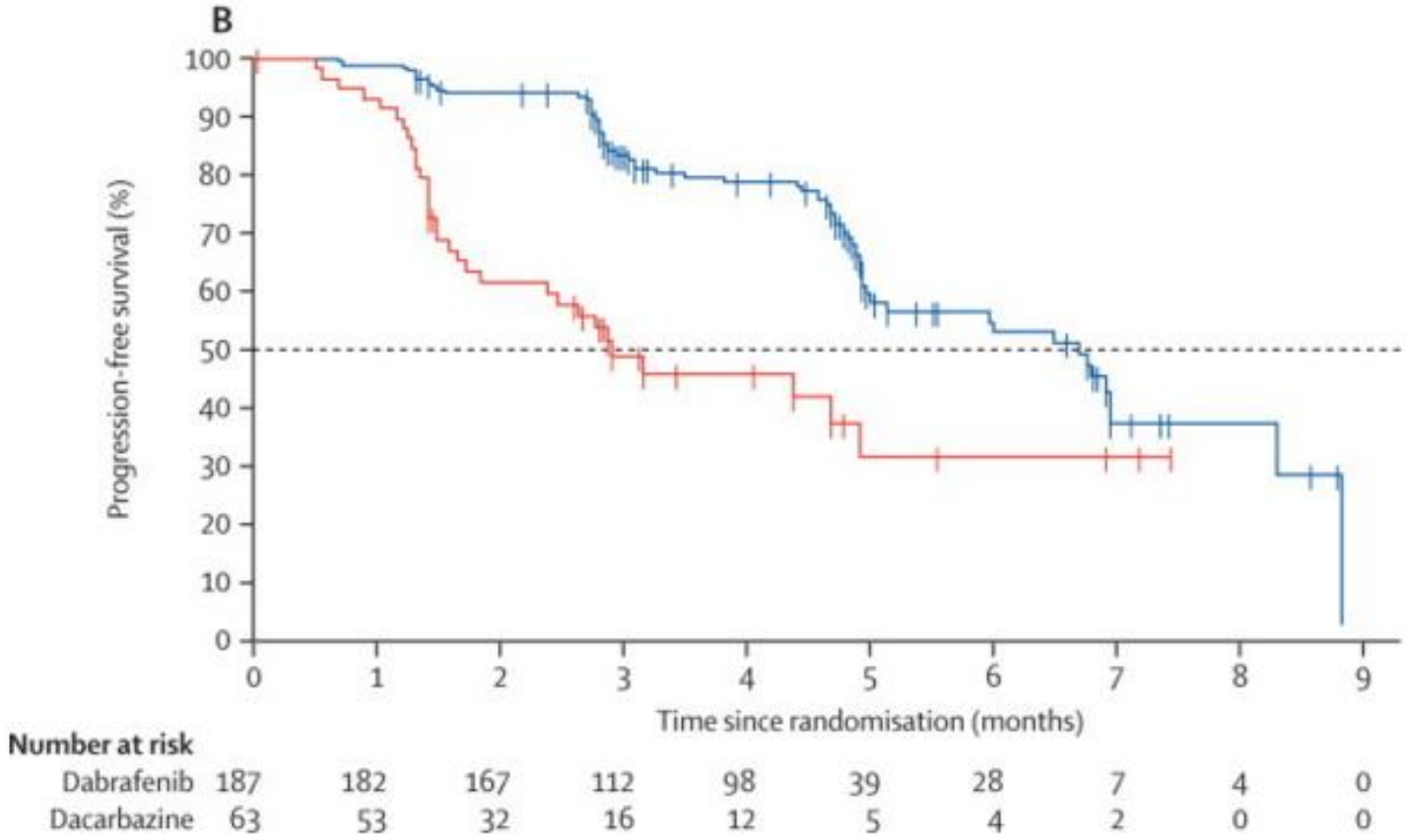
Somatic missense mutation in the BRAF gene is found in 60% of cutaneus melanoma

The most common BRAF mutation is substitution of glutamic acid for valine at codon 600 (*BRAF V600 E*)
80-90%
-other mutations: *BRAF V600K, BRAF V600R*



- BRAF-inhibitors
  - Vemurafenib / Dabrafenib
  - First-line therapy in patients with BRAF mutation
  - Risk of acquired restistance

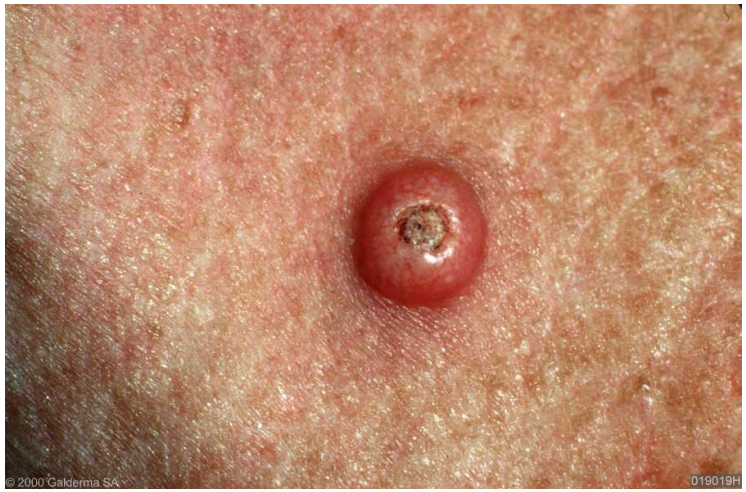
Dabrafenib vs dacarbazine



Median progression-free survival for dabrafenib of 6,7 months versus 2,9 months for dacarbazine (HR 0·35; 95% CI 0·20–0·61)

BRAF-inhibitors side effects

- Skin toxicity
  - photosensivity, rash, pruritus
- Arthralgias
- Fatigue
- Pyrexia
- Cutaneus squamous cell carcinoma
- Keratoacanthoma



Keratoacanthoma

Trametinib/binimetinib/cobimetinib

- MEK-inhibitors

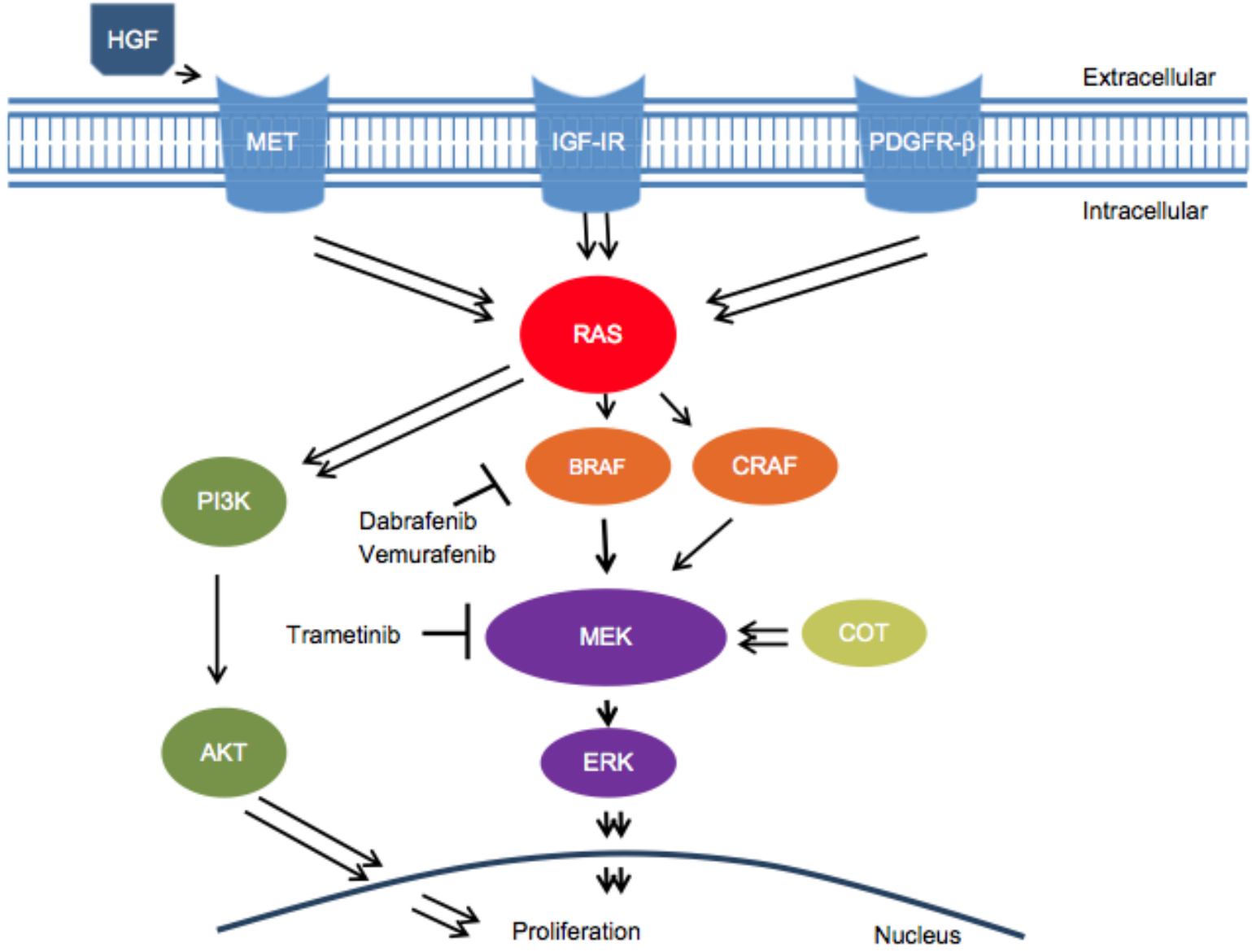


Figure 1 Redundancy of the MAPK signaling cascade and targeted inhibitors. Single arrows signify direct pathways. Double arrows reflect a culmination of multiple steps in the signaling cascade.

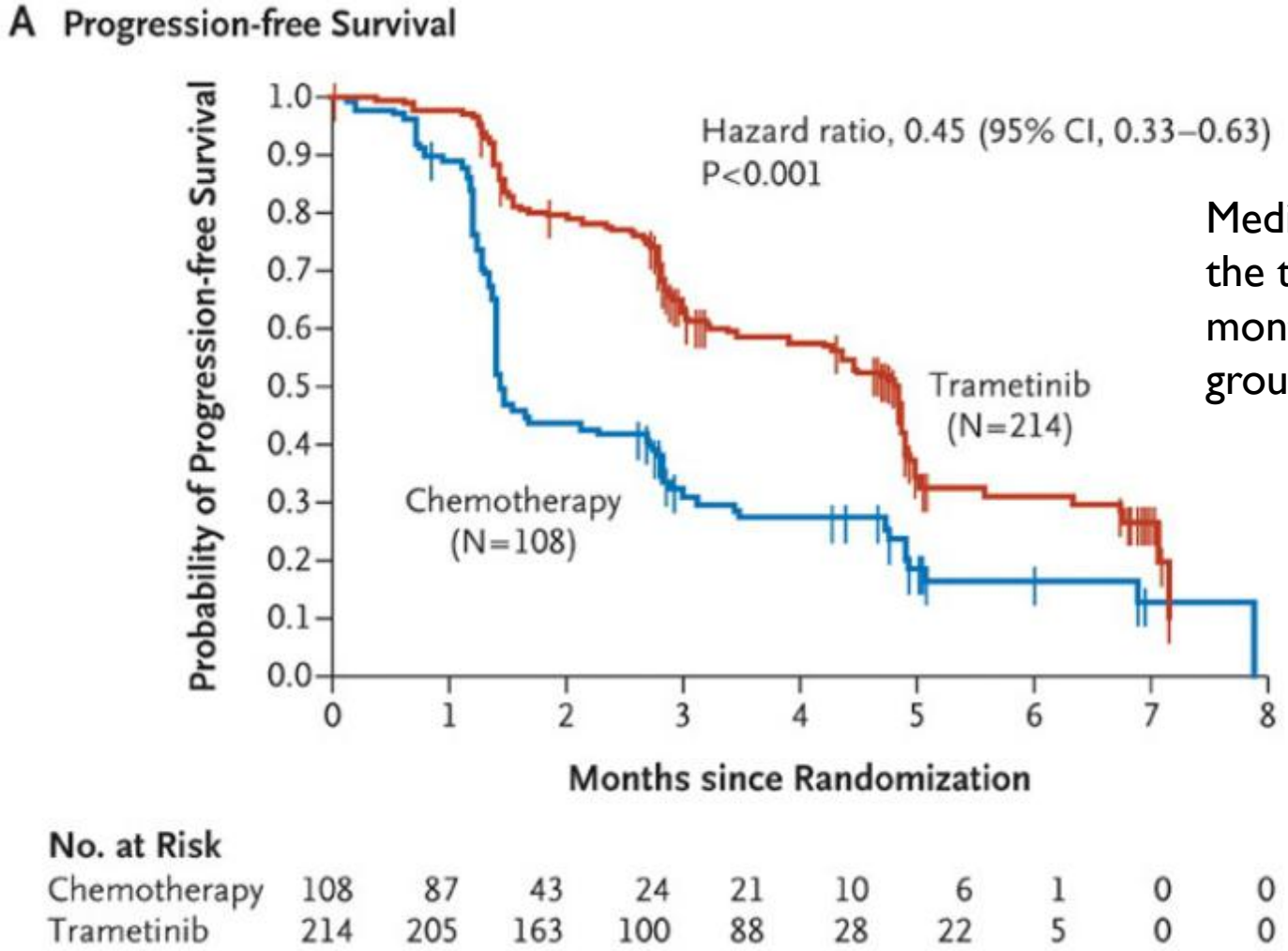
Note: Adapted from *Cancer Discov*, copyright 2013, 3(5), 487–490, Girotti MR, Marais R, Déjà vu: EGF receptors drive resistance to BRAF inhibitors, with permission from AACR.[59]

Abbreviations: HGF, human growth factor; IGF-IR, insulin-like growth factor 1 receptor; PDGFR-β, platelet-derived growth factor-β; PI3K, phosphoinositide 3-kinase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase.

Trametinib

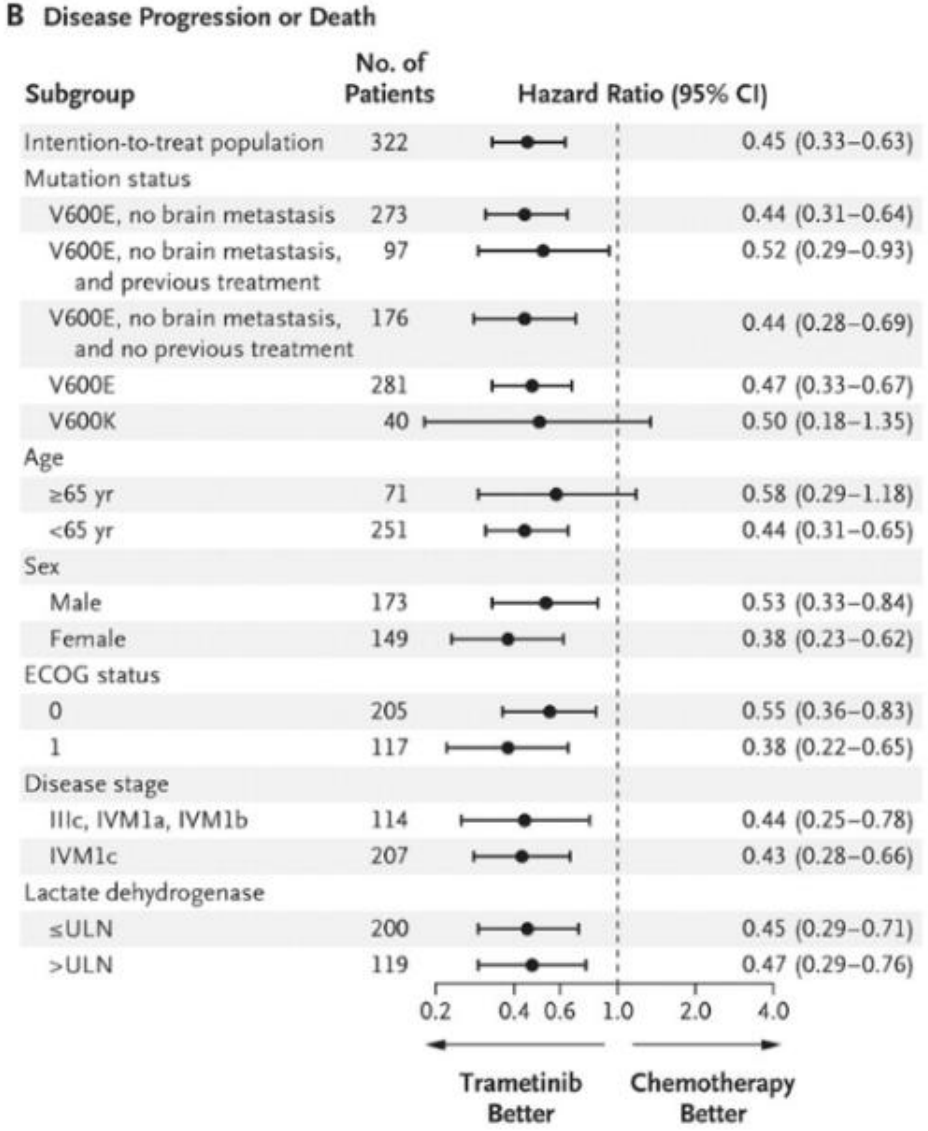
- inhibits MEK kinase 1 and 2 (mitogen-activated protein kinase), resulting in an inhibition of growth factor-mediated cell signaling and cellular proliferation in various cancers
- indicated as a single agent and in combination with dabrafenib
- Indicated in unresectable or metastatic melanoma with *BRAFV600E* or *V600K* mutations

Trametinib vs chemotherapy



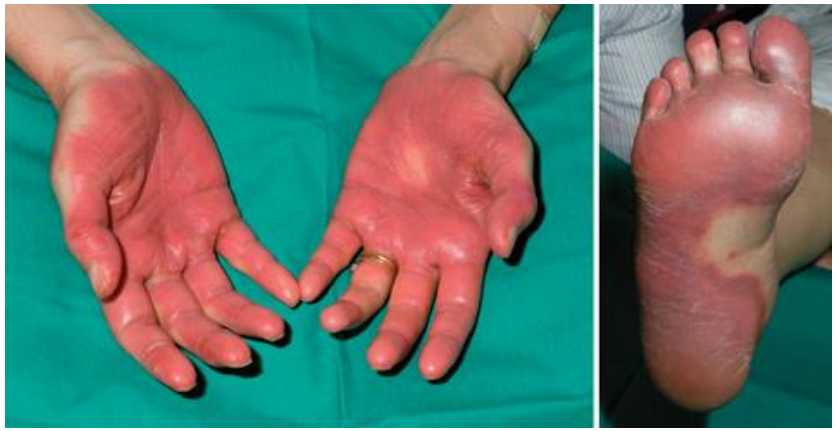
Median PFS was 4.8 months in the trametinib group and 1.5 months in the chemotherapy group

Trametinib vs chemotherapy



Trametinib side effects

- Skin toxicity (87%):
  - Rash, dermatitis acneiform rash, palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome-HFS), erythema,



- Diarrhea
- Peripheral edema
- Cardiomyopathy
- Ocular toxicity
  - retinal vein occlusion,

  retinal pigment epithelial detachment, uveitis, iritis
- Interstitial lung disease, pneumonitis

Combination BRAF + MEK inhibition (dabrafenib plus trametinib) vs dabrafenib+placebo

- Higher efficacy
  - Better ORR (67% vs 51%, 64% vs 51%)
  - Better median PFS (9,3 vs 8,8 months, 11,4 vs 7,3)
  - Better OS (6-month OS of 93% vs 85%, 12-month 72% vs 65%)
- Lower rates of cutaneous SCC/KA, skin papilloma, hiperkeratosis, HFS
- Higher rates of pyrexia
- Higher risk of dose discontinuation, dose modifications, interruption of treatment

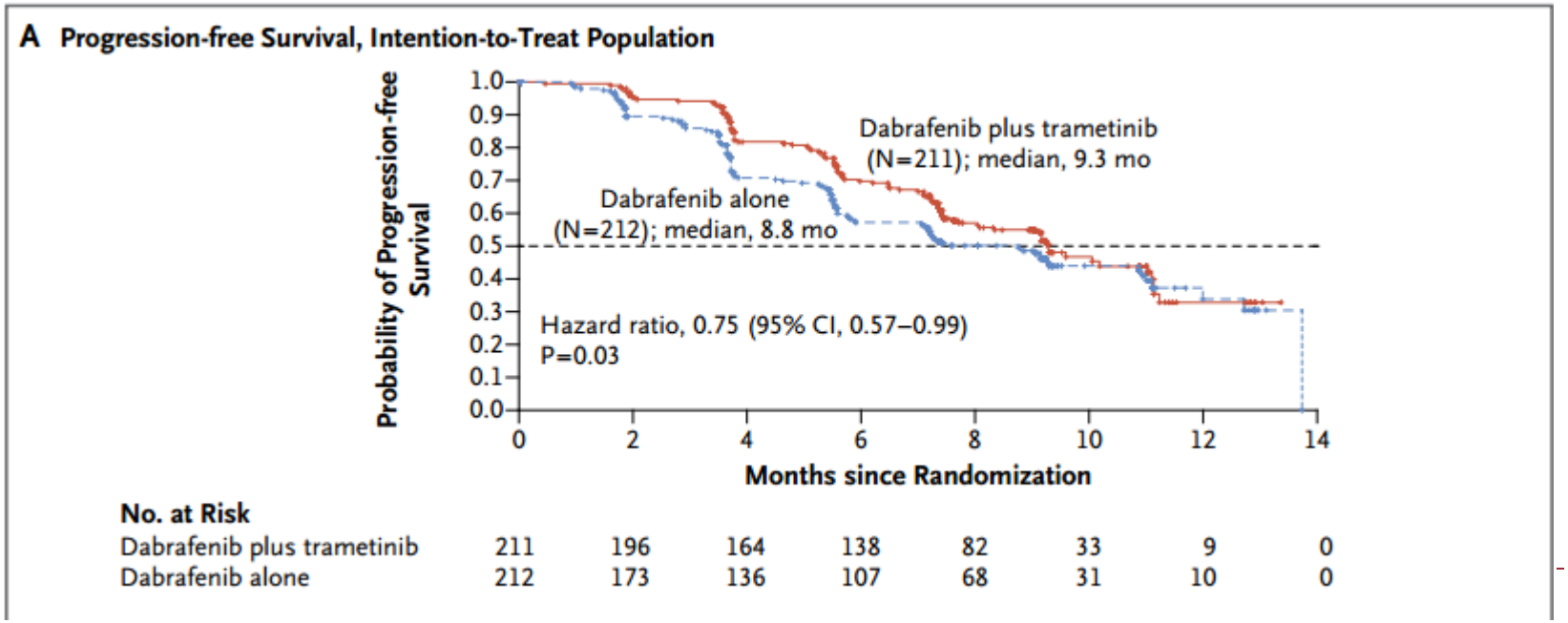
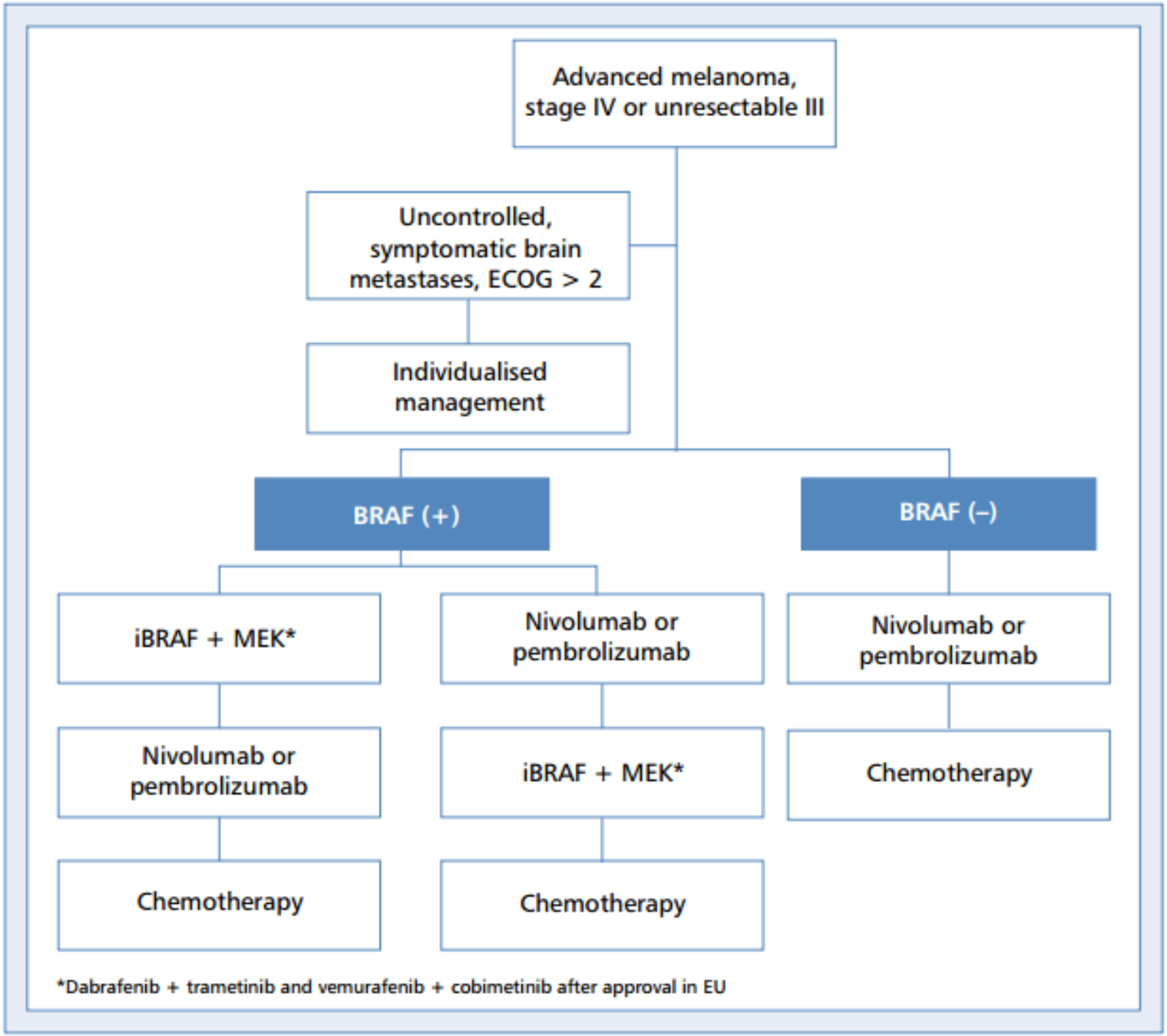


Table Treatment Characteristics and Endpoints to Consider in Tailoring Treatment for a Patient With Metastatic Melanoma

Desired Goal(s) of Care	Relevant Clinical Trial Endpoint to Consider	Treatment [Studies]					
		High-Dose IL-2[74,77,78]	Ipilimumab [18,27,36]	Pembrolizumab, Nivolumab [19,21,23,24,30,79]	Ipilimumab Plus Nivolumab [25,26]	BRAFi [4,53,54,56-59]	BRAFi Plus MEKi [56-58]
Cure (tumor eradication)	CR rate	6%	2%	3%–7%	5% (Near CR: 31%)	4%–9%	9%–13%
	Median CR duration	NR (> 3.5 yr)	NA	NA	NA	NA	NA
Prolonged survival (improved disease control)	Median OS	11 mo	10–12 mo	17 mo	39 mo	14–17 mo	NR
	2-year OS	25%	30%	43%–48%	75%	NA	NA
	5-year OS	NA	18%	NA	NA	NA	NA
	Median PFS	1.6 mo	< 3 mo	4–7 mo	NA	5–9 mo	9–11 mo
	1-year PFS	5%	20%–25%	30%–40%	40%	30%–35%	35%–45%
Symptom palliation (rapid tumor regression)	ORR	10%–15%	10%	28%–40%	53%	45%–51%	64%–76%
	Median time to response	NA	Slow (14–16 wk)	9 wk	< 12 wk	Rapid (< 8 wk)	Rapid (< 8 wk)
Improved quality of life (less toxicity)	Grade 3+ drug-related AE rate	80%	15%	11%–22%	53%	37%–63%	35%–65%
	Drug discontinuation rate	NA	NA	7%	21%	5%–12%	9%–13%

AE = adverse events; BRAFi = BRAF inhibitors; CR = complete response; IL-2 = interleukin-2; MEKi = MEK inhibitor; NA = not available; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.


Advanced melanoma, stage IV or unresectable III
Uncontrolled, symptomatic brain metastases, ECOG > 2
Individualised management
BRAF (+)
BRAF (–)
iBRAF + MEK*
Nivolumab or pembrolizumab
Nivolumab or pembrolizumab
Nivolumab or pembrolizumab
iBRAF + MEK*
Chemotherapy
Chemotherapy
Chemotherapy
*Dabrafenib + trametinib and vemurafenib + cobimetinib after approval in EU