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MOLECULAR DERMATOPATHOLOGY MELANOMA

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DISCLOSURE

I HAVE NOTHING TO DISCLOSE

IN·N·OUT BURGER

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1. Introduction to Molecular and Genetic Melanocytic Tumors.

2. Molecular prognostics and treatment of melanoma.

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INTRODUCTION

- Despite growth in genomics, gold standard for melanoma diagnosis still relies on histopathology.
- Initially melanoma were categorized based on histology – RGP and VGP growth phases.
- However categories now better distinguished by epidemiologic and genomic observations.

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WHO Classification of Melanoma

3rd Edition

- Superficial spreading melanoma
- Nodular melanoma
- Lentigo maligna melanoma
- Desmoplastic melanoma
- Nevoid melanoma
- Acral-lentiginous melanoma
- Mucosal melanoma
- UveaL melanoma
- Melanoma of childhood
- Melanoma arising from giant congenital nevus
- Melanoma arising from a blue nevus
- Persistent Melanoma

4th Edition

- Low CSD melanoma (SSM)
- High CSD melanoma (LMM)
- Desmoplastic melanoma
- Acral melanoma
- Mucosal melanoma
- Uveal melanoma
- Spitz melanoma
- Melanoma arising from giant congenital nevus
- Melanoma arising from a blue nevus

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	Low UV radiation exposure/CSD				High UV radiation exposure/CS	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma/SSM				High-CSD melanoma/LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate/low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate/high-grade dysplasias and melanocytomas	High-grade dysplasia/MIS	*BAP1*-inactivated melanocytoma/ MELTUMP	Deep penetrating melanocytoma/ MELTUMP	PEM/MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma/SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	**BRAF p.V600E**; *NRAS* *TERT*; *CDKN2A*; *TP53*; *PTEN*	*BRAF* or *NRAS* + *BAP1*	*BRAF*, *MAP2K1*, or *NRAS* + *CTNNB1* or *APC*	*BRAF* + *PRKAR1A* or *PRKCA*	*NRAS*; *BRAF (non-p.V600E)*; *KIT*; *NF1* *TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	*NF1*; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET* *TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11*

- WHO Classification of Skin Tumors 4th.

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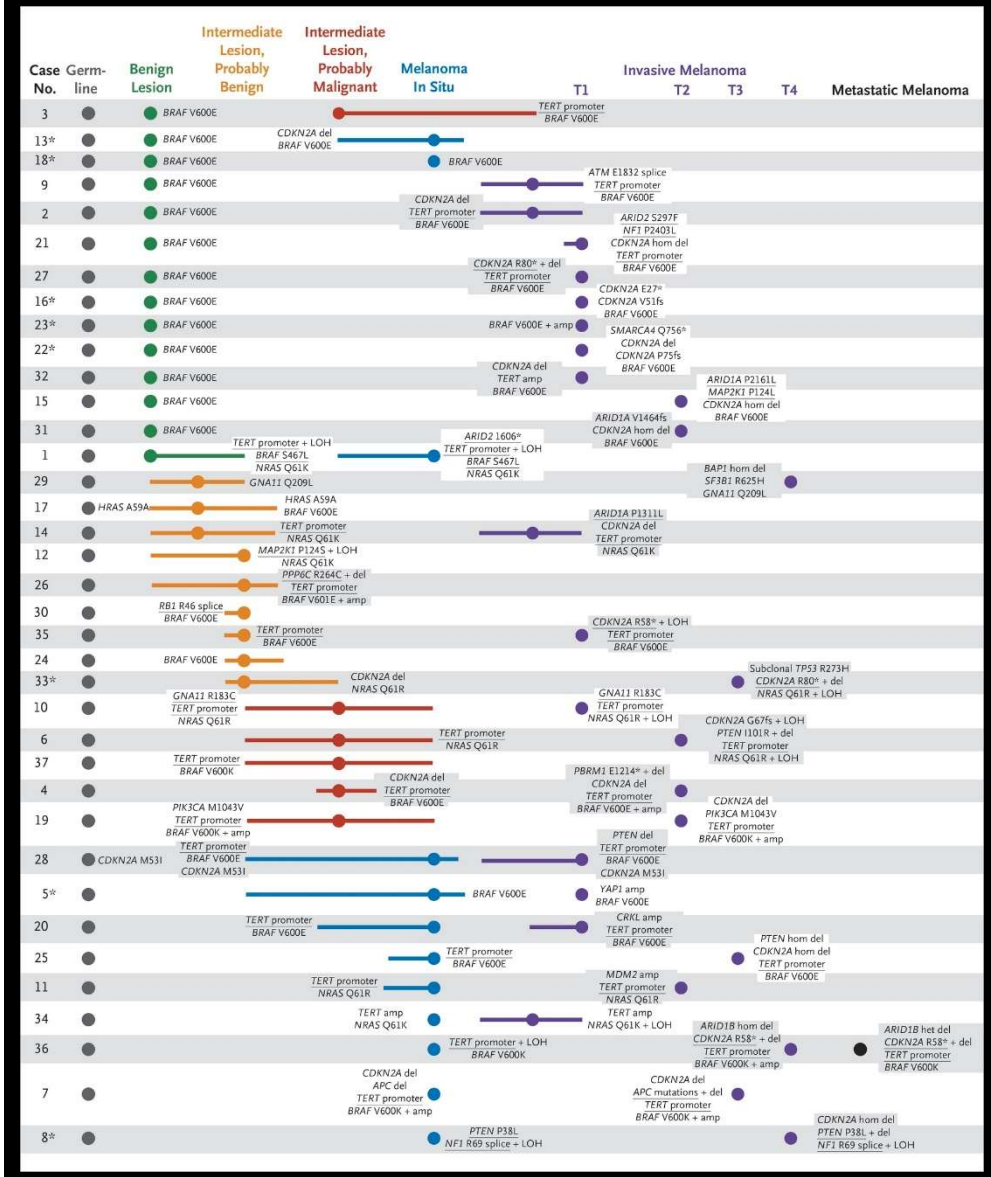
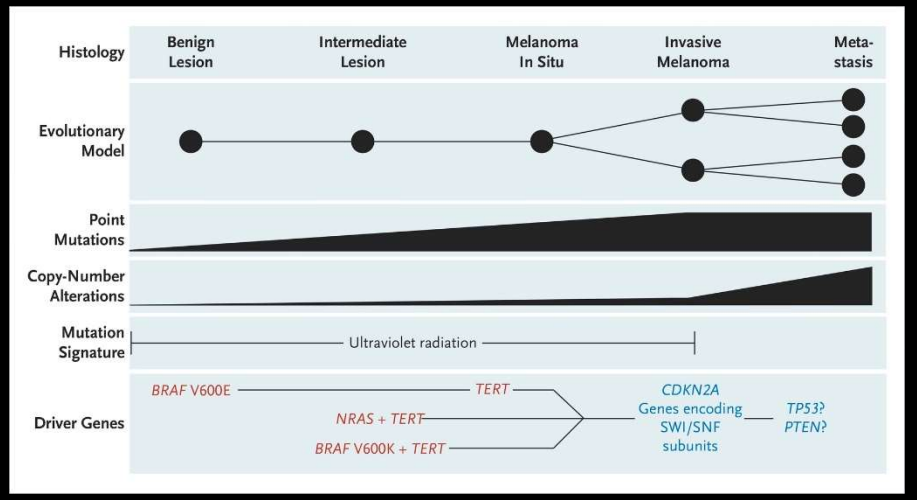
Low to no (or variable/incidental) UV radiation exposure / CSD					
IV	**V**	**VI**	**VII**	**VIII**	**IX**
Malignant Spitz tumour / Spitz melanoma	Acral melanoma	Mucosal melanoma	Melanoma in CN	Melanoma in BN	Uveal melanoma
Spitz naevus	? Acral naevus	? Melanosis	CN	Blue naevus	? Naevus?
Atypical Spitz tumour (melanocytoma)	IAMP / dysplasia	Atypical melanosis / dysplasia / IAMPUS	Nodule in CN (melanocytoma)	(Atypical) CBN (melanocytoma)	?
STUMP / MELTUMP	Acral MIS	Mucosal MIS	MIS in CN	Atypical CBN	?
Malignant Spitz tumour/ Spitz melanoma (tumorigenic)	Acral melanoma (VGP)	Mucosal lentiginous melanoma (VGP)	Melanoma in CN (tumorigenic)	Melanoma in blue naevus (tumorigenic)	Uveal melanoma
HRAS; ALK; ***ROS1***; ***RET***; ***NTRK1***; ***NTRK3***; ***BRAF***; ***MET***	***KIT***; ***NRAS***; ***BRAF***; ***HRAS***; ***KRAS***; ***NTRK3***; ***ALK***; ***NF1***	***KIT***, ***NRAS***, ***KRAS*** or ***BRAF***	***NRAS***; ***BRAF p.V600E*** (small lesions); ***BRAF***	***GNAQ***; ***GNA11***; ***CYSLTR2***	***GNAQ***, ***GNA11***, ***CYSLTR2***, or ***PLCB4***
CDKN2A	*CDKN2A*; *TERT*; *CCND1*; *GAB2*	***NF1***; *CDKN2A*; *SF3B1*; *CCND1*; *CDK4*; *MDM2*		*BAP1*; *EIF1AX*; *SF3B1*	*SF3B1*; *EIF1AX*; *BAP1*

- WHO Classification of Skin Tumors 4th.





- Cases included melanoma with precursor lesion
- Study defined the succession of genetic alterations during melanoma progression.
- It also identified an intermediate category with more than one genetic alteration – resolving the dysplastic/atypical nevi controversy.

- Shain et. al. The genetic evolution of Melanoma from Precursor Lesions. NEJM 2015.

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Table 1 | Common mutations and their role during melanoma progression

Pathway	Gene	Mutation	Subtype*	Progression phase‡	Role
MAPK	*BRAF*	V600E	Non-CSD	Naevi	Initiation
	BRAF	V600K, K601E and G469A, among other clustered nonV600E alterations	CSD	Intermediate and MIS lesions	Initiation
	NRAS	Q61R and Q61K, among other less common alterations affecting codon 61 or 12	CSD	Intermediate and MIS lesions	Initiation
	NF1	Disabling mutations occurring throughout the gene and deletions	CSD	MIS	Initiation
Telomerase	*TERT*	Promoter mutations affecting hg19 coordinates 1,295,228 or 1,295,250, among less common, nearby mutations	CSD and non-CSD	Intermediate and MIS lesions	Progression
RB	*CDKN2A*	Deletions and disabling mutations occurring throughout the coding region	CSD and non-CSD	Invasive melanoma	Progression
Chromatin remodelling	*ARID1A*, *ARID1B* and/or *ARID2*	Disabling mutations occurring throughout the protein	CSD and non-CSD	Invasive melanoma	Progression
PI3K	*PTEN*	Disabling mutations occurring throughout the protein and deletions	Non-CSD	Thicker invasive melanomas	Advanced progression
p53	*TP53*	Disabling mutations occurring throughout the protein	CSD	Thicker invasive melanomas	Advanced progression

ARID, AT-rich interaction domain; *CDKN2A*,cyclin-dependent kinase inhibitor 2A; CSD, chronically sun damaged; MIS, melanoma *in situ*; *NF1*, neurofibromin 1; *TERT*, telomerase reverse transcriptase. *Subtype refers to the melanoma subtype(s) predominantly associated with the mutation. ‡Progression phase refers to the earliest progression phase at which the mutation typically occurs.

- Shain et. al. From melanocytes to melanomas. Nat Rev Cancer 2016.

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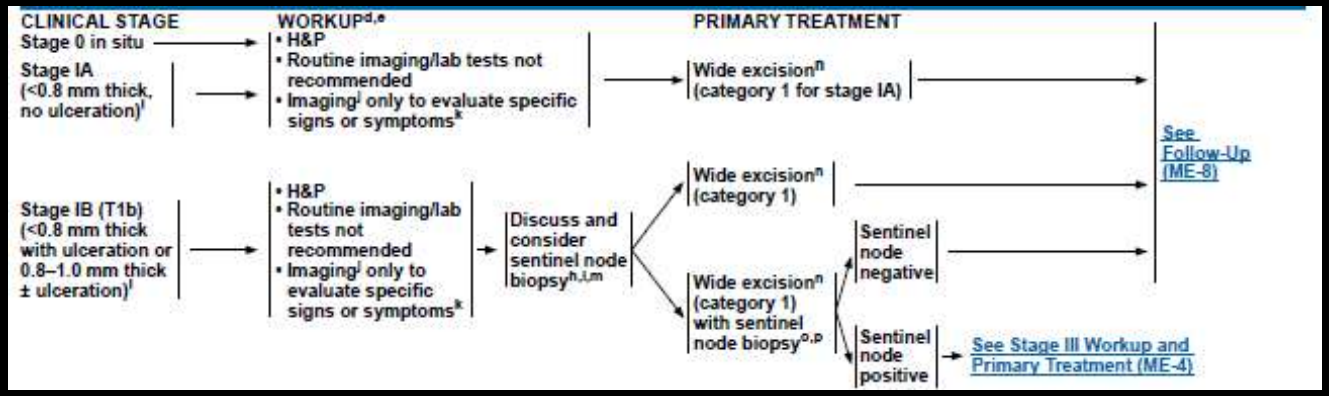
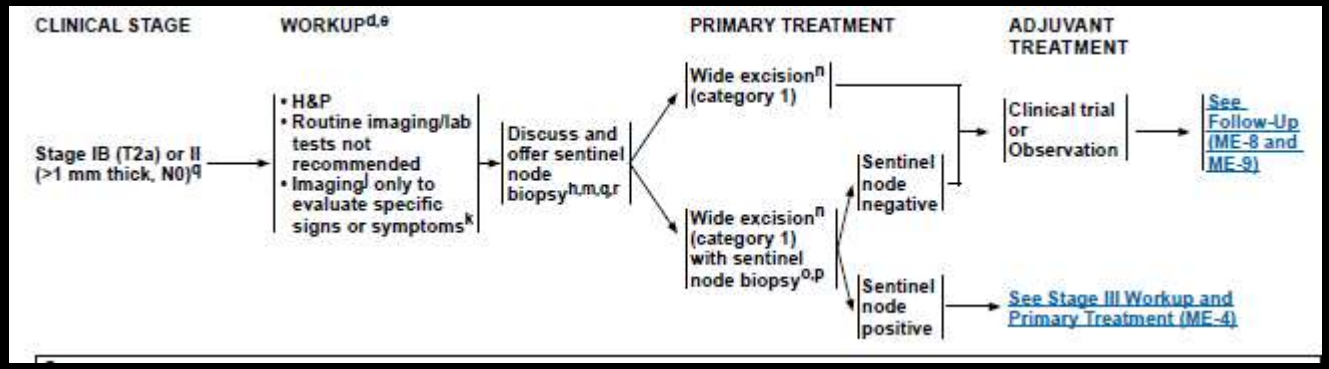
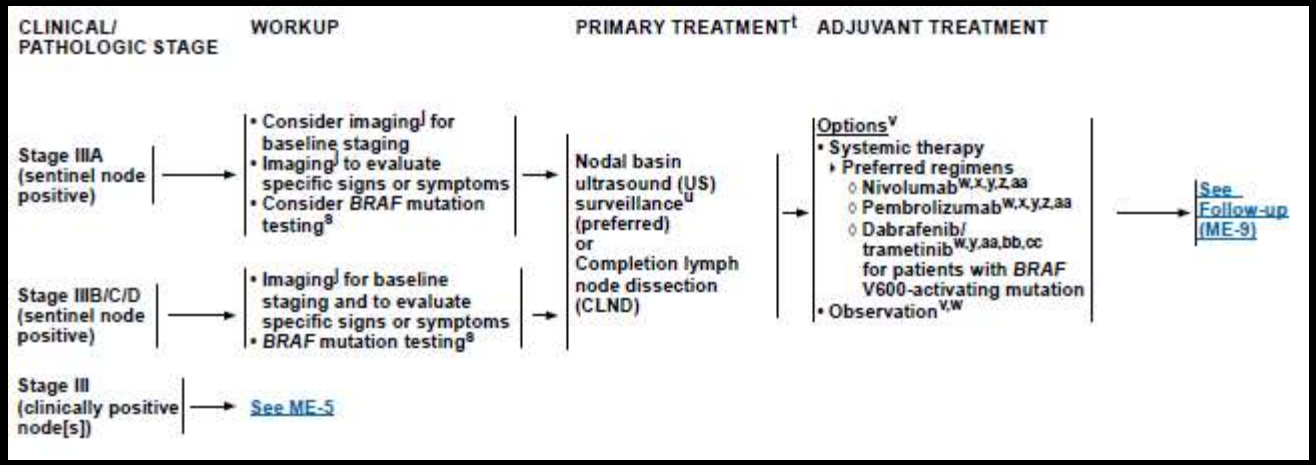
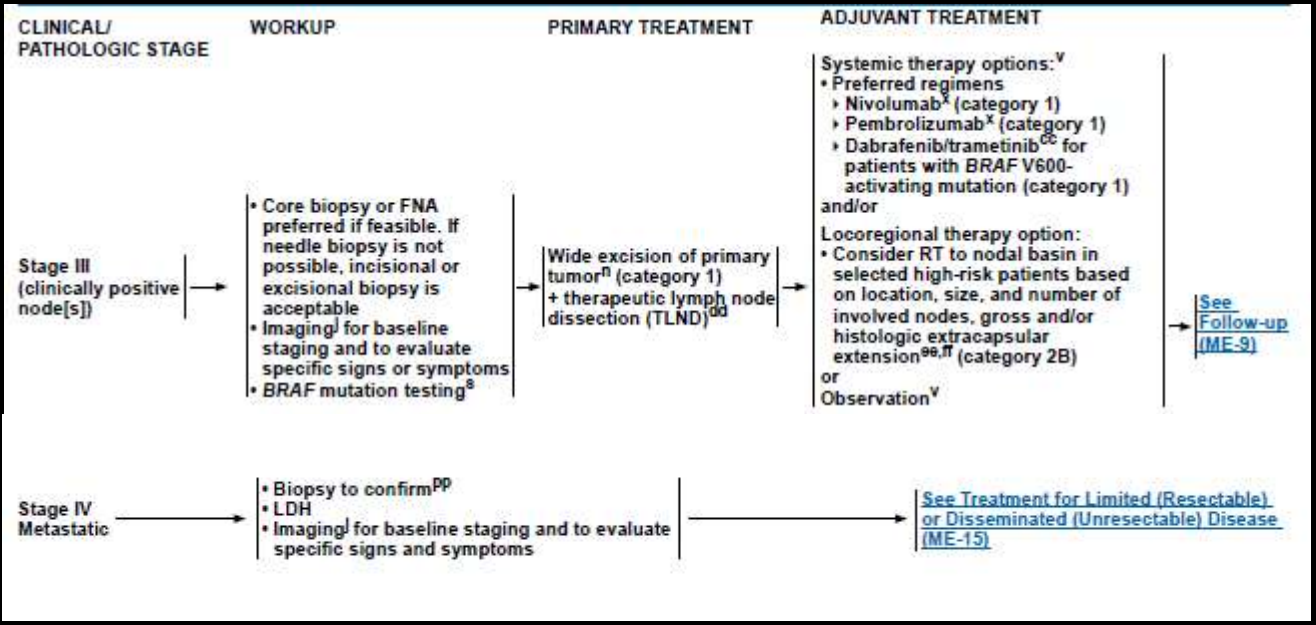
NCCN GUIDELINES






CLINICAL/ PATHOLOGIC STAGE
WORKUP
PRIMARY TREATMENT[t]
ADJUVANT TREATMENT
Stage IIIA (sentinel node positive)
• Consider imaging[j] for baseline staging
• Imaging[j] to evaluate specific signs or symptoms
• Consider BRAF mutation testing[s]
Nodal basin ultrasound (US) surveillance[u] (preferred) or Completion lymph node dissection (CLND)
Options[v]
• Systemic therapy
‣ Preferred regimens
◊ Nivolumab[w,x,y,z,aa]
◊ Pembrolizumab[w,x,y,z,aa]
◊ Dabrafenib/ trametinib[w,y,aa,bb,cc] for patients with BRAF V600-activating mutation
• Observation[v,w]
See Follow-up (ME-9)
Stage IIIB/C/D (sentinel node positive)
• Imaging[j] for baseline staging and to evaluate specific signs or symptoms
• BRAF mutation testing[s]
Stage III (clinically positive node[s])
See ME-5


CLINICAL/ PATHOLOGIC STAGE
WORKUP
PRIMARY TREATMENT
ADJUVANT TREATMENT
Stage III (clinically positive node[s])
• Core biopsy or FNA preferred if feasible. If needle biopsy is not possible, incisional or excisional biopsy is acceptable
• Imaging[j] for baseline staging and to evaluate specific signs or symptoms
• BRAF mutation testing[s]
Wide excision of primary tumor[n] (category 1) + therapeutic lymph node dissection (TLND)[dd]
Systemic therapy options:[v]
• Preferred regimens
‣ Nivolumab[x] (category 1)
‣ Pembrolizumab[x] (category 1)
‣ Dabrafenib/trametinib[cc] for patients with BRAF V600-activating mutation (category 1)
and/or
Locoregional therapy option:
• Consider RT to nodal basin in selected high-risk patients based on location, size, and number of involved nodes, gross and/or histologic extracapsular extension[ee,ff] (category 2B)
or
Observation[v]
See Follow-up (ME-9)
Stage IV Metastatic
• Biopsy to confirm[pp]
• LDH
• Imaging[j] for baseline staging and to evaluate specific signs and symptoms
See Treatment for Limited (Resectable) or Disseminated (Unresectable) Disease (ME-15)

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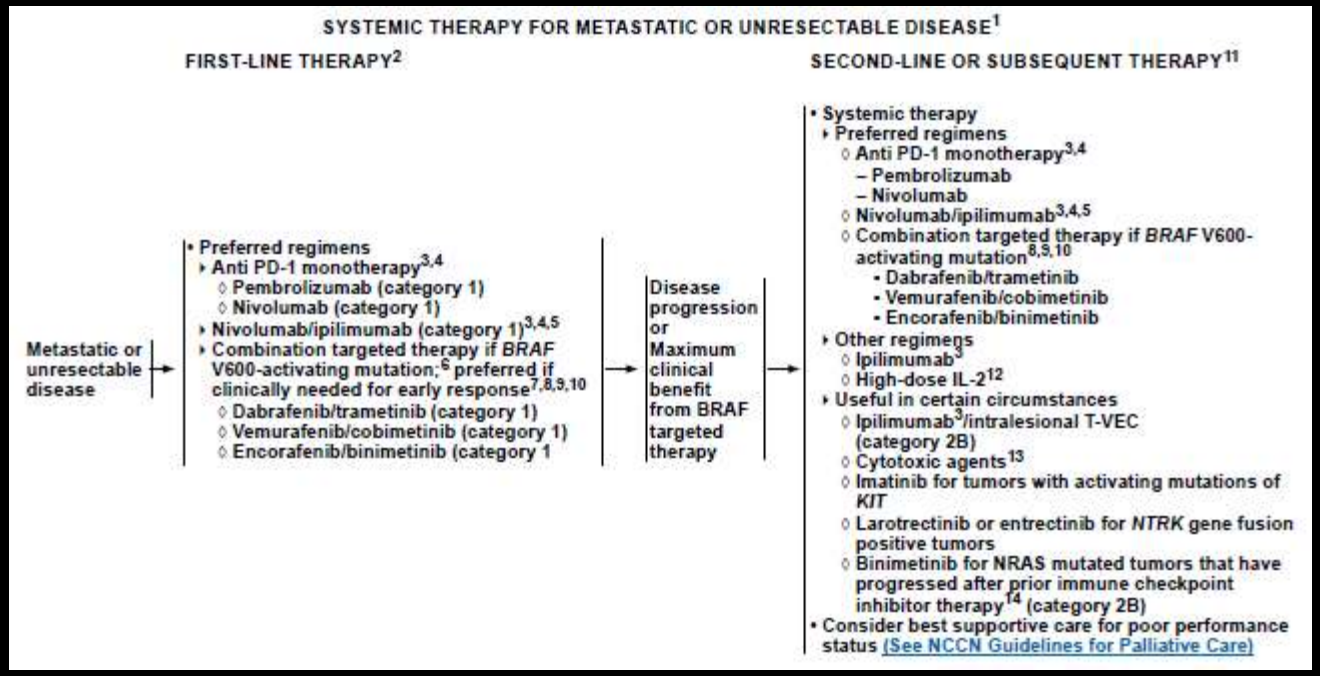

- There are many other clinical scenarios such as satellite/in transit/nodal recurrence and various tx options.

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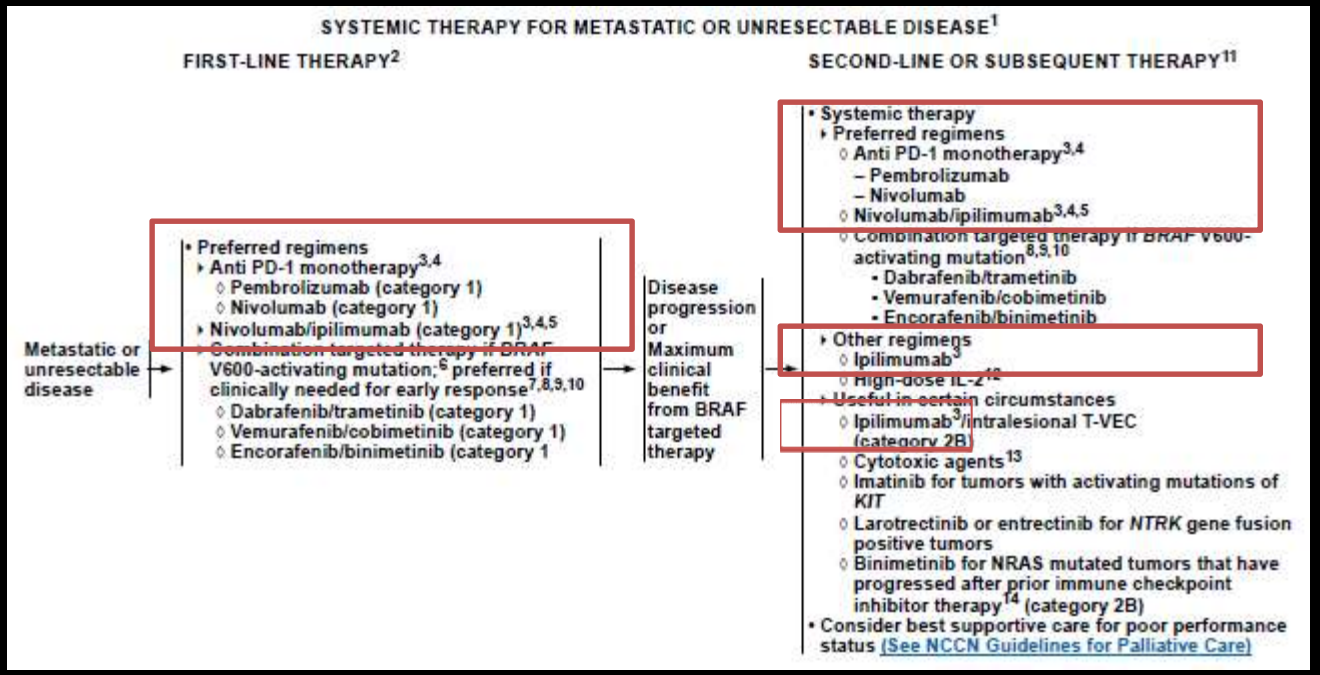
Checkpoint Inhibitors: CTLA-4 Ab and PD-1 and PD-L1 Blocking Ab



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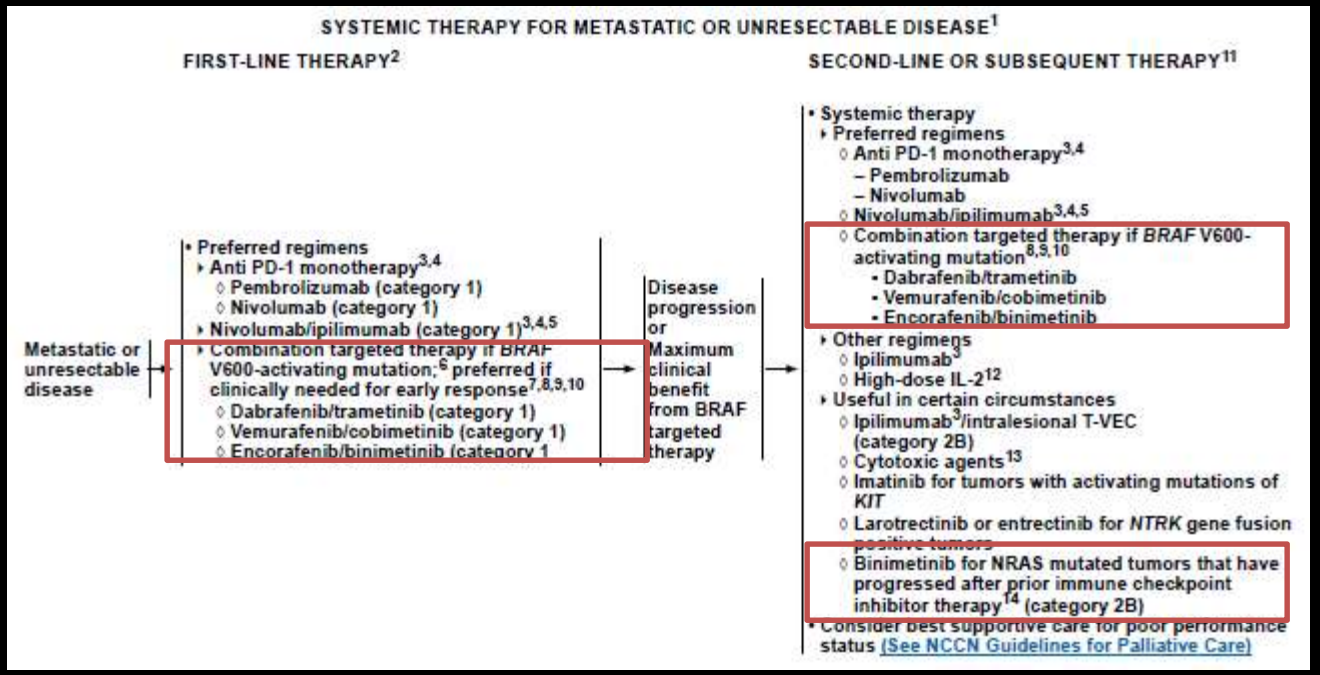
BRAF and MEK Inhibitors



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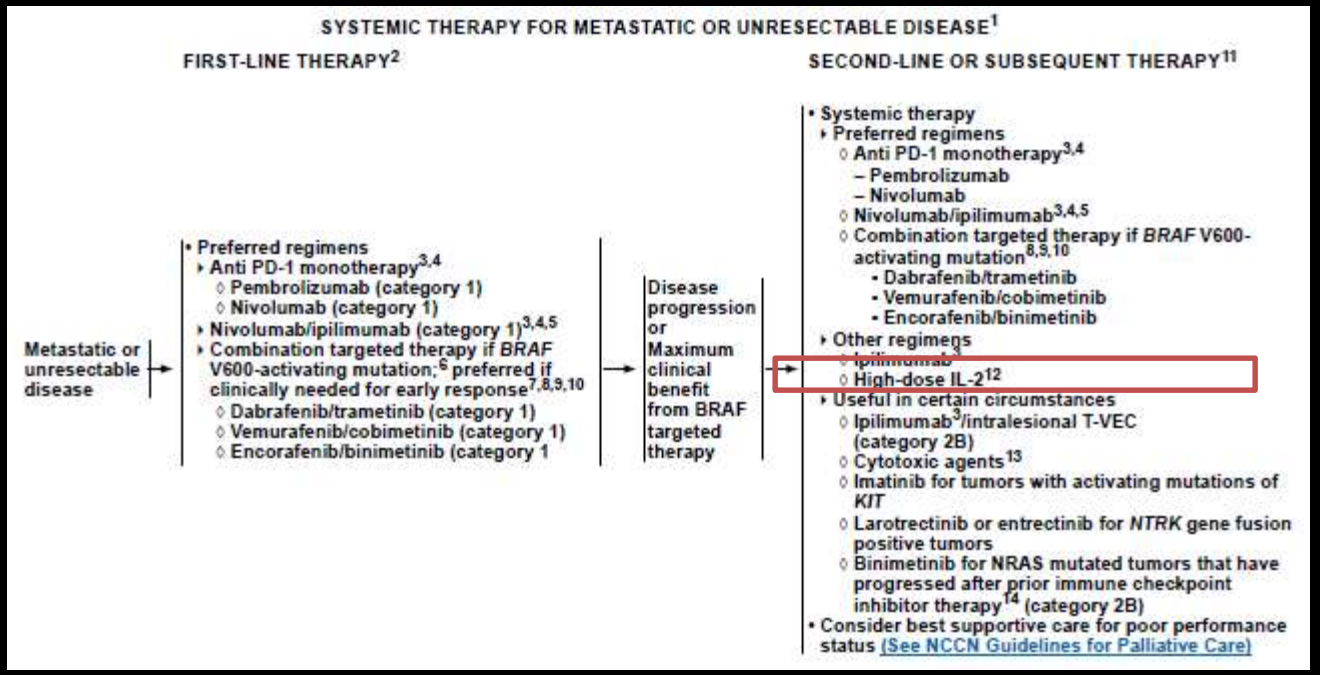
Interleukin-2



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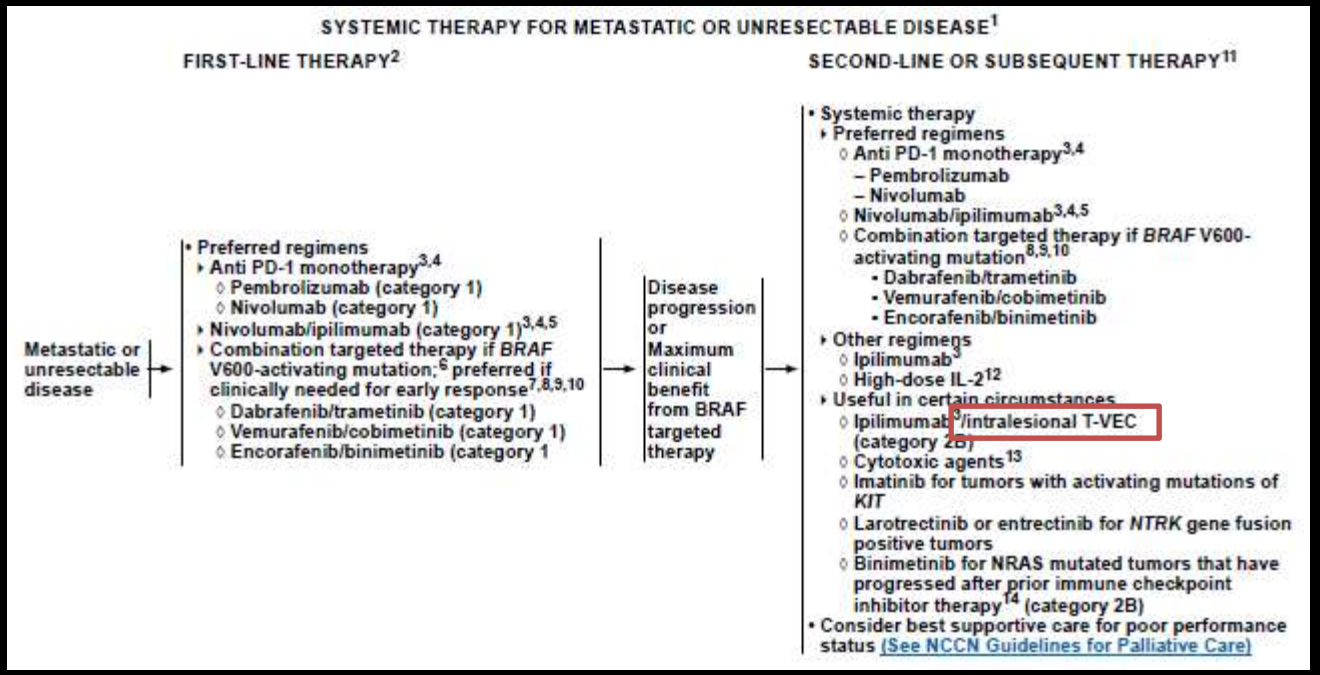
Intralesional T-VEC



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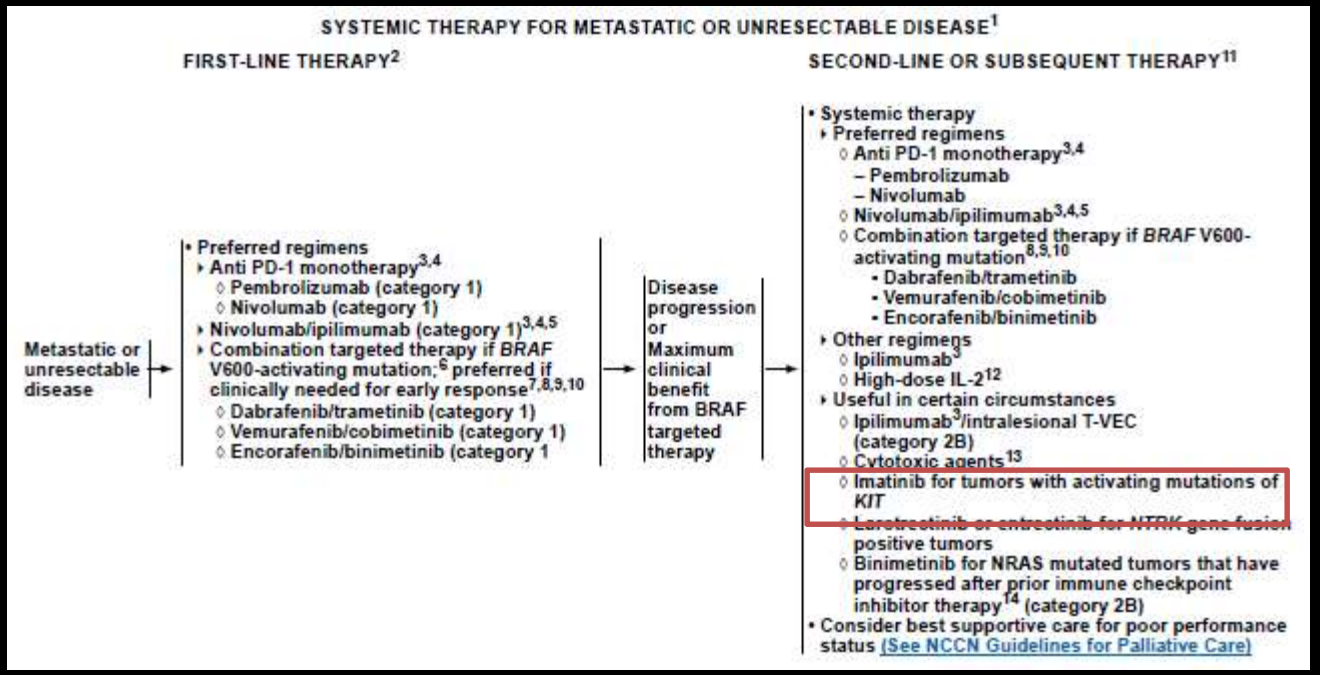
KIT Inhibitor



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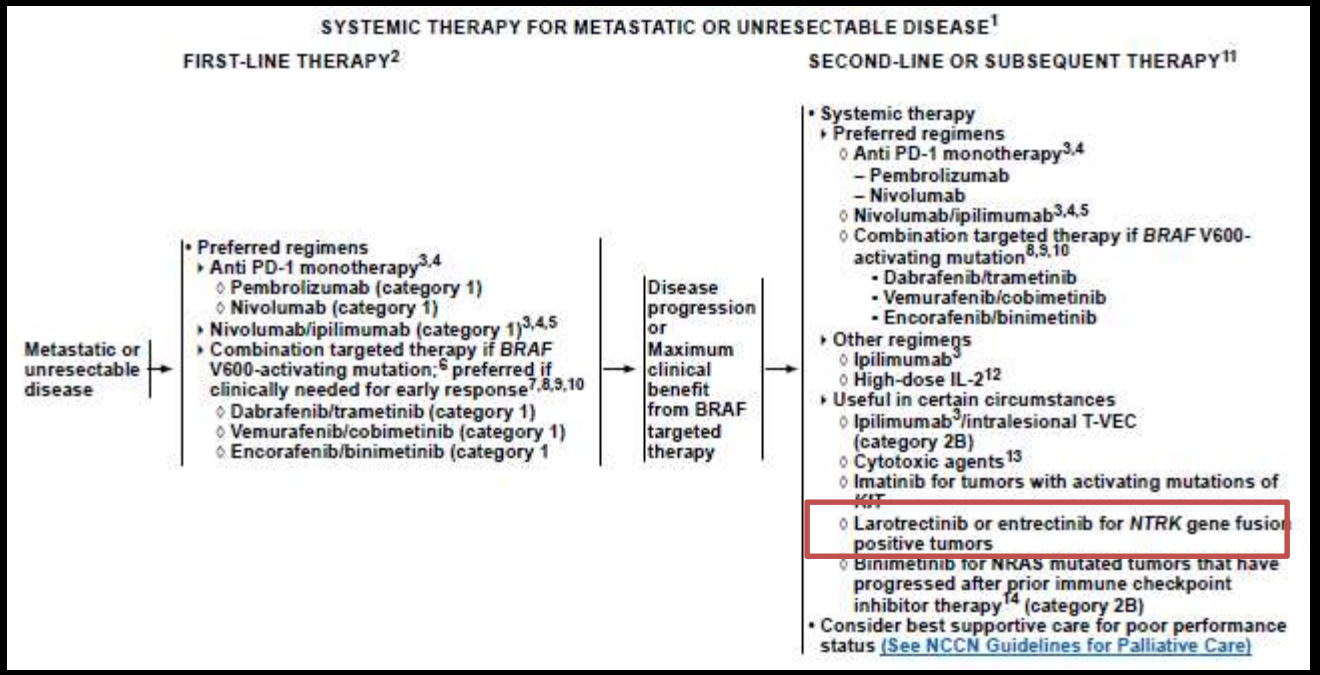
TRK Inhibitors



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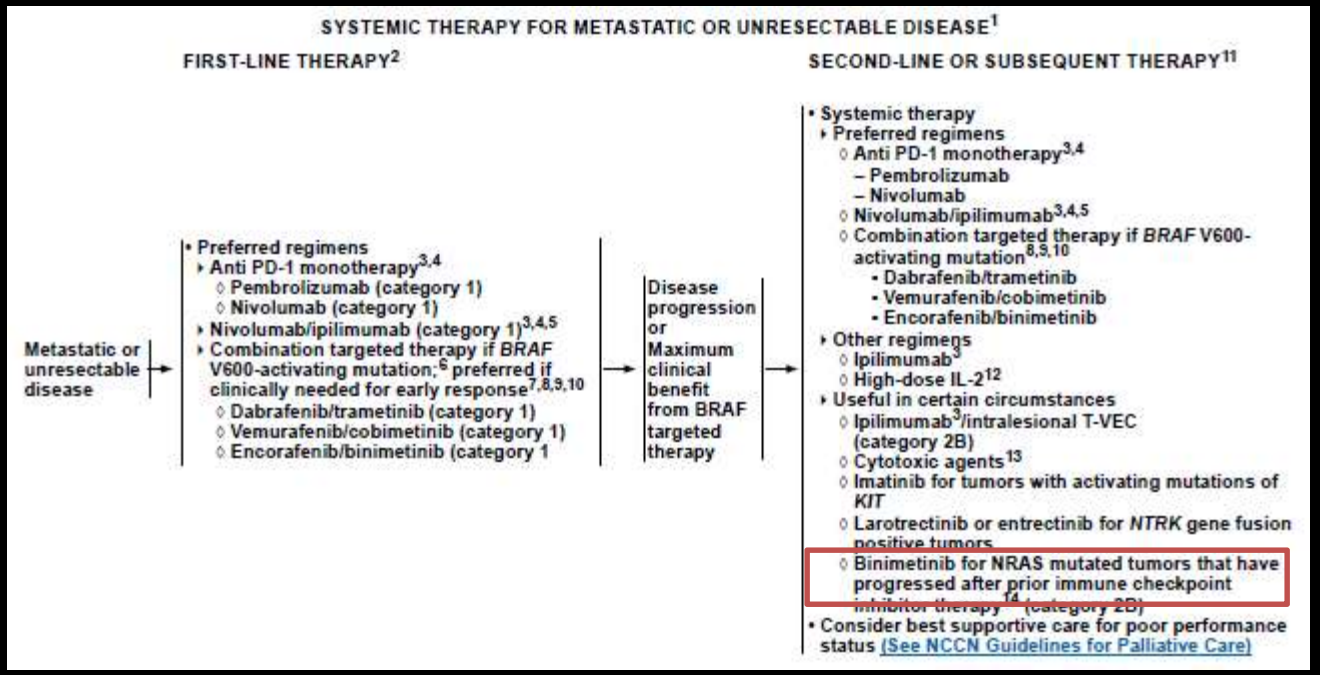
MEK Inhibitors for NRAS mutations



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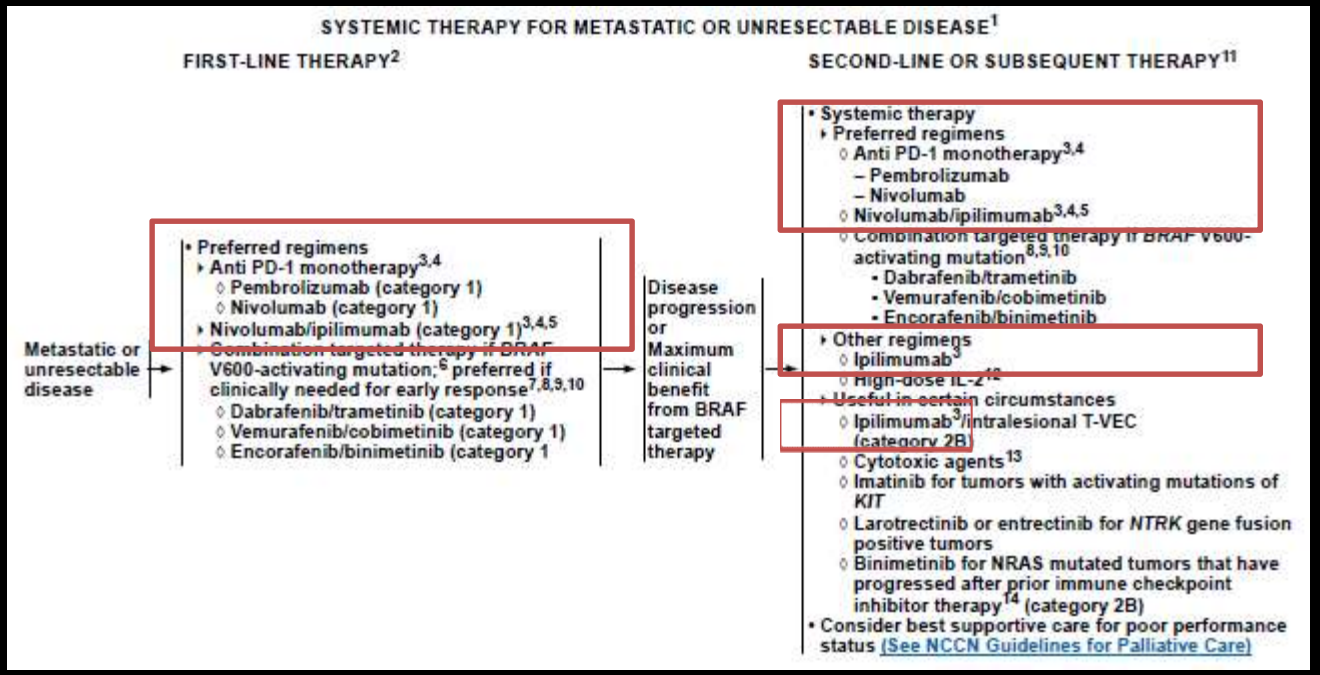
Checkpoint Inhibitors: CTLA-4 Ab and PD-1 and PD-L1 Blocking Ab



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Immune Checkpoint targeted therapy

- T-Cell activation introduction
- CTLA-4 Blocking Ab
  - Ipilimumab
- PD-1 Blocking Ab
  - Nivolumab
  - Pembrolizumab

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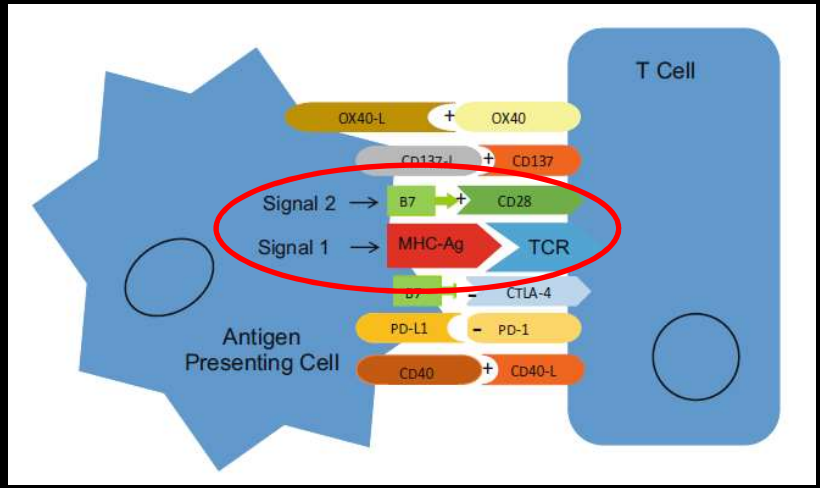
Immune Checkpoint targeted therapy



- Pathogen or Tumor antigen specific T-cell activation requires two signals:
  1. T-cell receptor (TCR) recognizes/binds to tumor associated antigen presented in association with MHC by antigen presenting cells.
  2. Costimulatory signal is provided by binding CD28 with B7-1(CD80) or B7-2(CD86) receptors.

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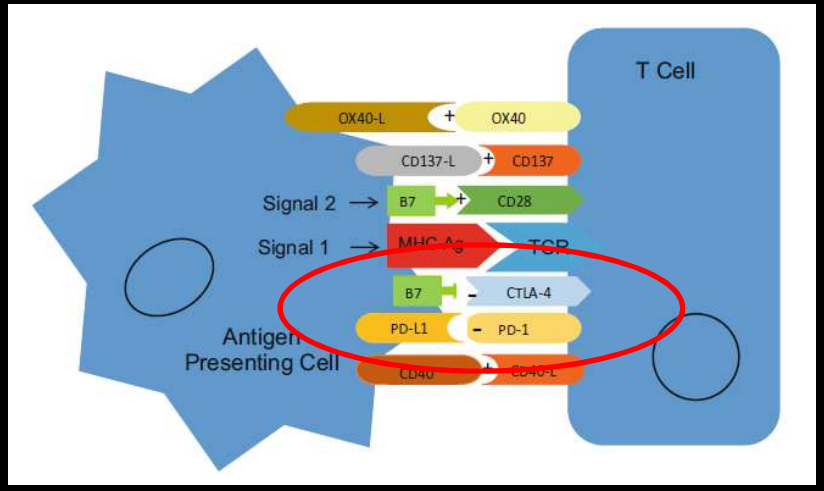
Immune Checkpoint targeted therapy



- Both signals are required for activation, differentiation, and proliferation of antigen – specific T cells which then migrate to the source of antigens in the periphery to elicit effector function (PROGRAM=KILL TUMOR CELLS!).
- T cell immunity is tightly regulated by check and balance systems involving many stimulatory and inhibitory molecules.

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Immune Checkpoint targeted therapy

- T-Cell activation introduction
- CTLA-4 Blocking Ab
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  - Nivolumab
  - Pembrolizumab

- Eggermont AM et al. NEJM 2016:375:1845-1855.
- Hodi FS et al. NEJM 2010:711-723.
- Robert C et al. NEJM 2011:2517-2526.
- Maio M et al. J Clin Oncol 2015:1191-1196
- Ascierto PA et al. Lancet Oncol 2017.

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Immune Checkpoint targeted therapy

Table 6. FDA-Approved Indications for Immune Checkpoint Inhibitor and BRAF/MEK Targeted Therapy in Cutaneous Melanoma

Agent	Treatment for Metastatic or Unresectable Disease	Adjuvant Therapy
Immune Checkpoint Inhibitors		
Ipilimumab[394]	Unresectable or metastatic melanoma	Cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy
Nivolumab[395]	Unresectable or metastatic melanoma	Melanoma with lymph node involvement or metastatic disease who have undergone complete resection
Pembrolizumab[396]	Unresectable or metastatic melanoma	Melanoma with involvement of lymph node(s) following complete resection
Nivolumab/ipilimumab[394,395]	Unresectable or metastatic melanoma	No FDA approval in this setting

- Current list of FDA approved ImmunoCheckpoint inhibitors.
- There are other anti-CTLA-4 and anti-PD-1/anti-PD-L1 drugs not approved or in development.

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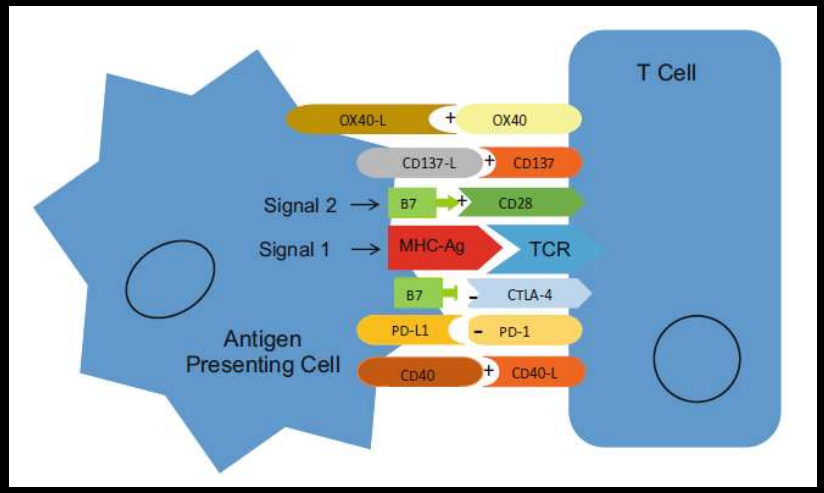
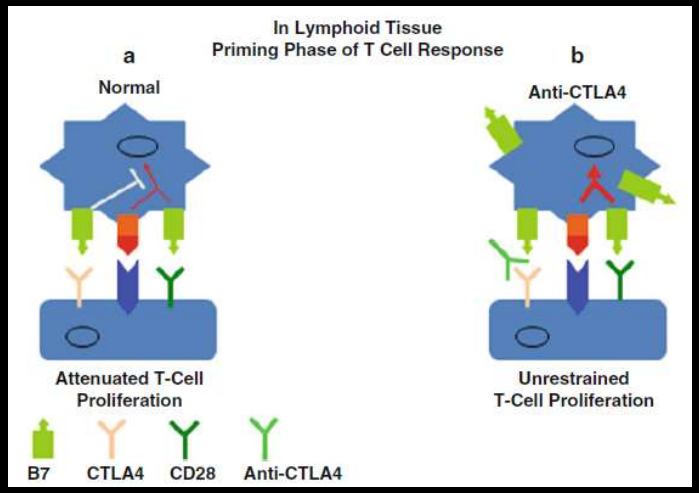
CTLA-4 Blocking Ab





- Immediately following T-cell activation, CTLA-4 is upregulated.
- CTLA-4 competes with CD28 for B7 thus interrupting the costimulatory signal and blunting T-cell response.
- Antibody blocking CTLA-4 therefore enhance antitumor immunity by sustaining T-cell response.

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CTLA-4 Blocking AB

Table 5. Immune Checkpoint Inhibitor and Targeted Therapy: Randomized Trial Data for Adjuvant Treatment

Trial		Stages Included[a]	Treatment Arms	Median Follow-up	Efficacy Analysis[b]			AEs[c]
Name and Reference	Phase Design				RFS or DFS	DMFS	OS	Any grade Grade 3–4 Grade 5
Immune Checkpoint Inhibitors								
EORTC 18071 NCT00636168 Eggermont 2016[384]	III DB RCT	IIIA >1 mm, IIIB/C no IT	HD-Ipi (n = 475) Pbo (n = 476)	5.3 y	5-y: 41% vs. 30% HR = 0.76 [0.64–0.89] *P* < .001	5-y: 48 vs. 39% HR = 0.76 [0.64–0.92] P = .002	5-y: 65% vs. 54% HR = 0.72 [0.58–0.88] *P* = .001	99% vs. 91% 54% vs. 26% 1.5 vs. 1.3%

- For stage 3 disease, ipilimumab improved Relapse Free Survival (RFS), Distant Mets Free Survival (DMFS), and Overall Survival (OS).
  - OS = the "gold standard" for measuring clinical benefits of a cancer drug. Measuring how long patients live compared to control. OS is a strong and precise endpoint, requiring having more patients and longer followups compared to other clinical trial endpoints.
  - RFS/DFS = survival without any signs or symptoms of the cancer.
  - DMFS = defined start point of the period to appearance of a distant mets.

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CTLA-4 Blocking AB

Table 9. Ipilimumab Trials in Advanced Melanoma[a]

Trial			Patients			Efficacy Results[b]			
Name and References	Phase Design	Median Follow-up (months)	Tx Naive	CNS Mets	Treatment Arms	Response Rate	PFS Median (months)	OS Median (months)	Grade 3-4 irAEs[c]
CA184-002 NCT00094653[403]	III RDB	21.0 27.8 17.2	0%[d]	12%[e]	Ipi + gp100 (n = 403) Ipi (n = 137) gp100 (n = 136)	6% *P* = .04 11% *P* = .001 2%	2.8 *P* < .05[f] 2.9 *P* < .001[f] 2.8	10.0 *P* < .001 10.1 *P* = .003 6.4	10%–15% 3%
CA184-024 NCT00324155[404,540]	III RDB	Min 36.6	100%	None	DTIC + ipi (n = 250) DTIC + pbo (n = 252)	15% *P* = .09 10%	ND[g] *P* = .0006[f] ND[g]	11.2 *P* < .001 9.1	38% 4%
CA184-169 NCT01515189[544]	III RDB	14.5 11.2	44%[d] 43%[d]	18%[e] 17%[e]	HD-ipi (n = 365) Ipi (n = 362)	15% 12%	2.8 *P* = .16 2.8	15.7 *P* = .04 11.5	30% 14%

- For unresectable and metastatic disease, ipilimumab improved Overall Survival (OS).

- PFS, progression free survival = how long person lives without the disease worsening.

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Immune Checkpoint targeted therapy

- T-Cell activation introduction
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  - Nivolumab
  - Pembrolizumab

- Weber J et al. NEJM 2017:1824-1835.
- Eggermont AM et al. NEJM 2018:1789-1801
- Harnid O et al. Eur J Cancer 2017:37-45
- Weber JS et al. Lancet Oncol 2015:375-384

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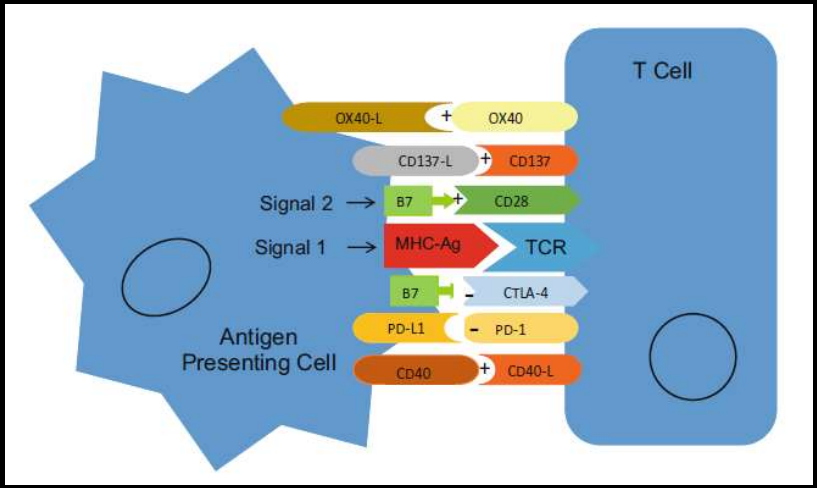
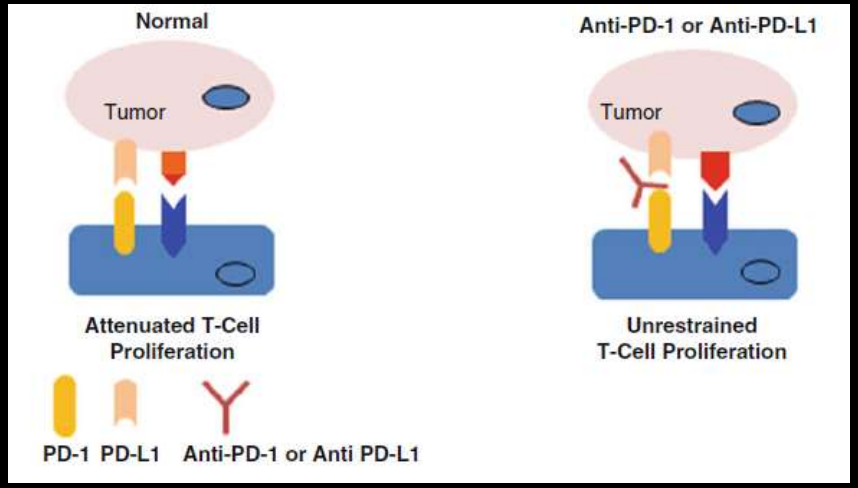
PD-1 and PD-L1 Blocking Ab





- PD-1 to PD-L1 binding leads to T cell exhaustion and deletion.
- Tumor cells upregulate PD-L1 evading immunosurveillance.
- Thus, anti-PD-1 or Anti-PD-L1 interrupts this mechanism, restoring anti-tumor immunity and sustained T-cell activation to kill tumor cells.

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PD-1 and PD-L1 Blocking Ab

- Current targeted therapies are associated with lower rates of toxicity than historical adjuvant tx options (IFNa, cytotoxic chemo).
- Although data is limited, so far, targeted therapies with Anti-PD-1 Ab (nivolumab and pembrolizumab) was associated with clinically meaningful and statistically significant improvement in relapse free survival, distant metastasis free survival, and overall survival in Stage III and IV.

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PD-1 and PD-L1 Blocking Ab

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Immune Checkpoint Inhibitors								
EORTC 18071 NCT00636168 Eggermont 2016[384]	III DB RCT	IIIA >1 mm, IIIB/C no IT	HD-Ipi (n = 475) Pbo (n = 476)	5.3 y	5-y: 41% vs. 30% HR = 0.76 [0.64–0.89] *P* < .001	5-y: 48 vs. 39% HR = 0.76 [0.64–0.92] P = .002	5-y: 65% vs. 54% HR = 0.72 [0.58–0.88] *P* = .001	99% vs. 91% 54% vs. 26% 1.5 vs. 1.3%
CheckMate 238 NCT02388906 Weber 2017[385]	III DB RCT	IIIB/C[d] IV	Nivo + Pbo (n = 453) HD-Ipi + Pbo (n = 453)	1.6 y	1-y: 71% vs. 61%[e] HR = 0.65 [0.51–0.83] *P* < .001	1-y: 80 vs. 73% HR = 0.73 [0.55–0.95]	NR	97% vs. 99% 25% vs. 55% 0 vs. 0.4%
KEYNOTE-054 NCT02362594 Eggermont 2018[386]	III DB RCT	IIIA >1 mm, IIIB/C no IT[f]	Pembro (n = 514) Pbo (n = 505)	1.2 y	1-y: 75% vs. 61% HR = 0.57 [0.43–0.74] *P* < .001	NR[g]	NR	93% vs. 90% 32% vs. 19% 0.2% vs. 0
BRAF-Targeted Therapy								
COMBI-AD NCT01682083 Long 2017[387]	III DB RCT	IIIA >1 mm, IIIB/C[h]	Dab + Tram (n = 438) Pbo (n = 432)	2.8 y	3-y: 58% vs. 39% HR = 0.47 [0.39–0.58] *P* < .001	NR[i] HR = 0.51 [0.40–0.65] Nominal *P* < .001	3-y: 86% vs. 77% HR = 0.57 [0.42–0.79] *P* = .0006[j]	97% vs. 88% 41% vs. 14% 0.2% vs. 0
BRIM8 NCT01667419 Maio 2018[393]	III DB RCT	IIC, IIIA >1 mm, IIIB/C no IT[k]	Vem (n = 250) Pbo (n = 248)	2.5 y, 2.8 y[l]	2-y: 62% vs. 53% HR = 0.65 [0.50–0.85] *P* = .0013	2-y: 72% vs. 65% HR = 0.70 [0.52–0.96] *P* = .027	2-y: 90% vs. 86% HR = 0.76 [0.49–1.18] *P* = .2165	NR 57% vs. 15% 0.4% vs. 0

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PD-1 and PD-L1 Blocking Ab

Table 10. Pembrolizumab Trials in Advanced Melanoma[a]

Trial			Patients			Efficacy Results[c]			Grade 3–4 Tx-Related AEs[d]
Name and References	Phase Design	Median Follow-up (months)	Tx Naive	Brain Mets[b]	Treatment Arms	Response Rate	PFS 2-year Rate	OS 2-year Rate	
KEYNOTE-002 NCT01704287[406,529]	II R, OL	28	None[e]	--	Pembro 2 mg/kg Q3W (n = 180)	22% *P* < .0001[f]	16% *P* < .0001	36% *P* = .117[f]	14%
					Pembro 10 mg/kg Q3W (n = 181)	28% *P* < .0001	22% *P* < .0001	38% *P* = .011	16%[g]
					Chemo (n = 179)	4%	<1%	30%	26%
KEYNOTE-006 NCT01866319[407,422]	III R, OL	22.9	34%[h]	9%	Pembro 10 mg/kg Q2W (n = 279)	37% *P* < .001[i]	31% *P* < .0001[i]	55% *P* = .0009[i]	17%
					Pembro 10 mg/kg Q3W (n = 277)	36% *P* < .001	28% *P* < .0001	55% *P* = .0008	17%
					Ipi 3 mg/kg Q3W x 4 doses (n = 278)	13%	14%	43%	20%

Table 11. Nivolumab Trials in Advanced Melanoma[a]

Trial			Patients			Efficacy Results[c]			Grade 3–4 Tx-Related AEs[d]
Name and References	Phase Design	Median Follow-up (months)	Tx Naive	CNS Mets[b]	Treatment Arms	Response Rate	Median PFS (months)	Median OS (months)	
CheckMate 037 NCT01721746[410,523]	III R, OL	~24	0[e]	20%	Nivo (n = 272)	27%	3.1 NS[f]	15.7 *P* = .716	14%
				14%	Chemo (n = 133)	10%	3.7	14.4	34%
CheckMate 066 NCT01721772[526,530]	III RDB	38[g]	100%	3.6%	Nivo (n = 210)	43% *P* < .001	5.1 *P* < .001	37.5 *P* < .001	15%
		39[g]			DTIC (n = 208)	14%	2.2	11.2	18%
CheckMate 067 NCT01844505 [408,421,531]	III RDB	47	100%	3.6%	Nivo/ipi, then nivo (n = 314)	58% *P* < .0001[h]	11.5 *P* < .0001[h]	NR *P* < .0001[h]	59%
		36			Nivo (n = 316)	45% *P* < .0001	6.9 *P* < .0001	36.9 *P* < .0001	22%
		19			Ipi (n = 315)	19%	2.9	19.9	28%
CheckMate 069 NCT01927419[409,528]	II RDB	25	100%	3%[g]	Nivo/ipi, then nivo (n = 95)	59% *P* < .0001	NR *P* < .0001	NR *P* = .26	54%
					Ipi (n = 47)	11%	3.0	NR	20%

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Adverse effects of Checkpoint Immunotherapies

Table 15. Checkpoint Immunotherapies: Treatment-Related Toxicities[a]

Study:	CheckMate 067 and 069[409,531]						KEYNOTE-006[407,422]			
Agent:	Ipilimumab		Nivolumab[b]		Ipilimumab + Nivolumab		Ipilimumab		Pembrolizumab	
Grade:	3–4	Any	3–4	Any	3–4	Any	3–5	Any	3–5	Any
All types	20–28	86–94	22	86	54–59	90–96	20[c]	73–74[c]	12–17[c]	76–80[c]
Diarrhea	6–11 ***		3 **		10 *****		3[c] **[c]		2–3[d] **[c]	
Colitis	2–8 *		1		8–13 **		6 *		3	
Nausea	1–2 **		0 *		1–2 ***		<1[c] *[c]		<1[c] *[c]	
Vomiting	<1 *		<1 *		1–2 **		0 *		<1	
Decreased appetite	<1 *		0 *		≤1 **		0 *		0 *	
Rash	≤2 ***		<1 **		3–4 ****		≤1[c] **[c]		0[c] **[c]	
Pruritus	<1 ****		<1 **		1–2 ****		<1[c] ***[c]		0[c] **[c]	
Maculopapular rash	<1 *		1 *		2–3 **		<1		<1	
Vitiligo	0[b] *[b]		<1 *		0[b] *		0		0 *	
Fatigue	≤1 *****		1 ****		4–5 ****		1[c] **[c]		≤1[c] ***[c]	
Pyrexia	<1 *		0 *		1–3 **		0		0	
Arthralgia[b]	0[b] *[b]		<1[b] *		1 *[b]		≤1[c] *[c]		<1[c] *[c]	
Myalgia	0 *		<1 *		<1 *		<1		<1	
Asthenia	1[b] *[b]		<1 *		<1[b] *[b]		1 *		<1 *	
Headache	<1 *		0 *		1–2 *		0		0	
Dyspnea	0		<1 *		1–2 *		<1		<1	
Cough	0 *		1 *		0 *		0		0	
Abdominal pain	1–2 *		0 *		<1 *		0 *		0	
Chills	0 *		0		0 *		0		0	
Elevated ALT	≤2 *		1		9–11 ***		1		<1	
Elevated AST	≤1 *		1		6–7 ***		1		<1	
Hypophysitis	2–4 *		<1		2 *		1		<1	
Hypothyroidism	0 *		0 *		<1 **		0[c] [c]		<1[c] *[c]	
Hyperthyroidism	0[b]		0		1[b] *[b]		<1		0	
Elevated lipase	≤4 *		5 *		10–11 **		-- --		-- --	
Elevated amylase	≤1		2 *		2–3 *		-- --		-- --	
Pneumonitis	<1		<1		1–2 *		-- --		-- --	
Creatinine increased	0		<1		≤1		0		0	

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Immune Checkpoint targeted therapy

- CTLA-4 Blocking Ab
  - Ipilimumab
- PD-1 Blocking Ab
  - Nivolumab
  - Pembrolizumab
- Checkpoint targeted therapy summary:
  - FDA approved for advanced stage melanomas.
  - Trials show promising results improving survival.
  - PD-1 Blocking Ab > CTLA-4 Blocking Ab (survival and AE)

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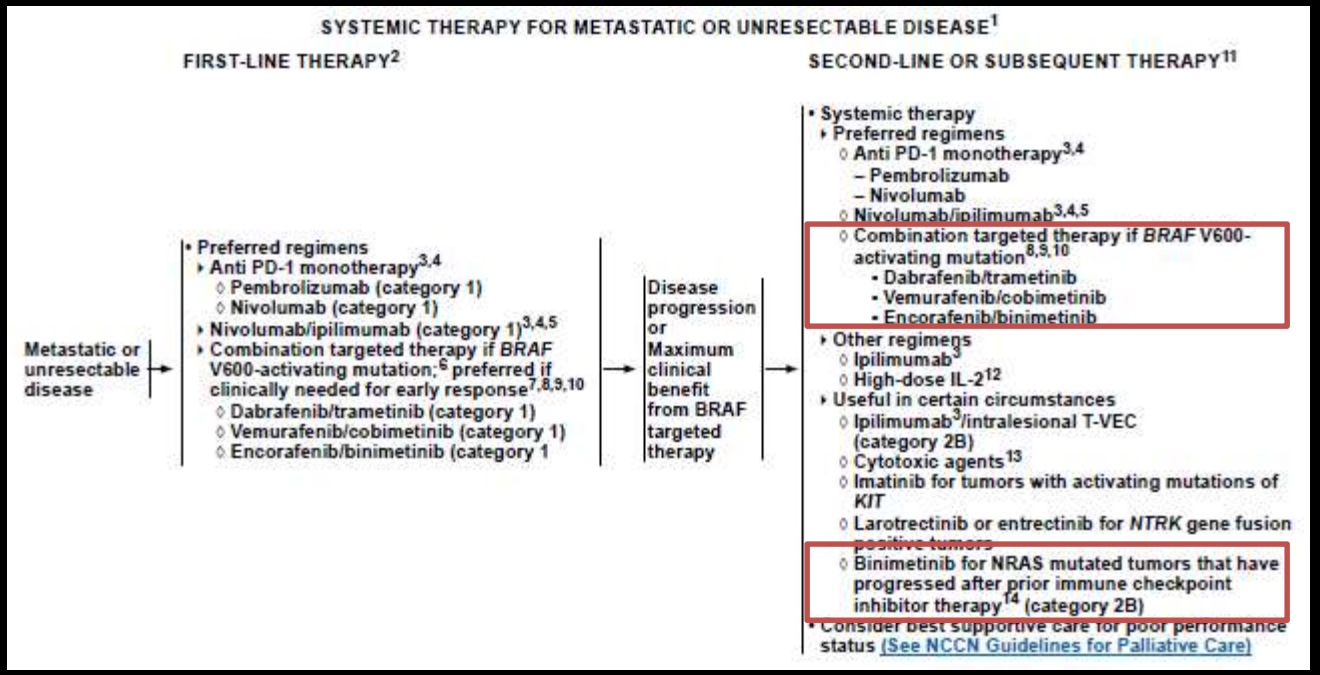
BRAF and MEK Inhibitors



- Daud A et al. J Clin Oncol 2016:34:Abstr 9510
- Schreuer M et al. Lancet Oncol 2017:464-472
- Johnson DB et al. J Clin Oncol 2014:3697-3704
- Flaherty KT et al. NEJM 2012:1694-1703
- Chen G et al. JAMA Oncol 2016:1056-1064
- Long GV et al. Ann Oncol 2017:1631-1639
- Robert C et al. NEJM 2015:30-39
- Dreno B et al. Ann Oncol 2017:1137-1155
- Dummer et al. Lancet Oncol 2018:1315-1327

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BRAF Inhibitors and MEK Inhibitors

- Dabrafenib
- Vemurafenib
- Encorafenib

- Trametinib
- Cobimetinib
- Binimetinib

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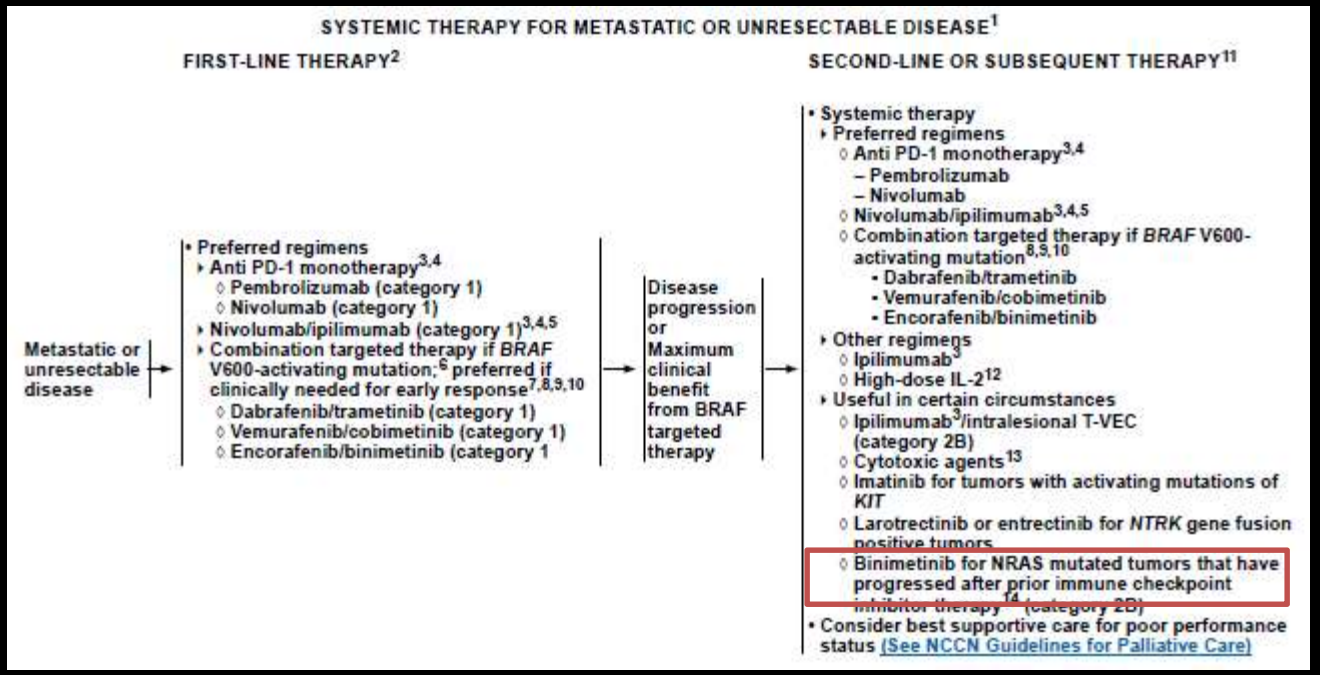
MEK Inhibitors for NRAS mutations



- Dummer et. al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomized, phase 3 trial Lancet Oncol 2017.

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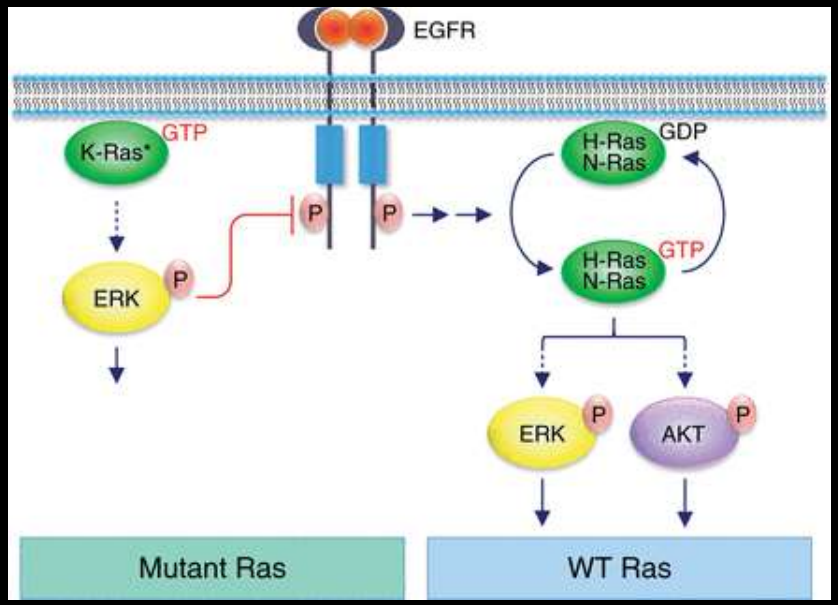
MEK Inhibitors for NRAS mutations

- Highest incidence of mutated RAS genes is found in tumors of exocrine pancreas, colon, and follicular and undifferentiated thyroid CA.
- About 15-20% of melanomas are believed to harbor a mutation in NRAS.
- NRAS mutation is low in acquired nevi but common in congenital nevi (~80%). This is in contrast to BRAF which are rare or absent in congenital nevi.
- NRAS mutations are reported in more commonly sun-exposed areas.
- Occurrence of BRAF and NRAS mutations in melanoma appear to be mutually exclusive events.

MEK Inhibitors for NRAS mutations

- Member of the small GTPase family of proteins.
- RAS protein is active upon binding to GTP.
- Mutant RAS interfere with ability to switch to the GDP bound inactive conformation.



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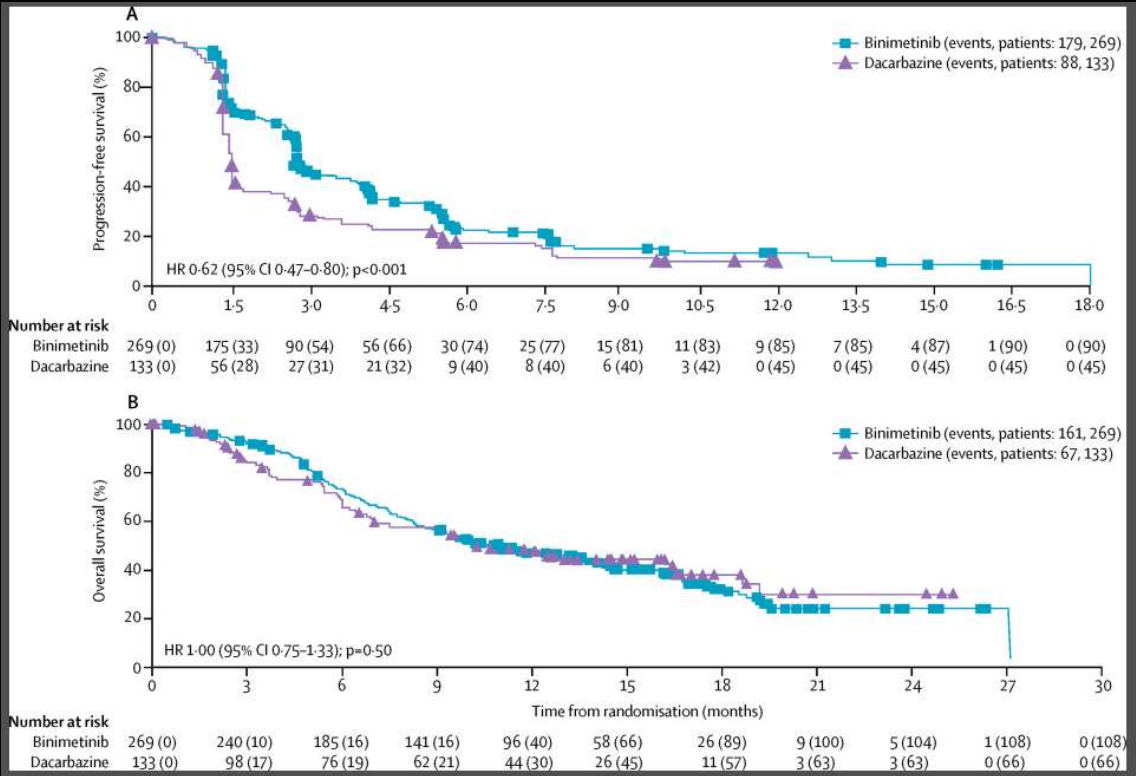
MEK Inhibitors for NRAS mutations



IMAGE

Binimetinib versus dacarbazine in patients with advanced *NRAS* -mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial

Lancet Oncology, The.

Dummer, Reinhard, Prof; Schadendorf, Dirk, Prof... Show all. Published March 31, 2017. Volume 18, Issue 4. Pages 435-445. © 2017.

Figure 2

Kaplan-Meier estimates of progression-free survival (A) and overall survival (B)
Stratified log-rank test and stratified Cox model using strata defined by American Joint Committee on Cancer stage, previous line immunotherapy, and Eastern Cooperative Oncology Group performance status, with one-sided p values. HR=hazard ratio.

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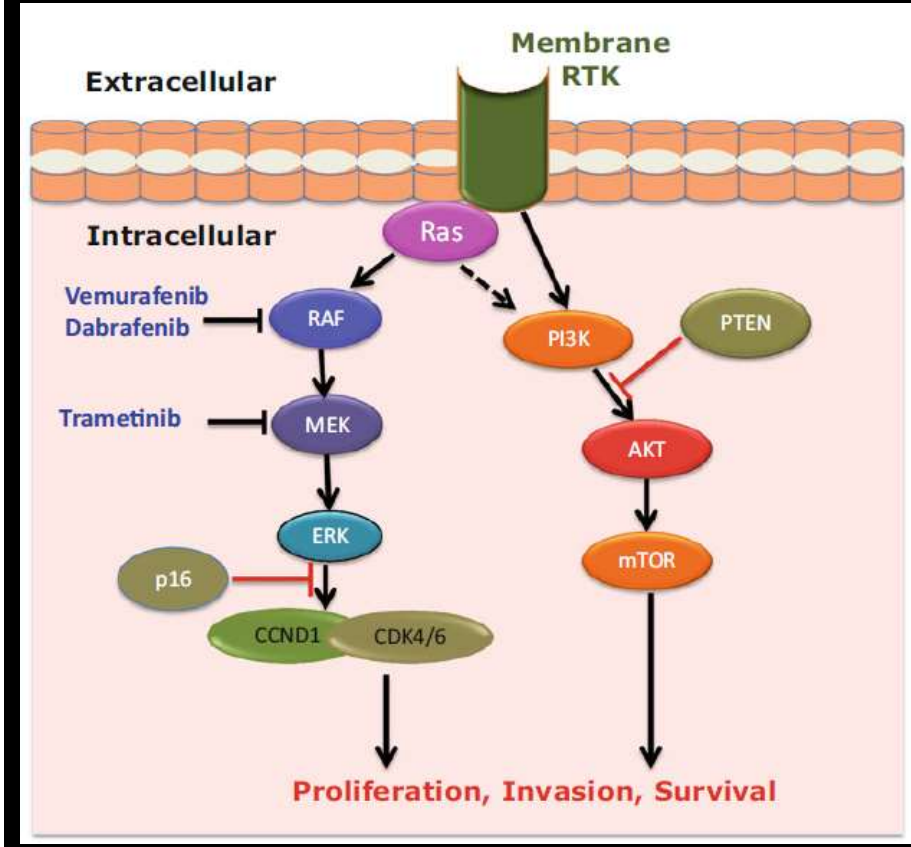
BRAF and MEK Inhibitors

- Davies et al. in 2002 (Nature 417:949-954) identified frequent BRAF mutations in human cancers including melanoma (66%).
- BRAF mutations frequently associated with melanomas from intermittently sun-exposed skin (trunk and extremities).
- Most common BRAF mutation is the V600E (substitution of Glu for Val). 75-90% of all BRAF-mutant melanomas.
- BRAF is one of the three RAF kinase isoforms.
- Part of the MAPK signal transduction pathway.

BRAF and MEK Inhibitors

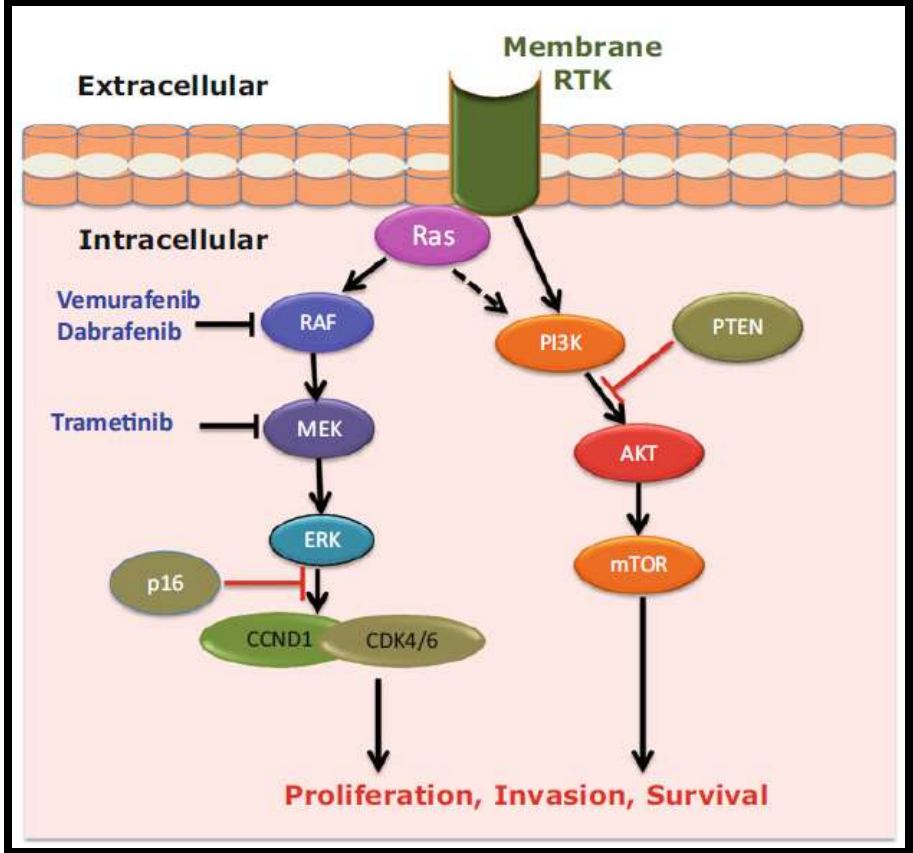


- Activation of membrane bound receptor changes inactive GDP-bound RAS to active GTP-bound state.
- RAS activates RAF.
- RAF activates MEK and ERK
- This causes upregulated cell proliferation and growth

BRAF and MEK Inhibitors

- Mutated BRAF causes constitutive activation of kinase activity.
- The V600E BRAF mutation has tenfold higher kinase activity than wild type.
- Inhibition of mutant BRAF in cell lines leads to decreased ERK activity, resulting in cell arrest, decreased transcription, and ultimately apoptosis. Logic for targeted therapy.
- Interestingly, BRAF mutations are also found in benign nevi.
- BRAF mutation only thought to be possible initial step in the development of malignancy. Thus additional genetic mutations are necessary for melanoma oncogenesis.

BRAF and MEK Inhibitors



- BRAF targeted monotherapy has issues with resistance.
  1. MEK-dependent resistance, acquisition of new mutations.
  2. MEK-independent resistance, upregulation of membrane receptor tyrosine kinase and bypass through mTOR pathway.

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BRAF and MEK Inhibitors

- BRAF monotherapy relapse within 6 months.
- Based on BRAF-inhibitor resistance, combined approach with MEK inhibitor suggests superior to BRAF inhibitory monotherapy.

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BRAF and MEK Inhibitors

Table 19. BRAF/MEK Inhibitor Combination in Advanced Melanoma[a]: Key Trials

Trial			Patients			Treatment Arms	Efficacy Results[b]			AEs Grade 3–4[c]
Name and References	Phase Design	Median follow-up (months)	Prior BRAFi	Tx Naive	Brain Mets		Response Rate	Median PFS (months)	Median OS (months)	
BRIM-7[607-609] NCT01271803	Ib OL, dose escalation	26	0[d]	Some[d]	NR[e]	Vem + cobi (n = 63)	87%	13.8	31.2	78%
		8	100%[d]	0[d]		Vem + cobi (n = 66)	15%	2.8	8.5	47%
NCT02296996[611]	II OL	6.8	100%[f]	0	68%	Dab + tram (n = 25)	32%	4.9	NR	8%
NCT01072175[527]	I/II OL	35.3	100%[g]	0	23%	Dab + tram (n = 26)	15%	3.6	10.0	61%
		27.4	100%[g]	0	9%	Dab + tram (n = 45)	13%	3.6	11.8	44%
NCT01072175 Part C[596,612]	II R	66.5	0		4%[e]	Dab (150 mg BID) + tram (2 mg QD) (n = 54)	76% *P* = .03	9.4 *P* < .001	25.0	67%
			0	Some[h]	13%[e]	Dab (150 BID) + tram (1 mg QD) (n = 54)	50% *P* = .77	9.2 *P* = .006	22.5	54%
			0		7%[e]	Dab (150 mg BID)	54%	5.8	20.2	47%
NCT01619774[610]	II	5.9	100%[g]	0	--[e]	Dab + tram (n = 23)	10%	3.0	10.2	71%
COMBI-d[411,603] NCT01584648	III RDB	20	0	100%	--[e]	Dab + tram (n = 211)	69% *P* = .0014	11.0 *P* = .0004	25.1 *P* = .0107	48%[i]
		16	0			Dab + pbo (n = 212)	53%	8.8	18.7	50%[i]
COMBI-v[412] NCT01597908	III R, OL	11	0	100%	--[e]	Dab + tram (n = 352)	64% *P* < .001	11.4 *P* < .001	NR *P* = .005	52%
		10	0			Vem (n = 352)	51%	7.3	17.2	63%
Co-BRIM[413,597,604] NCT01689519	III RDB	14.2; 18.5[j]	0	100%	<1%[e]	Vem + cobi (n = 247)	70% *P* < .0001	12.3 *P* < .0001	22.3 *P* = .005	75%
			0		<1%[e]	Vem + pbo (n = 248)	50%	7.2	17.4	61%
COLUMBUS[605,606] NCT01909453	III R, OL	32.1 (PFS) 36.8 (OS)	0	70%[k]	5%[e]	Encor + bini (n = 192)	64%	14.9 *P* < .0001[l]	33.6 *P* < .0001[l]	64%
			0	70%[k]	--[e]	Encor (n = 194)	52%	9.6 *P* = .0038[l]	23.5 *P* = .033[l]	67%
			0	70%[k]	2%[e]	Vem (n = 191)	41%	7.3	16.9	66%

- Dabrafenib/Trametinib
- Vemurafenib/Cobimetinib
- Encorafenib/Binimetinib

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BRAF and MEK Inhibitors

Table 21. BRAF and MEK Inhibitors: Toxicities[a]

Studies:	COMBI-d[b,524,603]				COMBI-v[412]				Co-BRIM[597]				COLUMBUS[606]					
Agent:	Dab		Dab/Tram		Vem		Dab/Tram		Vem		Vem/Cobi		Vem		Encor		Encor/Bini	
Grade:	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–4[c]	Any	3–4[c]	Any	3–4[c]	Any
All types	50	97	48	97	59	99	49	98	61	98	75	99	66	--	67	--	64	--
General, symptomatic:																		
Pyrexia	2	***	7	*****	1	**	4	*****	0	**	1	***	0	***	1	*	4	**
Chills	1	**	1	***	0	*	1	***	0	*	0	*	--	--	--	--	--	--
Headache	1	***	1	***	1	**	1	***	2	**	<1	**	1	**	3	***	2	***
Fatigue	1	****	2	****	2	***	1	***	3	***	5	****	2	***	1	***	2	***
Asthenia	1[b]	*b	<1[b]	*b	1	**	1	**	1	**	2	**	4	**	3	**	2	**
Decreased appetite	1[b]	*b	<1[b]	*b	0	**	1	*	<1	**	0	**	1	**	1	**	0	*
Peripheral edema	1	*	1	**	<1	*	<1	*	<1	*	0	*	1	*	0	*	2	*
Cough	0	**	0	**	0	*	0	**	0	*	0	*	1	*	1	*	1	*
General, lab results:																		
Hypertension	6	**	6	**	10	**	14	***	3	*	6	**	3	*	3	*	6	*
ALT increased	1	*	2	*	4	**	3	*	6	**	11	***	2	*	1	*	5	*
AST increased	1		3	*	3	*	1	*	2	*	9	**	2	*	1		2	*
GGT increased	--	--	--	--	--	--	--	--	10	**	15	**	3	*	5	*	9	**
Blood CPK increased	--	--	--	--	--	--	--	--	<1		12	****	0		0		7	***
Blood ALP increased	--	--	--	--	--	--	--	--	2	*	5	**	1	*	0		1	*
Lipase increased	--	--	--	--	--	--	--	--	1		3		1		1		2	
Anaemia	--	--	--	--	--	--	--	--	3	*	2	**	3	*	3	*	5	**
Musculoskeletal/Pain:																		
Arthralgia	0	***	1	***	4	*****	1	**	5	****	2	****	6	*****	9	****	1	***
Myalgia	0[b]	*b	<1[b]	*b	1	*	0	**	2	*	<1	**	1	**	10	***	0	**
Pain in extremity	--	--	--	--	<1	*	1	*	2	**	1	*	1	*	1	**	1	*
Pain	--	--	--	--	--	--	--	--	<1		0		0		4	*	1	
Musculoskeletal pain	--	--	--	--	--	--	--	--	<1	*	1		1	*	3	**	0	*

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BRAF and MEK Inhibitors

Table 21 (Continued)

Studies:	COMBI-d[b,524,603]				COMBI-v[412]				Co-BRIM[597]				COLUMBUS[606]					
Agent:	Dab		Dab/Tram		Vem		Dab/Tram		Vem		Vem/Cobi		Vem		Encor		Encor/Bini	
Grade:	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–4[c]	Any	3–4[c]	Any	3–4[c]	Any
Gastrointestinal:																		
Diarrhea	1	**	1	***	<1	****	1	***	1	***	7	******	2	***	2	*	3	****
Nausea	1	***	1	****	1	****	<1	***	1	***	1	****	2	***	4	****	2	****
Vomiting	1	*	1	***	1	**	1	***	1	*	2	***	1	**	5	***	2	***
Constipation	0[b]	*b	<1[b]	*b	<1	*	0	*	0	*	0	*	1	*	0	**	0	**
Cutaneous:																		
Rash	1	**	0	***	9	****	1	**	6	****	5	****	3	***	2	**	2	*
Pruritis	0[b]	*b	0[b]	*b	1	**	0	*	<1	**	1	**	0	*	1	**	1	*
Rash maculo-papular	--	--	--	--	--	--	--	--	5	**	7	**	4	*	1	*	0	
Rash generalized	--	--	--	--	--	--	--	--	1		<1		4	*	1	*	0	
Alopecia	0	***	1	*	<1	****	0	*	<1	***	<1	**	0	****	0	******	0	*
Dry skin	0[b]	*b	0[b]	*b	<1	**	0	*	0	**	1	**	0	**	0	***	0	**
Hyperkeratosis	1	****	0	*	1	**	0		2	***	<1	*	0	***	4	****	1	**
Keratosis pilaris	--	--	--	--	0	*	0		0	*	0		0	**	0	**	0	
Palmoplantar erythrodysesthesia syndrome	--	--	--	--	<1[d]	**d	0[d]	d	<1		0	*	1	*	14	*****	0	*
Palmoplantar keratoderma	1	**	1	*					0	*	0		1	**	2	***	0	*
Skin papilloma	0	**	0		1	**	0		<1	*	0	*	0	**	0	*	0	*
Photosensitivity reaction	0		0		<1	**	0		0	**	3	***	1	**	0		1	
Keratoacanthoma	1	*	2		--	--	--	--	9	*	1		3	*	0	*	1	
cSCC					<1		0		13	*	4		4	*	0		0	
Basal cell carcinoma	1	*	3		--	--	--	--	2		6	*	1		1		0	

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BRAF and MEK Inhibitors

- BRAF monotherapy and MEK monotherapy is not beneficial.
- BRAF inhibitor and MEK inhibitor combined therapy is showing promising results for targeted therapy of advanced melanoma.
- There is great interest in investigating combined BRAF inhibitors with inhibitors of the mTOR pathway.

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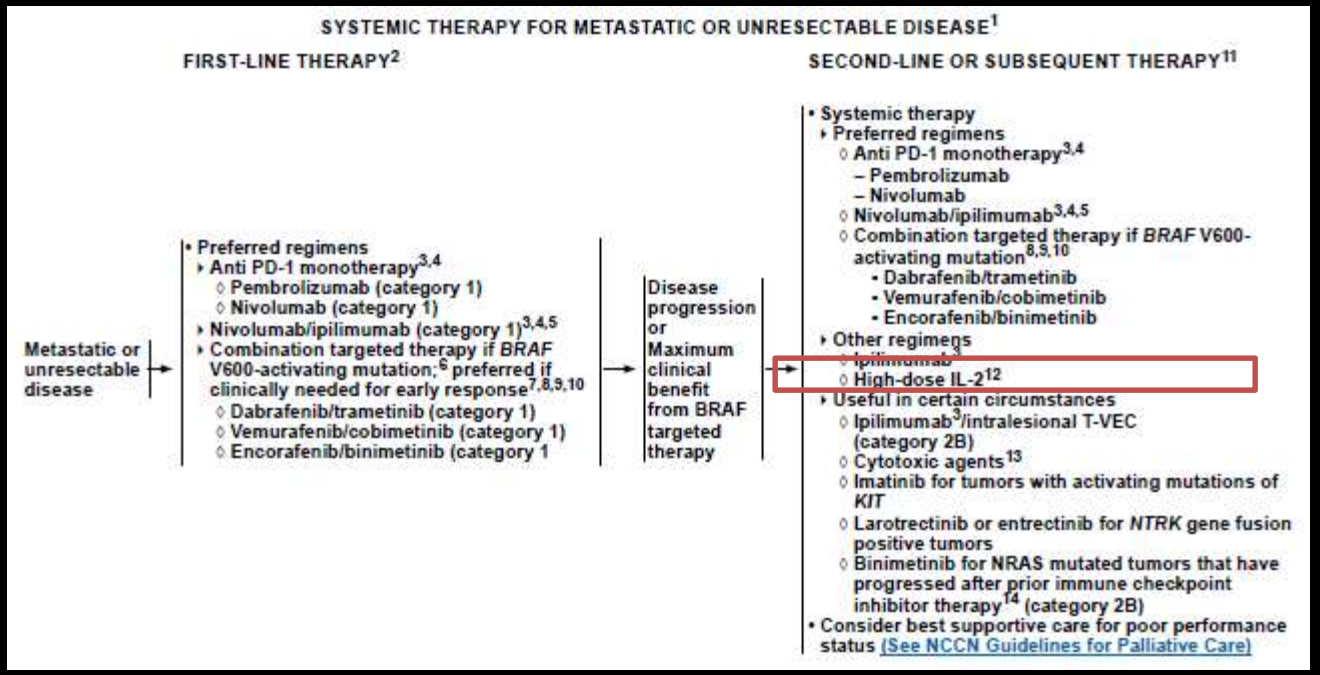
Interleukin-2



- Boyd KU et al. J Surg Oncol 2011:711-717
- Weide B et al. Cancer Immuno Immunother 2011:487-493

Interleukin-2

- Antitumor activity of IL-2 is believed to be immune based; however, exact mechanism is unclear.
  - Binding of IL-2 receptor expressed on immune cells, IL-2 induces a cytokine cascade:
    - interferons
    - Interleukins
    - Tumor necrosis factors
  - These cytokines further stimulate proliferation and differentiation of B and T cells, monocytes/macrophages, and NK cells.
- Through stimulation of the immune system, IL-2 induces antitumor cytotoxicity (nonspecific and ?specific).

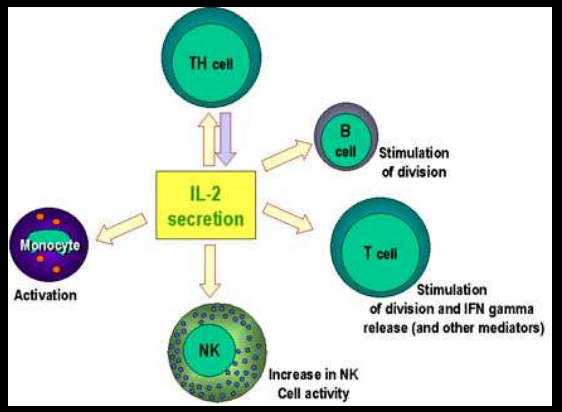
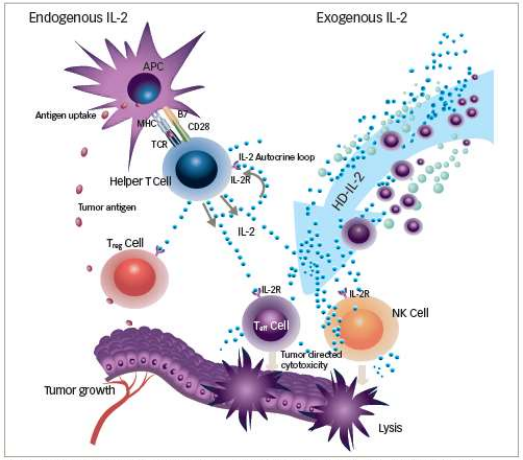


Figure 1: Dual mechanism of action of interleukin-2



APC = antigen-presenting cell; HD-IL-2 = high-dose interleukin; NK = natural killer; MHC = major histocompatibility complex. TCR = T cell receptor. Source: Prometheus.

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Interleukin-2

- High dose IL2 has been used to treat metastatic melanoma.
- Overall response rare (ORR) are modest at <20%.
- But those with complete response (<10%) tend to have high rates of long term survival.
- Median OS is usually 11-12 mo with 10% achieving long term survival >5years.

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Interleukin-2

- IL-2 however is associated with significant toxicities.
- Therefore, due to low response rate and high toxicity, IL-2 is less preferred compared to checkpoint inhibitors and BRAF-targeted options.
- However, Intralesional IL-2 injection is far less toxic and has high complete response rate for cutaneous lesions.

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Interleukin-2

Table 8. Intralesional Injection

Injection Agent	Key Published Clinical Studies	Response Rates	
		Injected Lesions	Uninjected Lesions
Talimogene laherparepvec (T-VEC)	• Phase III trial[450,451]	≥50% decrease in size: 64%	• ≥50% decrease in size: • 32% of non-visceral • 15% of visceral
Interleukin-2	• >5 non-comparative studies, including several phase II trials[452,453] and retrospective/observational analyses[463-466] • 2014 systematic reviews and meta-analysis[454]	CR: 67%–96% •80% for dermal •73% for subcutaneous	No responses seen in two phase 2 trials
Bacillus Calmette-Guérin (BCG)	• >10 prospective pilot/retrospective studies[a] • 1 prospective randomized study[459]	CR: •90% for dermal •45% for subcutaneous	Occasional responses observed
Rose Bengal	• Phase I trial[461] • Phase II trial[462]	OR: 46%–58%	OR: 27%

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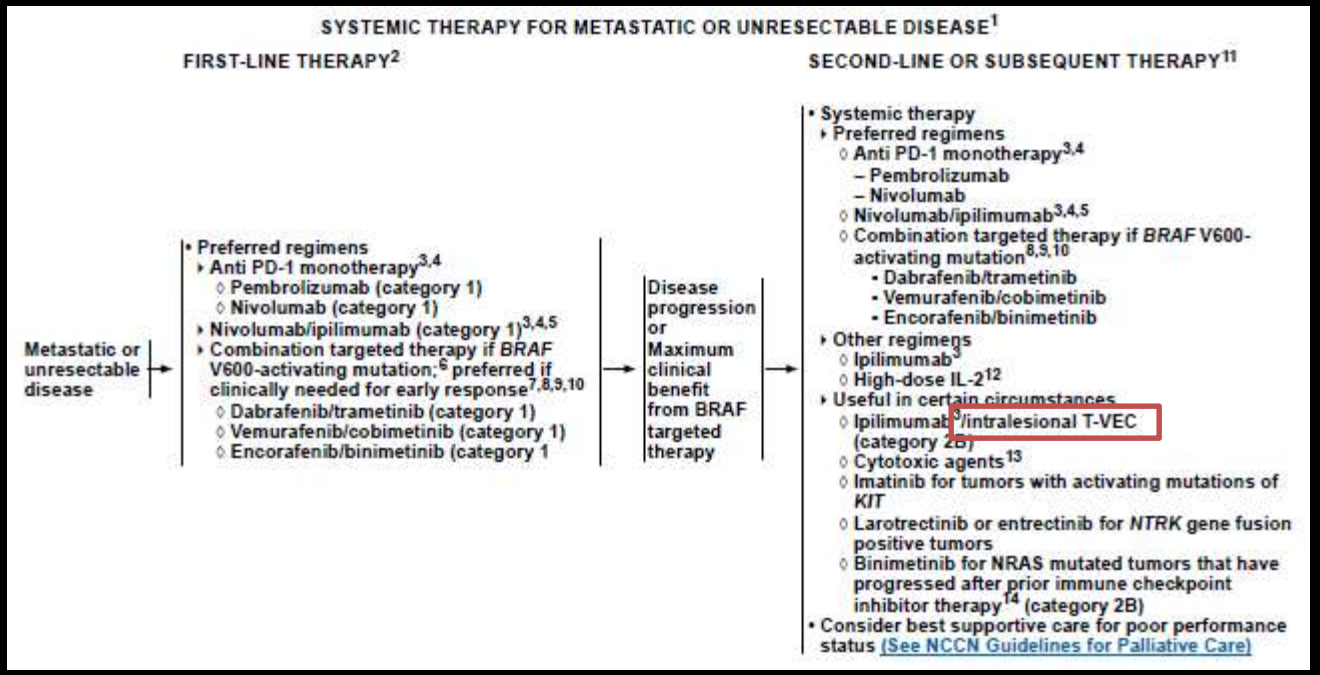
Intralesional T-VEC



- Andtbacka RH et al. J clin Oncol 2015:2780-2788
- Andtbacka RHI et al. ASCO meeting Aabstracts 2015;33:TPS9094

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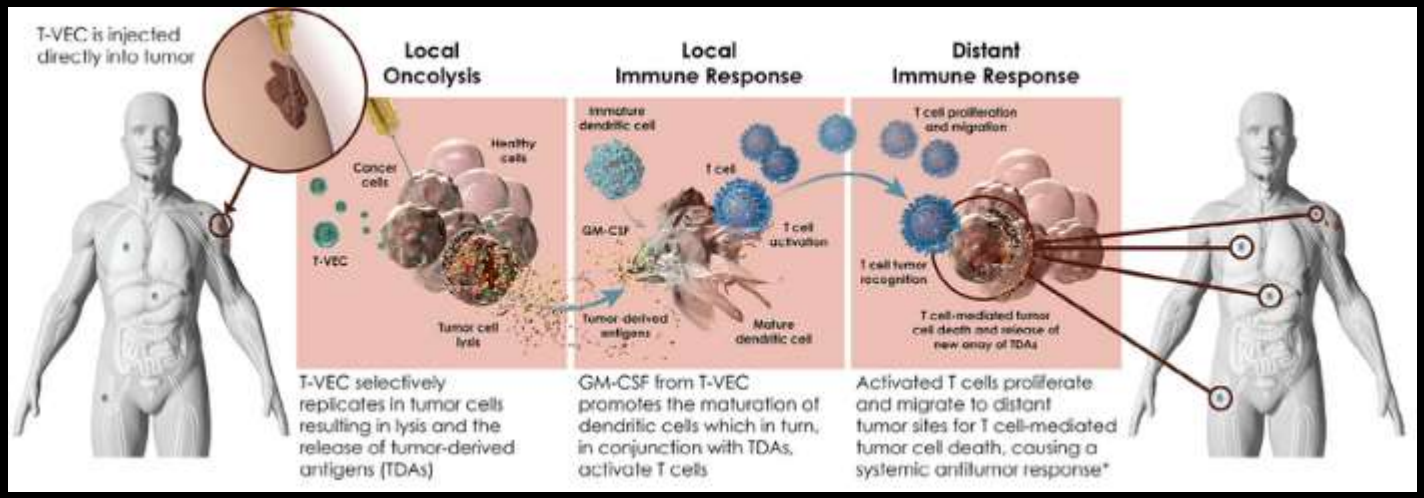
Intralesional T-VEC

- Talimogene laherparepvec (T-VEC), is an agent that uses modified herpes simplex virus to induce tumor cell lysis and to deliver localized expression of GM-CSF to injected lesions.



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Intralesional T-VEC

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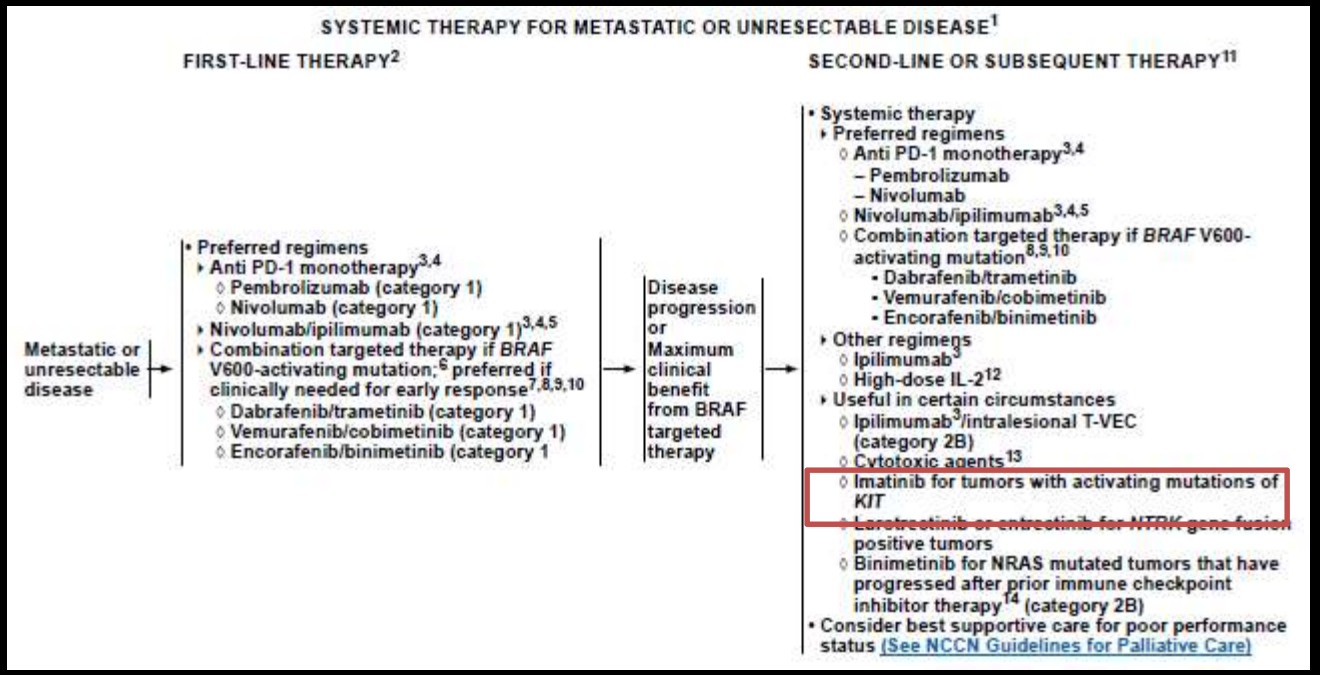
KIT Inhibitor



- Lee et al. Multicenter Trial of Korean Cancer Study Group (UN10-06) Oncologist 2015.
- Guo et al. Phase II TEAM Trial. Ann Oncol 2017
- MORE REFERENCES NEEDED

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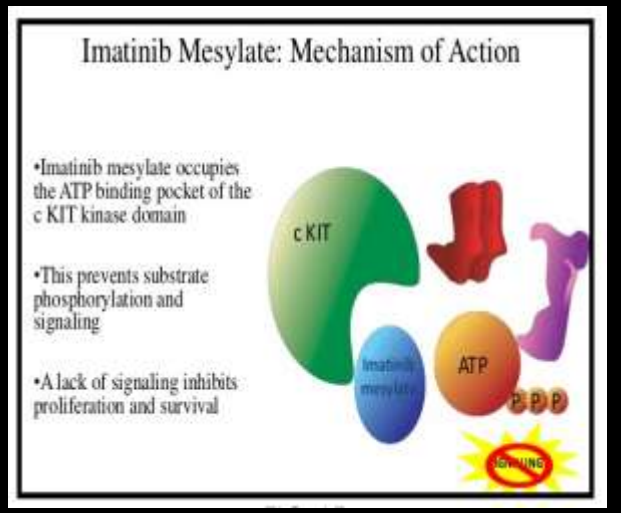
KIT Inhibitor

- KIT mutations are rarely seen in melanoma and mostly associated with mucosal and acral subtypes.
- KIT is a transmembrane receptor tyrosine kinase activating MAPK, PI3K, phospholipase C-gamma, and JAK/STAT pathways.
- Two most common KIT mutations are L576P(34%) and K642E(15%) in exon 11 and 13, respectively.
- Most KIT mutations occur in exon 11 (70%) which encodes a domain that inhibits the receptor.

KIT Inhibitor

- This results in constitutive activation of the associated signaling pathway.
- Imatinib designed to inhibit kinase activity



- KIT mutations or increased copy number of KIT is seen in 39% mucosal melanoma, 36% acral melanomas, and 28% of melanomas on high cumulative sun-damaged skin, unlike BRAF and NRAS mutation associated melanomas.

KIT Inhibitor

- In metastatic melanomas Phase II studies with imatinib or nilotinib inhibitors of KIT demonstrated 17%-30% ORR and 35%-57% Disease control rate.
- In phase II study in 43 Asian patients with metastatic melanoma with KIT mutation or amplification were treated with imatinib:
  - 23% partial response.
- In phase II study in 9 Asian patients with metastatic melanoma with KIT aberration were treated with nilotinib:
  - 2 patients had partial response.

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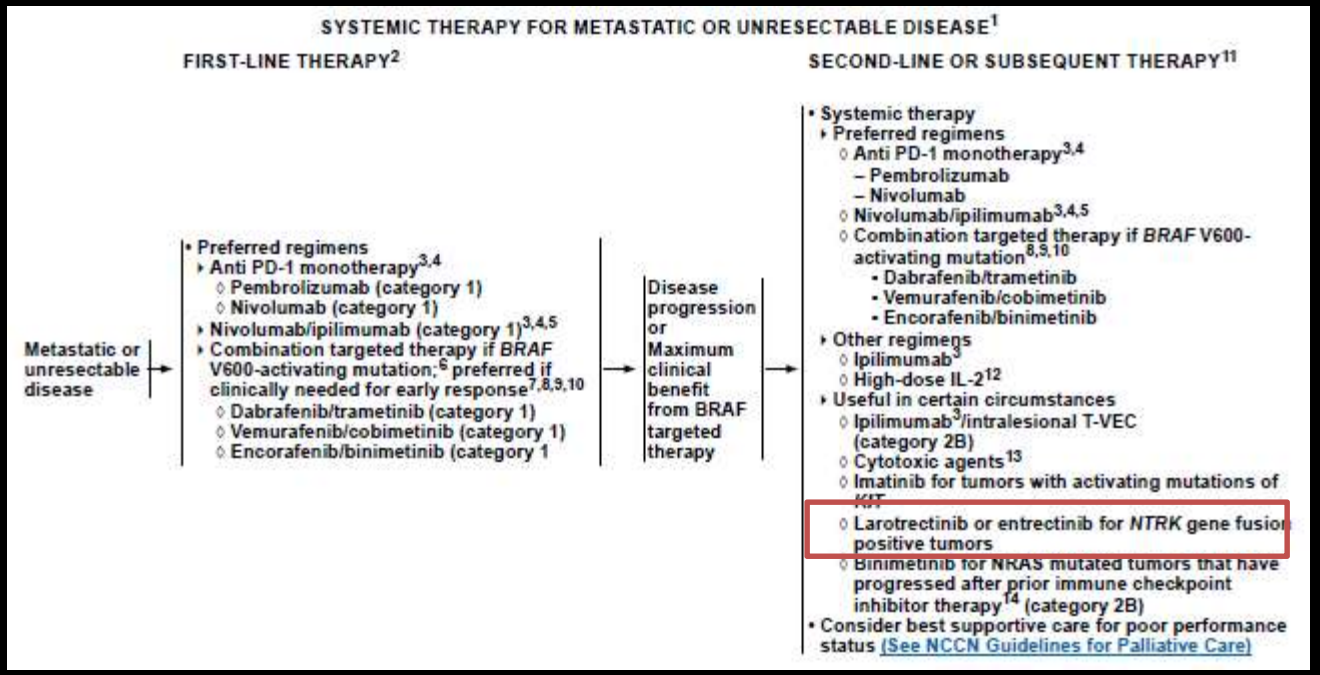
TRK Inhibitors



- Drilon A et. al. Efficacy of Larotrectinib in TRK fusion-positive cancers in adults and Children. N Engl J Med 2018.
- Drilon A. et al. Safety and antitumor activity of the multitargeted Pan-TRK, ROS1, and ALK inhibitor entrectinib. Combined results from two phase 1 trials (ALKA-3720991 and STARTRK-1) Cancer Discov 2017.

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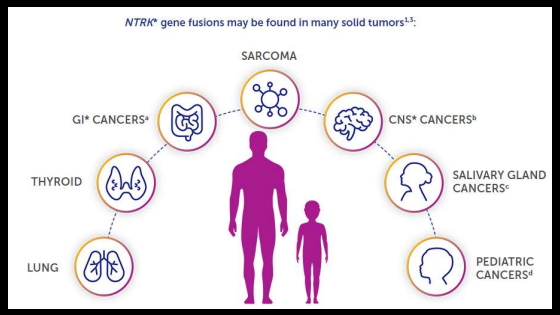
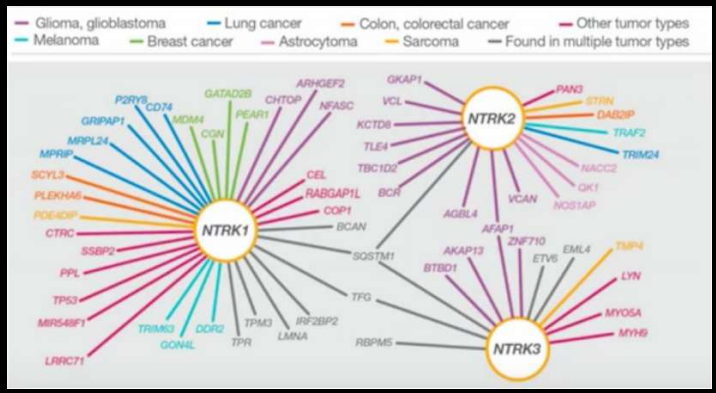
TRK Inhibitors

- Neurotrophic Receptor Tyrosine Kinase Genes:
  - NTRK1, NTRK2, NTRK3.
- Melanoma and other diverse cancers have shown recurrent chromosomal fusion events involving the carboxy-terminal kinase domain of TRK and various upstream amino-terminal partners.





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TRK Inhibitors

Article | Published: 08 May 2017

Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients

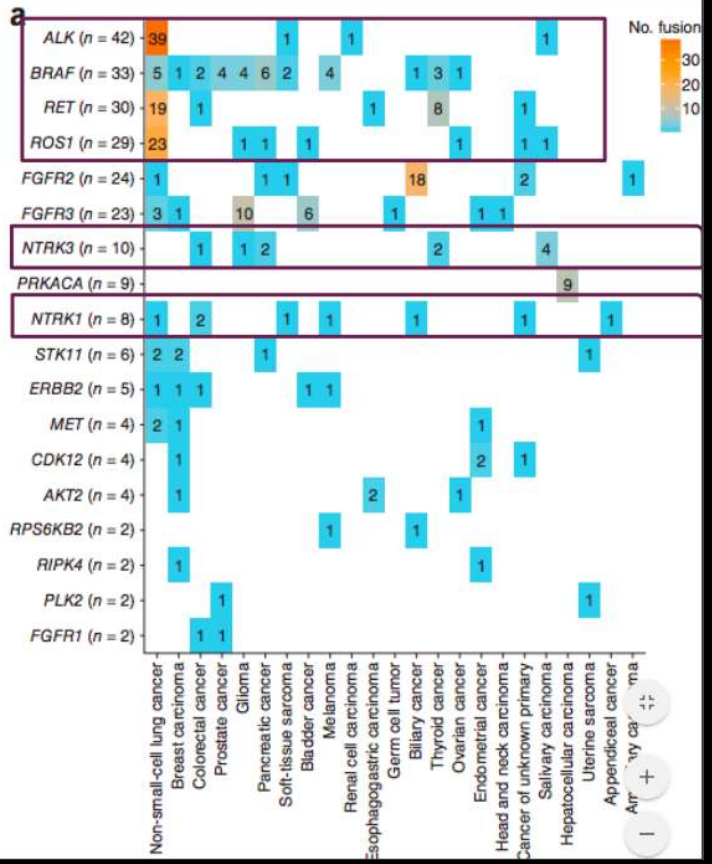
Ahmet Zehir, Ryma Benayed [...] Michael F Berger

Nature Medicine **23**, 703–713 (2017) | Download Citation

Among metastatic cancers, gene fusions were reported in 1,597 individuals (15%)

The most famous gene fusions: *ALK, RET, ROS*

Behind them : *NTRK3 and NTRK1*



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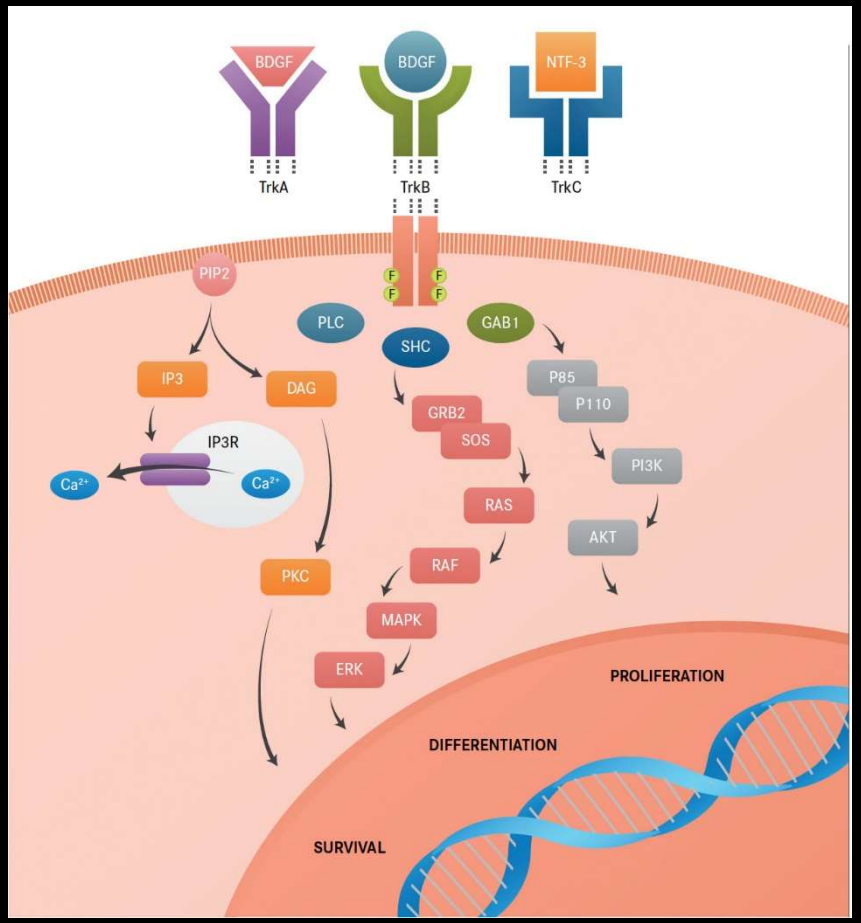
TRK Inhibitors

- Fusion leads to overexpression of the chimeric protein and constitutive ligand-independent activation.



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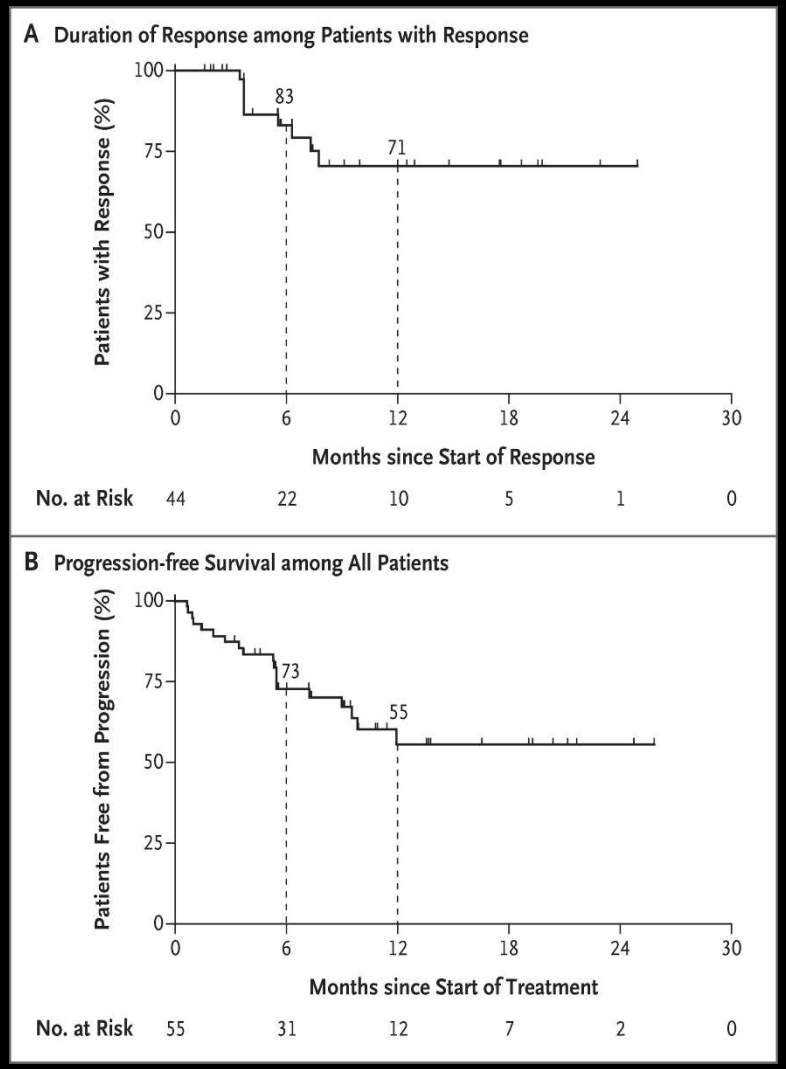
TRK Inhibitors

- Larotrectinib Kaplan-Meier Plots of Duration of Response among 44 patients with a Response and Progression-free Survival among all 55 patients.



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TRK Inhibitors

- Entrectrinib notably also used for NSCLC with ROS1 rearrangement .

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	Low UV radiation exposure / CSD				High UV radiation exposure / CS	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma / SSM				High-CSD melanoma / LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate / low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate / high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS	*BAP1*-inactivated melanocytoma / MELTUMP	Deep penetrating melanocytoma / MELTUMP	PEM / MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma / SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	***BRAF* p.V600E**; ***NRAS*** *TERT*; *CDKN2A*; *TP53*; *PTEN*	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS***; ***BRAF* (non-p.V600E)**; ***KIT***; ***NF1*** *TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET* *TERT*; *NFKBIE*; ***NRAS***; *PIK3CA*; ***PTPN11***

Low to no (or variable/incidental) UV radiation exposure / CSD					
IV	**V**	**VI**	**VII**	**VIII**	**IX**
Malignant Spitz tumour / Spitz melanoma	Acral melanoma	Mucosal melanoma	Melanoma in CN	Melanoma in BN	Uveal melanoma
Spitz naevus	? Acral naevus	? Melanosis	CN	Blue naevus	? Naevus?
Atypical Spitz tumour (melanocytoma)	IAMP / dysplasia	Atypical melanosis / dysplasia / IAMPUS	Nodule in CN (melanocytoma)	(Atypical) CBN (melanocytoma)	?
STUMP / MELTUMP	Acral MIS	Mucosal MIS	MIS in CN	Atypical CBN	?
Malignant Spitz tumour/ Spitz melanoma (tumorigenic)	Acral melanoma (VGP)	Mucosal lentiginous melanoma (VGP)	Melanoma in CN (tumorigenic)	Melanoma in blue naevus (tumorigenic)	Uveal melanoma
HRAS; ALK; ***ROS1***; ***RET***; ***NTRK1***; ***NTRK3***; ***BRAF***; ***MET*** *CDKN2A*	***KIT***; ***NRAS***; ***BRAF***; ***HRAS***; ***KRAS***; ***NTRK3***; *ALK*; ***NF1*** *CDKN2A*; *TERT*; *CCND1*; *GAB2*	***KIT***, ***NRAS***, ***KRAS*** or ***BRAF*** ***NF1***; *CDKN2A*; *SF3B1*; *CCND1*; *CDK4*; *MDM2*	***NRAS***; ***BRAF p.V600E*** (small lesions); ***BRAF***	***GNAQ***; ***GNA11***; ***CYSLTR2*** *BAP1*; *EIF1AX*; *SF3B1*	***GNAQ***, ***GNA11***, ***CYSLTR2***, or ***PLCB4*** *SF3B1*; *EIF1AX*; *BAP1*

- WHO Classification of Skin Tumors 4th.