Major Changes in Systemic Therapy for Advanced Melanoma

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National Comprehensive Cancer Network®

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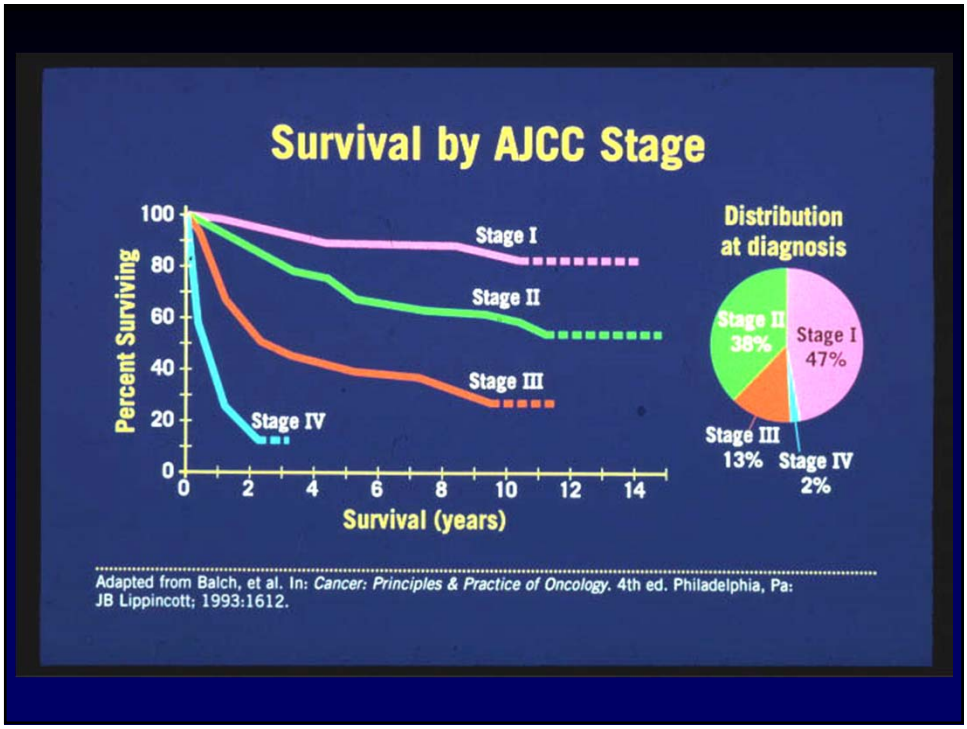
Featuring:

- Updates on immune checkpoint therapies and new targeted therapies
- FDA approval for combination ipilimumab + nivolumab
- FDA approval for high-dose ipilimumab for resected, high-risk melanoma
- FDA approval for talimogene laherparepvec (T-VEC)
- FDA approval for cobimetinib in combination with vemurafenib



Case Study

- **2013:** 45-year-old man – "mole" on the midback became pruritic, bled
  - Biopsy: melanoma, 3.5 mm depth, ulcerated, mitotic index 4/mm^2
  - Wide local excision and sentinel node biopsy of right axilla: 2 sentinel nodes + Completion node dissection: 12 nodes negative
  - Staging: T4B N2A M0

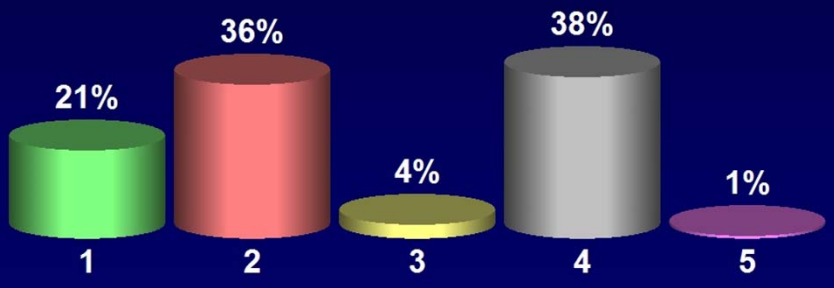
- **Jan 2015**: patient noticed two lumps under skin between wide local excision site and axilla.
  - Core biopsy: Positive for melanoma
  - Molecular assay: Positive for BRAF V600E mutation
  - Imaging: bilateral lung nodules (new) and subcentimeter, but new liver lesion. Brain MRI negative.
  - Performance status 0; LDH within normal limits; mild hypertension on lisinopril, but no other medical problems

LDH, lactate dehydrogenase

Audience Polling Results

What is the best treatment option?

1. Pembrolizumab (anti-PD-1) monotherapy
2. Dabrafenib + trametinib targeted therapy
3. High-dose interleukin-2 (IL-2)
4. Anti-CTLA-4 (ipilimumab) + nivolumab (anti-PD-1) combination immunotherapy
5. Intratumoral T-VEC



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NCCN Guidelines Version 2.2016 Melanoma

SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE

FIRST-LINE THERAPY

- Immunotherapy
  - Anti PD-1 monotherapy
    - Pembrolizumab
    - Nivolumab (category 1)
  - Nivolumab/ipilimumab
- Targeted therapy if BRAF mutated; preferred if clinically needed for early response
  - Combination therapy (preferred)
    - Dabrafenib/trametinib (category 1)
    - Vemurafenib/cobimetinib (category 1)
  - Single agent therapy
    - Vemurafenib (category 1)
    - Dabrafenib (category 1)
- Clinical trial

Metastatic or unresectable disease → Disease progression or Maximum clinical benefit from *BRAF* targeted therapy

PERFORMANCE STATUS (PS)

PS 0-2 →

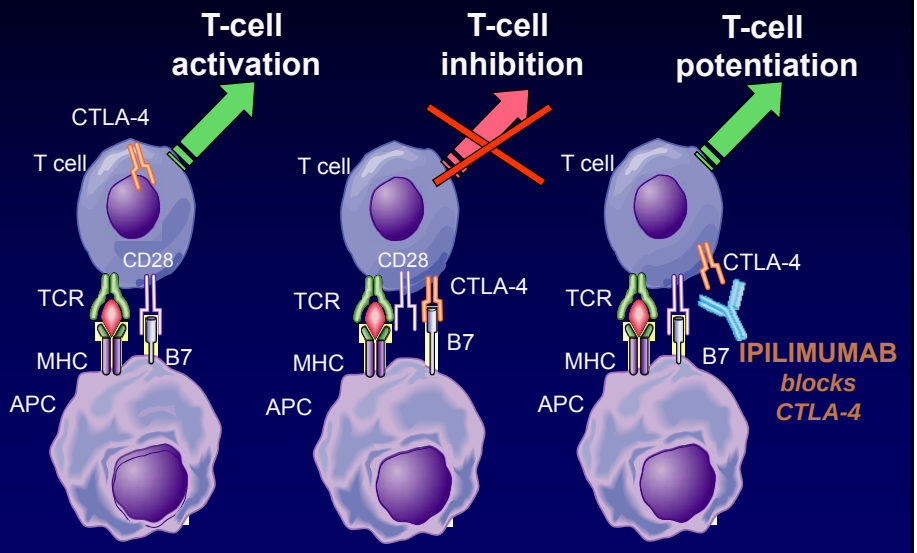
SECOND-LINE OR SUBSEQUENT THERAPY

- Anti PD-1 monotherapy
  - Pembrolizumab
  - Nivolumab
- Nivolumab/ipilimumab
- Ipilimumab (category 1)
- Targeted therapy if *BRAF* mutated
  - Combination therapy (preferred)
    - Dabrafenib/trametinib
    - Vemurafenib/cobimetinib
  - Single agent therapy
    - Vemurafenib
    - Dabrafenib
- High-dose IL-2
- Biochemotherapy (category 2B)
- Cytotoxic agents
- Imatinib for tumors with activating mutations of *C-KIT*
- Clinical trial

PS 3-4 → Consider best supportive care (See NCCN Guidelines for Pailliative Care)

ME-E 1 of 6

Ipilimumab: Mechanism of Action



APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor

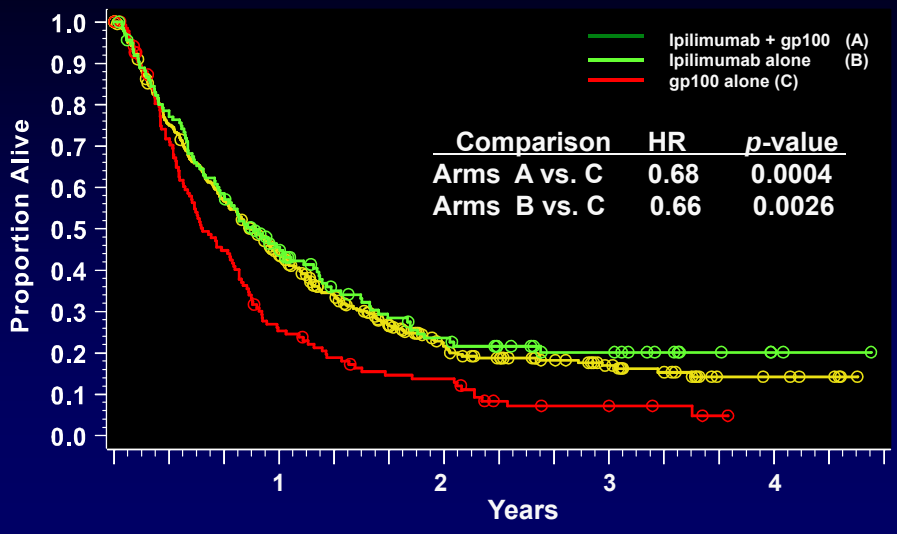
Ipilimumab Registration Trials

- **Second Line MDX010-20 Trial in HLA-A2 Positive Disease (N=650)**
  - **3 arms 3:1:1 (ipilimumab + gp100 vaccine, ipilimumab alone, gp100 alone)**
  - **1st study in metastatic melanoma to demonstrate OS benefit in large randomized placebo-controlled trial**
- **First Line CA184-024 Trial, Randomized Placebo Control (N=500)**
  - **Ipilimumab + DTIC vs Placebo + DTIC**
  - **OS advantage for Ipilimumab + DTIC versus Placebo + DTIC**

DTIC, dacarbazine; gp100, glycoprotein 100 peptide vaccine.

Hodi FS, et al. N Engl J Med 2010;363:711-723; Robert C, et al. N Engl J Med 2011;364:2517-2526.

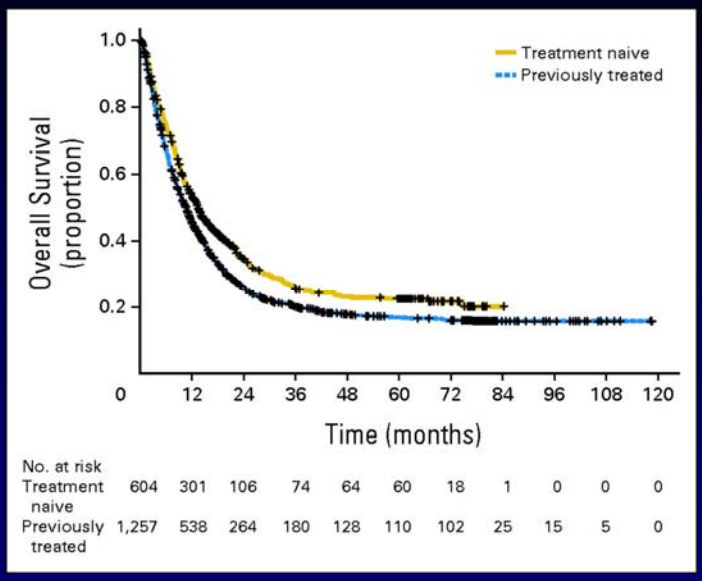
Overall Survival



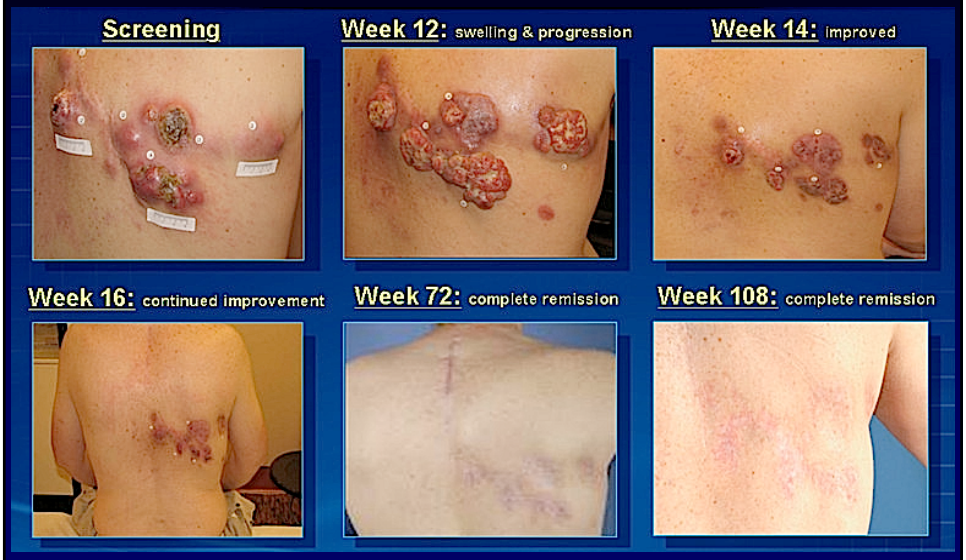
Hodi FS, et al. N Engl J Med 2010;363:711-723.

Pooled Analysis of Long-term Survival Data from Phase II and III Trials of Ipilimumab in Unresectable or Metastatic Melanoma

Schadendorf D, et al. J Clin Oncol 2015;33:1889-1894.



Ipilimumab Patterns of Response



Hoos A, et al. J Natl Cancer Inst 2010;102:1388-1397.

(Images courtesy of Jedd D. Wolchok, MD, MSKCC)

Immune-related Adverse Events (irAEs) Associated with Ipilimumab

Skin:
- Pruritus
- Rash

Gastrointestinal
- Diarrhea
- Abdominal Pain
- Blood in stool
- Bowel perforation
- Peritoneal signs

Liver
- ↑ AST/ALT, Bilirubin

Endocrine
- Fatigue
- Headache
- Mental status changes
- Hypotension
- Abnormal thyroid function tests/serum chemistries

Neurological
- Uni- or bilateral weakness
- Sensory alterations
- Paresthesias

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Ipilimumab Immune-Mediated Adverse Reactions Management Guide. 2015. http://bit.ly/1MewYCy

Immune-related Adverse Events (irAEs) Associated with Ipilimumab
Management of Gastrointestinal irAEs

Mild toxicity: Evaluate for other causes of symptoms
Symptomatic therapy

Moderate toxicity: 4-6 stools/day over baseline, abdominal pain, blood in stool

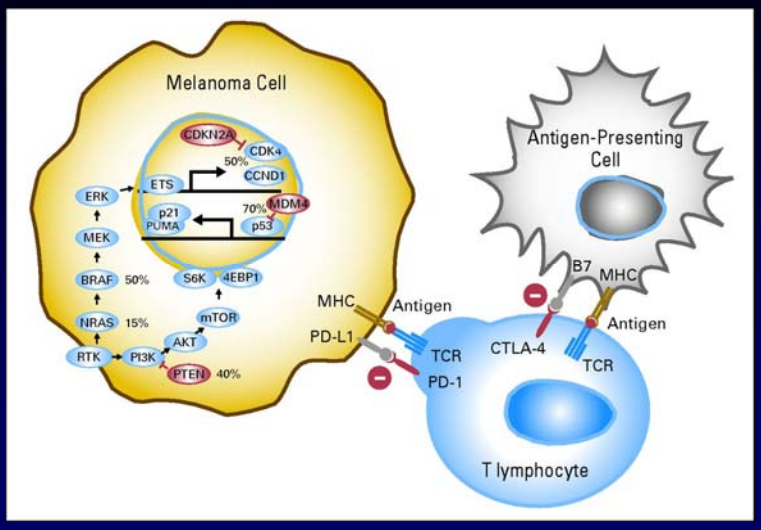
- Withhold ipilimumab
- Consider anti-diarrheal medication/nutritional modification
- If symptoms persist >1 week, prednisone at 0.5 mg/kg/day or equivalent

Severe toxicity: ≥7 stools/day over baseline, peritoneal signs consistent with perforation, ileus, fever

- Discontinue ipilimumab
- Evaluate for bowel perforation
- Consider endoscopy
- Steroids at 1-2 mg/kg/day (of prednisone or equivalent) until improvement, then taper over a month

National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0. NCI, NIH, DHHS; 2009. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html.
http://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=2265ef30-253e-11df-8a39-0800200c9a66&type=display.

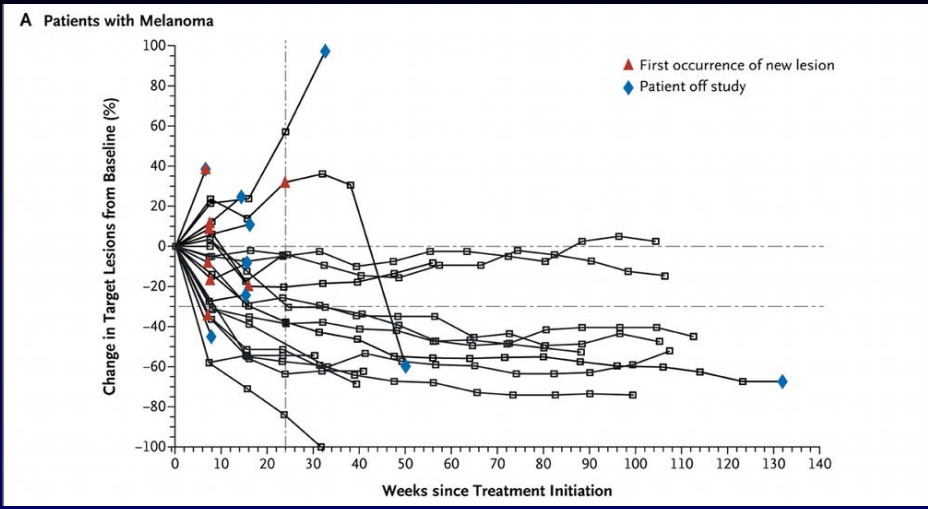
Therapeutic Biology of Melanoma



McArthur GA, et al. J Clin Oncol 2013;31:499-506.

MHC, major histocompatibility complex; TCR, T-cell receptor

Activity of Anti–Programmed Death 1 (PD-1) Antibody (Nivolumab) in Patients with Refractory Melanoma



Complete/partial Response (CR/PR): **33/107 (31%)**
Stable Disease (SD): **7/107 (7%)**

Topalian SL, et al. N Engl J Med 2012;366:2443-2454.
Topalian SL, et al. J Clin Oncol 2014;32:1020-1030.

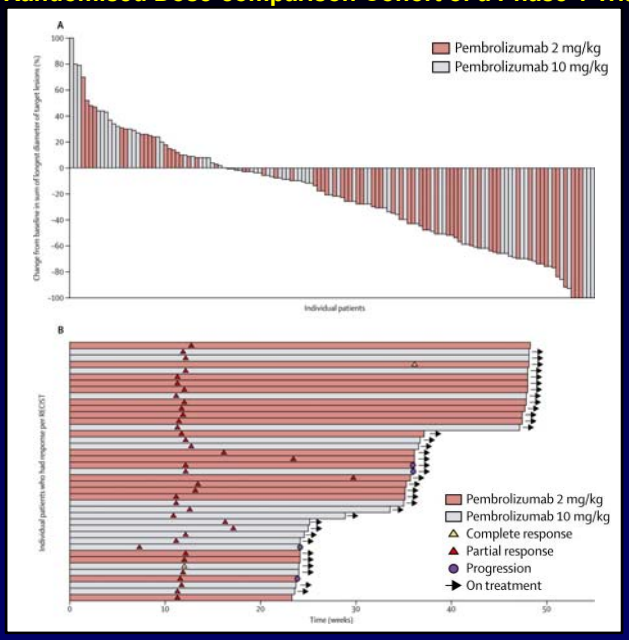
Anti-PD-1 (Pembrolizumab) in Ipilimumab-refractory Melanoma

- **173 patients with melanoma that progressed after ≥2 doses of ipilimumab**
- **Allocated randomly to pembrolizumab IV every 3 weeks at 2 or 10 mg/kg**
- **With both doses: Safety profile similar**
  ORR 26%

FDA approved pembrolizumab for: unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

Robert C, et al. Lancet 2014;384:1109-1117.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125514s004s006lbl.pdf

Pembrolizumab (anti-PD-1) in Ipilimumab-refractory Advanced Melanoma: a Randomised Dose-comparison Cohort of a Phase 1 Trial



Robert C, et al. Lancet 2014;384:1109-1117.

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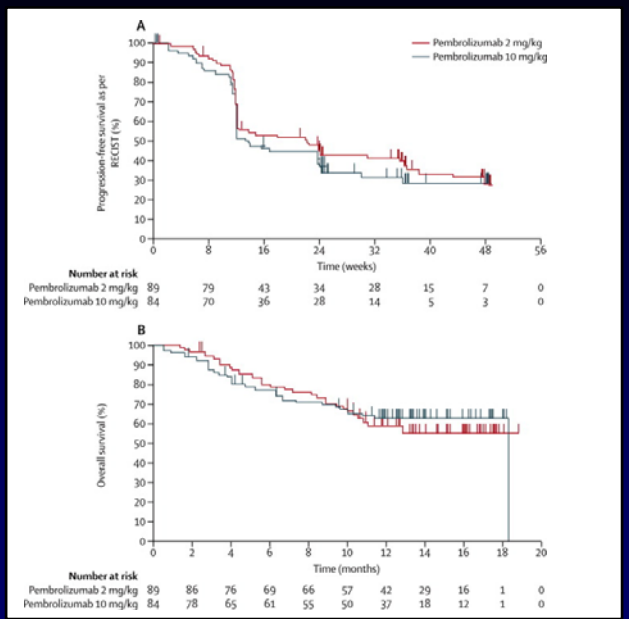


Robert C, et al. Lancet 2014;384:1109-1117.

Adverse Reactions in >10% of Patients Treated with 2 mg/kg Anti-PD-1 (Pembrolizumab)

	All grade (%)	Grade 3 (%)
Fatigue	47	7
Peripheral edema	17	1
Chills	14	0
Nausea	30	0
Constipation	21	0
Diarrhea	20	0
Vomiting	16	0
Cough	30	1
Dyspnea	10	2
Pruritis	30	0
Rash	29	0
Vitiligo	11	0
Arthralgia	20	0
Myalgia	14	1
Headache	15	0
Anemia	14	5
Insomnia	14	0
Upper respiratory infection	11	1

There were no Grade 5 AEs reported. Of the >10% AEs, none were reported as Grade 4

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125514s004s006lbl.pdf

Nivolumab in Previously Untreated Melanoma Without BRAF Mutation

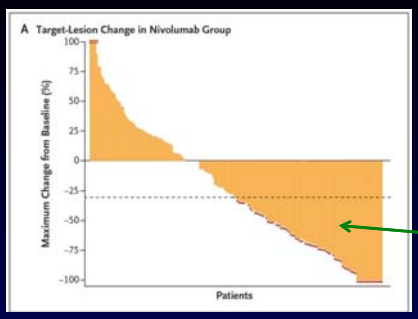
418 patients with metastatic melanoma

Previously untreated, BRAF mutation negative, Performance Score 0-1

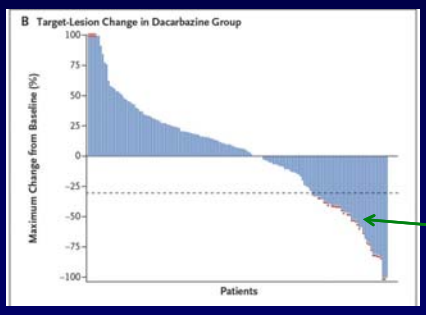
Randomly assigned to:

- **Nivolumab 3 mg/kg every two weeks and dacarbazine-matched placebo every 3 weeks (N = 210)**
- **Dacarbazine 1000 mg/m^2 every three weeks and nivolumab-matched placebo every 2 weeks (N = 208)**

Robert C, et al. N Engl J Med 2015;372:320-330.

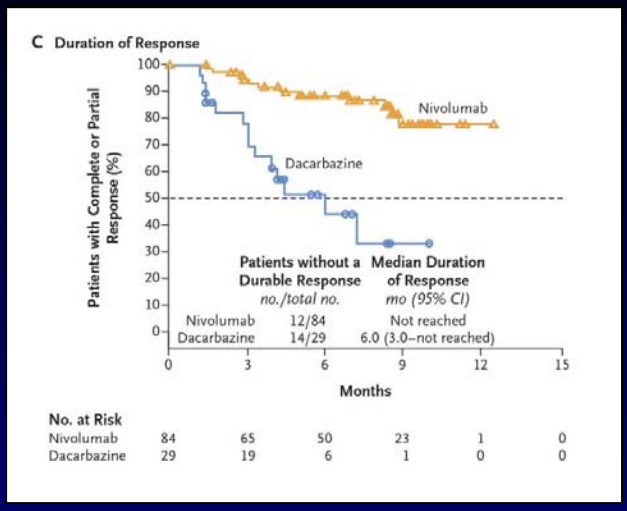


Nivolumab objective response rate = 40%

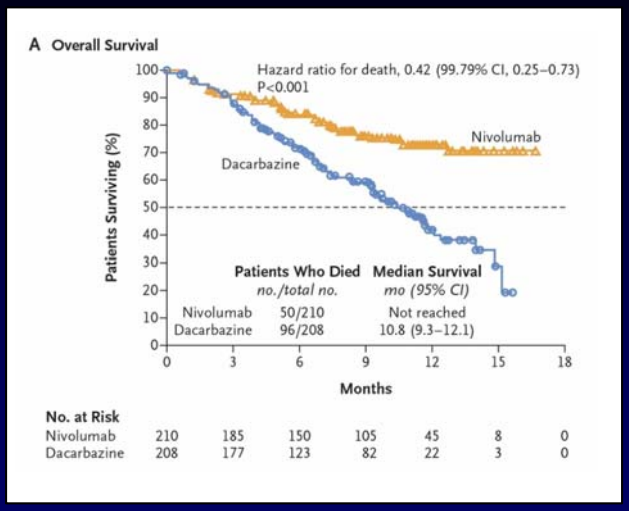


Dacarbazine objective response rate = 14%

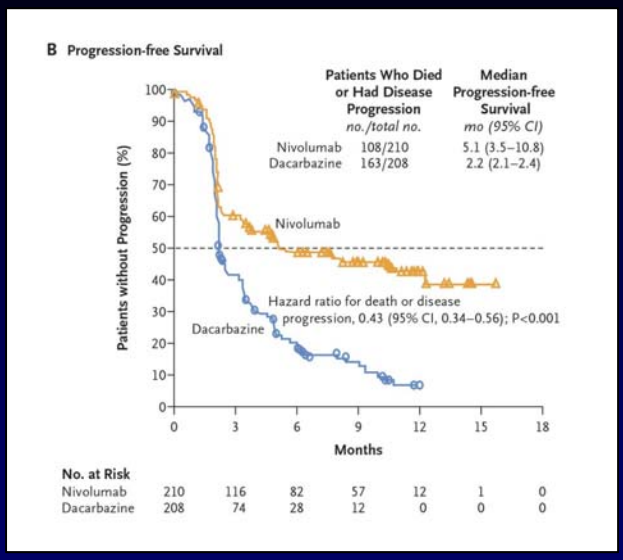
Robert C, et al. N Engl J Med 2015;372:320-330.



Robert C, et al. N Engl J Med 2015;372:320-330.



Robert C, et al. N Engl J Med 2015;372:320-330.



Robert C, et al. N Engl J Med 2015;372:320-330.

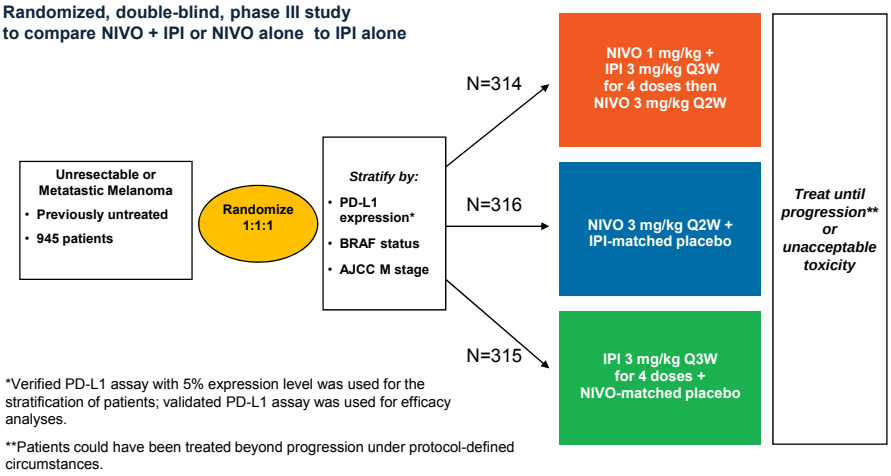
Tumor Staining for PD-L1: Correlation with Response to Therapy with Anti-PD-1 or Anti-PD-L1

	Overall Response Rate	
	PD-L1 Positive	PD-L1 Negative
Topalian (NEJM 2012)	9/25	0/17
Grosso (ASCO 2013)	7/16	3/18
Herbst (ASCO 2013)	13/33	8/61
Robert (NEJM 2015)	53%	33%*

*PD-L1 negative or indeterminate

Topalian SL, et al. N Engl J Med 2012;366:2443-2454.
Grosso J, et al. ASCO Meeting Abstracts 2013;31:3016.
Herbst RS, et al. ASCO Meeting Abstracts 2013;31:3000.
Robert C, et al. N Engl J Med 2015;372:320-330.

CA209-067 Study Design



*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

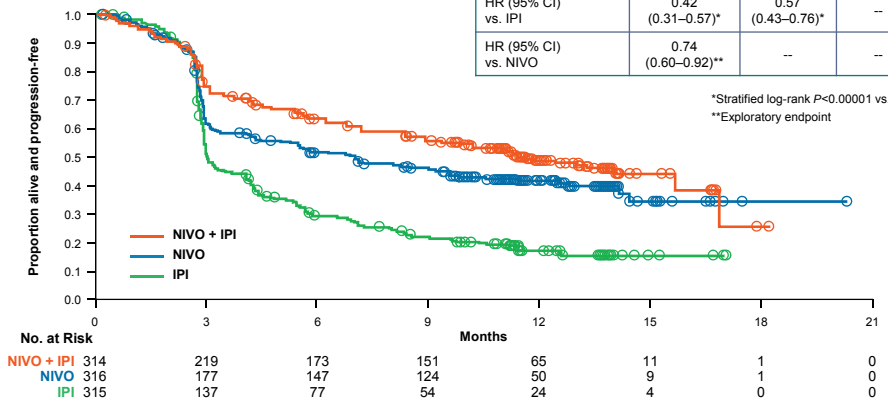
**Patients could have been treated beyond progression under protocol-defined circumstances.

AJCC, American Joint Committee on Cancer; IPI, ipilimumab; NIVO, nivolumab; Q2W, every 2 weeks; Q3W, every 3 weeks.
Larkin J, et al. N Engl J Med 2015;373:23-34.

CA209-067 Co-primary Endpoint: Progression-Free Survival (Intent-to-Treat)

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (95% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--

*Stratified log-rank $P<0.00001$ vs. IPI
**Exploratory endpoint



No. at Risk								
NIVO + IPI	314	219	173	151	65	11	1	0
NIVO	316	177	147	124	50	9	1	0
IPI	315	137	77	54	24	4	0	0

IPI, ipilimumab; NIVO, nivolumab.
Larkin J, et al. N Engl J Med 2015;373:23-34.

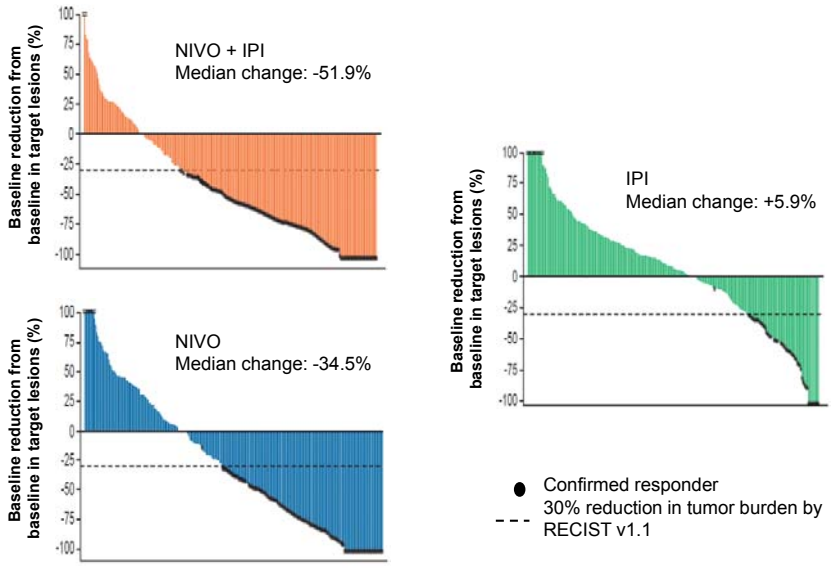
CA209-067 Response to Treatment

	NIVO + IPI (n=314)	NIVO (n=316)	IPI (n=315)
ORR, % (95% CI)*	**57.6** (52.0–63.2)	**43.7** (38.1–49.3)	**19.0** (14.9–23.8)
Two-sided *P* value vs IPI	<0.001	<0.001	--
Best overall response — %			
Complete response	11.5	8.9	2.2
Partial response	46.2	34.8	16.8
Stable disease	13.1	10.8	21.9
Progressive disease	22.6	37.7	48.9
Unknown	6.7	7.9	10.2
Duration of response (months)			
Median (95% CI)	NR (13.1, NR)	NR (11.7, NR)	NR (6.9, NR)

*By RECIST v1.1.

IPI, ipilimumab; NIVO, nivolumab; NR, not reached; ORR, objective response rate; RECIST, response evaluation criteria in solid tumors.
Larkin J, et al. N Engl J Med 2015;373:23-34

CA209-067 Tumor Burden Change From Baseline



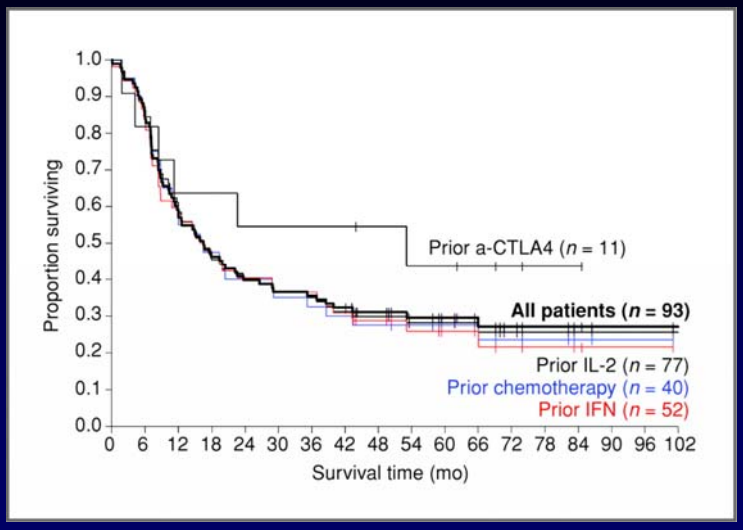
IPI, ipilimumab; NIVO, nivolumab; RECIST, response evaluation criteria in solid tumors.
Larkin J, et al. N Engl J Med 2015;373:23-34

CA209-067 Conclusions

- NIVO alone and NIVO + IPI significantly improved PFS and ORR vs. IPI alone in patients with previously untreated melanoma
  - NIVO + IPI resulted in numerically longer PFS and a higher ORR vs. NIVO alone
  - In patients whose tumors have ≥5% PD-L1 expression, both NIVO alone and NIVO + IPI resulted in a similar prolongation in PFS, although ORR was numerically higher with NIVO + IPI
- Based upon available evidence, the combination represents a means to improve outcomes vs. NIVO alone, particularly for patients whose tumors have <5% PD-L1 expression

IPI, ipilimumab; NIVO, nivolumab; PFS, progression-free surbibal; ORR, objective response rate.
Larkin J, et al. N Engl J Med 2015;373:23-34

Overall Survival of Patients Receiving Cell Transfer Based on Prior Treatment Received



Rosenberg SA, et al. Clin Cancer Res 2011;17:4550-4557.

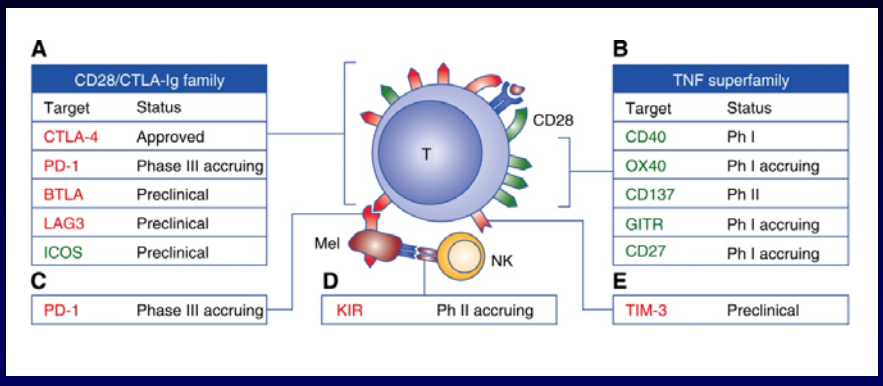
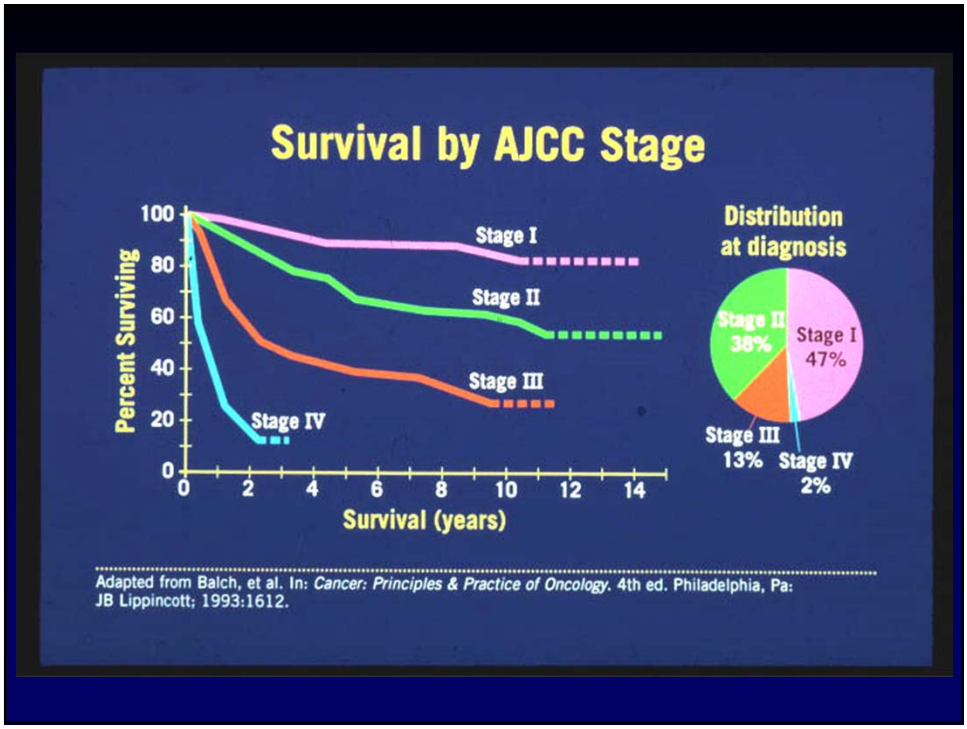


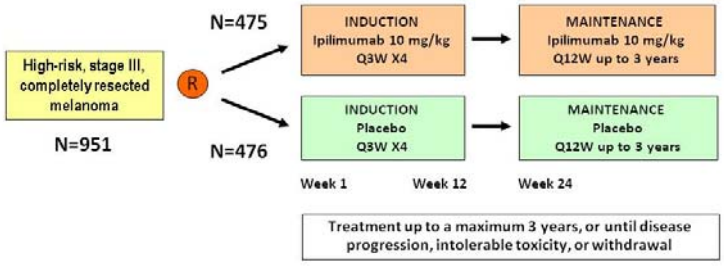
Figure 1 from Naidoo, J. *British Journal of Cancer*. 2014. Advance Online Publication doi:10.1038/bjc.2014.348



Ipilimumab vs Placebo after Complete Resection of Stage III Melanoma

LBA 9008, presented By Alexander Eggermont at 2014 ASCO Annual Meeting

EORTC 18071/CA184-029: Study Design



Stratification factors:

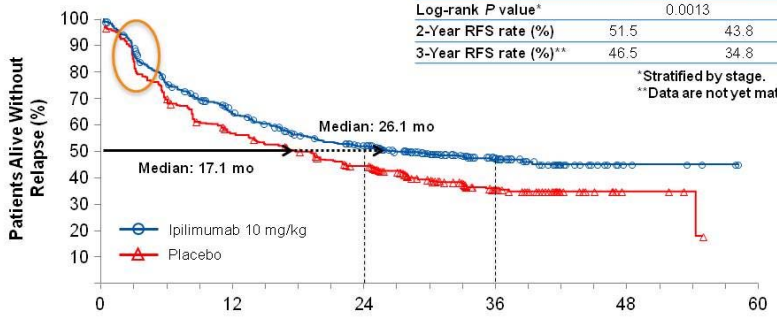
- Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC ≥4 positive lymph nodes)
- Regions (North America, European countries and Australia)

Eggermont AM, et al. Lancet Oncol 2015;16:522-530.

Primary Endpoint: Recurrence-free Survival (IRC)

	Ipilimumab	Placebo
Events/patients	234/475	294/476
HR (95% CI)*	0.75 (0.64–0.90)	
Log-rank *P* value*	0.0013	
2-Year RFS rate (%)	51.5	43.8
3-Year RFS rate (%)**	46.5	34.8

*Stratified by stage.
**Data are not yet mature.



Patients at Risk

	O	N					
Ipilimumab	234	475	276	205	67	5	0
Placebo	294	476	260	193	62	4	0

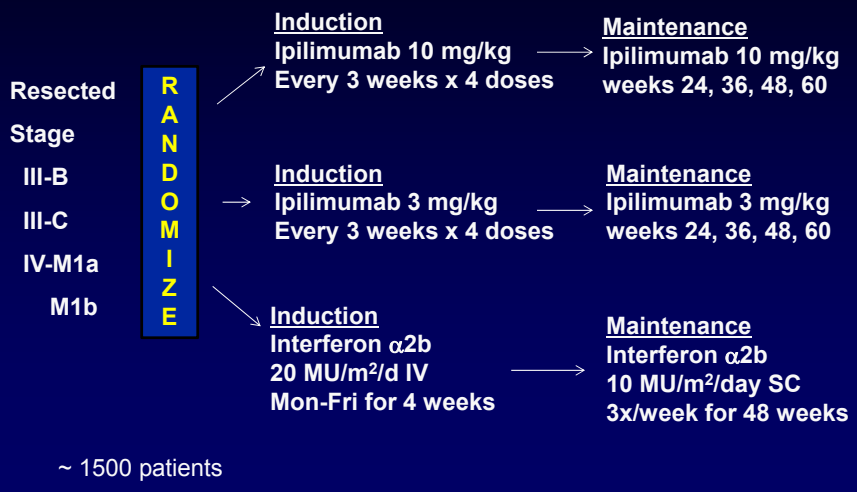
Presented By Alexander Eggermont at 2014 ASCO Annual Meeting
Eggermont AM, et al. Lancet Oncol 2015;16:522-530.

Deaths Related to Study Drug

- Five patients (1.1%) died due to drug-related AEs in the ipilimumab group:
  - Three patients with colitis (2 with gastrointestinal perforations)
  - One patient with myocarditis
  - One patient with Guillain-Barré syndrome
- No deaths related to study drug were reported in the placebo group

Presented By Alexander Eggermont at 2014 ASCO Annual Meeting
Eggermont AM, et al. Lancet Oncol 2015;16:522-530.

ECOG 1609: Phase III Trial of Ipilimumab Versus Interferon for Resected, High-risk Melanoma



~ 1500 patients

https://clinicaltrials.gov/ct2/show/NCT01274338

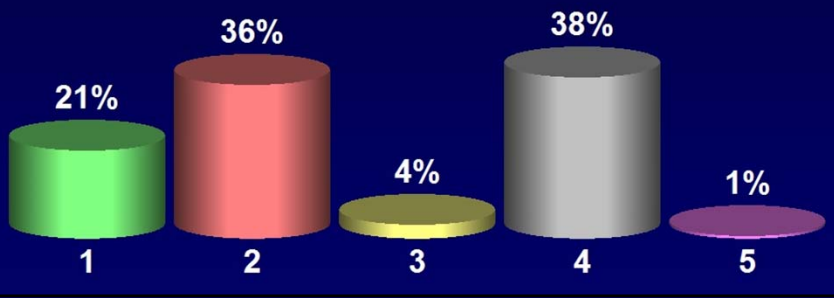
Case Study

- **2010:** 50-year-old man – melanoma excised left calf, 0.66 mm depth, no ulceration. Staging T1Ac N0 M0.
- **Fall 2015:** Patient noticed fullness left groin.
  Fine-needle aspiration biopsy: positive for melanoma.
  Left inguinal lymph node dissection: 9 nodes, 3 positive for melanoma, largest 3.5 cm without extracapsular extension.
  Staging workup including PET/CT: negative.
- Staging T1 N2B M0, stage IIIB.

Audience Polling Results

What is the best treatment option?

1. Pembrolizumab (anti-PD-1) monotherapy
2. Dabrafenib + trametinib targeted therapy
3. High-dose interleukin-2 (IL-2)
4. Anti-CTLA-4 (ipilimumab) + nivolumab (anti-PD-1) combination immunotherapy
5. Intratumoral T-VEC



Case Study (cont)

- Ipilimumab (10 mg/kg) adjuvant therapy started. Eight days after the first dose, patient developed red rash, intensely pruritic.
- Topical potent steroid cream and antihistaminics administered. Rash gradually subsided but the day 22 dose was skipped. The patient received another dose of ipilimumab on day 42.
- Six days later, the patient had abrupt onset eye pain, hyphema. A diagnosis of anterior uveitis was made and prednisone 1 mg/kg/day started. Eye pathology worsened, with edema of extraocular muscles (myositis) causing proptosis and increased intraocular pressure.
- Infliximab 5 mg/kg administered with rapid reduction in pain, intraocular pressure. Gradual taper of prednisone (5 mg reduction every 5 days).

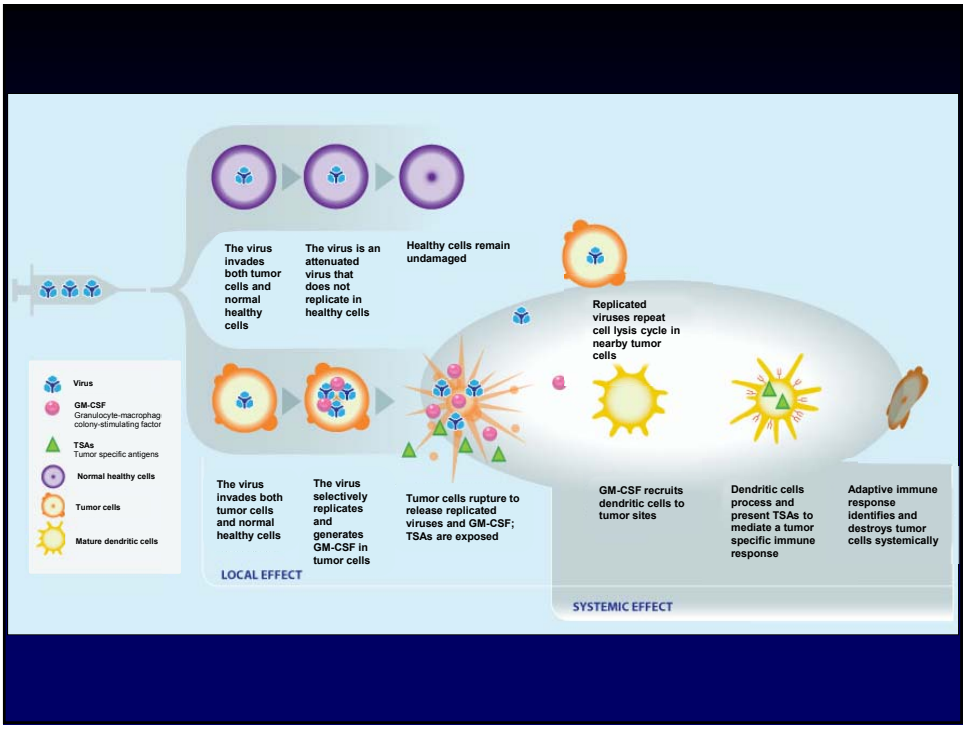
National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Melanoma

HIGH-DOSE IPILIMUMAB

[s]Adjuvant ipilimumab is associated with improvement in recurrence-free survival. Its impact on overall survival has not been reported. The recommended dose of ipilimumab (10 mg/kg) was associated with adverse events which led to the discontinuation of treatment in 52% of patients. There was a 1% drug-related mortality rate.

[t]The clinical trial excluded patients with sentinel lymph node metastases ≤1 mm in size and who did not undergo CLND. The decision to use ipilimumab should be based on risk of recurrence balanced against the risk of treatment-related toxicity. It is unclear whether the decision should be based on CLND.



Talimogene Laherparepvec (T-VEC) Improves Durable Response Rate in Patients with Advanced Melanoma

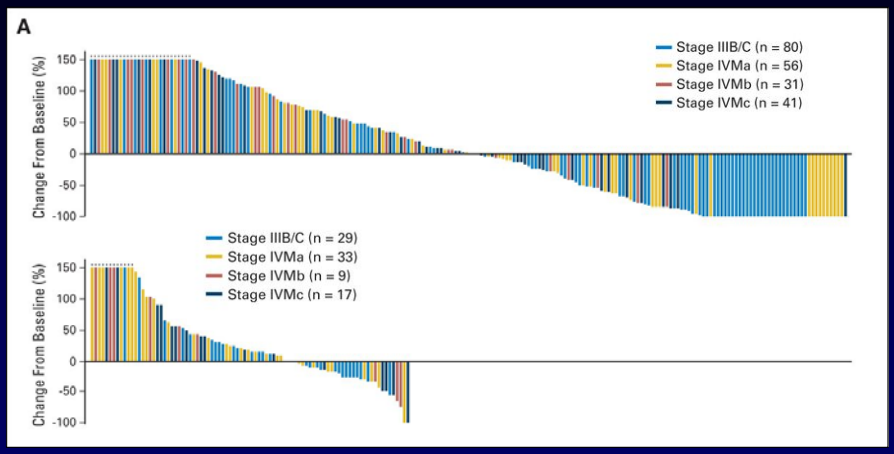
Patients with injectable melanoma that was not surgically resectable (N=436) randomized to:

- T-VEC (n=295) intralesional injection week 0, 3, then every 2 weeks
- GM-CSF (n=141) 125 mcg/m^2 SC days 1-14 every 28 days

	T-VEC (n=295)	GM-CSF (n=141)	p value
Durable Response	48 (16%)	3 (2.1%)	< 0.001
CR	32 (10.8%)	1 (<1%)	
PR	46 (15.6%)	7 (5%)	
ORR	26.4%	5.7%	< 0.001

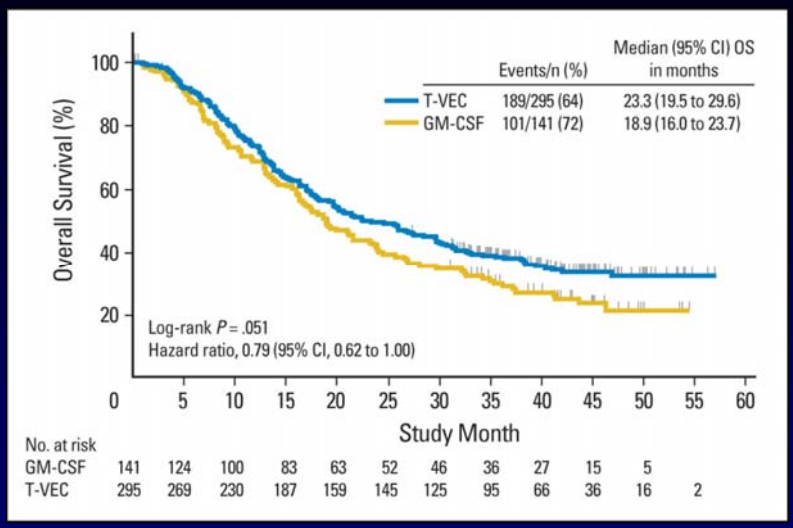
GM-CSF, granulocyte macrophage colony-stimulating factor.
Andtbacka RH, et al. J Clin Oncol 2015;33:2780-2788.

Antitumor Activity of Talimogene Laherparepvec (T-VEC)



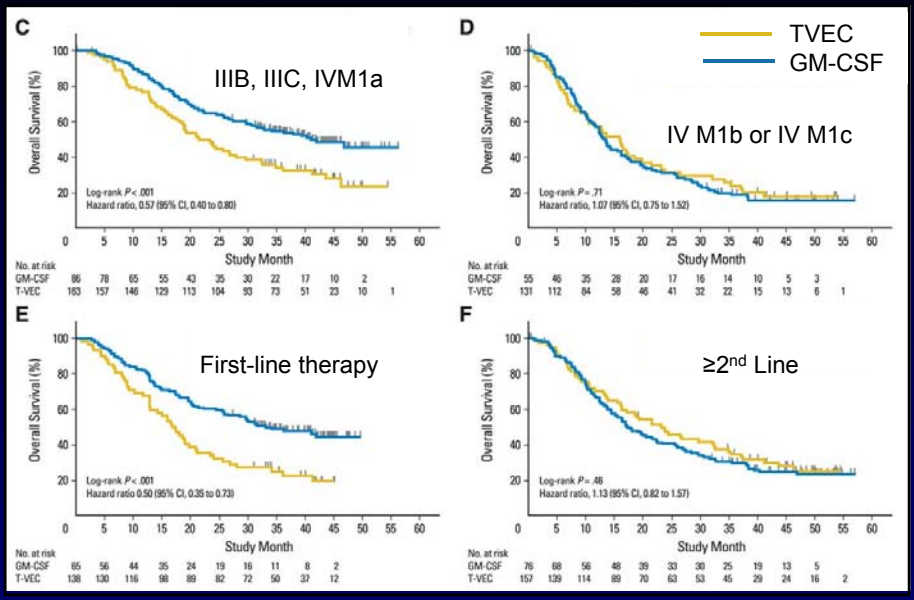
Andtbacka RH, et al. J Clin Oncol 2015;33:2780-2788.

Primary Analysis of Overall Survival (OS) in Intent-to-treat Population



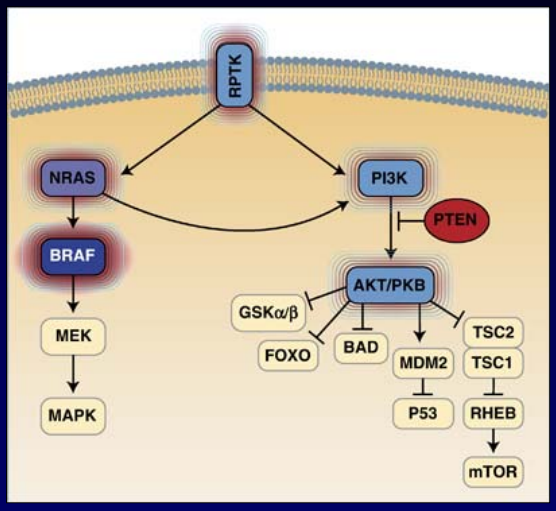
GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, Talimogene Laherparepvec
Andtbacka RH, et al. J Clin Oncol 2015;33:2780-2788.

Outcomes in Patient Subgroups



GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, Talimogene Laherparepvec
Andtbacka RH, et al. J Clin Oncol 2015;33:2780-2788.

Kinase Signaling Pathways in Melanoma



Davies MA, et al. Oncogene 2010;29:5545-5555.

NCCN Guidelines Version 2.2016 Melanoma

SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE

FIRST-LINE THERAPY

- Immunotherapy
  - Anti PD-1 monotherapy
    - Pembrolizumab
    - Nivolumab (category 1)
  - Nivolumab/ipilimumab
- Targeted therapy if BRAF mutated; preferred if clinically needed for early response
  - Combination therapy (preferred)
    - Dabrafenib/trametinib (category 1)
    - Vemurafenib/cobimetinib (category 1)
  - Single agent therapy
    - Vemurafenib (category 1)
    - Dabrafenib (category 1)
- Clinical trial

Metastatic or unresectable disease →

PERFORMANCE STATUS (PS)

Disease progression or Maximum clinical benefit from *BRAF* targeted therapy

PS 0-2 →

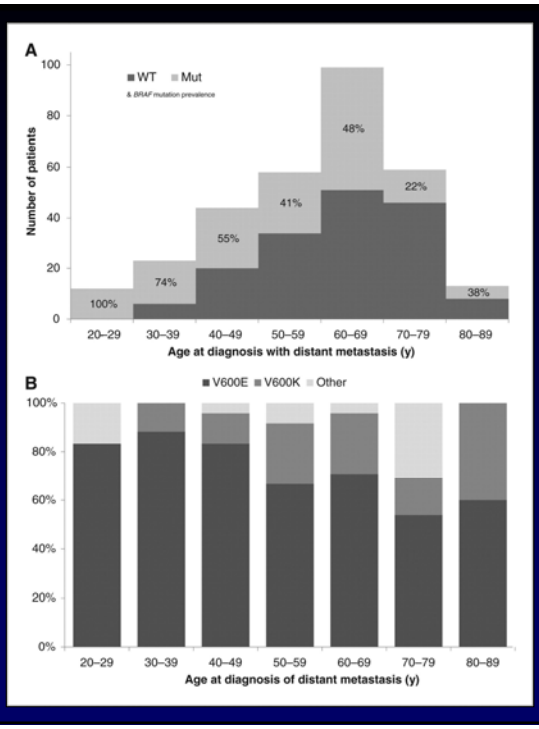
SECOND-LINE OR SUBSEQUENT THERAPY

- Anti PD-1 monotherapy
  - Pembrolizumab
  - Nivolumab
- Nivolumab/ipilimumab
- Ipilimumab (category 1)
- Targeted therapy if *BRAF* mutated
  - Combination therapy (preferred)
    - Dabrafenib/trametinib
    - Vemurafenib/cobimetinib
  - Single agent therapy
    - Vemurafenib
    - Dabrafenib
- High-dose IL-2
- Biochemotherapy (category 2B)
- Cytotoxic agents
- Imatinib for tumors with activating mutations of *C-KIT*
- Clinical trial

PS 3-4 → Consider best supportive care (See NCCN Guidelines for Paillative Care)

ME-E 1 of 6

Age at Diagnosis of Metastatic Melanoma and Prevalence of BRAF Mutation (N = 308)



Menzies AM, et al. Clin Cancer Res 2012;18:3242-3249.

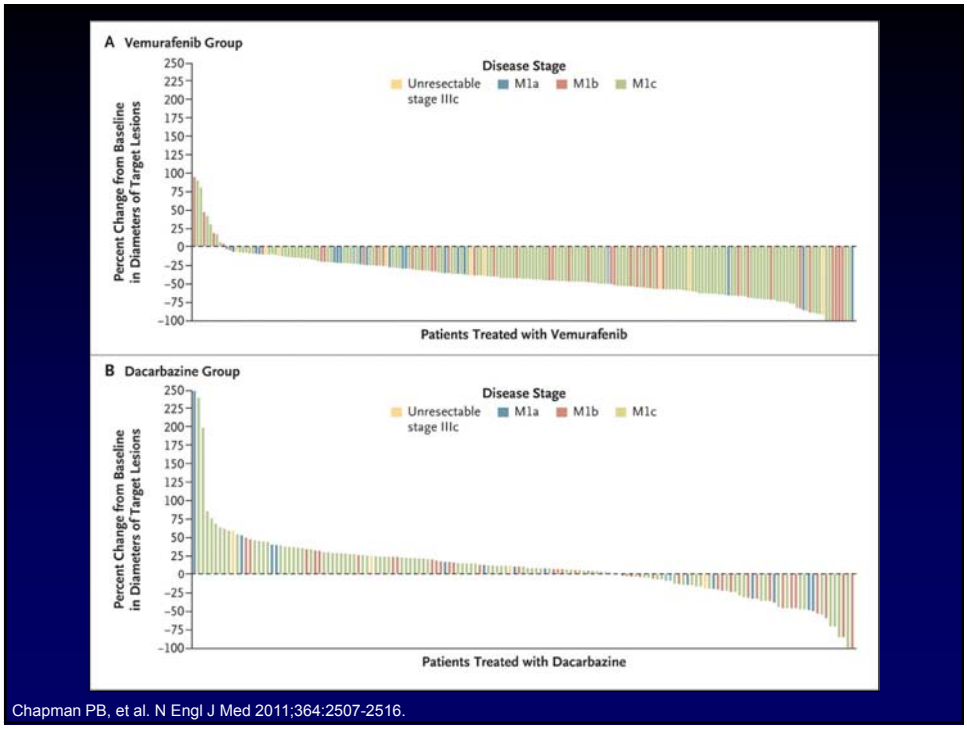
Phase III trial of Vemurafenib Versus Dacarbazine in Metastatic Melanoma

Previously untreated patients with metastatic melanoma

2107 patients screened; 675 patients randomized

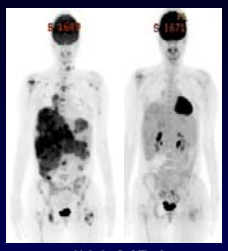
Vemurafenib (n = 337) **vs.** **Dacarbazine (n = 338)**
960 mg oral BID **1000 mg/m^2 every 3 weeks**

Chapman PB, et al. N Engl J Med 2011;364:2507-2516.

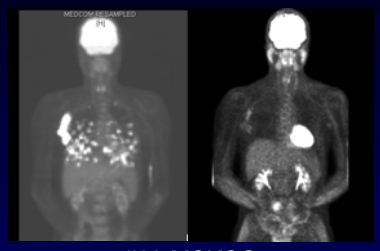


Chapman PB, et al. N Engl J Med 2011;364:2507-2516.

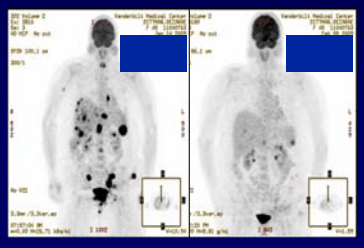
PET Scans at Baseline and Day 15 After Vemurafenib

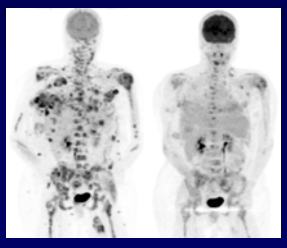


#69 MDA



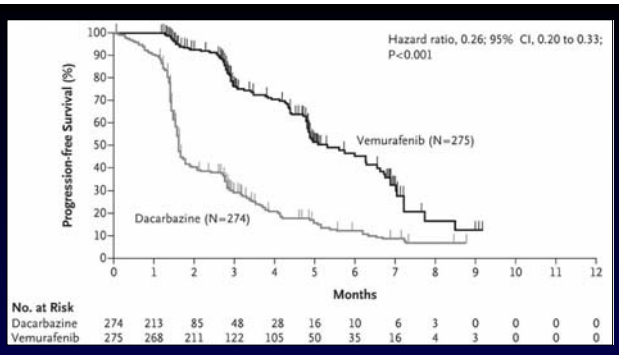
#63 MSKCC



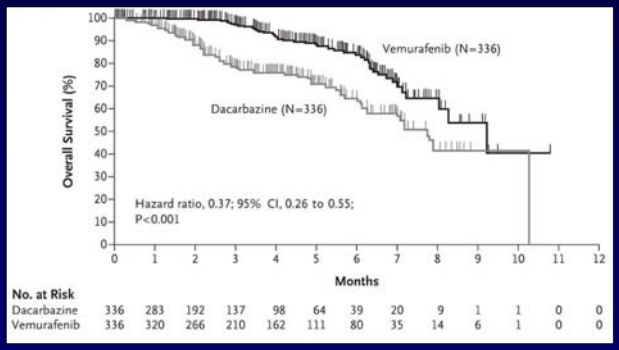


Chapman PB et al. Presented at ECCO 15/ESMO 34. Sept 20-24, 2009. Berlin, Germany. Abstract 6 BA.

Progression-free Survival



Overall Survival



Chapman PB, et al. N Engl J Med 2011;364:2507-2516.

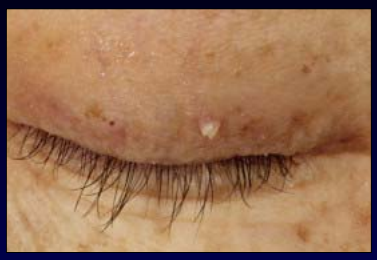
Adverse Events in 618 Patients

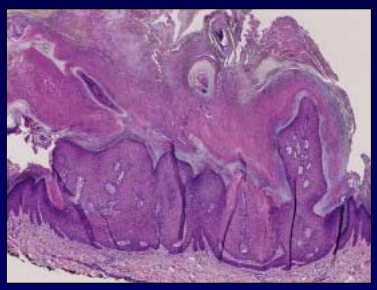
Adverse Event	Vemurafenib (N=336)†	Dacarbazine (N=282)
	no. of patients (%)	
Arthralgia		
Grade 2	60 (18)	1 (<1)
Grade 3	11 (3)	2 (<1)
Rash		
Grade 2	33 (10)	0
Grade 3	28 (8)	0
Fatigue		
Grade 2	38 (11)	33 (12)
Grade 3	6 (2)	5 (2)
Cutaneous squamous-cell carcinoma‡		
Grade 3	40 (12)	1 (<1)
Keratoacanthoma§		
Grade 2	7 (2)	0
Grade 3	20 (6)	0
Nausea		
Grade 2	25 (7)	32 (11)
Grade 3	4 (1)	5 (2)
Alopecia		
Grade 2	26 (8)¶	0
Pruritus		
Grade 2	19 (6)	0
Grade 3	5 (1)	0

Adverse Event	Vemurafenib (N=336)†	Dacarbazine (N=282)
	no. of patients (%)	
Hyperkeratosis		
Grade 2	17 (5)	0
Grade 3	4 (1)	0
Diarrhea		
Grade 2	16 (5)	4 (1)
Grade 3	2 (<1)	1 (<1)
Headache		
Grade 2	15 (4)	5 (2)
Grade 3	2 (<1)	0
Vomiting		
Grade 2	9 (3)	14 (5)
Grade 3	4 (1)	3 (1)
Neutropenia		
Grade 2	1 (<1)	4 (1)
Grade 3	0	15 (5)
Grade 4	1 (<1)	8 (3)
Grade 5	0	1 (<1)

Chapman PB, et al. N Engl J Med 2011;364:2507-2516.

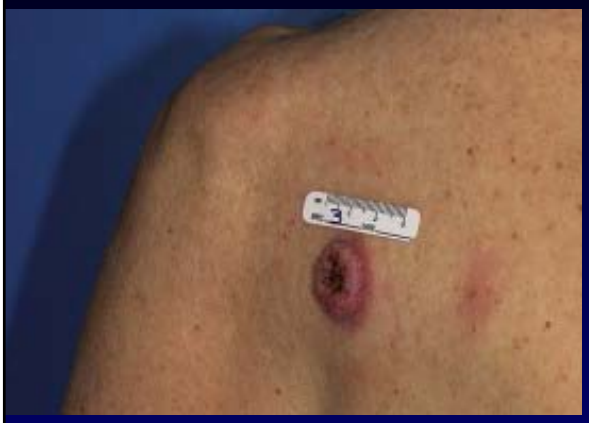
Verrucal Keratosis

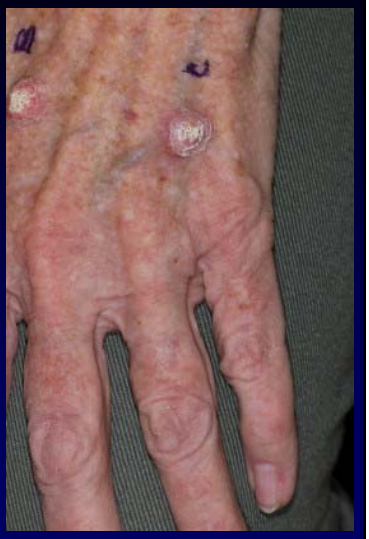




Macdonald JB, et al. J Am Acad Dermatol 2015;72:221-236

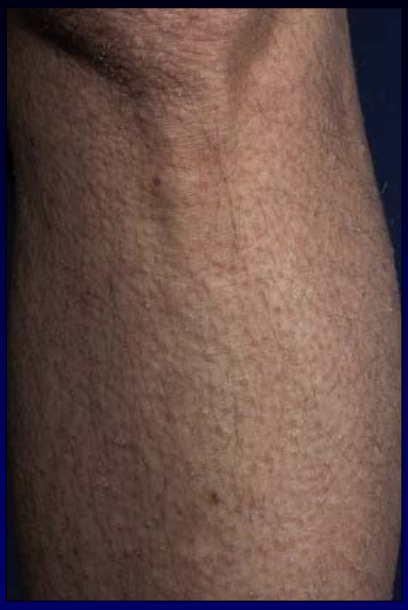
Well-differentiated Squamous Cell Carcinomas





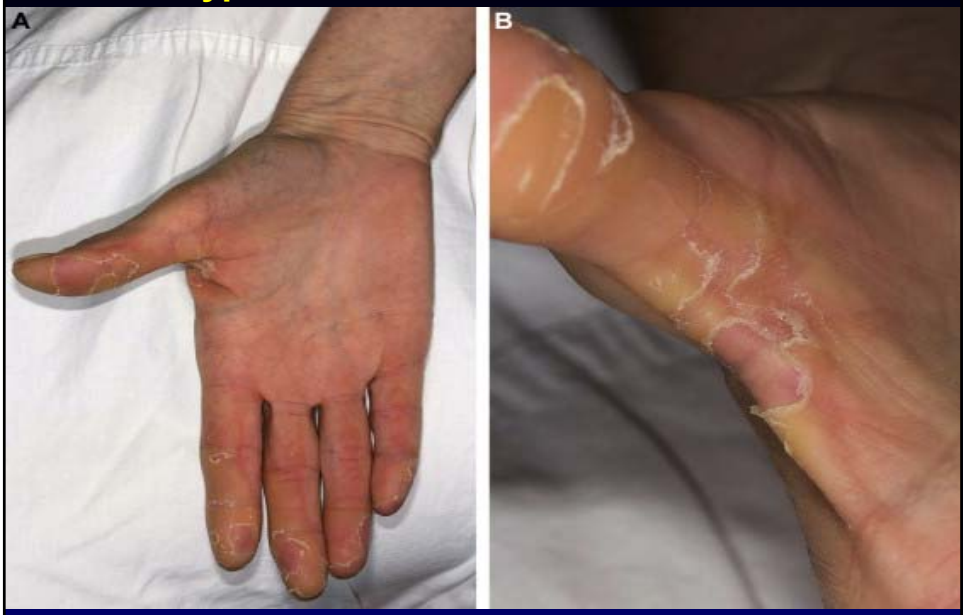
Macdonald JB, et al. J Am Acad Dermatol 2015;72:221-236

Keratosis Pilaris-like Reaction

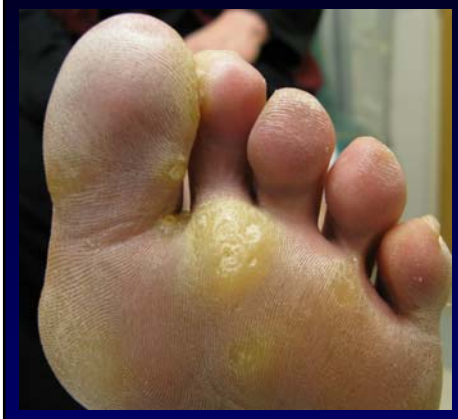


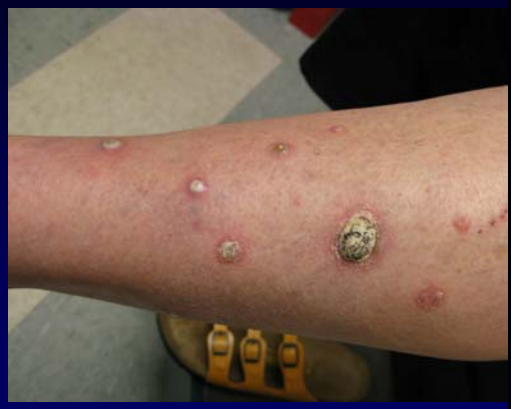
Macdonald JB, et al. J Am Acad Dermatol 2015;72:221-236

Hyperkeratotic Hand-foot Reaction



Macdonald JB, et al. J Am Acad Dermatol 2015;72:221-236



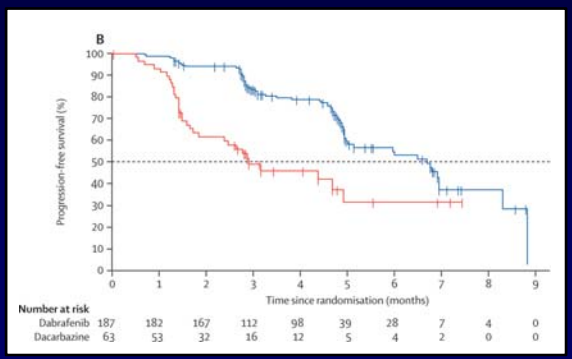


(Images courtesy of John A. Thompson, MD, FHCRC/SCCA)

Dabrafenib in BRAF-mutated Metastatic Melanoma

733 patients enrolled; 250 randomized

	Dabrafenib 150 mg oral BID (n=187)	Dacarbazine 1000 mg/m^2 IV every 3 weeks (n=63)
CR	6 (3%)	1 (2%)
PR	87 (47%)	3 (5%)



Progression-free Survival

Hauschild A, et al. Lancet 2012;380:358-365.

COMBI-d: Study Design

n=947 screened

- BRAF V600E/K
- Unresectable stage IIIC/IV
- Treatment naïve
- ECOG PS 0/1
- No brain mets, unless
  - Treated
  - Stable > 12 wks

Stratification
- BRAF mut V600E v K
- LDH (>ULN v ≤ ULN)

n=423

dabrafenib + placebo
150 mg BID+placebo once daily
n=212

dabrafenib + trametinib
150 mg BID + 2 mg once daily
n=211

Primary Analysis (PFS)

Final Analysis (OS)

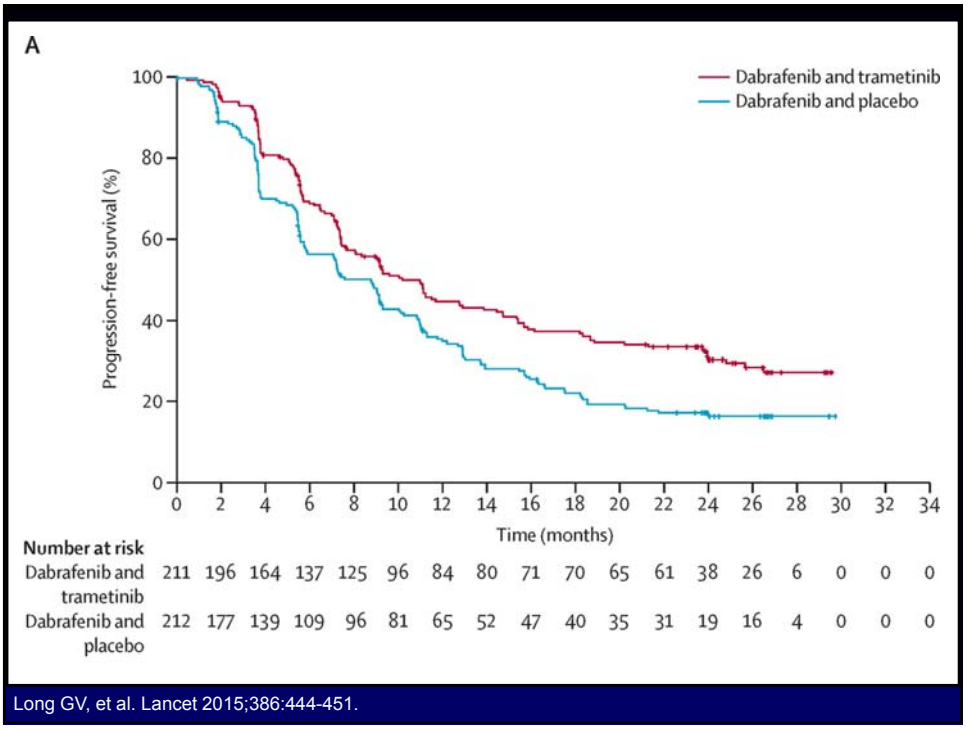
Pre-planned Interim OS

Primary Endpoint = Investigator-assessed PFS

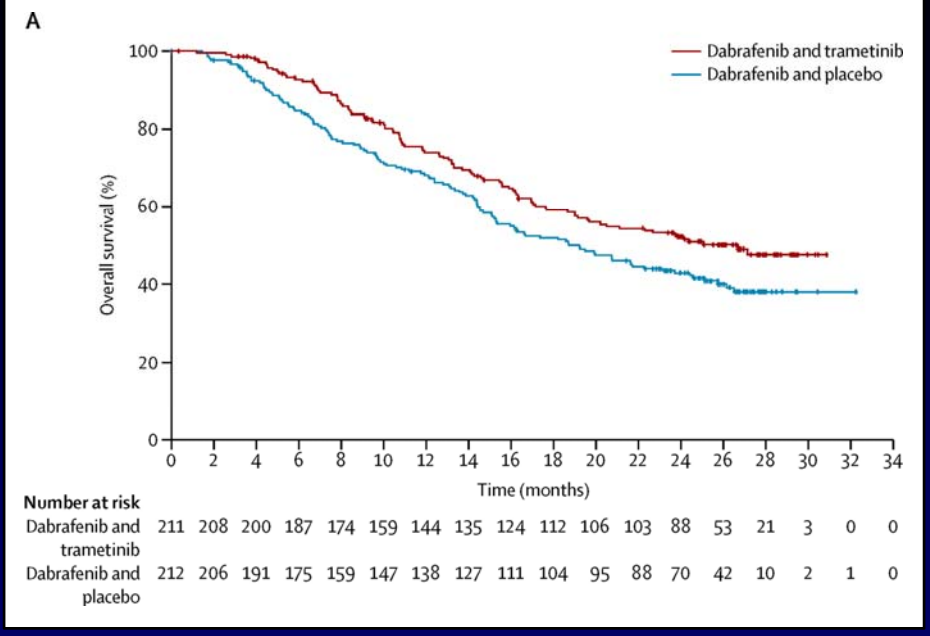
Secondary Endpoints = Overall Survival, Overall Response Rate, Duration of Response

Safety

Presented By Georgina Long at 2014 ASCO Annual Meeting



Long GV, et al. Lancet 2015;386:444-451.



Long GV, et al. Lancet 2015;386:444-451.

	Dabrafenib + Trametinib (n=211)	Dabrafenib (n=212)	p value
Median PFS (months)	11.0	8.8	0.0004
Median OS (months)	25.1	18.7	0.0107
2-year OS	51%	42%	
CR	16%	13%	
PR	53%	40%	

After cessation of study treatment, 33% of patients in the dabrafenib/trametinib arm and 51% of patients in the dabrafenib arm received other treatments, most commonly ipilimumab.

In the dabrafenib/trametinib group, fever and flu-like reaction were more common, but cutaneous squamous cell cancers and hyperkeratosis were less common.

Long GV, et al. Lancet 2015;386:444-451.

Pyrexia: Temp ≥ 38.5° C is common (~55%) with combined dabrafenib and trametinib (less frequent with BRAF monotherapy ~20%).

Onset often 2-4 weeks following the start of therapy

May be associated with chills, night sweats, rash, dehydration, electrolyte abnormalities, and ↓blood pressure. Stopping dabrafenib at the onset of pyrexia will often interrupt the episode, and treatment can be resumed with full-dose dabrafenib upon resolution of pyrexia and pyrexia-related symptoms.

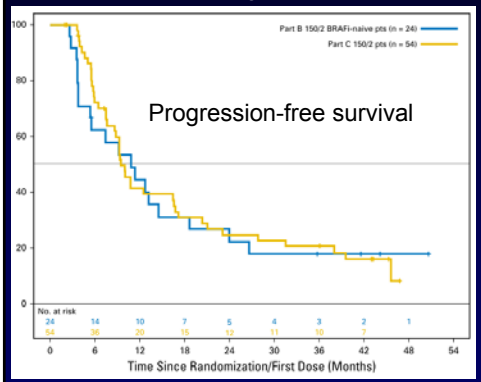
Upon re-exposure to dabrafenib, pyrexia events may recur, but grade >3 events are uncommon (21%).

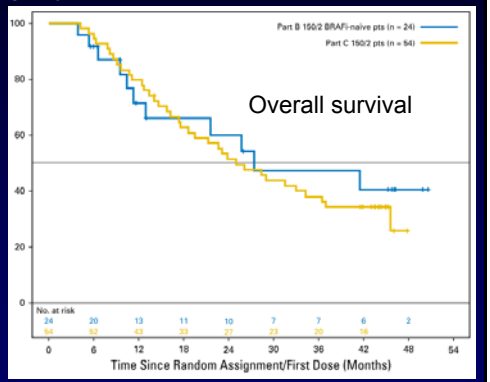
For prolonged or severe pyrexia not responsive to discontinuation of dabrafenib, prednisone (10 mg/day) may be used. Patients with pyrexia should be advised to use antipyretics as needed and increase fluid intake.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Melanoma (Version 3.2015).

Overall Survival and Durable Responses with Dabrafenib + Trametinib

- A Phase I/II study of dabrafenib and trametinib contained four parts (A, B, C, D).
- This analysis includes patients who were BRAF inhibitor naïve and received dabrafenib 150 mg BID + trametinib 2 mg/day.

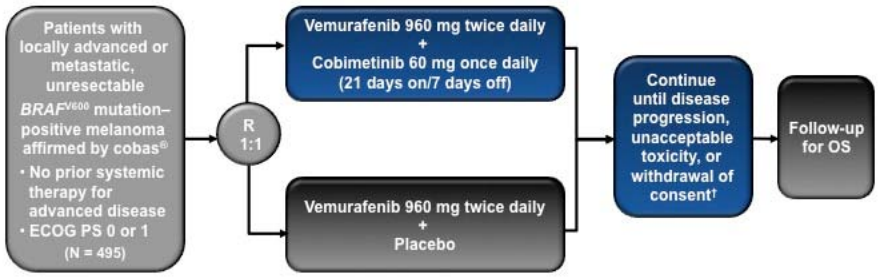




- Baseline prognostic features for good outcome: normal LDH, fewer metastases
- Normal baseline LDH and CR associated with 3-year OS rate >60%

LDH, lactate dehydrogenase level.
Long GV, et al. J Clin Oncol 2016. [Epub Jan 2016]

coBRIM (GO28141) Phase 3 Study of Cobimetinib in Combination With Vemurafenib vs Vemurafenib Alone in *BRAF*^{V600}-Mutated Metastatic Melanoma: **Trial Overview**



Primary endpoint

- Investigator-assessed PFS per RECIST v1.1

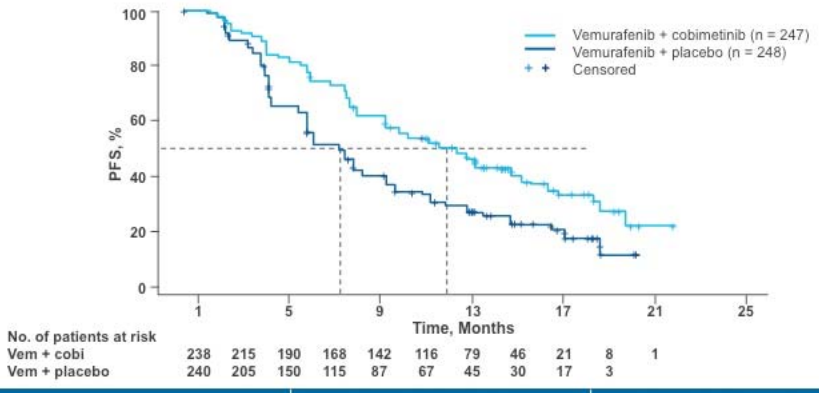
Secondary endpoints

- OS, ORR per RECIST v1.1, DOR, IRC-assessed PFS, and safety

DOR, duration of response; IRC, independent review committee; PS, performance score; R, randomized; RECIST, response evaluation criteria in solid tumours.

Larkin J, et al. N Engl J Med 2014;371:1867-1876.
Larkin JMG, et al. ASCO Meeting 2015;33:abstr 9006.

coBRIM (GO28141) Phase 3 Study of Cobimetinib in Combination With Vemurafenib vs Vemurafenib Alone in *BRAF*^{V600}-Mutated Metastatic Melanoma: **Investigator-Assessed PFS in the ITT Population (01/16/15 Cutoff)†**



	Vemurafenib + Placebo	Vemurafenib + Cobimetinib
PFS events, n (%)	180 (72.6)	143 (57.9)
Median PFS (95% CI), months	7.20 (5.55-7.49)	12.25 (9.46-13.37)
Stratified hazard ratio (95% CI)	0.58 (0.460-0.719)	

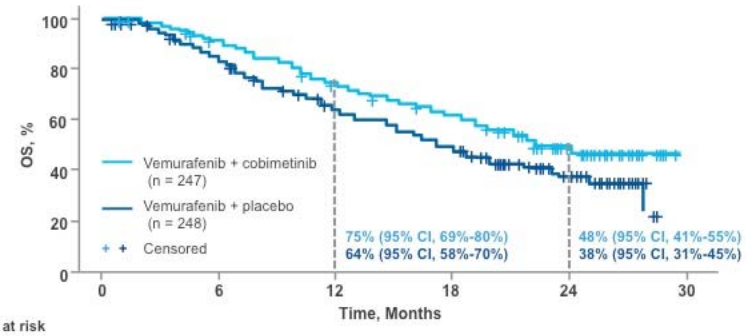
Larkin JMG, et al. ASCO Meeting 2015;33:abstr 9006.

coBRIM (GO28141) Phase 3 Study of Cobimetinib in Combination With Vemurafenib vs Vemurafenib Alone in *BRAF*^{V600}-Mutated Metastatic Melanoma: **Best Confirmed Response Rate and Duration of Response (01/16/15 Cutoff)**†

	Vemurafenib + Placebo (n = 248)	Vemurafenib + Cobimetinib (n = 247)
Objective confirmed response		
Patients with objective response, n (%) (95% CI)	124 (50.0) (43.61-56.39)	172 (69.6) (63.49-75.31)
Difference in objective response rates (95% CI)	19.64 (10.95-28.32)	
Best response, n (%)		
Complete response	26 (10.5)	39 (15.8)
Partial response	98 (39.5)	133 (53.8)
Duration of response		
Patients with an event, n (%)	73 (58.9)	84 (48.8)
Median (95% CI), months	9.23 (7.52-12.78)	12.98 (11.10-16.62)
Range, months	1.77-17.68	2.86-20.11

Larkin JMG, et al. ASCO Meeting 2015;33:abstr 9006.

coBRIM (GO28141) Phase 3 Study of Cobimetinib in Combination With Vemurafenib vs Vemurafenib Alone in *BRAF*^{V600}-Mutated Metastatic Melanoma: **Final OS (08/28/15 Cutoff)**†



No. of patients at risk

Vem + cobi	247	232	210	192	169	152	139	107	48	14
Vem + placebo	248	230	194	165	142	126	106	71	41	11

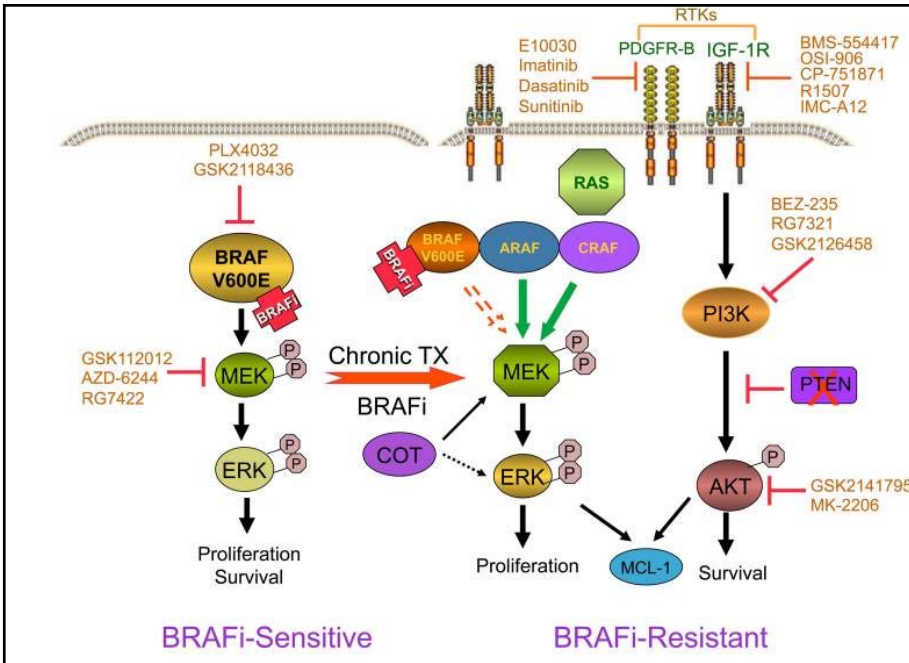
	Vemurafenib + Placebo (n = 248)	Vemurafenib + Cobimetinib (n = 247)
Patients with events, n (%)	141 (56.9)	114 (46.2)
Median OS (95% CI) months	17.4 (15.0-19.8)	22.3 (20.3-NE)
Hazard ratio (95% CI)	0.70 (0.55-0.90)	
P value	0.005	
Median follow-up, months	18.5	

Atkinson, V. Presented at 2015 Society for Melanoma Research.

Toxicities of Vemurafenib + Cobimetinib

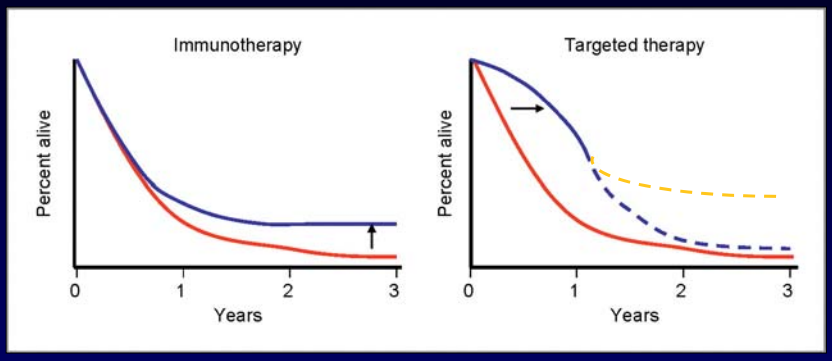
Adverse Event	Rate	Monitoring
Cutaneous malignancies	6% cSCC or keratocanthoma, 4.5% bcc, 0.8% second primary melanoma	*Dermatological exam at baseline and every 2 months*
Hemorrhage	13% all grades, 1.2% grade 3-4	
Cardiomyopathy	26% grade 2-3 decrease in LVEF; safety not established for LVEF <50%	*LVEF at baseline, after 1 month, then every 3 months*
Serous retinopathy	26% all grades	*Ophthalmological exam at regular intervals and for new/worse visual disturbances*
Hepatic toxicity	Grade 3-4: ALT 11%, AST 7%, bilirubin 1.6%, ALP 7%	*Monitor LFTs monthly*
Rhabdomyolysis	12% grade 3-4 CPK elevations	*Serum CPK and creatinine levels at baseline, then periodically during therapy*
Rash	16% grade 3-4	
Photosensitivity	47% all grades, 4% grade 3	

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; bcc, basal cell carcinoma; CPK, creatinine phospho kinase; cSCC, cutaneous squamous cell carcinoma; LFTs, liver function tests; LVEF, left ventricular ejection fraction.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206192s000lbl.pdf



AZD6244, selumetinib; BRAFi, BRAF inhibitor; GSK2118436, dabrafenib; GSK112012, trametinib; PLX4032, vemurafenib; RG7422, apitolisib
Villanueva J, et al. Cancer Res 2011;71:7137-7140.

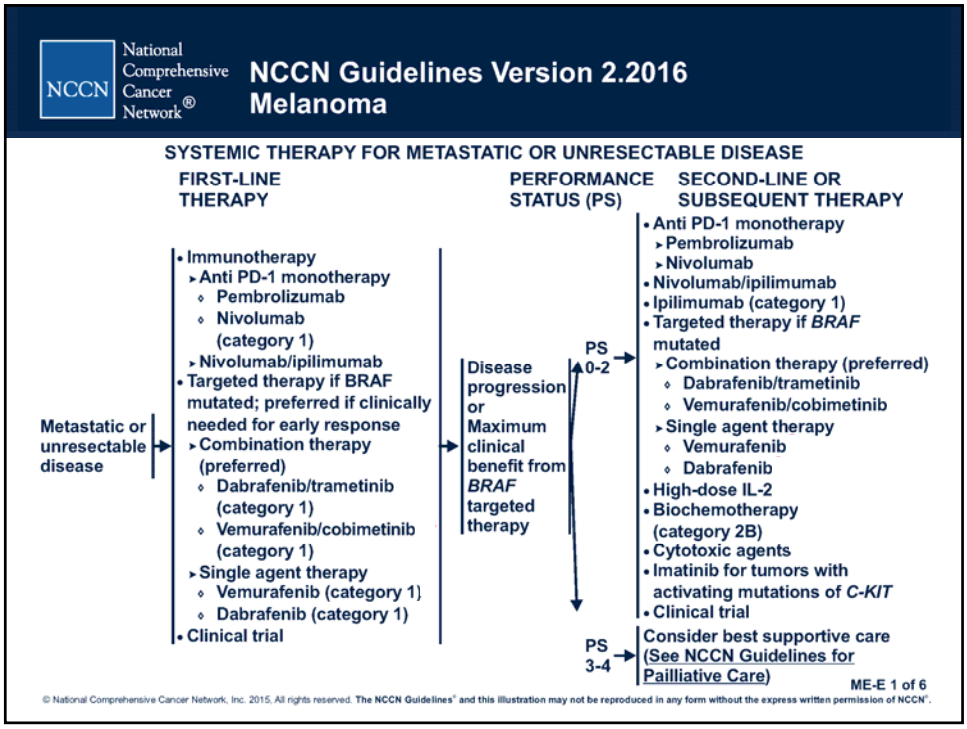
Effects of Immunotherapy and Targeted Therapy on Melanoma Survival Curves



Ribas A et al. Clin Cancer Res 2012;18:336-341.

NCCN Recommendations for Metastatic or Unresectable Melanoma: First-line Systemic Therapy

	BRAF Mutated	BRAF Wild-type
Preferred if need early response	• BRAF/MEK inhibitor combination (preferred): ▪ Dabrafenib/trametinib ▪ Vemurafenib/cobimetinib • BRAF inhibitor monotherapy (vemurafenib or dabrafenib)	• Anti-PD-1 monotherapy (nivolumab or pembrolizumab) • Ipilimumab/nivolumab combination • Clinical trial
All other cases	• Anti-PD-1 monotherapy (nivolumab or pembrolizumab) • Ipilimumab/nivolumab combination • Clinical trial	



Unanswered questions:

Optimal duration of therapy?

Biomarkers to predict response?

Combination vs sequential therapy?

Role of T-cell therapies?

Thank You

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