Current Topics in Melanoma

Sanjay Rao, MD FRCPC

FPON Webcast

October 15, 2015

Disclosures

- I have received honoraria and travel support from Bristol-Myers Squibb (BMS)
- I have received honoraria and travel support from Roche
- I have received honoraria from Novartis
- I have served on advisory boards for BMS, Roche, Novartis, and Merck
- Some of the slides in this presentation are the property of BMS and/or Novartis and/or Roche; I have obtained permission to use those slides
- I may mention off-label use of some drugs; any discussion of off-label use has not been supported or encouraged by drug manufacturers

Objectives

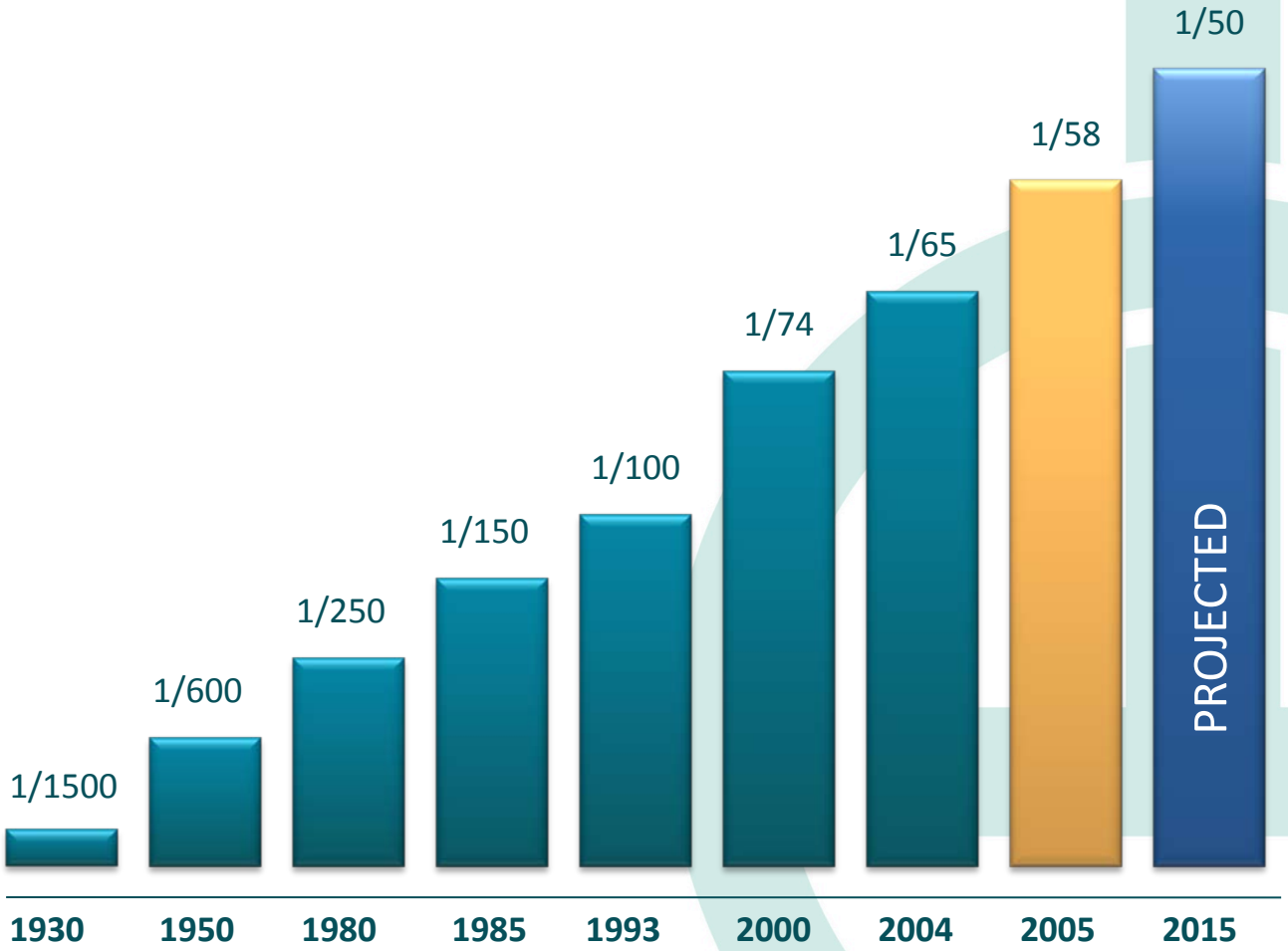
- Understanding basic concepts of melanoma classification, diagnosis and management
- Understanding recent advances in management of metastatic disease
- Understanding at a general level the toxicities of new therapies and their management

Background

- Melanoma is projected to account for 3.6% of new cancer cases in Canada
  - But 8% in 15-29 age group and 6% in 30-49 age group
- Incidence rates in some areas are rising among young people (particularly young women)
- About 85% are localized; 10% involve regional nodes; 5% present with distant mets (US SEER data)
- Benefit of adjuvant therapies is uncertain
- Until recently, metastatic disease had poor outcomes, with disease course little modified by available agents
  - In 2015, projected melanoma mortality is 20%; 2/3 of those will be men

Canadian cancer statistics source: Canadian Cancer Society 2015
http://www.cancer.ca/~/media/cancer.ca/CW/publications/Canadian%20Cancer%20Statistics/Canadian-Cancer-Statistics-2015-EN.pdf

Lifetime Risk of Developing Melanoma is Increasing



(From CheckPoint module 2A) U.S. statistics.
Rigel DS, et al. *CA Cancer J Clin* 2010; 60(5):301-16.

Classification of Melanoma

Changing Perspectives

- Morphological and anatomical descriptors losing favor
- As molecular biology and genetics advance, new classifications emerge
- New therapies directed at molecular targets
- Continued exploration of relationship between melanoma and immune system

Melanoma Classification

- Classification formerly descriptive
  - Nodular, SSM, lentigo maligna, acral, mucosal, choroidal, etc.
  - These subtypes now have no significant bearing on prognosis or management
- Now interest in identification of characteristic mutations
  - Cutaneous → BRAF
  - Mucosal → c-KIT
  - Ocular / uveal → GNAQ/GNA11
- May eventually have multiple gene “signature”

Management of Non-Metastatic Melanoma: Typical Approaches

Cutaneous Melanoma: Localized

- Early-stage disease
  - –Surgery a mainstay
    - Excisional bx → wide ex (+/- SLNB)
  - –Typically no adjuvant treatment indicated

Cutaneous Melanoma: Localized

- Synoptic pathology report highlights:
  - Breslow depth
  - Presence of ulceration
  - Mitotic rate
  - Presence of in-transit metastases or satellite lesions

Cutaneous Melanoma: Regional Nodal Metastases

- Surgery as above; may include more extensive node dissection
- Adjuvant interferon could be offered

Mucosal Melanoma

- Staging and treatment protocols not well-established due to rarity
  - Incidence 2 per million vs 150 per million for cutaneous in US[1]
- Can arise in any mucosal area, but more commonly:
  - Head and neck (nasal/sinus)
  - Gastrointestinal (anorectal)
  - Genitourinary (vulvovaginal)
- Value of sentinel node biopsy, adjuvant therapy unknown

[1]Mihajlović et al. Int J Clin Exp Pathol 2012;5(8):739-753

Ocular Melanoma

- Incidence 2-8 per million per year in Caucasians
- Multidisciplinary evaluation required
- No proven benefit of any one primary treatment modality over another
  - Can be surgery and/or radiation
- Risk of metastasis increases with increasing thickness of primary tumor
- 50% of patients who develop metastases will have liver metastases only

Uveal melanoma UK national guidelines. Nathan et al. European Journal of Cancer (2015);51:2404–2412

Cutaneous Melanoma: Adjuvant Interferon

- Considered a standard adjuvant treatment
  - In BC, for resected clinically node-positive patients, but can be prescribed more broadly
- Problems
  - Several randomized trials of varying design, and which provided inconsistent results
  - Subsequent aggregate analyses suggest modest relapse-free and OS benefit, possibly limited to clinically node-positive patients
  - Mucosal, acral, ocular not well represented
  - Toxicity

Adjuvant Treatment - Now

- Trials are underway looking at adjuvant targeted therapy, anti-CTLA4 antibodies, and vaccine (cutaneous melanoma only)
- EORTC 18071[1] – ipilimumab vs placebo (OS data not mature)
  - Evaluated in higher-risk stage 3 melanoma patients post-complete regional node dissection
  - RFS-3 significantly higher for ipi group (46.5 vs 34.8%; p=0.0013)
  - mRFS 26.1 vs 17.1 months
  - 5 deaths in ipi group

Eggermont et al. Lancet Oncology 2015;16(5):522-30

Adjuvant Treatment - Now

- Other trials:
  - BRIM-8: p3 vemurafenib vs placebo in resected $BRAF^{V600}$-mutant stage 2C or 3 cutaneous melanoma
  - E1609: p3 ipilimumab vs interferon-α_{2b} in resected stage 3 and 4 (M1a and M1b only)
  - MAVIS: p3 polyvalent melanoma vaccine (POL-103A) vs placebo in resected stage 2b/c and 3

Progress in Management of Advanced Melanoma

Past Treatments for Metastatic Melanoma

Treatment

Dacarbazine (DTIC)

- In large randomized trials, Response rate (RR) of <15%

Temozolomide

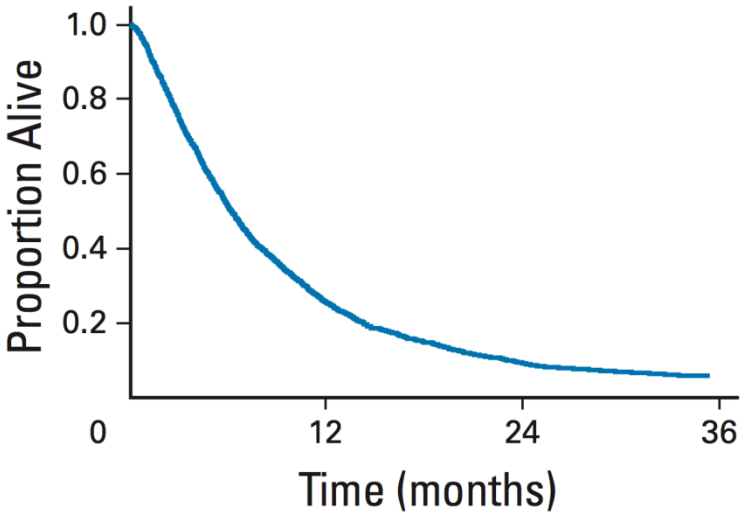
- Similar to DTIC

IL-2

- RR of 15-20%
- A minority are durable responses
- Highly toxic treatment

Survival[1]

- Median OS: 6.2 months
- One year OS: 25.5% (95% CI, 23.6% to 27.4%)



OS=overall survival.

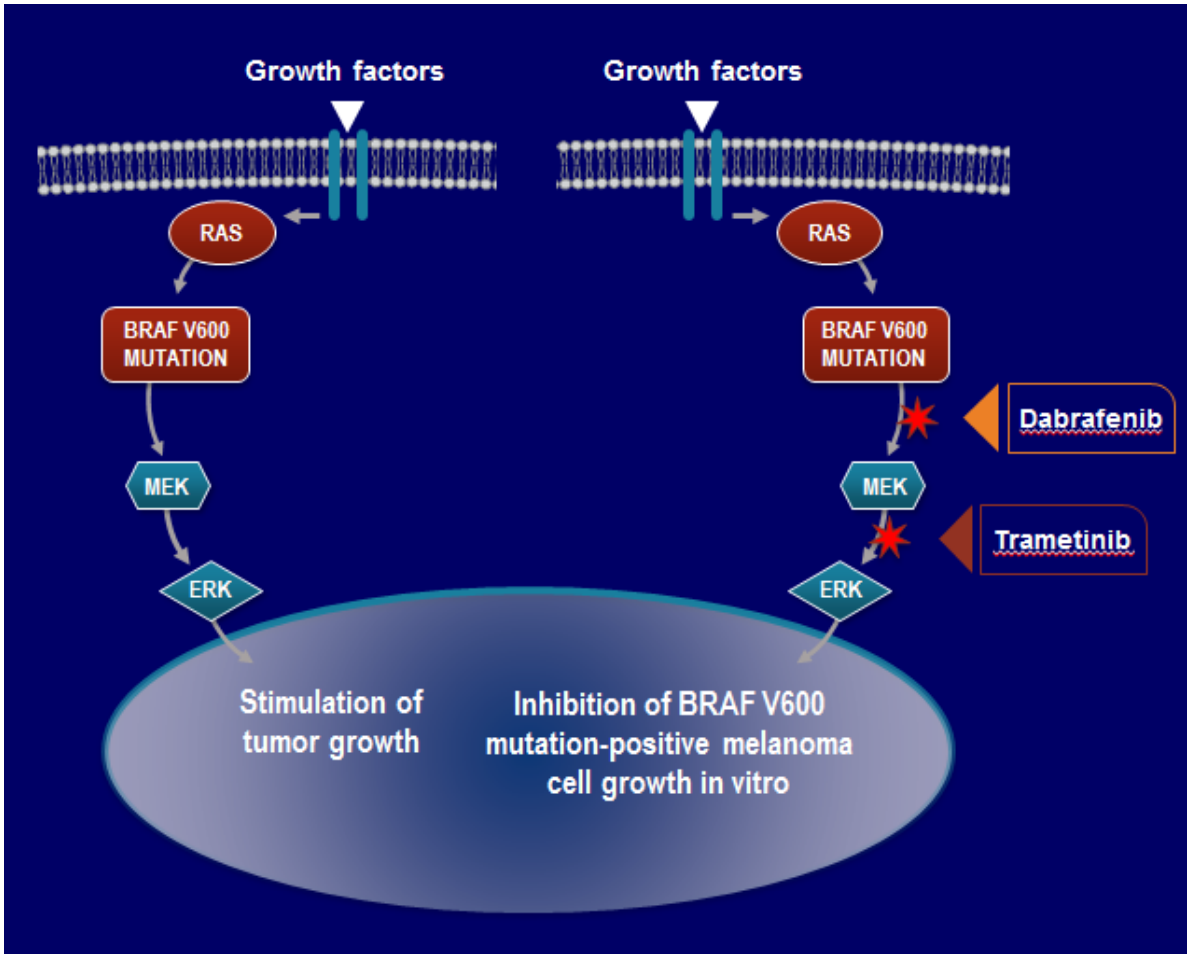
1. Korn, JCO. 2008 Feb 1; 26(4)

Advanced melanoma

- Recent advances include immunotherapy and targeted therapy
- It is now standard to evaluate tumors for $BRAF^{V600}$ and other mutations
  - 40-60% of cutaneous melanomas will be BRAF mutated
  - KIT and NRAS routinely in near future?

Targeted Therapies: BRAF and MEK inhibition

Mechanism of Action: BRAF and MEK inhibitors



Tafinlar (dabrafenib) Product Monograph. GlaxoSmithKline Inc., March 4, 2015.

http://gsksource.com/gskprm/en/US/images/gsk_content/TAFMEK/FBP/map-k-pathway/index.html#

BRIM3 Study Design in Previously Untreated Patients With Metastatic Melanoma

Multicenter, randomized, open-label, Phase 3 study of vemurafenib vs. dacarbazine in previously untreated patients with *BRAF*^{V600E} mutation-positive* unresectable stage IIIC or IV melanoma[1,2]

Patients	Treatment
• Aged ≥18 years • No prior systemic therapy • Enrollment: N=675	**Vemurafenib** 960 mg BID (n=337) vs. **Dacarbazine** 1000 mg/m2 IV q3w (n=338)

Primary objectives

- OS, PFS

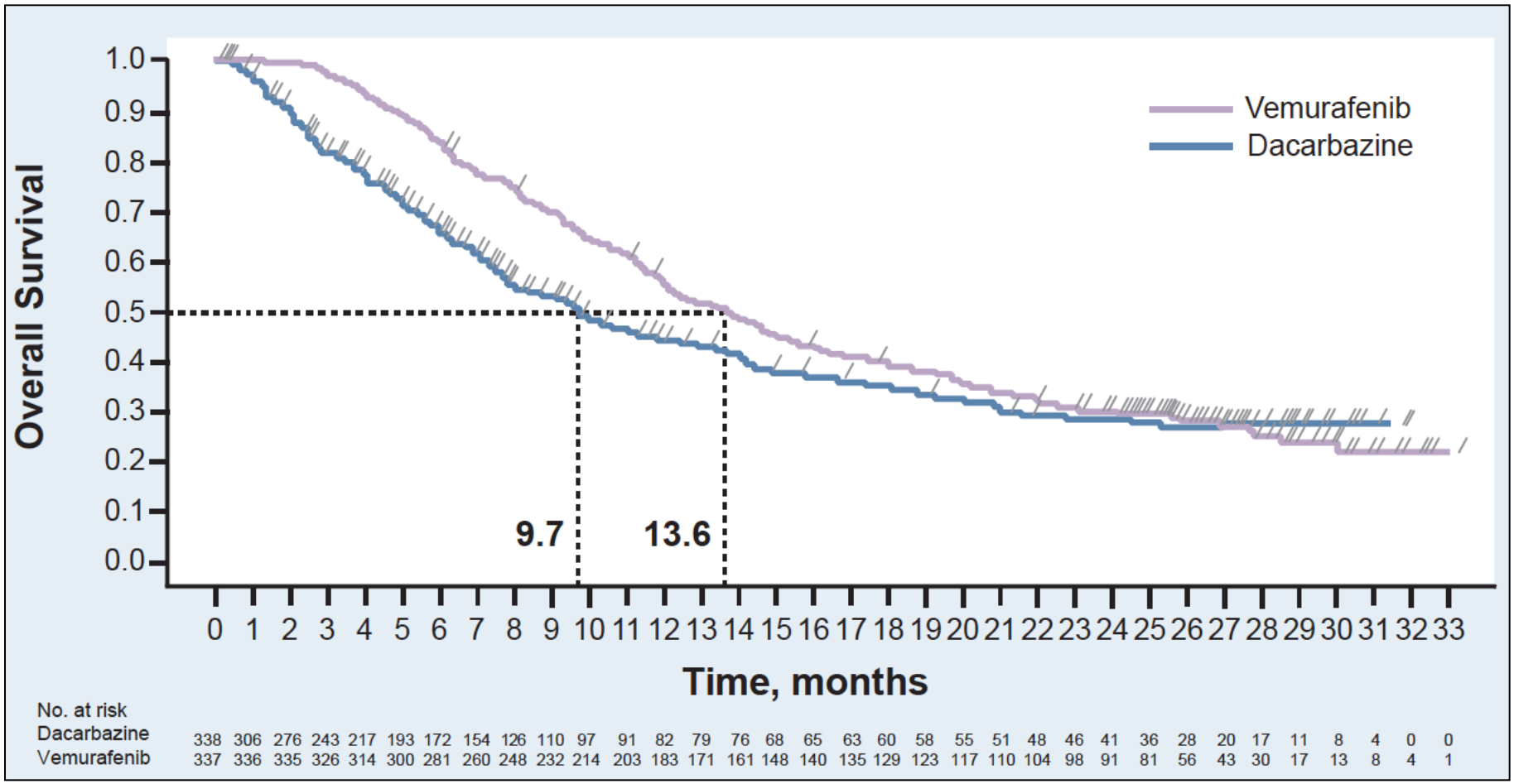
Secondary objectives

- BORR, DOR, TTF, safety

*Determined by cobas® 4800 *BRAF*^{V600} Mutation Test
BID = twice daily; BORR = best overall response rate; DOR = duration of response; IV = intravenous; OS = overall survival; PFS = progression-free survival; TTF = time to treatment failure.

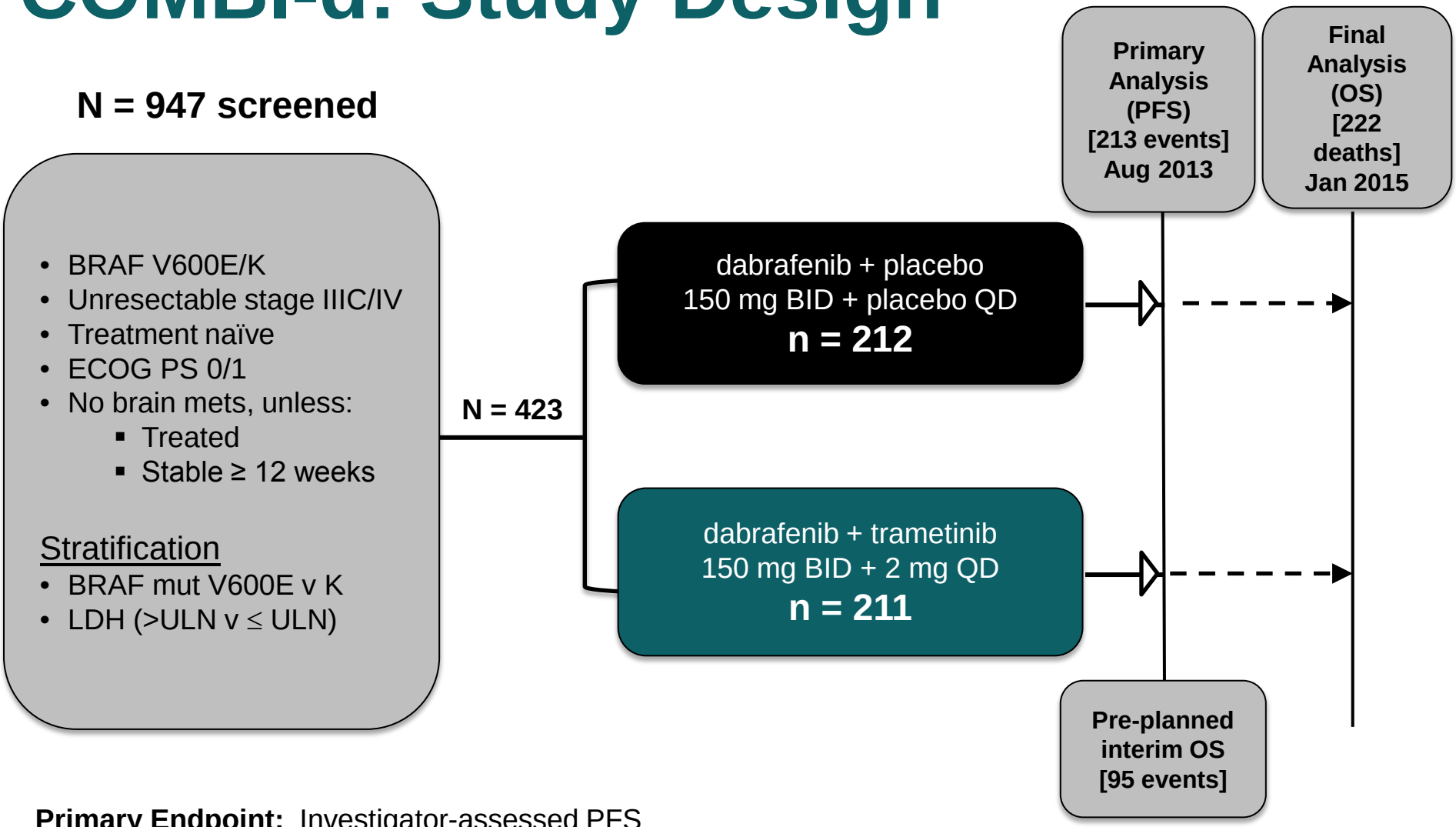
1. Chapman PB, *et al. N Engl J Med* 2011;364:2507–16.
2. NCT01006980. www.clinicaltrials.gov (last accessed July 8, 2013).

Overall Survival (December 30, 2012 Cut-off) Censored At Crossover[1]



1. Presented by Alex Hauschild as a poster at SMR 2013. Vemurafenib Improves Overall Survival Compared With Dacarbazine in Advanced BRAFV600-Mutated Melanoma: Updated Results From a Phase 3 Randomized, Multicenter Trial.

COMBI-d: Study Design

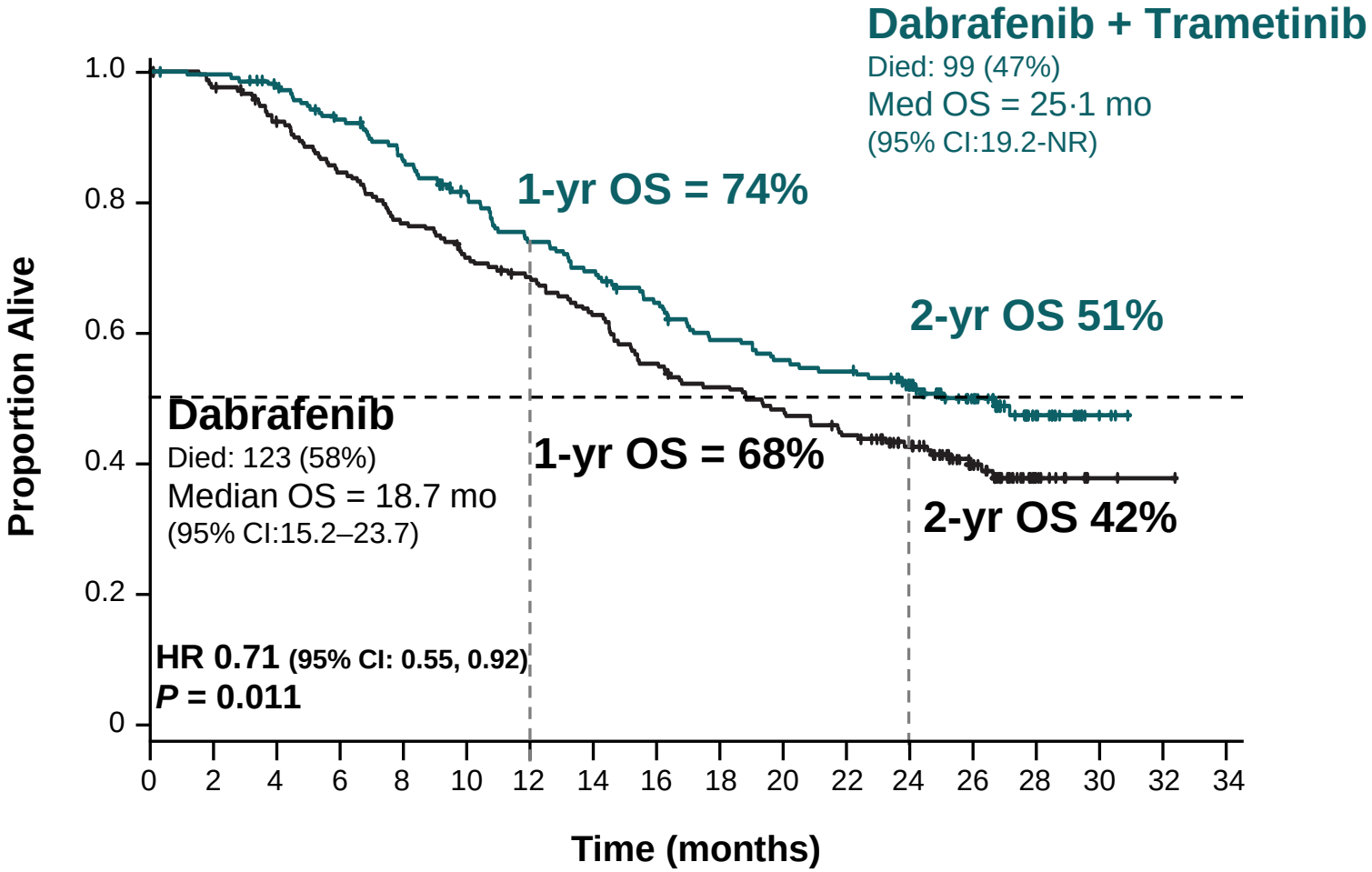


Primary Endpoint: Investigator-assessed PFS

Secondary Endpoints: OS, overall response rate (ORR), duration of response, safety

Long GV, et al. *Lancet* epub 31 May 2015.

COMBI-d: Overall Survival



Number at risk

Dabrafenib + trametinib	211	208	200	187	174	159	144	135	124	112	106	103	88	53	21	3	0	0
Dabrafenib + placebo	212	206	191	175	159	147	138	127	111	104	95	88	70	42	10	2	1	0

Dabrafenib+Trametinib med follow up 20 mo (range 0-30 mo); Dabrafenib med follow up 16 mo (range 0-32 mo).

Long GV, et al. *Lancet* epub 31 May 2015.

COMBI-v: Most common AEs by grade
≥20% of patients (all grades)

Preferred term, n (%)	Dabrafenib + trametinib (n=350)*			Vemurafenib (n=349)*		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Any event	343 (98)	167 (48)	16 (5)	345 (99)	198 (57)	23 (7)
Pyrexia	184 (53)	15 (4)	0	73 (21)	2 (<1)	0
Nausea	121 (35)	1 (<1)	0	125 (36)	2 (<1)	0
Diarrhoea	112 (32)	4 (1)	0	131 (38)	1 (<1)	0
Chills	110 (31)	3 (<1)	0	27 (8)	0	0
Fatigue	101 (29)	4 (1)	0	115 (33)	6 (2)	0
Headache	101 (29)	3 (<1)	1 (<1)	77 (22)	2 (<1)	0
Vomiting	101 (29)	4 (1)	0	53 (15)	3 (<1)	0
Hypertension	92 (26)	48 (14)	0	84 (24)	32 (9)	1 (<1)
Arthralgia	84 (24)	3 (<1)	0	178 (51)	15 (4)	0
Rash	76 (22)	4 (1)	0	149 (43)	30 (9)	0
Pruritus	30 (9)	0	0	75 (21)	3 (<1)	0
Alopecia	20 (6)	0	0	137 (39)	1 (<1)	0
Hyperkeratosis	15 (4)	0	0	86 (25)	2 (<1)	0
Photosensitivity	13 (4)	0	0	78 (22)	1 (<1)	0
Skin papilloma	6 (2)	0	0	80 (23)	2 (<1)	0

***Two subjects (dabrafenib + trametinib) and three subjects (vemurafenib) were excluded from safety population because they were randomised but not dosed.**

Robert C, et al. N Engl J Med 2015;372:30–9; Robert C, et al. Oral presentation at ESMO 2014, Abstract LBA4_PR

COMBI-v: BRAFi- or MEKi-related AEs

Preferred term, n (%)	Dabrafenib + trametinib n=350	Vemurafenib n=349
BRAF inhibitor-related adverse events*		
Pyrexia	184 (53)	73 (21)
cuSCC + KA	5 (1)	63 (18)
Hyperkeratosis	15 (4)	86 (25)
Skin papilloma	6 (2)	80 (23)
Hand-foot syndrome†	14 (4)	87 (25)
Alopecia	20 (6)	137 (39)
Photosensitivity and sunburn	15 (4)	124 (36)
Non-cutaneous malignancies	3 (<1)	2 (<1)
New primary melanoma	2 (<1)	7 (2)
MEK inhibitor-related adverse events#		
Diarrhoea	112 (32)	131 (38)
Hypertension	92 (26)	84 (24)
Acneiform rash	22 (6)	20 (6)
Ejection fraction decrease	29 (8)	0 (0)
Chorioretinopathy	2 (<1)	1 (<1)

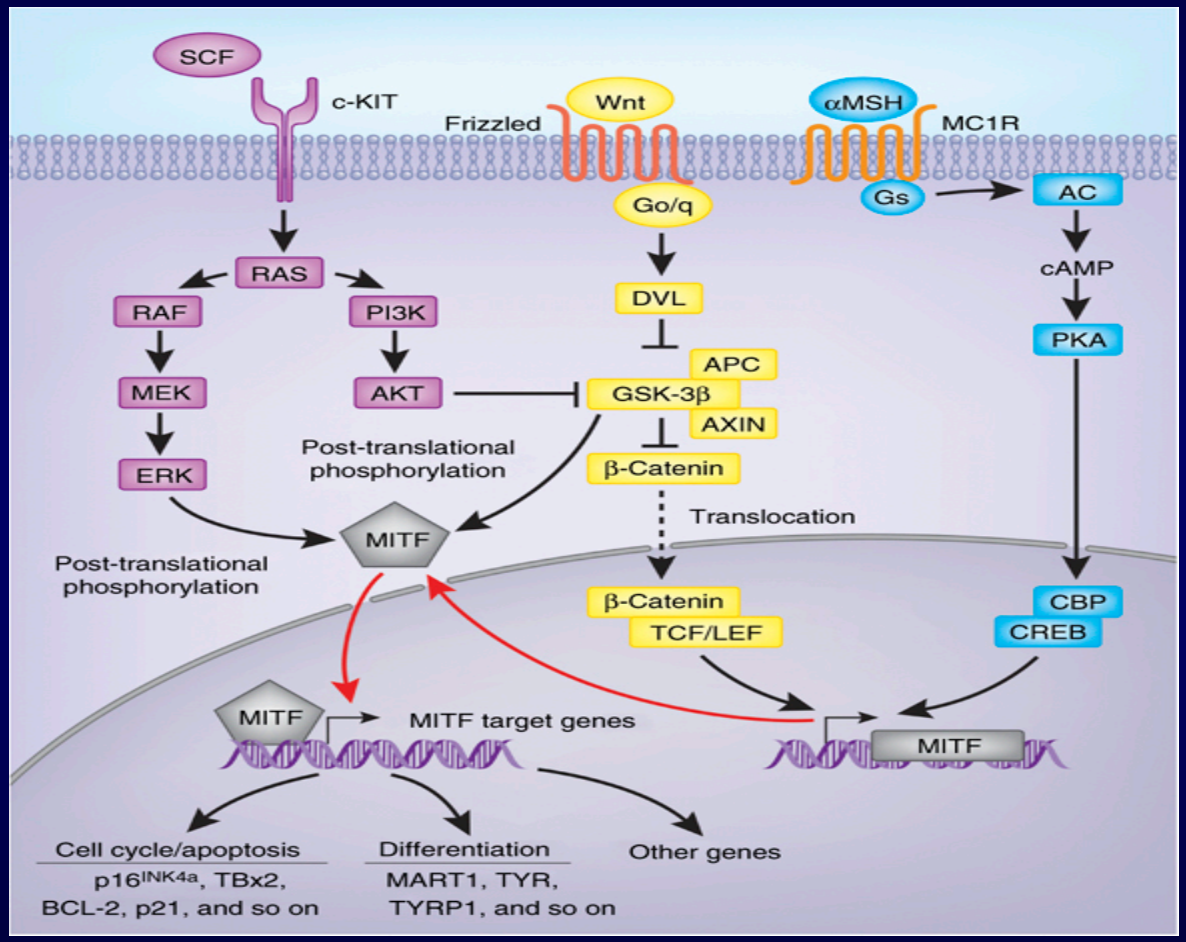
*AEs indicated are those typically associated with BRAF inhibitors; †Hand–foot syndrome includes PPE and palmoplantar keratoderma. # AE's indicated are those typically associated with MEK inhibitors
CuSCC=cutaneous squamous cell carcinoma; KA=keratoacanthoma.
Robert C, *et al.* Oral presentation at ESMO 2014, Abstract LBA4_PR.

BRAF/MEK inhbitor toxicity

- Manufacturer prescribing information contains toxicity management info
- Typical strategies:
  - Supportive care
  - Dose interruption and subsequent reduction
  - Steroids
- Rechallenge is often possible, but in some cases should not be attempted
  - Eg, ILD, some grade 3-4 toxicities
- In some cases, one drug can be continued but not the other
  - Eg, discontinuation of MEK inhibitor but possible continuation of BRAF inhibitor if significant EF decrease or symptomatic CHF

Targeted Therapies: KIT inhibition

c-KIT Mutation in Melanoma



Journal of Investigative Dermatology (2008) **128**, 2575–2595

KIT inhibition

- KIT mutation seems to be more relevant than KIT amplification
- Melanoma phenotypic subtypes most likely to demonstrate KIT mutation are:
  - Mucosal (1.5% overall incidence; 15-40% mutation incidence)
  - Acral (2-3% incidence; 10-35% mutation incidence)
  - Chronically sun-damaged (high incidence; 15% mutation incidence)
- There are no phase 3 studies
- While KIT inhibitor therapy use is accepted in KIT-mutated tumors, its use would be considered off-label

Garido et al. Journal of Investigative Dermatology (2010) 130, 20–27

KIT inhibition

- Response rates vary from 15-40%
- Responses may be more likely in patients whose tumors have particular KIT mutations
  - Eg, mutations in exons 11, 13, and 17
- Median PFS tends to be just a few months, but may be longer in responding patients
- If the best means of identifying suitable patients can be determined, a randomized trial is needed

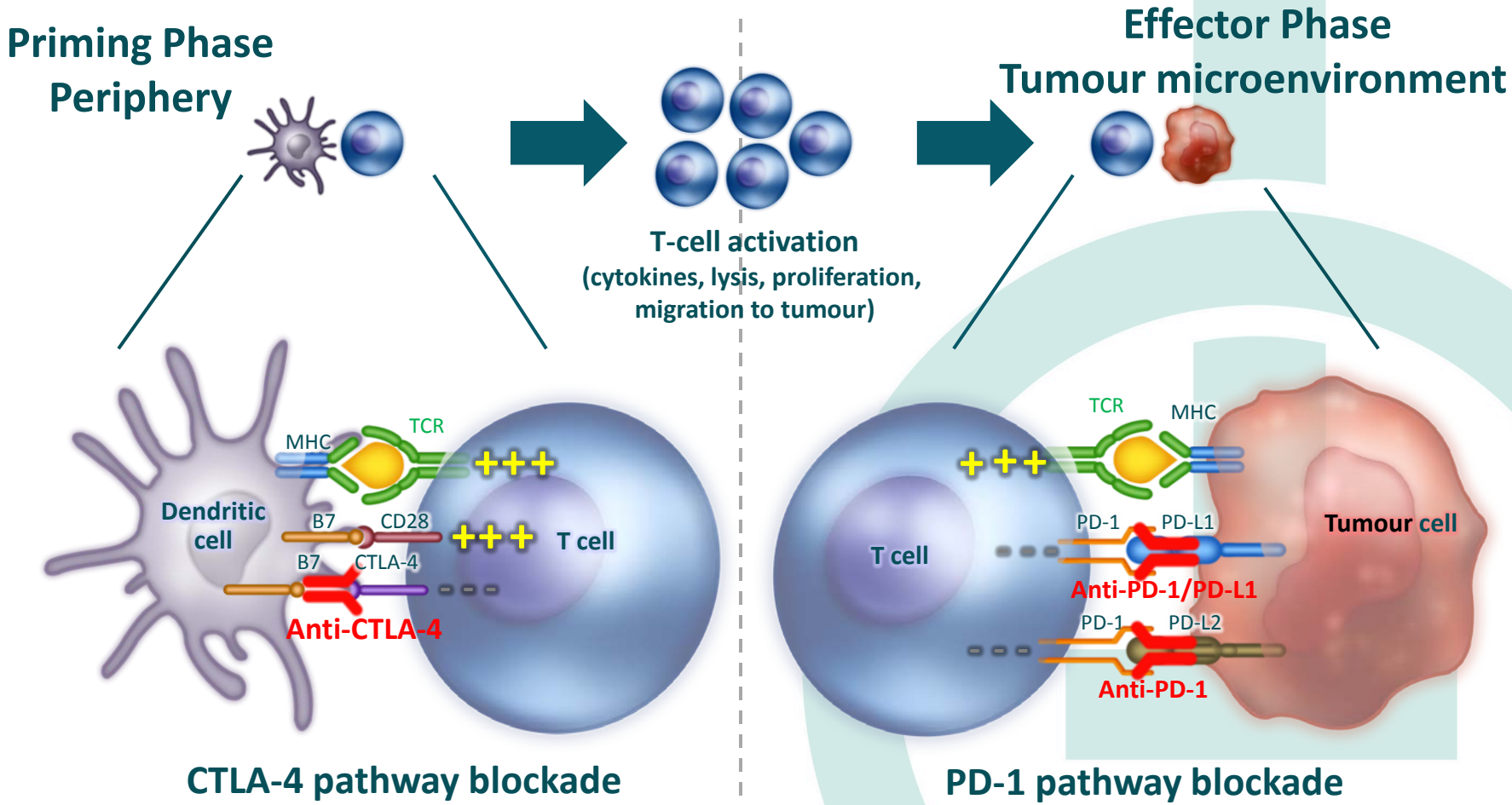
Garido et al. Journal of Investigative Dermatology (2010) 130, 20–27

Checkpoint Inhibitors

Checkpoint Inhibitors

- Currently two classes:
  - Anti-CTLA-4 antibodies
  - Anti-PD-1 antibodies

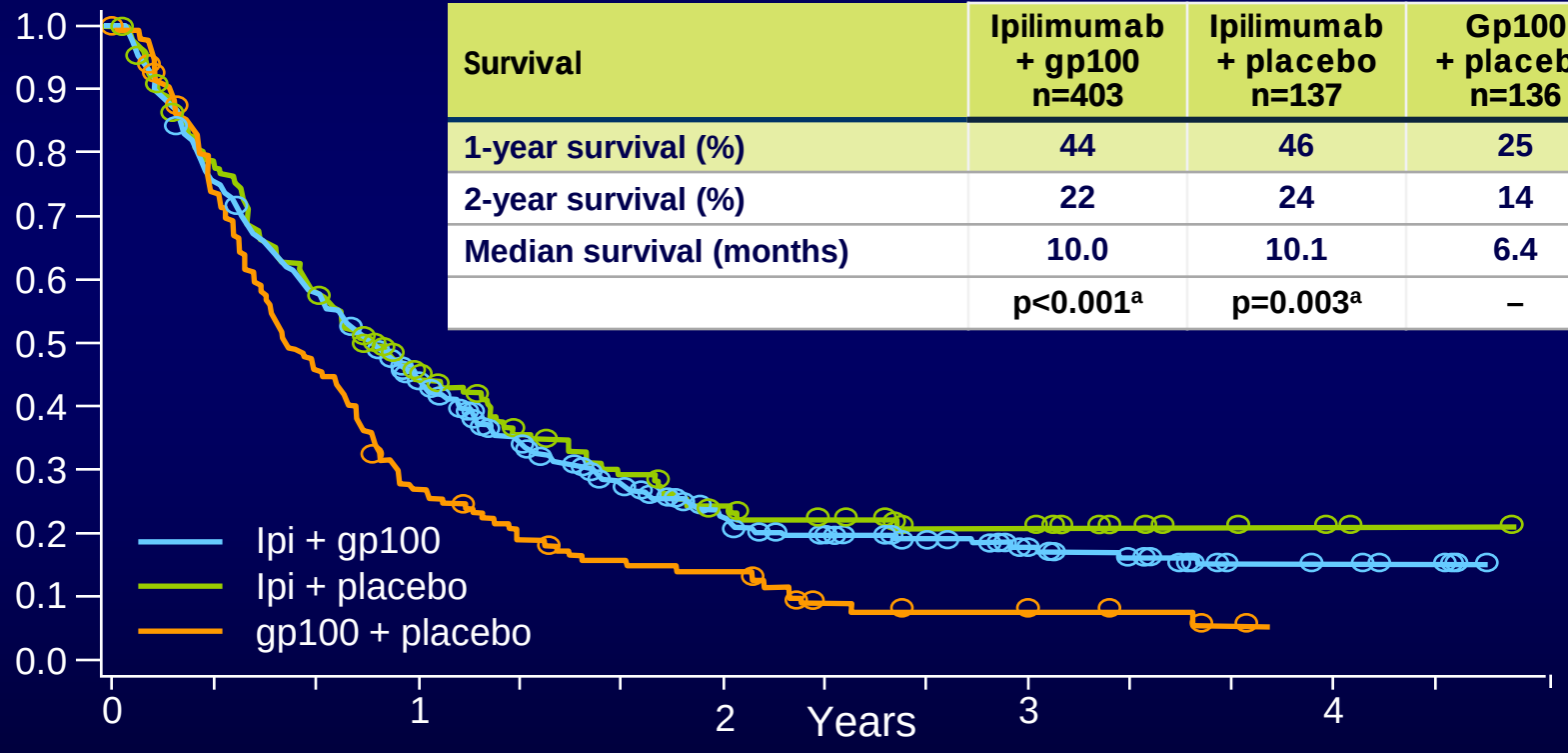
Immuno-oncology: Blocking CTLA-4 and PD-1 Pathways with Monoclonal Antibodies



CTLA-4=cytotoxic T-lymphocyte antigen-4; PD-1=programmed cell death 1; PD-L1/2=PD ligand 1/2; TCR=T cell receptor.
Adapted from Wolchock J, *et al*. Oral presentation at ASCO 2013 (Abstract 9012).

MDX-020: Pivotal Phase III Trial

First phase III trial to demonstrate
overall survival advantage in metastatic melanoma



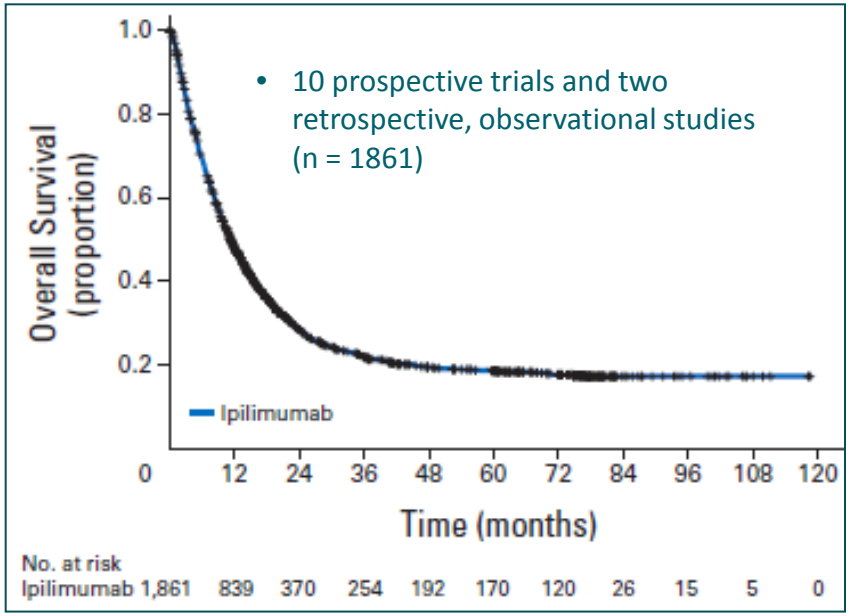
Survival	Ipilimumab + gp100 n=403	Ipilimumab + placebo n=137	Gp100 + placebo n=136
1-year survival (%)	44	46	25
2-year survival (%)	22	24	14
Median survival (months)	10.0	10.1	6.4
	p<0.001[a]	p=0.003[a]	–

Overall Survival was the Primary Endpoint in this Trial

Hodi FS, et al: *N Engl J Med* 2010; 363(8):711-723/BMS
Also presented at ASCO 2010 (Plenary Session, Abstract #4).

Long-Term Survival with Ipilimumab in Melanoma

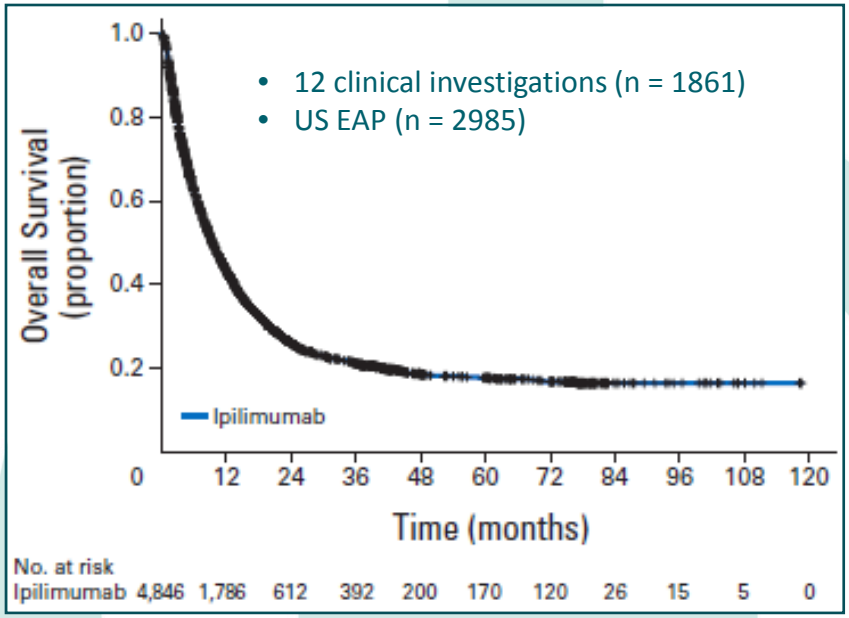
Pooled Analysis: Phase III and Phase II Trials



Median OS: 11.4 months
(95% CI, 10.7-12.1 months)

3-year survival rate: 22%
(95% CI, 20% to 24%)

Pooled Analysis: Phase III, Phase II Trials and EAP

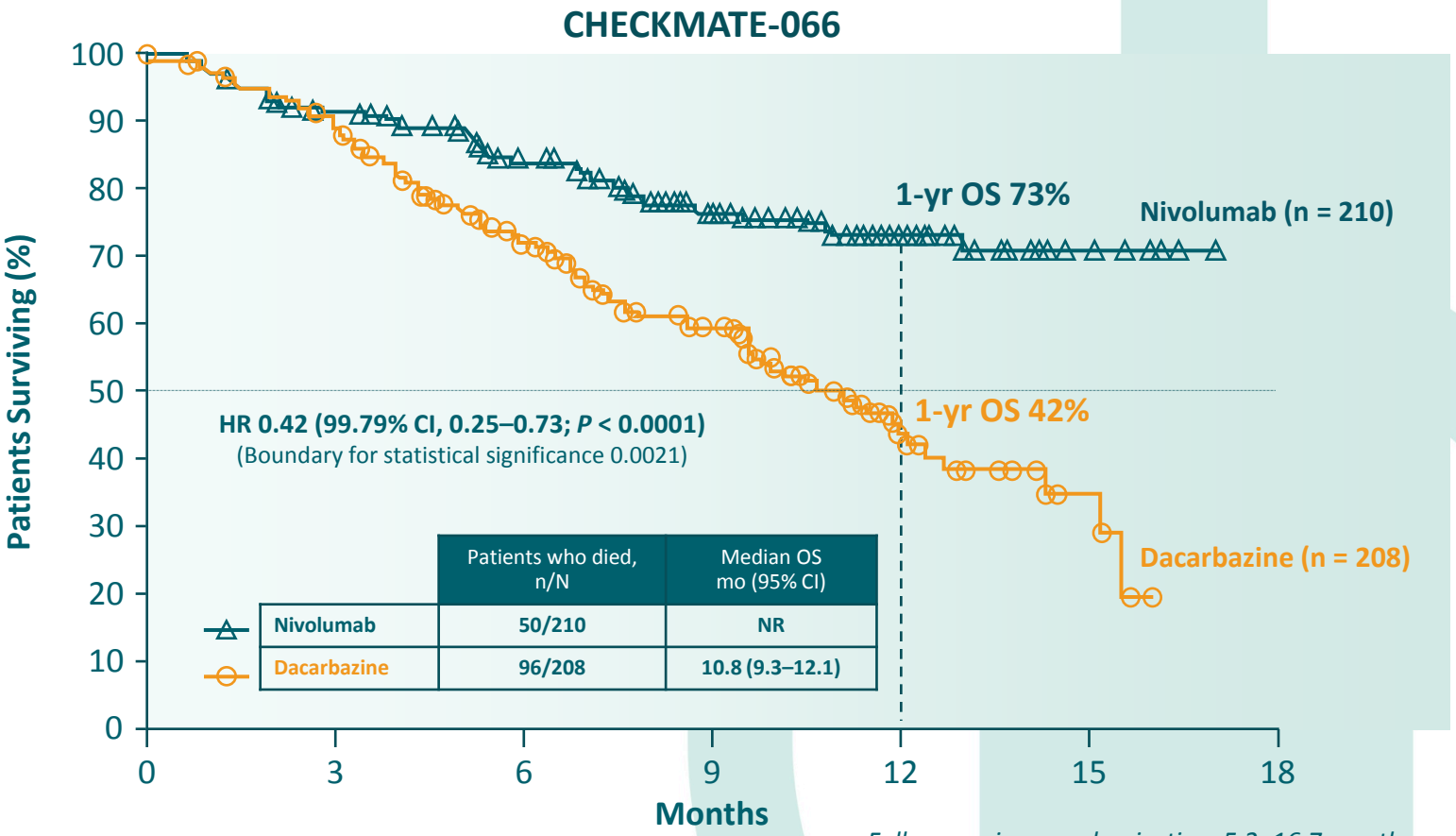


Median OS: 9.5 months
(95% CI, 9.0-10.0 months)

3-year survival rate: 21%
(95% CI, 20% to 22%)

Schadendorf D, *et al.* J Clin Oncol. 2015 Feb 9.

Nivolumab Improved Overall Survival vs. Dacarbazine in Melanoma



Follow-up since randomization: 5.2–16.7 months.

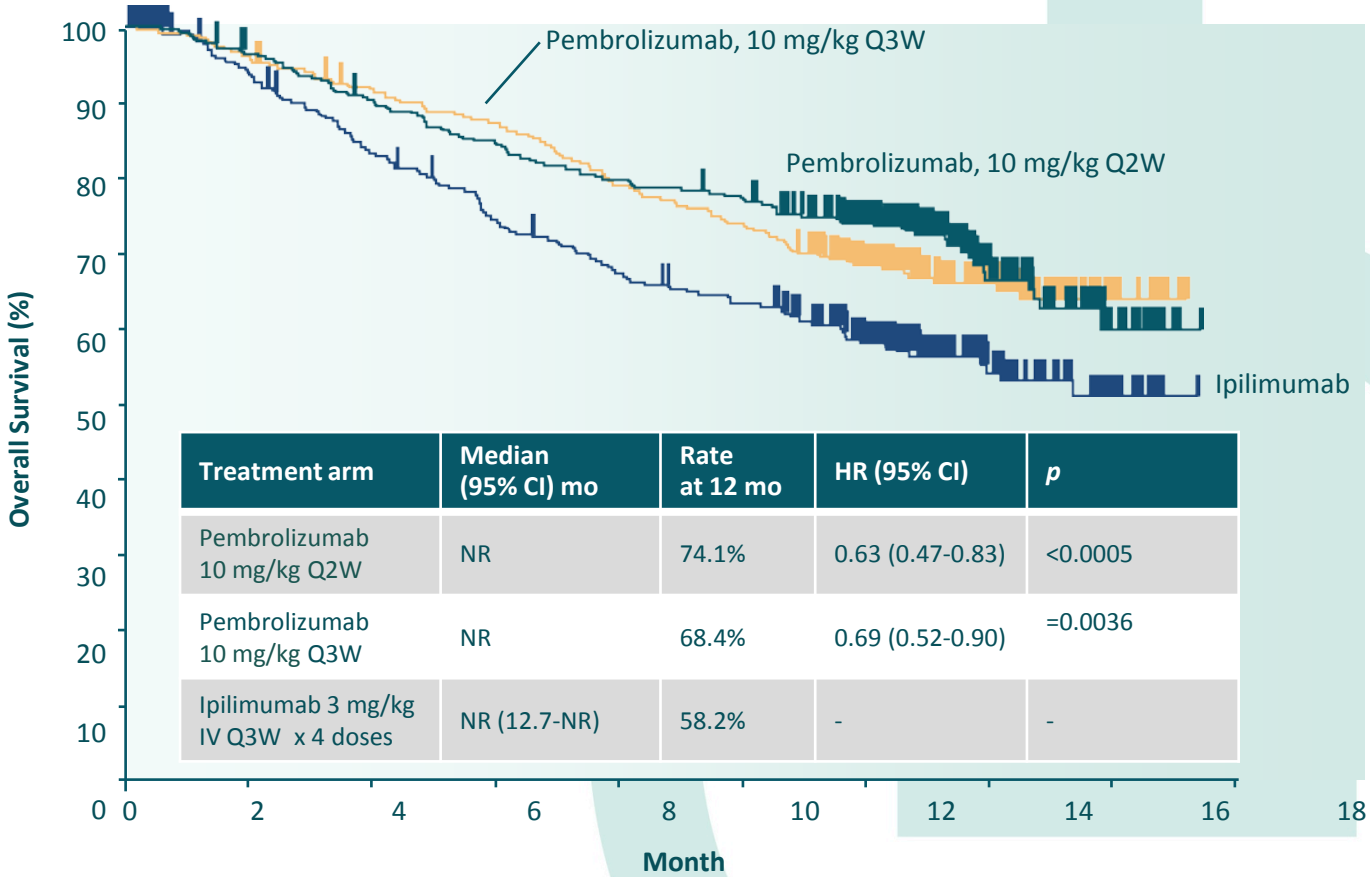
Patients at Risk

Nivolumab	210	185	150	105	45	8	0
Dacarbazine	208	177	123	82	22	3	0

NR = not reached.
Based on 5 August 2014 database lock.

Robert C *et al*. *N Engl J Med*. 2015 Jan 22;372(4):320-30

Pembrolizumab Showed Improved OS (RECIST v1.1) vs. Ipilimumab in Melanoma



Treatment arm	Median (95% CI) mo	Rate at 12 mo	HR (95% CI)	*p*
Pembrolizumab 10 mg/kg Q2W	NR	74.1%	0.63 (0.47-0.83)	<0.0005
Pembrolizumab 10 mg/kg Q3W	NR	68.4%	0.69 (0.52-0.90)	=0.0036
Ipilimumab 3 mg/kg IV Q3W x 4 doses	NR (12.7-NR)	58.2%	-	-

No. at Risk

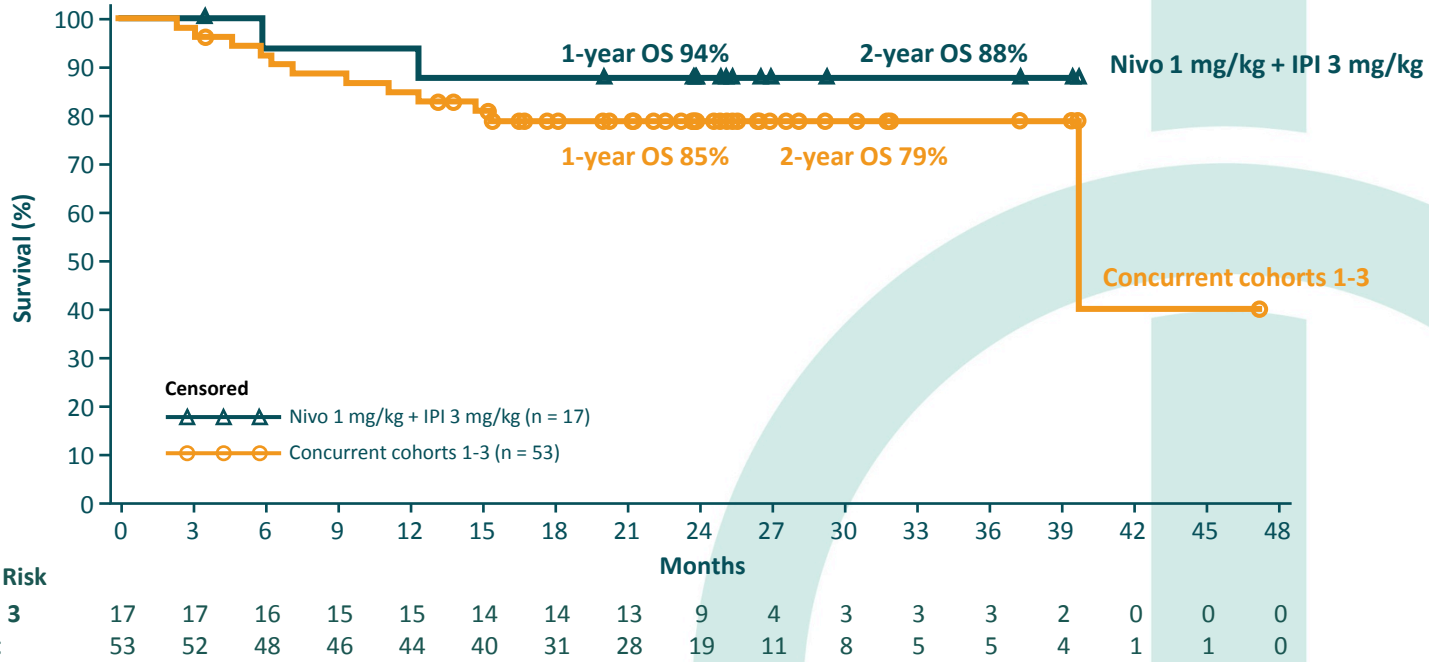
Pembrolizumab, Q2W	279	266	248	233	219	212	177	67	19	0
Pembrolizumab, Q3W	277	266	251	238	215	202	158	71	18	0
Ipilimumab	278	242	212	188	169	157	117	51	17	0

NR=not reached

Robert C, *et al. N Engl J Med* 2015; Apr 19. [Epub ahead of print].

Nivolumab Plus Ipilimumab in a Concurrent Regimen in Patients with Advanced Melanoma Showed 79-88% OS at 2 Years

Nivolumab 1 mg/kg Q3W×4 and ipilimumab 3 mg/kg Q3W×4, followed by nivolumab 3 mg/kg Q2W regimen selected for further evaluation



Patients at Risk																
Nivo 1 + IPI 3	17	17	16	15	15	14	14	13	9	4	3	3	3	2	0	0	0
Concurrent	53	52	48	46	44	40	31	28	19	11	8	5	5	4	1	1	0

- Data from a phase 1 trial (CA209-004) of nivolumab plus ipilimumab on a concurrent or sequenced regimen[1]
- 62% of patients had grade 3/4 AEs on the concurrent regimen; there were no new safety signals and most events were manageable using standard protocols[1]
- Historical 1-year survival rates with ipilimumab and nivolumab monotherapy in patients with advanced melanoma were 45.6% (phase 3)[2] and 62% (phase 1), respectively[3,a]

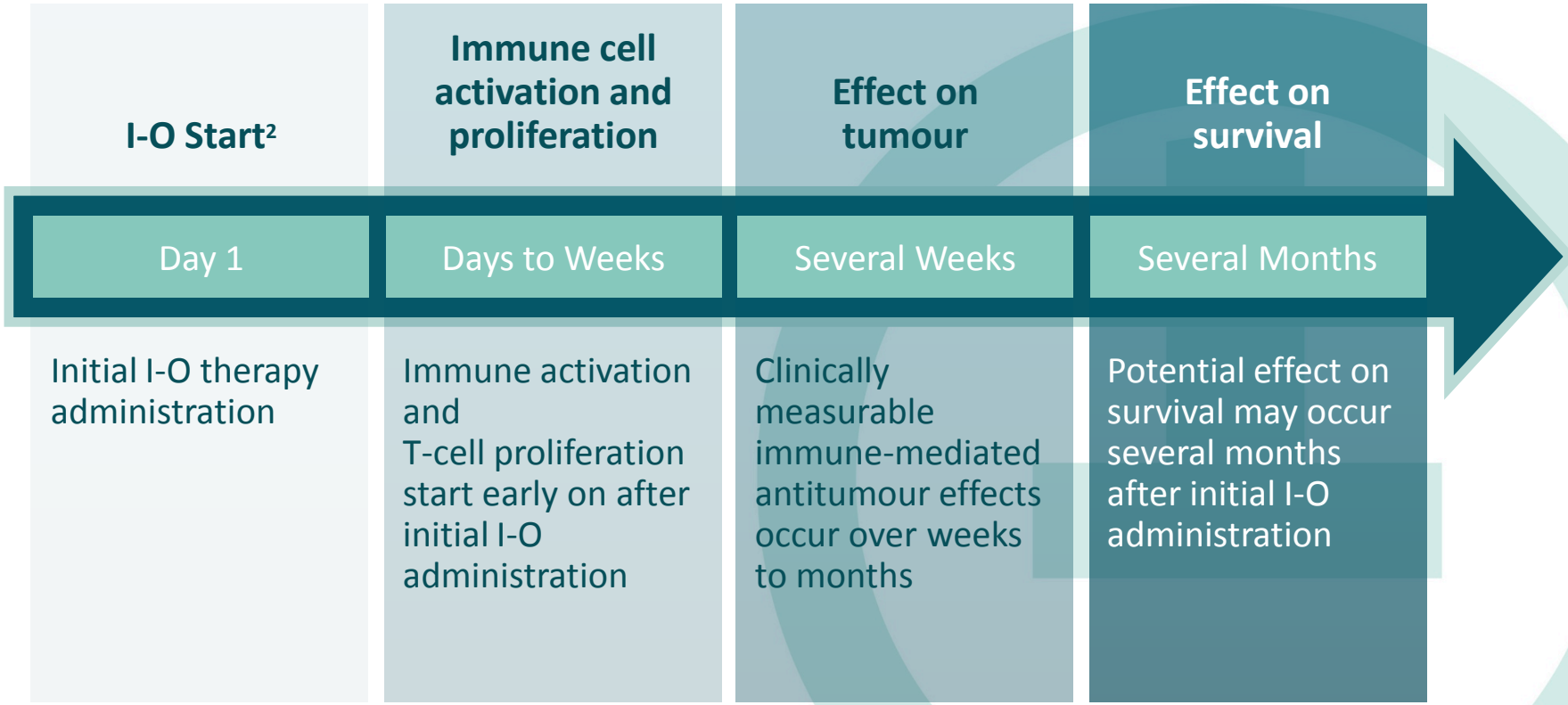
[a]Data from separate, noncomparative trials; use cross-trial comparisons with caution in the absence of data from a randomized, comparative trial.
Q3W, every 3 weeks.

1. Adapted from Sznol M, *et al*. Presented at: ASCO 2014. Oral presentation 9003. 2. Hodi FS, et al. *N Engl J Med*. 2010;363:711-723.
3. Sznol M, *et al. J Clin Oncol.* 2013;31(suppl):abstract CRA9006.

Checkpoint Inhibitor Response Patterns

Response to I-O Therapy is a Multi-step Process that May Impact Response Kinetics

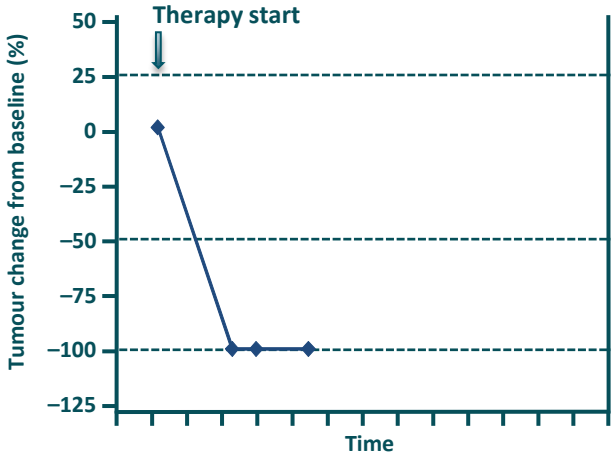
Therapies that affect the immune system may not induce a measurable impact on tumour growth immediately after administration[1]



1. Hoos A, Britten CM. *OncoImmunology*. 2012;1:334-339; 2. Hoos A, *et al*. *J Natl Cancer Inst*. 2010;102:1388-1397.

Potential Tumour Response Patterns to Therapy

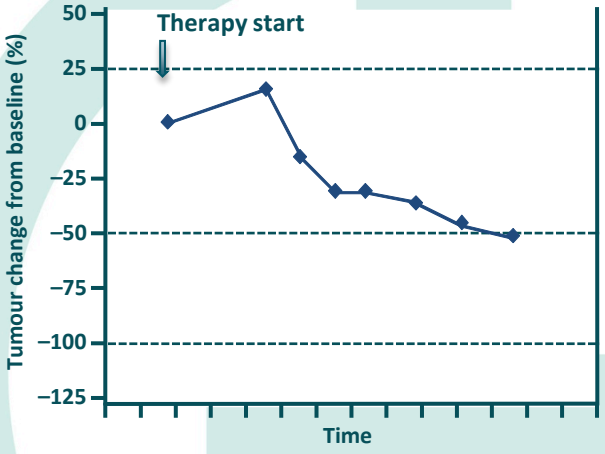
Response in baseline lesions typically seen with chemotherapy, but also I-O therapies and targeted therapies. Captured by existing RECIST and WHO criteria



----- Thresholds for response or progressive disease (RECIST)

Graphs for illustrative purposes showing responses to ipilimumab in advanced melanoma

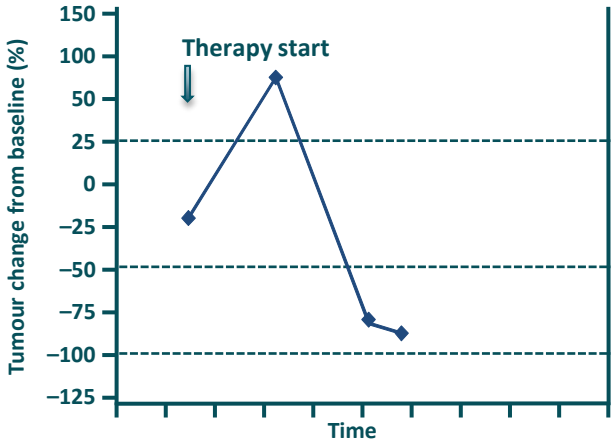
"Stable disease": Slow, steady decline in tumour volume seen with chemotherapy, targeted and I-O therapies. Captured by existing RECIST and WHO criteria



Adapted from Wolchok JD, *et al*. *Clin Cancer Res* 2009;15:7412–7420; Hoos A, *et al*. *Annals of Oncology* 2012;23(suppl 8): viii47–viii52.

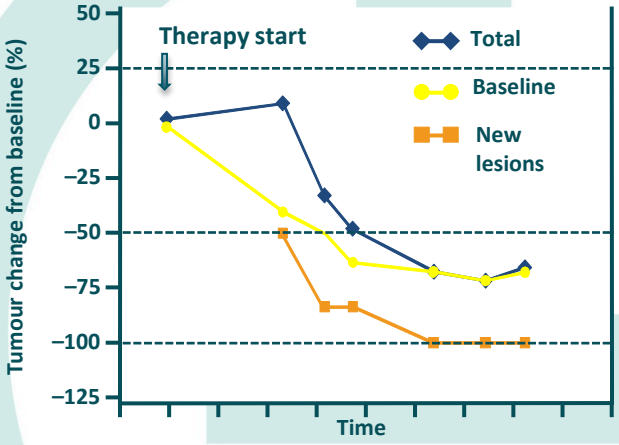
Potential Tumour Response Patterns to Therapy

Response after initial increase in tumour volume; novel and specific to I-O therapy RECIST or WHO criteria may not be appropriate to assess



Some vaccines may not follow similar patterns of response as other I-O therapies

Reduction in tumour burden after appearance of new lesions; novel and specific to I-O therapy, RECIST or WHO criteria may not be appropriate to assess



Adapted from Wolchok JD, *et al*. *Clin Cancer Res* 2009;15:7412–7420; Hoos A, *et al*. *Annals of Oncology* 2012;23(suppl 8): viii47–viii52.

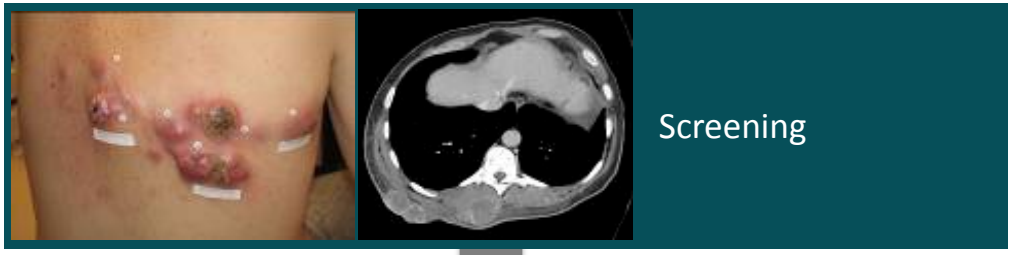
Pseudo-progression: Inflammation Causes Swelling, May Appear as Tumour Growth or New Lesions Upon Imaging[1]

Considerations when evaluating true progression vs. pseudo-progression

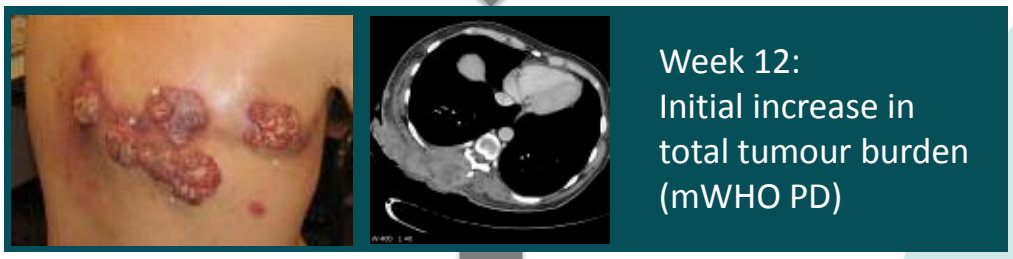
	May indicate progression	May indicate pseudo-progression
Performance status	Deterioration of performance	Remains stable or improves
Systemic symptoms	Worsen	May or may not improve
Symptoms of tumour enlargement	Present	May or may not be present
Tumour burden **Baseline** **New lesions**	Increase Appear and increase in size	Increase followed by response Appear then remain stable and/or subsequently respond
Biopsy may reveal	Evidence of tumour growth	Evidence of T-cell infiltration

1. Wolchok JD, *et al*. *Clin Cancer Res*. 2009;15:7412-7420; 2. Topalian SL, *et al. N Engl J Med*. 2012;366:2443-2354;
3. Eisenhauer EA, *et al*. *Eur J Cancer*. 2009;45:228-247; 4. Chow LQ. Am Soc Clin Oncol Educ Book. 2013:280-285;
5. American Cancer Society. Lung Cancer. http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-diagnosis. Accessed September 30, 2013.

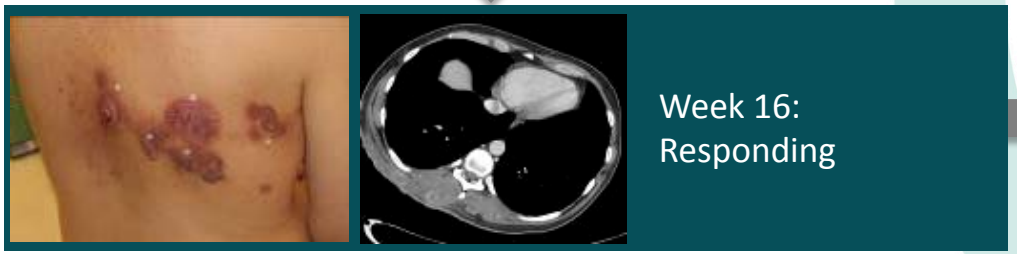
Example of Evolution of Response to CTLA-4 Inhibition



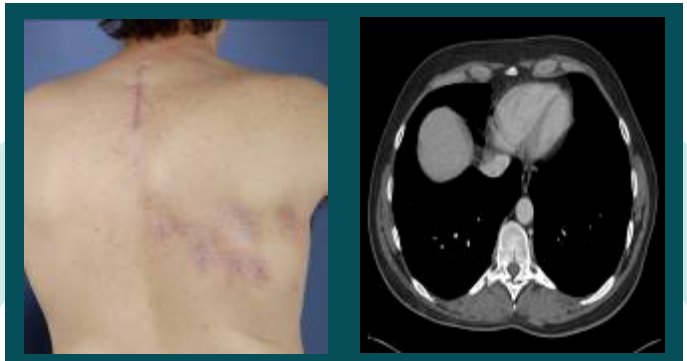
Screening



Week 12:
Initial increase in total tumour burden (mWHO PD)



Week 16:
Responding



Week 96:
Durable and ongoing response without signs of irAEs

irAE = immune-realted adverse events

Harmankaya K, *et al.* Presented at the World Meeting of Interdisciplinary Melanoma/Skin Cancer Centers: November 19 - 21, 2009; Berlin, Germany.

Checkpoint Inhibitor Toxicity

Key Considerations on Management of Immune-related Events

Result from enhanced or excessive immune activity

Early diagnosis and appropriate management is essential

Health care team and patient education for early recognition

Delayed irAEs may occur

Can be severe or life-threatening, may involve various organs

Multidisciplinary team approach is required for optimal management

Patients should be instructed to report potential AEs as soon as possible

Unless an alternate etiology has been identified, consider all symptoms and signs as potential irAE

Systemic high-dose corticosteroids* may be required for severe events

*with or without additional immunosuppressive therapy

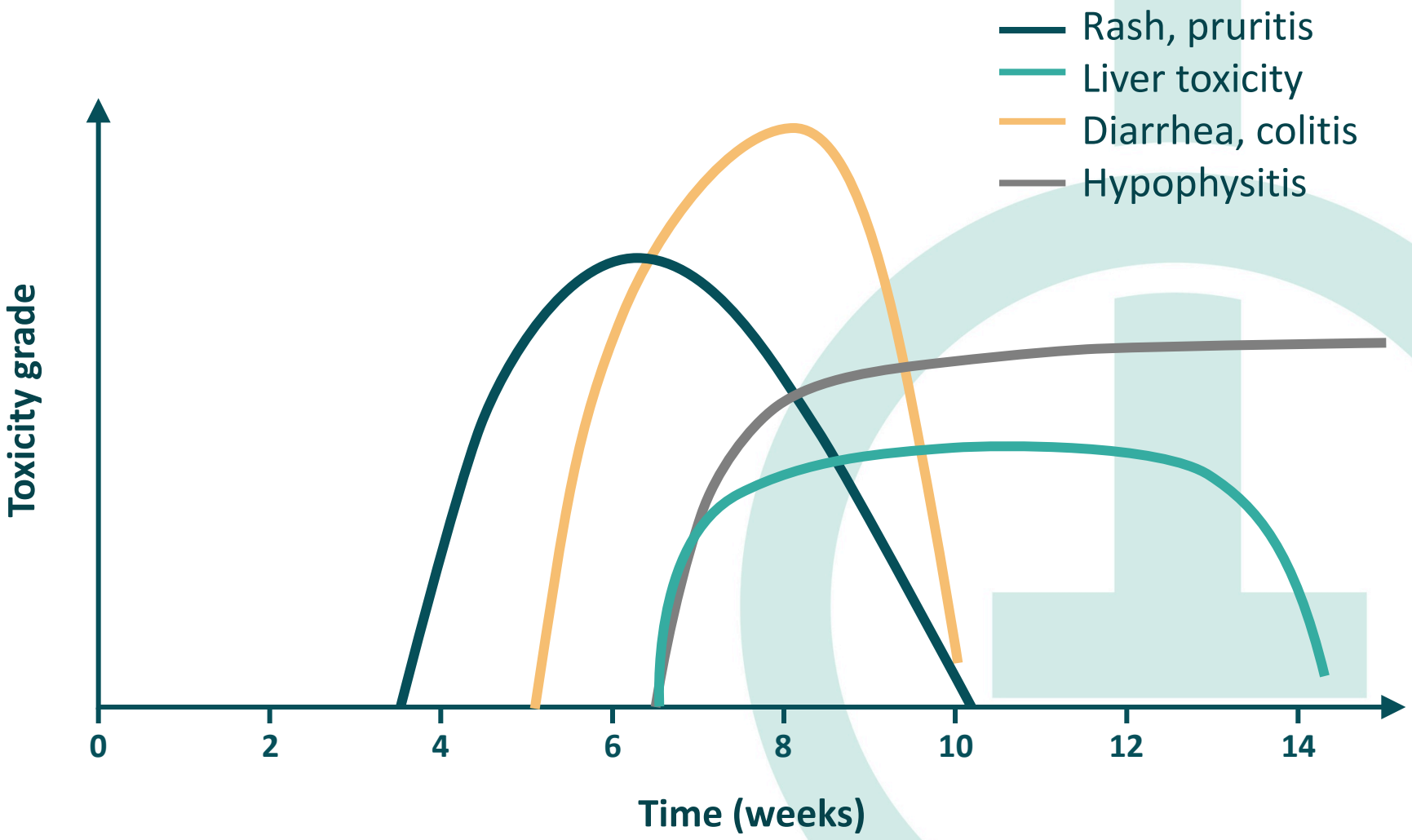
Bristol-Myers Squibb. YERVOY (ipilimumab) Immune-related Adverse Reactions (IrAR) Management Guide and online Tool at https://www.yervoy.co.uk/;
Bristol-Myers Squibb. YERVOY (ipilimumab) SmPC updated July 2013, available at http://www.ema.europa.eu.

Immune Related Adverse Events with Checkpoint Inhibition are Uncommon

Drug	Target	Phase of study	Most frequent toxicities			
				Any grade	Grade 3	Grade 4
Ipilimumab	CTLA-4	I, II, III	Gastrointestinal	15.3-35.1%	7.6%	<0.5%
			Dermatologic	43.5%	1.5%	<0.3%
				Any grade	Grade 3-4	
Nivolumab Pembrolizumab MPDL3280A MEDI4736	PD-1 or PD-L1	I, II, III	Rash	9-26%	<1.0%	
			Pruritus	8-24%	0.0 - 1.0%	
			Diarrhoea	8-19%	0.2-2.6%	
			Fatigue	16-36%	1.0-7.0%	
			Pneumonitis	1-5%	0.0-1.0%	
			Headache	7-8%	0.0 - 0.4%	
			Asthenia	5-10%	0.4 – 2.0%	
			Dyspnea	4-7%	0.3 – 7.0%	
			Anemia	2-4%	0.0 – 3.0%	

Hodi FS, et al. N Engl J Med 2010; 363(8):711-23. Ribas A et al., ASCO 2014 oral presentation, J Clin Oncol 32:5s, 2014 (suppl; abstr LBA9000). Topalian S, et al. J Clin Oncol. 2014. Long et al., SMR. 2014; Herbst et al., Nature Volume: 515, Pages:563–567. Larkin J et al., N Engl J Med 2015; ePub ahead of print. May 31, 2015. Robert C et al. *N Engl J Med*. 2015 Jan 22;372(4):320-30. Brahmer J et al. N Engl J Med 2015; ePub ahead of print. June 17, 2015. Paz-Arez L et a., Oral presentation. Presented at ASCO 2015. Spira AI, et al: Presented at ASCO 2015; Oral Presentation. Garon EB et al. N Engl J Med 2015; 372:2018-2028.

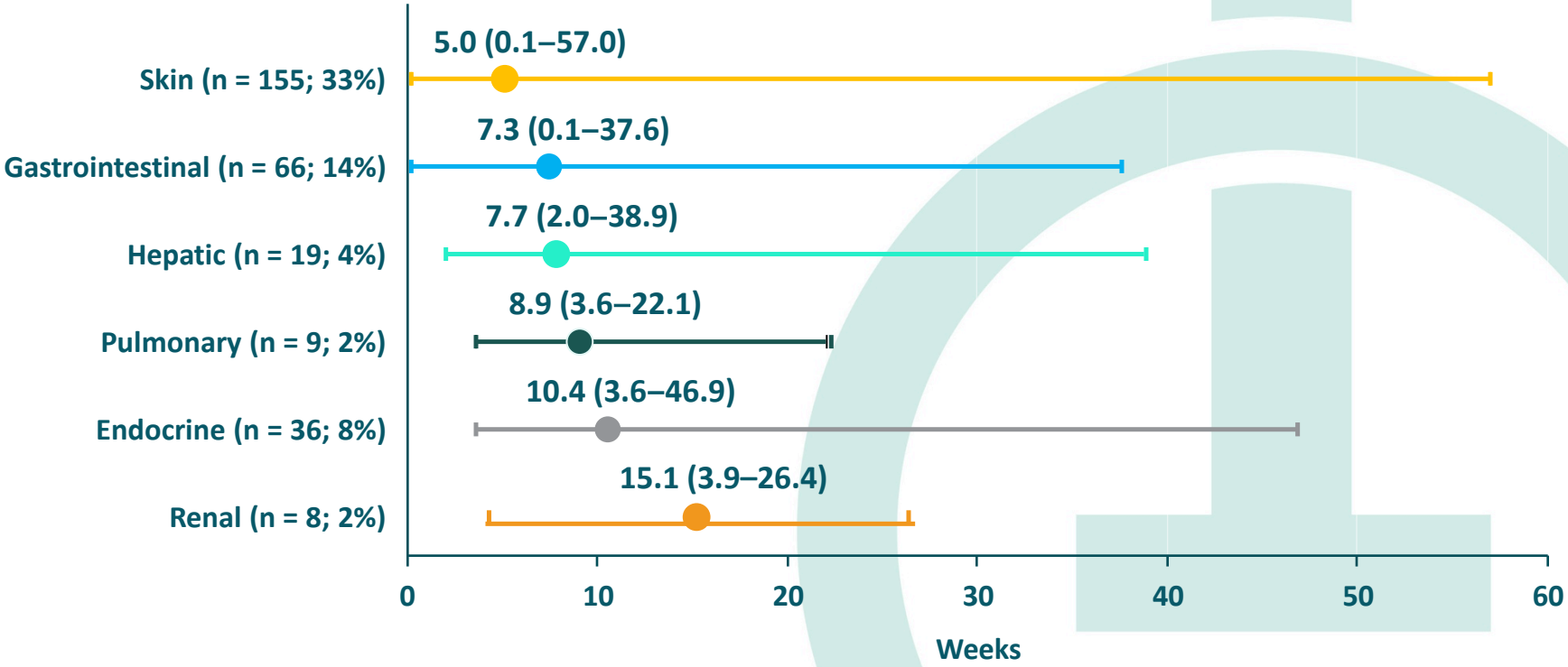
Kinetics of irAEs: Example for Ipilimumab



Weber JS, et al. *J Clin Oncol* 2012; 30(21):2691-7.

Kinetics of irAEs: Example for Nivolumab

Time to onset of select treatment-related AEs (any grade; n = 474)



Median time to onset for treatment-related select AEs ranged from 5.0 weeks for skin AEs to 15.1 weeks for renal AEs

Circles represent median; bars signify ranges. The kinetics of AEs presented on the slide are for melanoma but may not reflect the kinetics of AEs in other tumor types.
Weber JS, et al. Presentation at ASCO 2015.

Stepwise Approach to Using I-O Agents in Clinic

1 BASELINE ASSESSMENT | 2 EDUCATION | **3 MONITORING** | 4 EARLY RECOGNITION | 5 IiAE Management

- Initiate treatment according to prescribing Product Monograph
- Careful ongoing clinical assessment is necessary for early identification of irAEs
- irAEs can be severe or life-threatening if not identified early
- irAEs can occur any time
- Keep in mind that toxicity does not equal response
- Early recognition is key
- Consider all symptoms and signs as potential irAE
- Refer to organ-specific algorithms for the management of irAEs

Stepwise Approach to Using I-O Agents in Clinic

1 BASELINE ASSESSMENT | 2 EDUCATION | 3 MONITORING | 4 EARLY RECOGNITION | **5 irAE Management**

The majority of immune-related AEs are manageable and reversible with drug interruption corticosteroid.

Steroid taper is generally required over at least one month.

Grade	Management	Continue the drug?
Low (gr 1)	Monitor closely	Continue (except for pneumonitis consider delay)
Moderate (gr 2)	Symptomatic management Monitor closely Oral corticosteriods if persistent toxicity	Delay the dose Resume IO drug when AEs resolve to grade ≤ 1 or baseline
High (gr 3-4)	Administer high dose IV Corticosteroids Symptomatic management Monitor closely Involve specialist consultant*	Discontinue I-O Drug permanently (Delay in some situations)

* In the event of grade 3 or 4 toxicity for practitioners in non-tertiary centres, consult with an oncologist or consider transfer to a tertiary centre

GI Adverse Event Algorithm

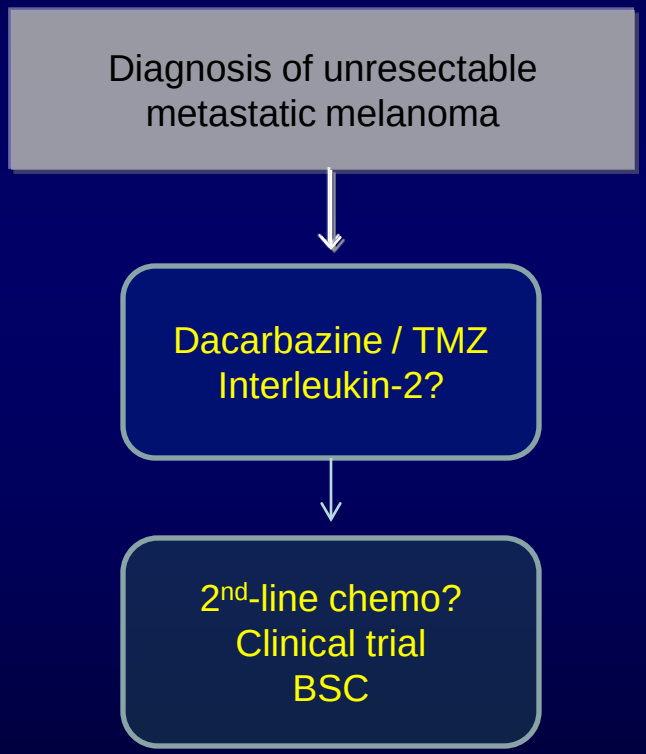
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 **Diarrhea:** < 4 stools/day over baseline; **Colitis:** asymptomatic	• Continue I-O therapy • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately **If worsens**: • Treat as Grade 2 or 3-4
Grade 2 **Diarrhea:** 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; not interfering with ADL **Colitis:** abdominal pain; blood in stool	• Delay I-O therapy • Symptomatic treatment	**If improves to grade 1:** • Resume I-O therapy **If persists > 5-7 days or recurs:** • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy **If worsens or persists > 3-5 days with oral steroids:** • Treat as Grade 3-4
Grade 3-4 **Diarrhea (G3):** ≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 hrs; interfering with ADL **Colitis (G3):** severe abdominal pain, medical intervention indicated, peritoneal signs **G4:** life-threatening, perforation	• Discontinue I-O therapy • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	**If improves:** • Continue steroids until Grade 1, then taper over at least 1 month **If persists > 3-5 days, or recurs after improvement:** • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis.

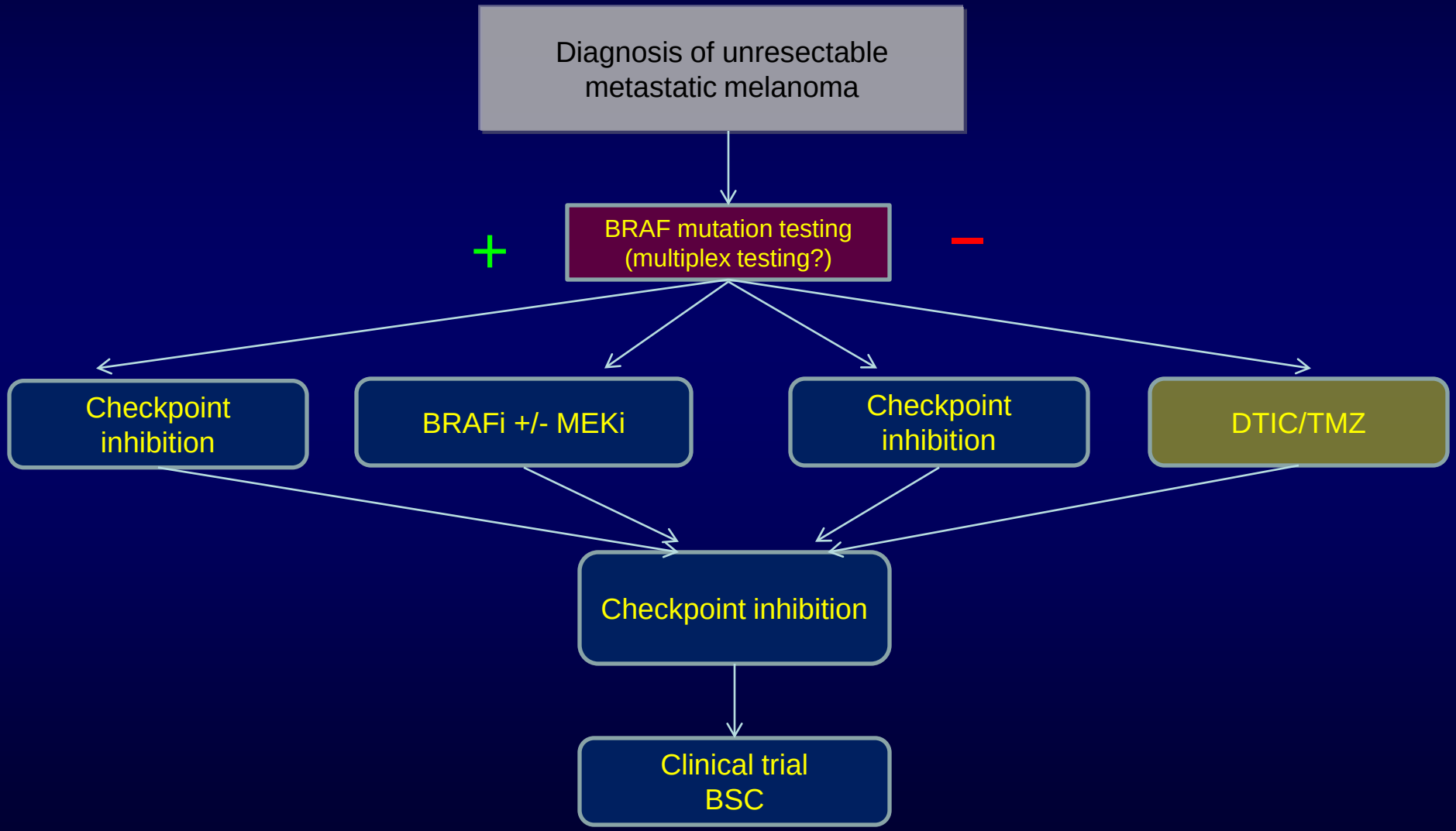
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Summary

Metastatic Melanoma: Historically



Metastatic Melanoma: Today



Conclusion

- Many aspects of melanoma management are changing
- New treatments offer substantial improvements over previous options and new hope, but at the potential cost of considerable toxicity
  - Education, monitoring, and early intervention are important
- Future strategies may feature less toxicity

Genetic Testing in Melanoma: Prevalence of Mutations and Testing Recommendations[1]

Melanoma Subtype	Mutations, %					Testing Recommendations	
	BRAF	*NRAS*	*KIT*	*GNAQ/11*	*BAP1*	First Step	Second Step
Cutaneous (non-CSD)	45	15-20	~1	NS	NR	*BRAF* ± *NRAS*	*KIT*
Cutaneous (CSD)	5-30	10-15	2-17	NS	NR	*BRAF* ± *NRAS*	*KIT*
Acral	10-15	10-15	15-20	NS	NR	*BRAF, KIT* ± *NRAS*	NS
Mucosal	5	5-10	15-20	NS	NR	*BRAF, KIT* ± *NRAS*	NS
Uveal	NS	NS	NS	80	50	Gene expression profiling or monosomy 3 determination[a]	NS
From an unknown primary	50	20	NS	NS	NS	*BRAF, NRAS*	*KIT; GNAQ, GNA11,* monosomy 3

[a] Gene expression profiling and monosomy 3 analysis of primary uveal melanomas have been used as prognostic tests for metastatic risk; these tests currently do not have a defined role in patients with metastatic disease.