"Black is the New Black" or "How I learned to stop worrying and love melanoma (with apologies to Dr. Strangelove)"

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Presenter Disclosure

- **Faculty/Speaker: Ralph Wong**

- **Relationships with financial sponsors:**
  - **No conflicts to disclose**

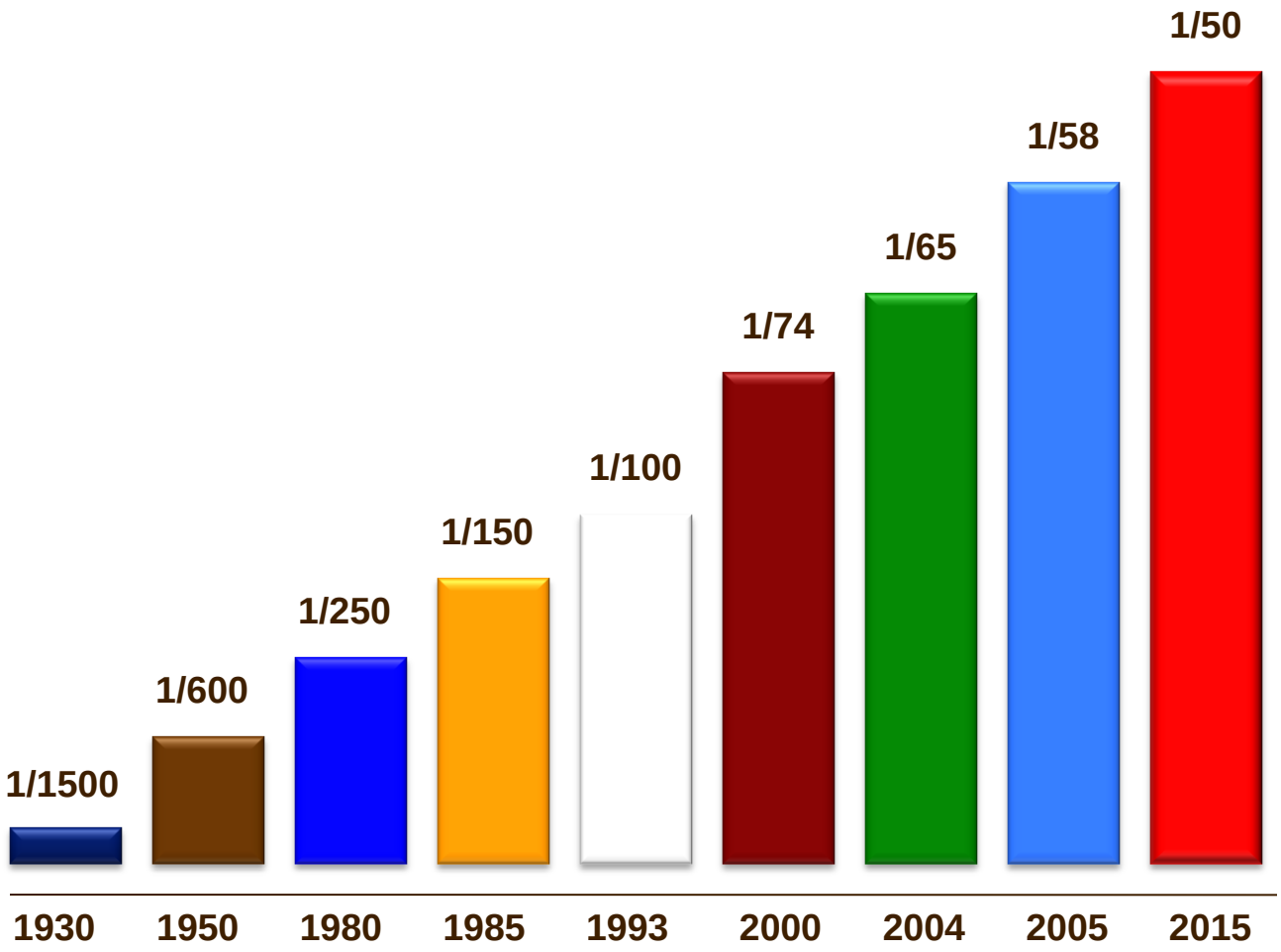
Learning Objectives

- Describe the epidemiology and health care burden of melanoma
- Discuss the overall management of melanoma
- Explain the new Adjuvant therapies that will be used in Canada and how they will impact on the natural history of the disease

Epidemiology

- incidence of melanoma has increased at a rate exceeding all other cancers except lung cancer in women

Lifetime Risk of Developing Melanoma



[a]US Statistics

Rigel DS, et al. CA Cancer J Clin. 2010;60(5):301-316.

Projected Prevalence of Melanoma in Canada

Projected Annual Number of Cutaneous Melanoma Cases in Canada By Province, Gender and Year (2004 to 2031)

Patient-Based Incidence Approach (Low Annual Percent Change Scenario)

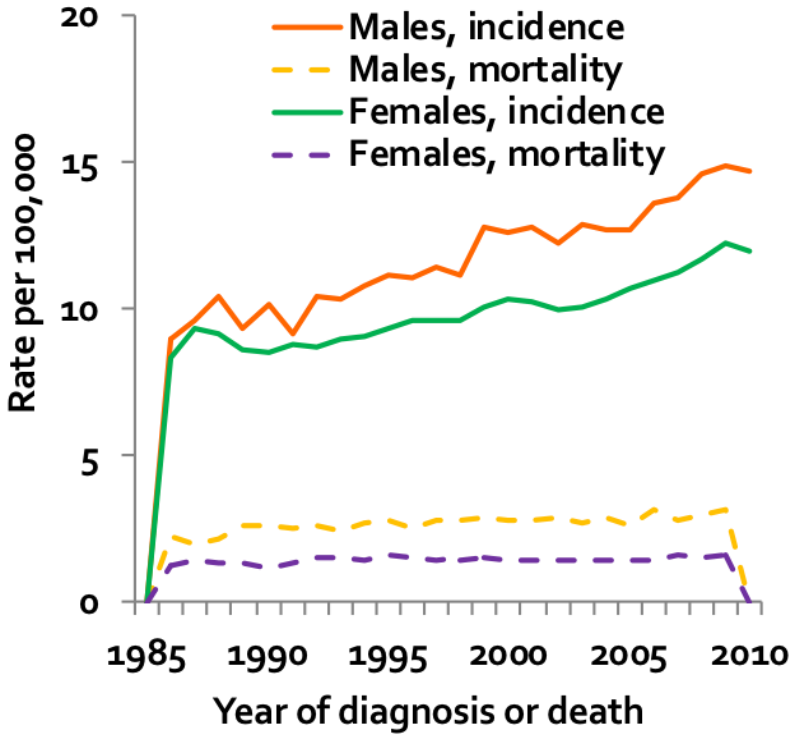
	2004			2011			2016			2021			2026			2031		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
BC	359	304	663	447	361	808	522	407	929	599	451	1,050	679	497	1,175	757	545	1,301
AB	229	222	452	267	238	505	316	268	585	366	299	665	420	334	753	474	370	843
SK	52	60	112	66	65	132	73	69	142	80	72	152	88	77	165	95	82	177
MB	73	54	127	81	65	146	92	71	163	103	77	180	114	84	198	124	91	215
ON	978	885	1,863	1,236	999	2,235	1,453	1,131	2,585	1,671	1,261	2,932	1,907	1,397	3,304	2,137	1,540	3,677
QC	383	311	694	494	412	907	567	453	1,020	631	489	1,120	696	523	1,219	758	552	1,310
NB	56	51	107	71	65	136	82	72	153	91	77	168	101	82	184	109	87	197
NF&L	27	29	56	36	32	68	40	35	76	44	38	82	48	41	89	52	43	95
PEI	10	16	26	15	18	32	17	19	36	19	21	40	21	23	44	23	25	47
NS	94	99	193	117	106	223	134	117	251	150	128	277	167	138	305	180	147	327
YK NWT	2	2	4	2	2	4	3	2	5	3	2	5	3	2	6	4	3	6
NV	2	2	4	3	2	5	3	3	6	3	3	6	4	3	7	4	4	8
Canada	1	1	2	1	1	2	1	1	2	1	1	3	1	1	3	1	1	3
	2,268	2,035	4,303	2,835	2,367	5,202	3,303	2,649	5,952	3,762	2,919	6,681	4,249	3,203	7,452	4,717	3,491	8,208

Note: Calculated numbers are not rounded and thus may appear not to add appropriately.

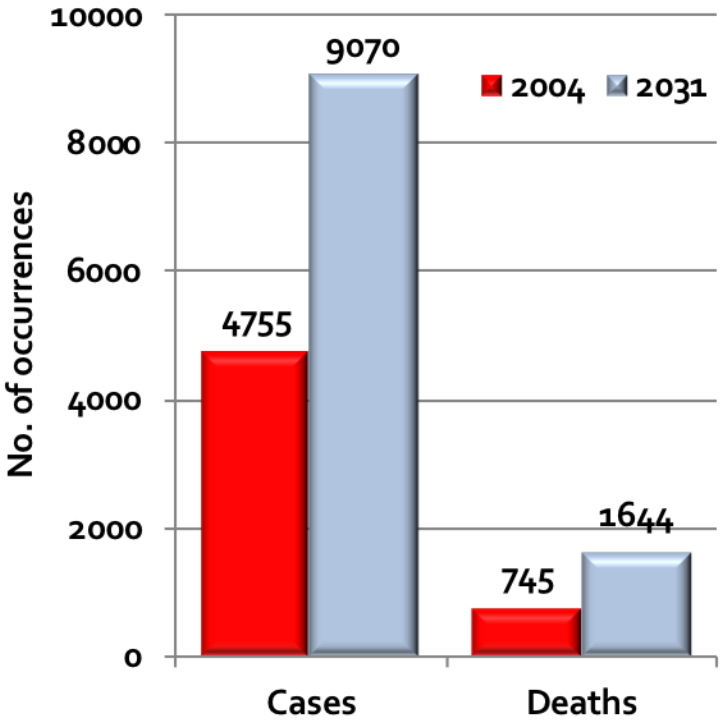
Canadian Partnership Against Cancer. The economic burden of skin cancer in Canada: current and projected. Last update Feb 2010; Available at: partnershipagainstcancer.ca

Epidemiology: Incidence and Mortality (Canada)

Age-standardized incidence and mortality rates of melanoma in Canada[1]



Projected incidence and mortality in Canada*[2]



*Based on low annual percent change scenario

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics: Canadian Cancer Statistics, 2014; 2. Canadian Partnership Against Cancer. The economic burden of skin cancer in Canada: current and projected. Last update Feb 2010; Available at: partnershipagainstcancer.ca

Epidemiology

- median age 45-55 yrs. (25% before age 40)
  - second most common tumour in women aged 20-35 yrs.
  - leading cause of cancer death in women aged 25-30 yrs.

Economic burden of melanoma in Canada (direct & indirect costs)

Cost	2004		2031	
	$ (millions)	% of total	$ (millions)	% of total
Primary care	1.76	0.4	3.35	0.5
Hospital-based day surgery	17.01	3.8	36.75	5.3
Hospital inpatient care	10.78	2.4	24.62	3.5
Total direct costs	29.55	6.7	64.72	9.3
Mortality	410.07	92.5	624.78	89.8
Morbidity	3.86	0.9	6.46	0.9
Total indirect costs	413.93	93.3	631.24	90.7
Total costs	443.48	100	695.96	100

In 2004 constant dollars

Canadian Partnership Against Cancer. The economic burden of skin cancer in Canada: current and projected. Last update Feb 2010; Available at: partnershipagainstcancer.ca

Incidence and Mortality

	Incidence	Deaths	5 yr. Net Survival[1]
Canada			
Total	7200 (12th)	1250	88%
Males	4000 (7th)	790	85%
Females	3200 (7th)	450	92%
Manitoba			
Total	220 (12th)	30	-
Males	110 (7th)	20	-
Females	100 (7th)	10	-

[1]Net survival is estimated using age-standardized relative survival ratios

Canadian Cancer Statistics 2017.

Conditional Net Survival

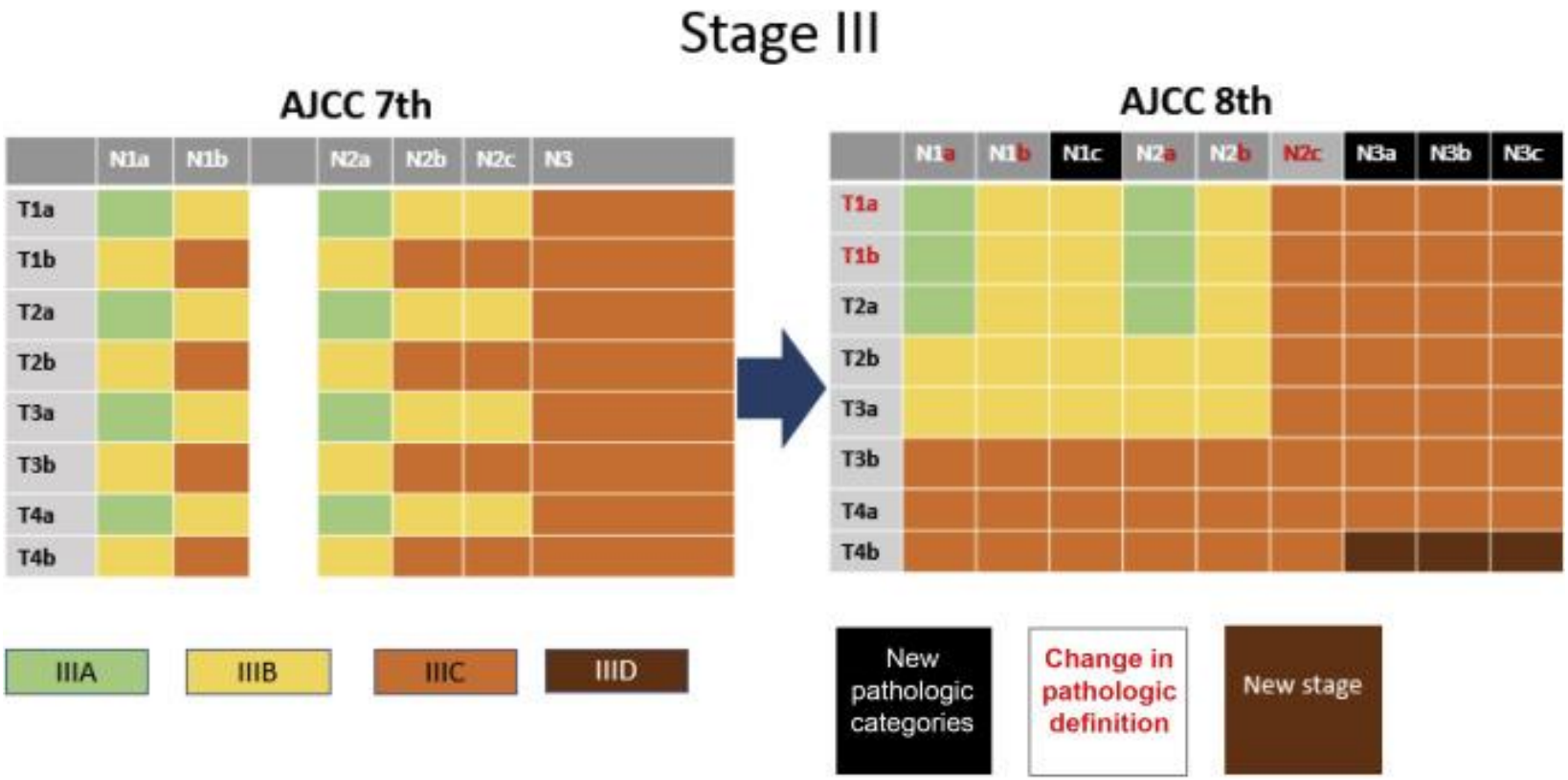
Conditional Net Survival (%)						
Year	0	1	2	3	4	5
Melanoma	88	91	93	95	95	97

[1]Net survival is estimated using age-standardized relative survival ratios

AJCC 8th Edition

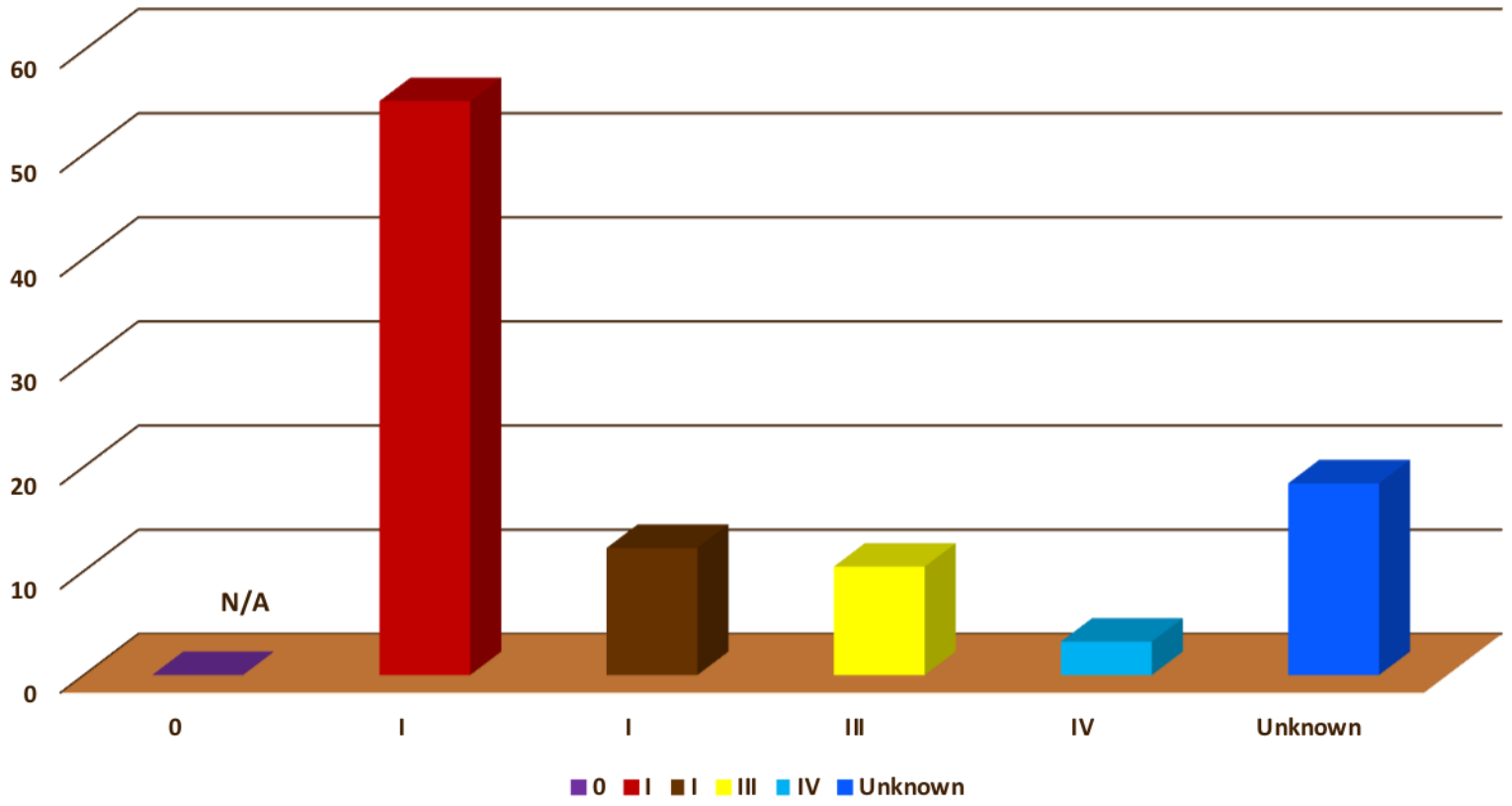
- New Staging system implemented 2017
- Significant changes particularly in Stage III disease

AJCC 8th Edition Staging



Grob et al. EJC 2018;91: 168-170.

Melanoma Stage at Diagnosis



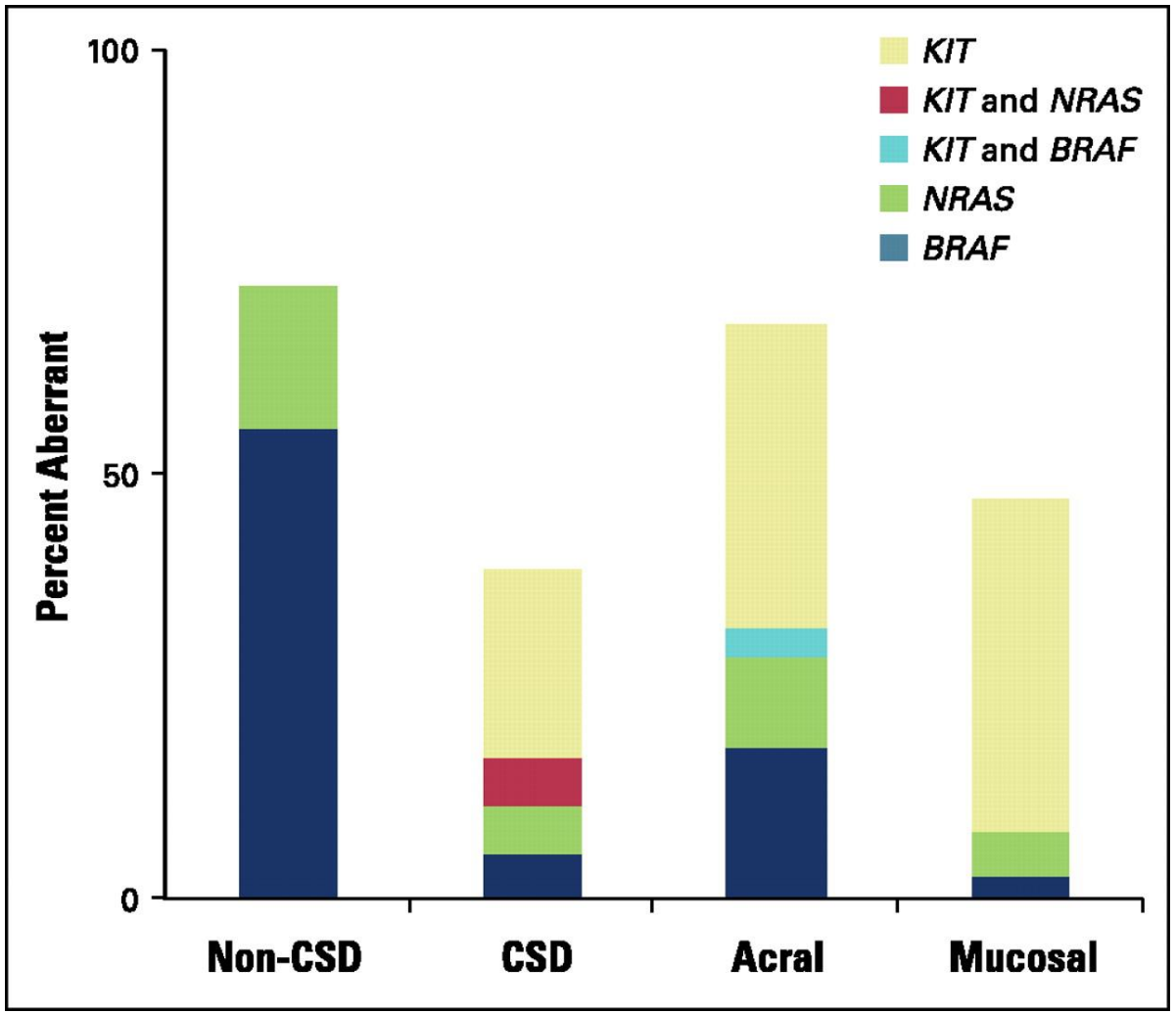
Canadian Cancer Stats 2018.

Melanoma Subtypes

- **Common subtypes listed;**
  - **superficial spreading melanoma**
  - **nodular melanoma**
  - **lentigo maligna melanoma**

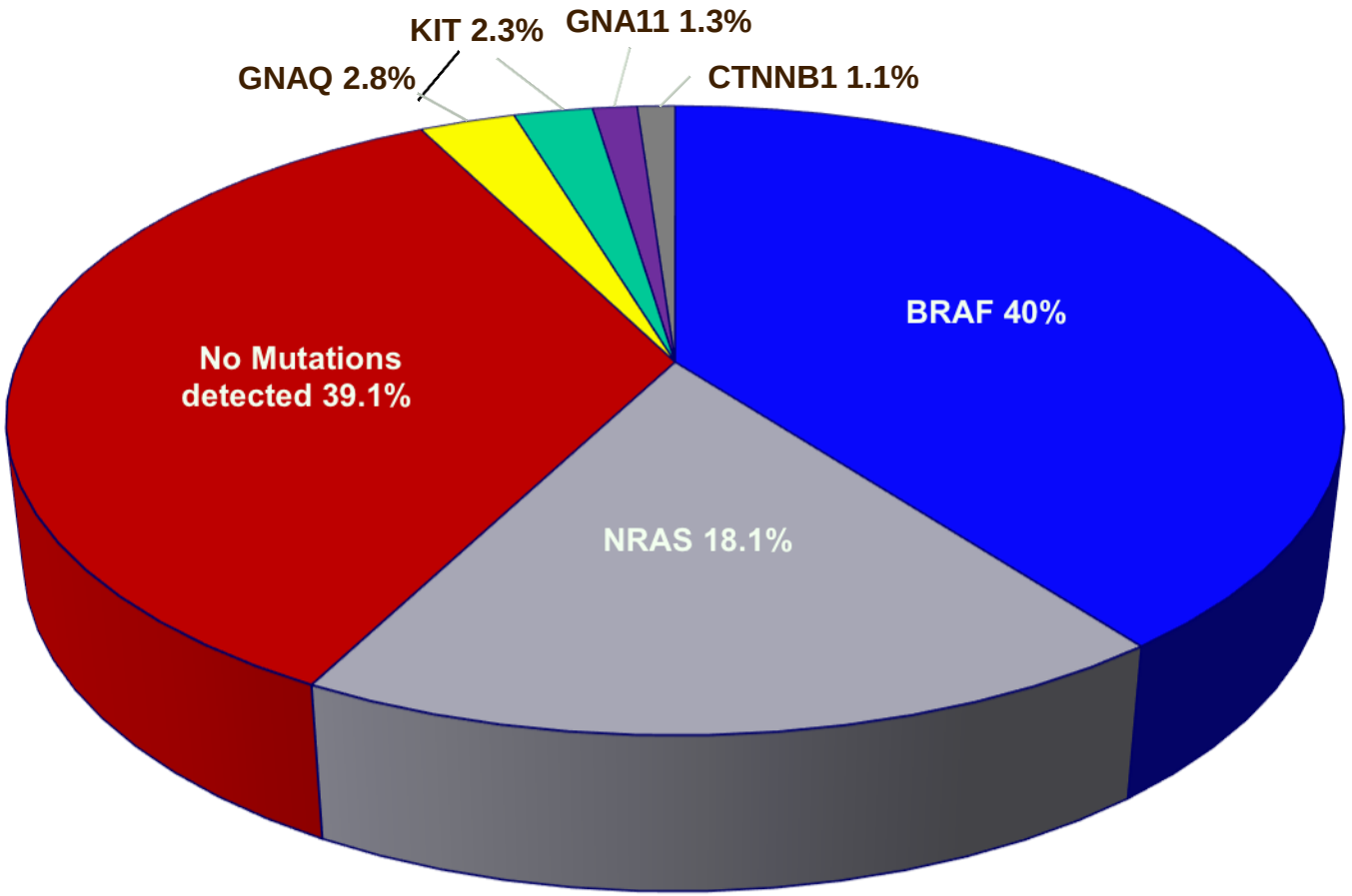
- **Have little if any prognostic significance independent of tumour thickness, interpretation is subjective and prone to interobserver variation, and their use is principally for clinicopathological correlation**

Four Melanoma subtypes



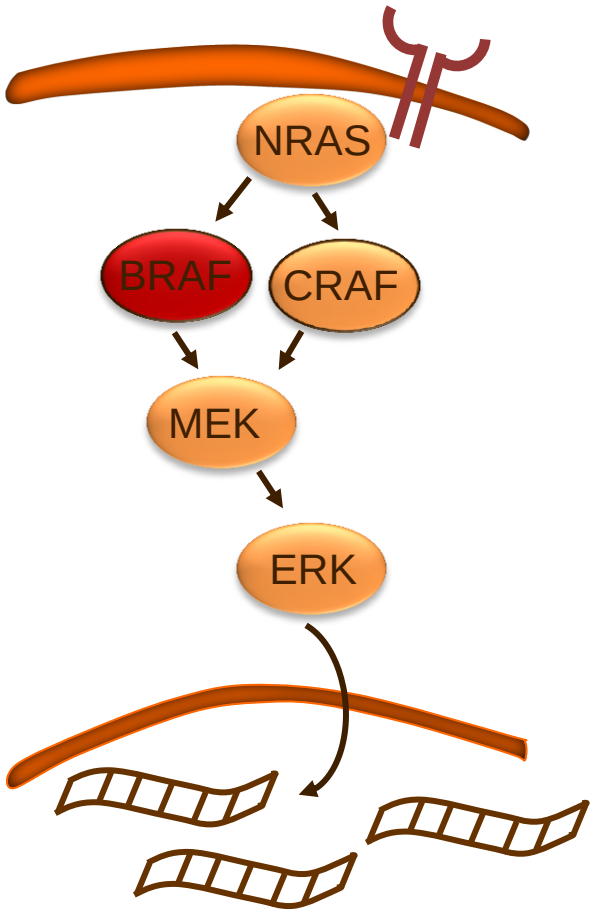
Curtin J A et al. JCO. 2006;24: 4340-46.

Spectrum of Oncogenic Driver Mutations in Melanoma



Meador et al. Clin Can Res. 2014;20(9): 2264-2275.

BRAF Mutations: Biology and Practice

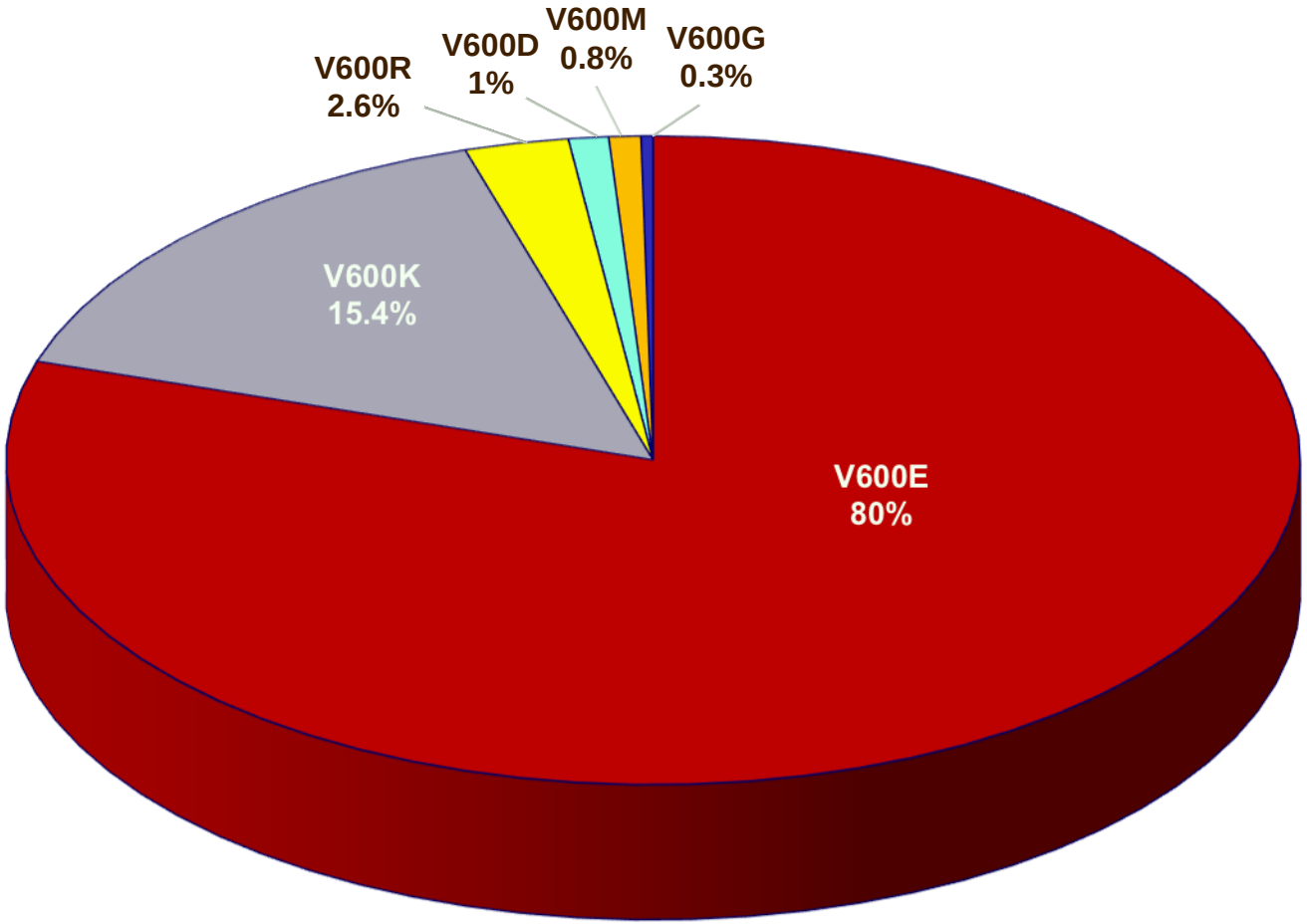


BRAF Mutation, %	N = 677
All BRAF mutations	47
V600E	72
V600K	23
V600R/L	4
Non-V600	2

- Stable across primary to metastatic melanoma
- Detectable in formalin-fixed, paraffin-embedded tumor samples

Jakob J. et al. ASCO 2011. Abstract 8500.

Relative Frequency of BRAF Mutations in Melanoma



Meador et al. Clin Can Res. 2014;20(9): 2264-75.

Therapy

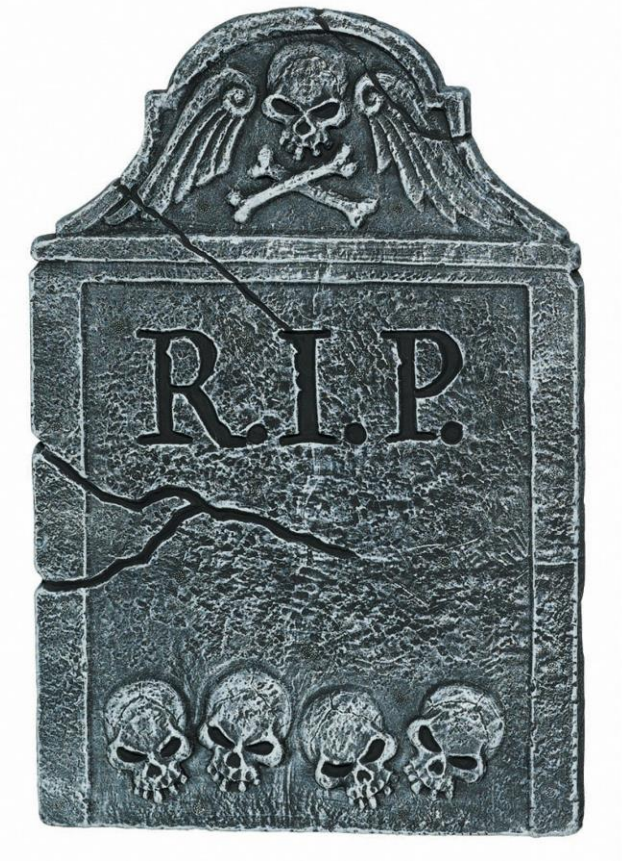
Surgery

- **Melanoma is predominately a surgical disease**
  - **Wide excision**
  - **Sentinel Nodes**
  - **Completion lymphadenectomy when appropriate**
  - **? surgery for oligometastatic disease**

Radiation

- **Limited role in the management of melanoma**
  - **Regional lymph node basin under certain situations**
  - **SRS with CNS metastases**
  - **To potentially generate an abscopal response**

Systemic Therapy



Chemotherapy
(1976-2014)

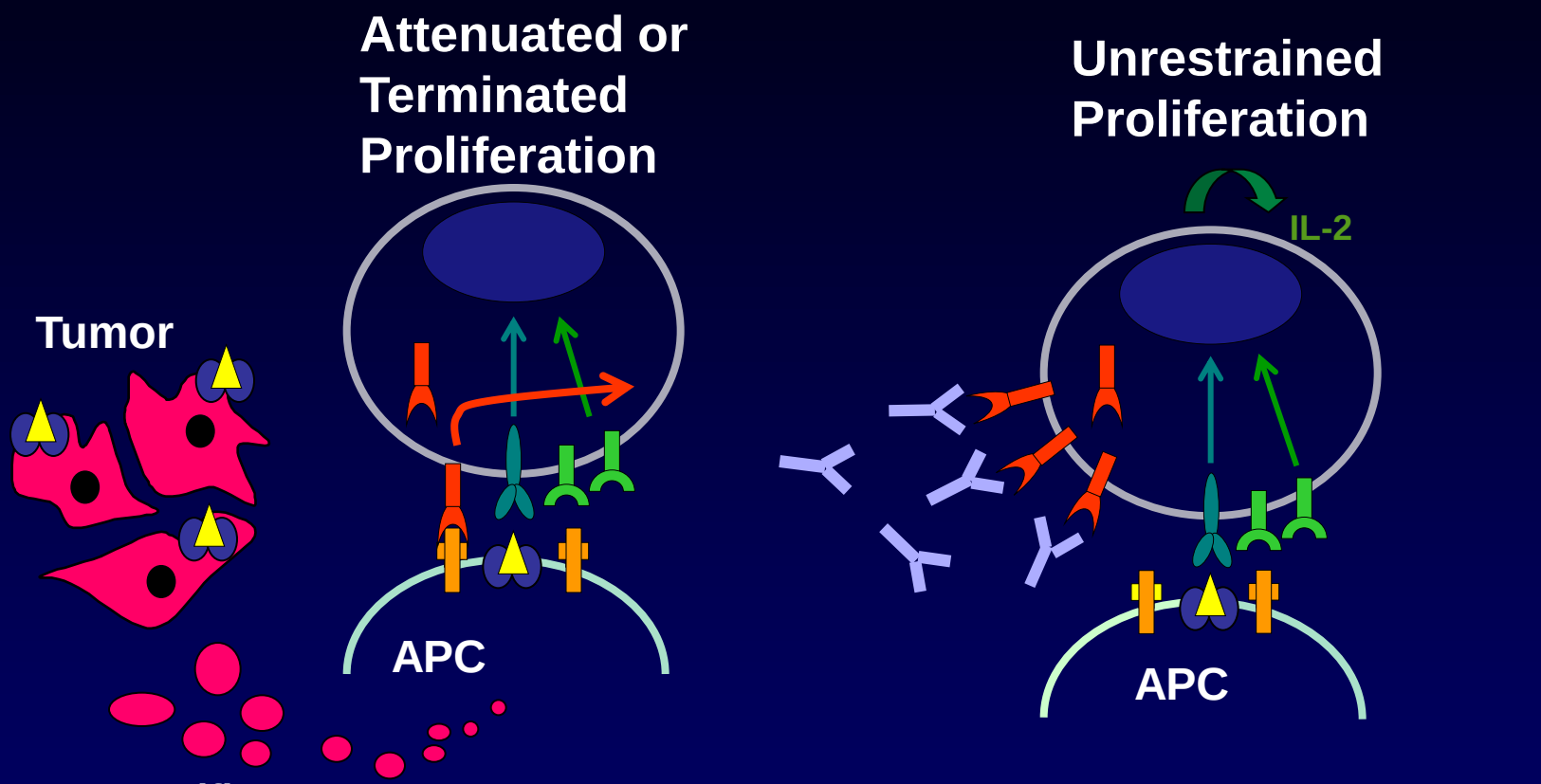
New Therapies

- **In the past seven years there has been a revolution in the management of metastatic melanoma with the approval of a number of new drugs**

The NEW “Tsunami”

- **Ipilimumab (Yervoy™)**
- **Vemurafenib (Zelboraf™)**
- **Cobimetinib (Cotellec ™)**
- **Dabrafenib (Tafinlar™)**
- **Trametinib (Mekinist™)**
- **Nivolumab (Opdivo™)**
- **Pembrolizumab (Keytruda™)**

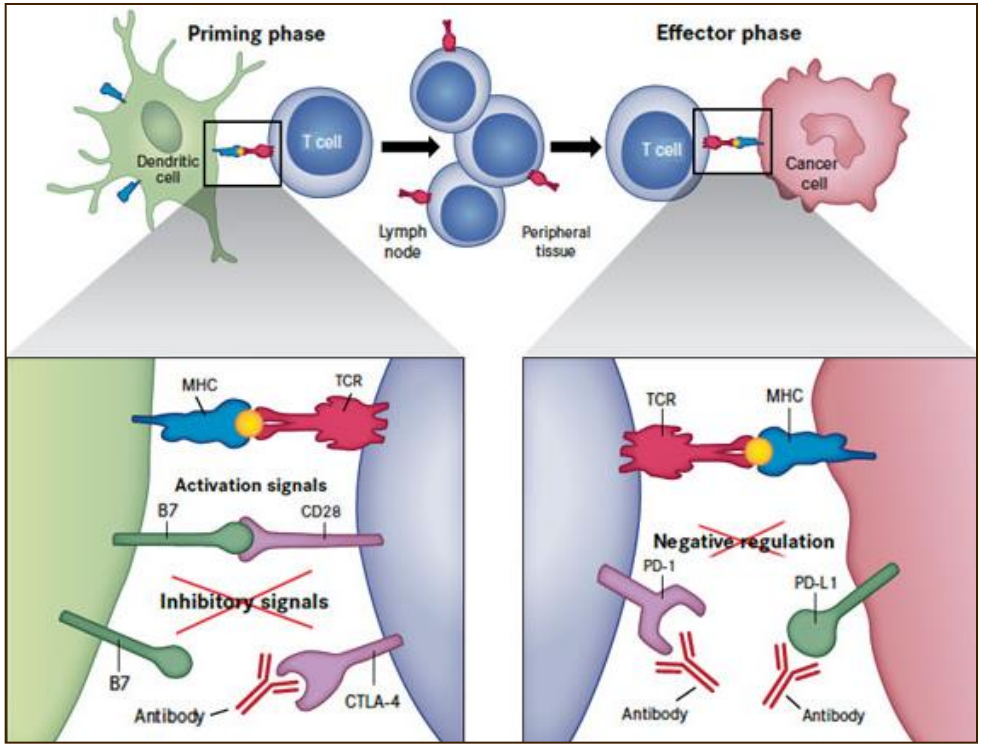
CTLA-4: Mechanism of Action (MoA)



Adapted from Chambers CA, et al. *Annu Rev Immunol*. 2001;19: 565-94.

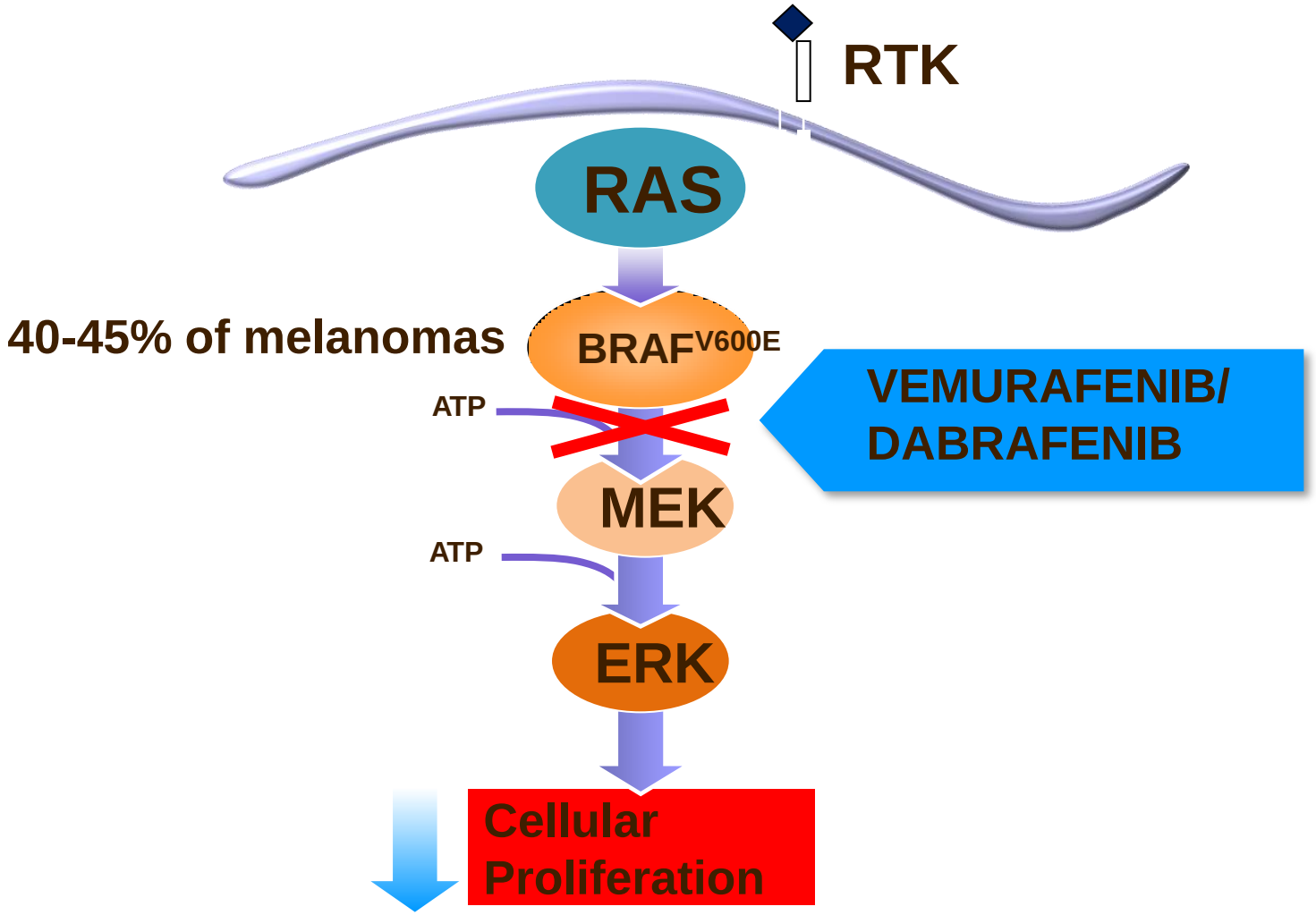
PD-1 and PD-L1 Antibodies

- PD-1 – inhibitory receptor found on activated lymphocytes and monocytes and is associated with tumour immune escape
- Binds with PD-L1 on tumour cells
- Interaction between PD-1 and PD-L1 suppresses the cytotoxic T-cell response



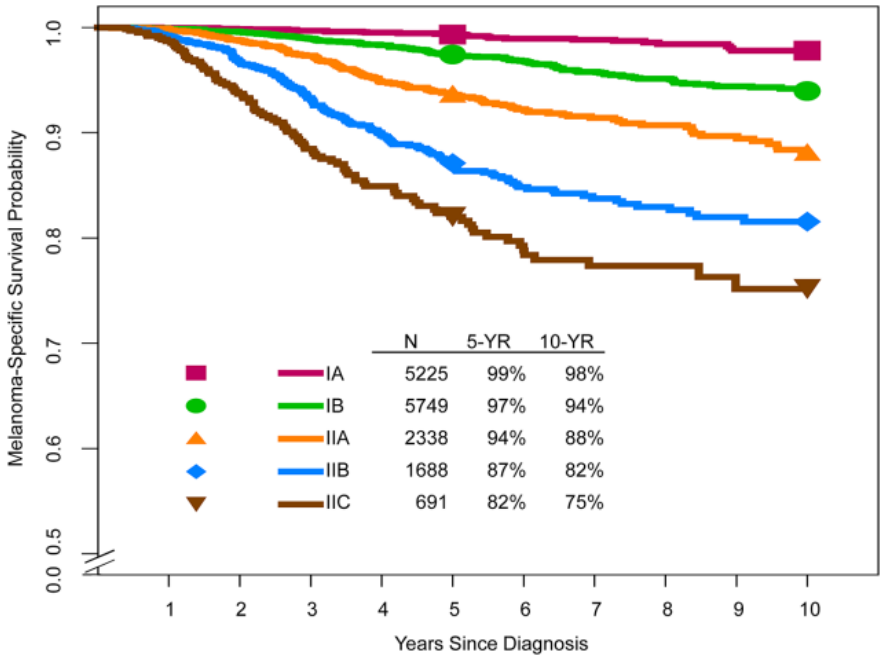
Adapted from NEJM. 2012;366(26):2517

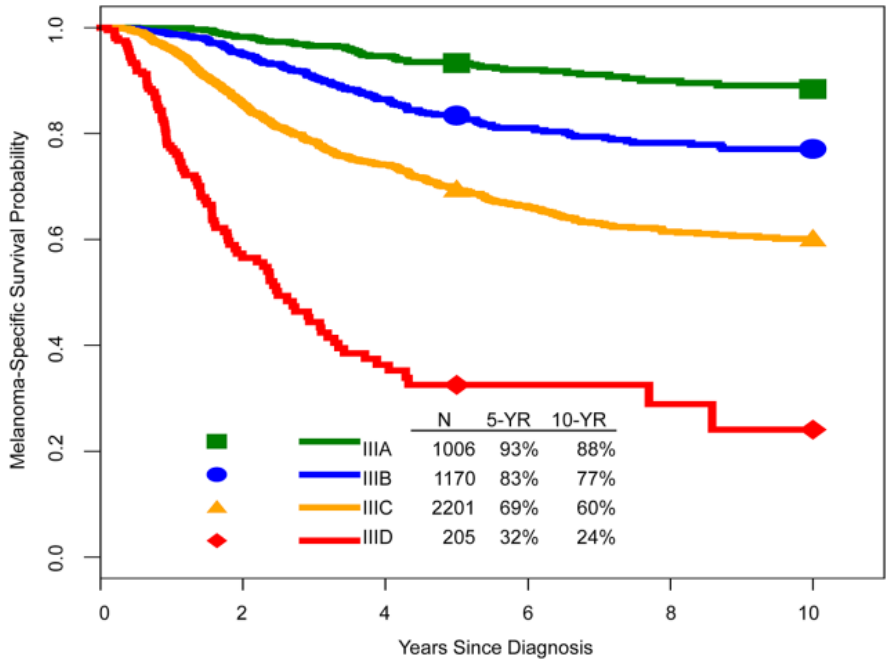
Vemurafenib and Dabrafenib inhibits $BRAF^{V600E}$ Kinase



Adjuvant Therapy

Who Needs Adjuvant Therapy? Survival in High Risk Melanoma AJCC 8th Edition





Gershenwald JE et al. CA Cancer J Clin. 2017;67(6): 472-92.

Benefits of Interferons (EFS, OS)

Overall Risk		
Dose	**Event Free Survival**	**Overall Survival**
High (N=1196)	0.83 (0.72-0.96)	0.93 (0.80-1.08)
Peg-IFN (N=1256)	0.83 (0.76-1.00)	0.96 (0.82-1.11)
Intermediate (N=2243)	0.84 (0.74-0.95)	0.91 (0.79-1.04)
Low (N=2732)	0.85 (0.77-0.94)	0.86 (0.77-0.96)
Very low (N=484)	0.99 (0.80-1.23)	0.96 (0.76-1.21)
Overall (95%CI)	0.86 (0.81-0.91)	0.90 (0.85-0.97)

Problems

- Toxic
- Expensive
- One year of therapy
- Not widely accepted

Ipilimumab verses placebo

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

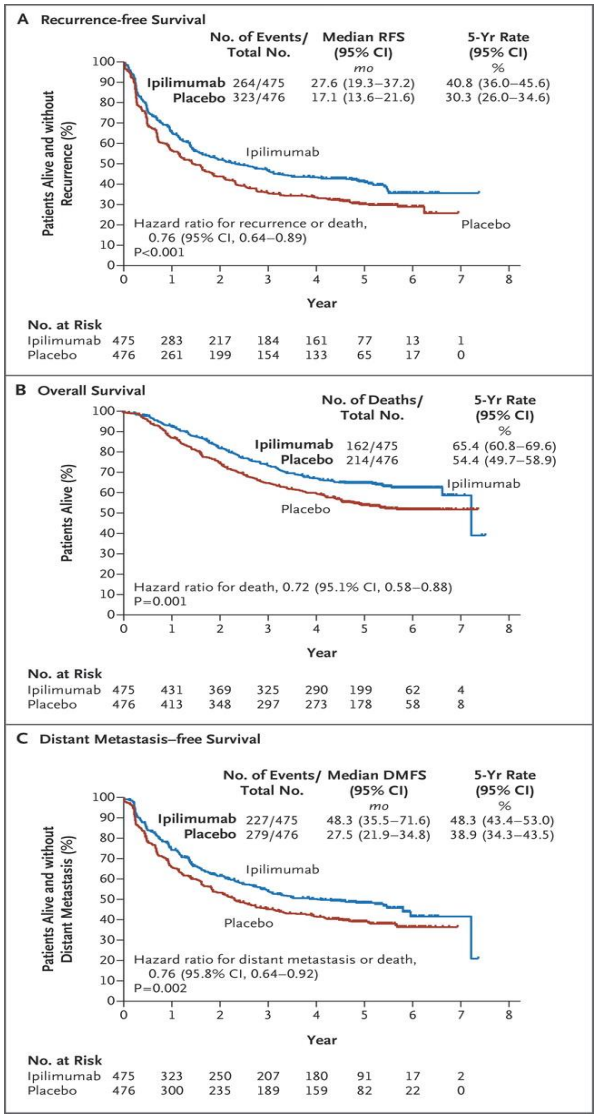
Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy

A.M.M. Eggermont, V. Chiarion-Sileni, J.-J. Grob, R. Dummer, J.D. Wolchok, H. Schmidt, O. Hamid, C. Robert, P.A. Ascierto, J.M. Richards, C. Lebbé, V. Ferraresi, M. Smylie, J.S. Weber, M. Maio, L. Bastholt, L. Mortier, L. Thomas, S. Tahir, A. Hauschild, J.C. Hassel, F.S. Hodi, C. Taitt, V. de Pril, G. de Schaetzen, S. Suciu, and A. Testori

Eggermont et al NEJM. 2016;375:1845-55.

- **Stage IIIA with metastasis > 1mm; any Stage IIIB or IIIC (no in-transit metastases)**
- **CLND required**
- **Ipilimumab 10 mg/kg**

Results



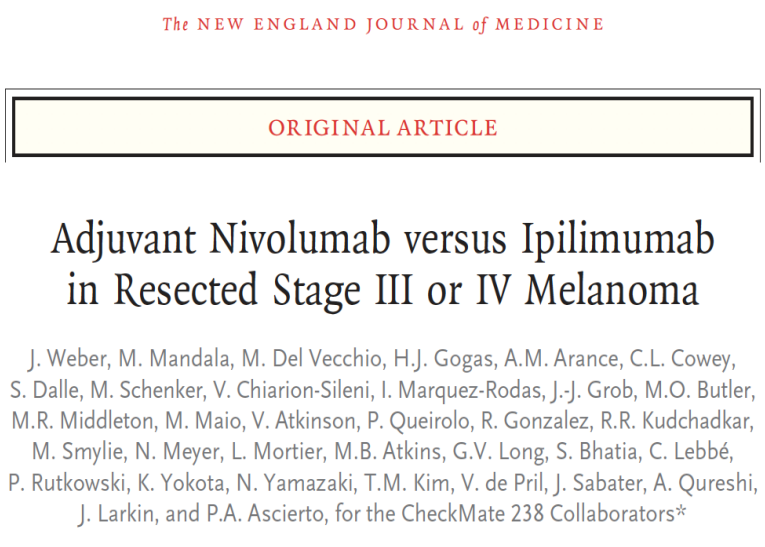
Eggermont et al NEJM. 2016;375: 1845-1855.

ISSUES

- Dose of ipilimumab is 10 mg/kg
- Toxicity
  - 41 % Grade 3-5 toxicity
- 5 deaths (1.1%)

PD-1 inhibition

Nivolumab[1]



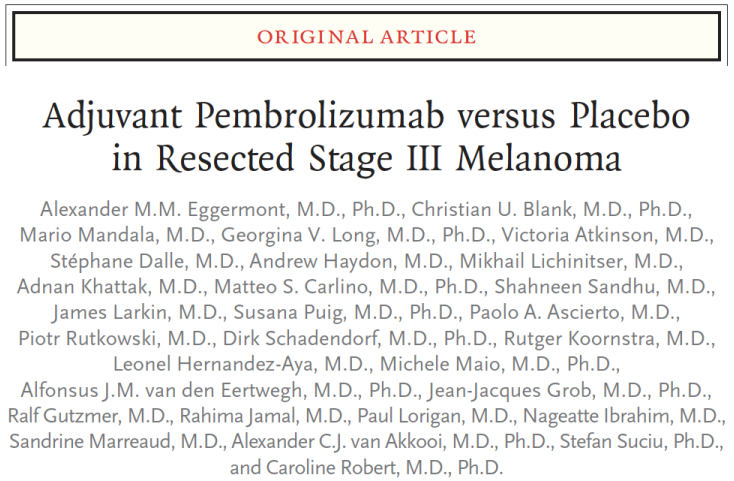
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma

J. Weber, M. Mandala, M. Del Vecchio, H.J. Gogas, A.M. Arance, C.L. Cowey, S. Dalle, M. Schenker, V. Chiarion-Sileni, I. Marquez-Rodas, J.-J. Grob, M.O. Butler, M.R. Middleton, M. Maio, V. Atkinson, P. Queirolo, R. Gonzalez, R.R. Kudchadkar, M. Smylie, N. Meyer, L. Mortier, M.B. Atkins, G.V. Long, S. Bhatia, C. Lebbé, P. Rutkowski, K. Yokota, N. Yamazaki, T.M. Kim, V. de Pril, J. Sabater, A. Qureshi, J. Larkin, and P.A. Ascierto, for the CheckMate 238 Collaborators*

Pembrolizumab[2]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma

Alexander M.M. Eggermont, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Mario Mandala, M.D., Georgina V. Long, M.D., Ph.D., Victoria Atkinson, M.D., Stéphane Dalle, M.D., Andrew Haydon, M.D., Mikhail Lichinitser, M.D., Adnan Khattak, M.D., Matteo S. Carlino, M.D., Ph.D., Shahneen Sandhu, M.D., James Larkin, M.D., Susana Puig, M.D., Ph.D., Paolo A. Ascierto, M.D., Piotr Rutkowski, M.D., Dirk Schadendorf, M.D., Ph.D., Rutger Koornstra, M.D., Leonel Hernandez-Aya, M.D., Michele Maio, M.D., Ph.D., Alfonsus J.M. van den Eertwegh, M.D., Ph.D., Jean-Jacques Grob, M.D., Ph.D., Ralf Gutzmer, M.D., Rahima Jamal, M.D., Paul Lorigan, M.D., Nageatte Ibrahim, M.D., Sandrine Marreaud, M.D., Alexander C.J. van Akkooi, M.D., Ph.D., Stefan Suciu, Ph.D., and Caroline Robert, M.D., Ph.D.

1. Weber et al. NEJM. 2017;377: 1824-35.
2. Eggermont et al. NEJM. 2018;378: 1789-1801.

PD-1 inhibition

Nivolumab[1]

- Verses ipilimumab
- 906 patients
- Stage IIIB, IIIC, IV NED
- CLND required
- Nivolumab 3 mg/kg q2 wks. x one year

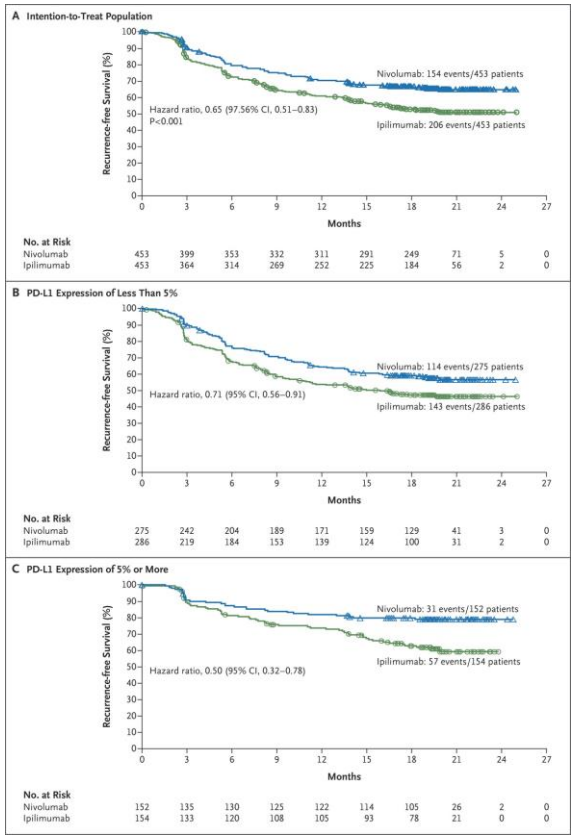
Pembrolizumab[2]

- Verses placebo
- 1019 patients
- Stage IIIA (>1mm), IIIB, IIIC, no in-transit mets
- CLND required
- Pembrolizumab 200 mg q3 wks. x 18 doses

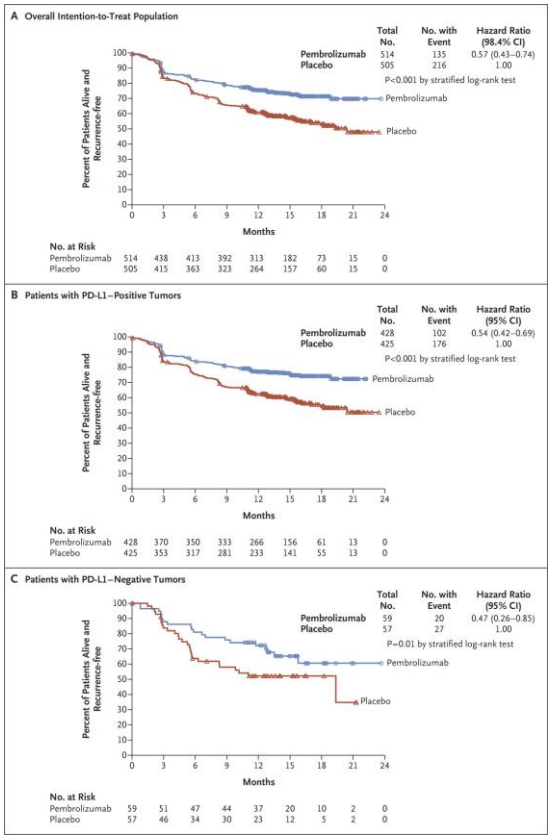
1. Weber et al. NEJM. 2017;377:1824-35.
2. Eggermont et al. NEJM. 2018;378: 1789-1801.

PD-1 inhibition

Nivolumab[1]



Pembrolizumab[2]



1. Weber et al. NEJM. 2017;377: 1824-35.
2. Eggermont et al. NEJM. 2018;378: 1789-1801.

Approvals

- **FDA**
  - **Nivolumab December 20, 2017**
    - **lymph node involvement, Stage IV NED**
  - **Pembrolizumab accepted for a sBLA July 25, 2018**
- **EMA**
  - **Nivolumab July 31, 2018**
    - **lymph node involvement, Stage IV NED**
- **Canada**
  - **Nivolumab NOC expected mid November 2018**
  - **Pembrolizumab refused to reveal their date**

ISSUES

- Different patient populations enrolled
- Different control arms
- CLND required for enrollment
- Cost

Targeted Therapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

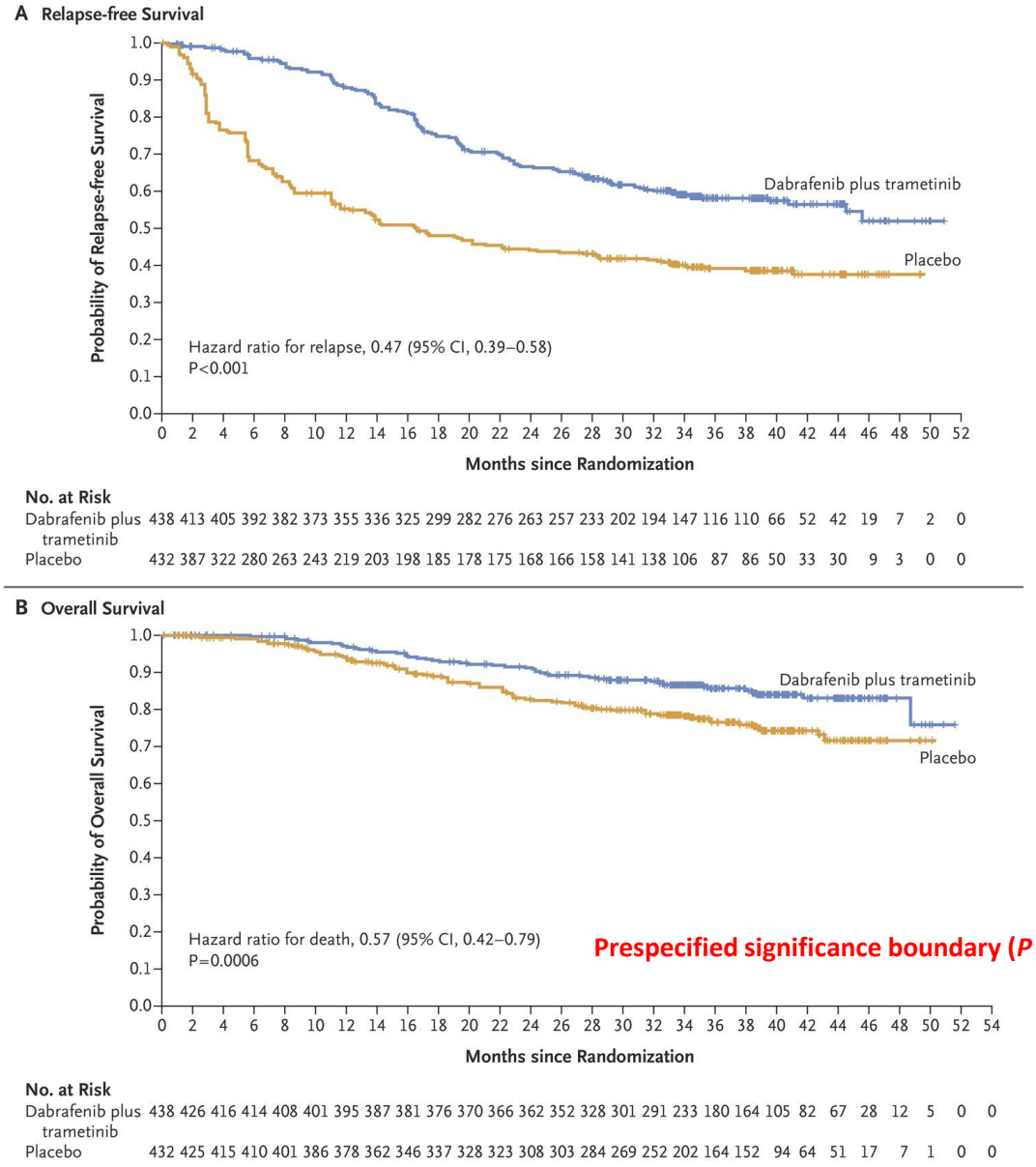
Adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma

G.V. Long, A. Hauschild, M. Santinami, V. Atkinson, M. Mandalà, V. Chiarion-Sileni, J. Larkin, M. Nyakas, C. Dutriaux, A. Haydon, C. Robert, L. Mortier, J. Schachter, D. Schadendorf, T. Lesimple, R. Plummer, R. Ji, P. Zhang, B. Mookerjee, J. Legos, R. Kefford, R. Dummer, and J.M. Kirkwood

Long GV et al. NEJM. 2017;377: 1813-23.

COMBI - AD

- Verses placebo
- 870 patients, Braf V600E and V600K
- Dabrafenib 150 mg po bid + trametinib 2 mg OD x one year
- Stage IIIA (>1mm), IIIB, and IIIC
- CLND required



Prespecified significance boundary (*P* = .000019)

Long GV et al. NEJM. 2017;377: 1813-23.

Approvals

- **FDA**
  - **April 30, 2018**
  - **Stage III V600E and V600K**
- **EMA**
  - **August 29, 2018**
  - **Stage III V600 positive**
- **Canada**
  - **Health Canada NOC fall 2018**
  - **Available through Managed Access Program for Stage III patients. Stage IV NED on a case by case basis.**

Adjuvant Therapy - Issues

- What to do with Braf V600 positive melanomas?
- What to do with patients who relapse after completion of therapy?
  - before 6 months
  - between 6-12 months
  - after 12 months

- What about high risk Stage II patients?
- What about nivolumab/ipilimumab combination?

Take Home Messages

- **Melanoma carries a significant health burden despite being relatively uncommon**
- **Adjuvant therapy will be changing significantly in the new year with new therapies that change the natural course of the disease**
- **Some concerns exist regarding the translation of the clinical trials under the new staging system**