The case for adjuvant BRAF-targeted therapy in high-risk melanoma

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Relevant Disclosures

- Advisory Board/Consulting:
  - Novartis
  - Amgen
  - Merck
  - Array
  - Syndax
  - Replimmune

- Research Sponsorship:
  - Amgen
  - Merck

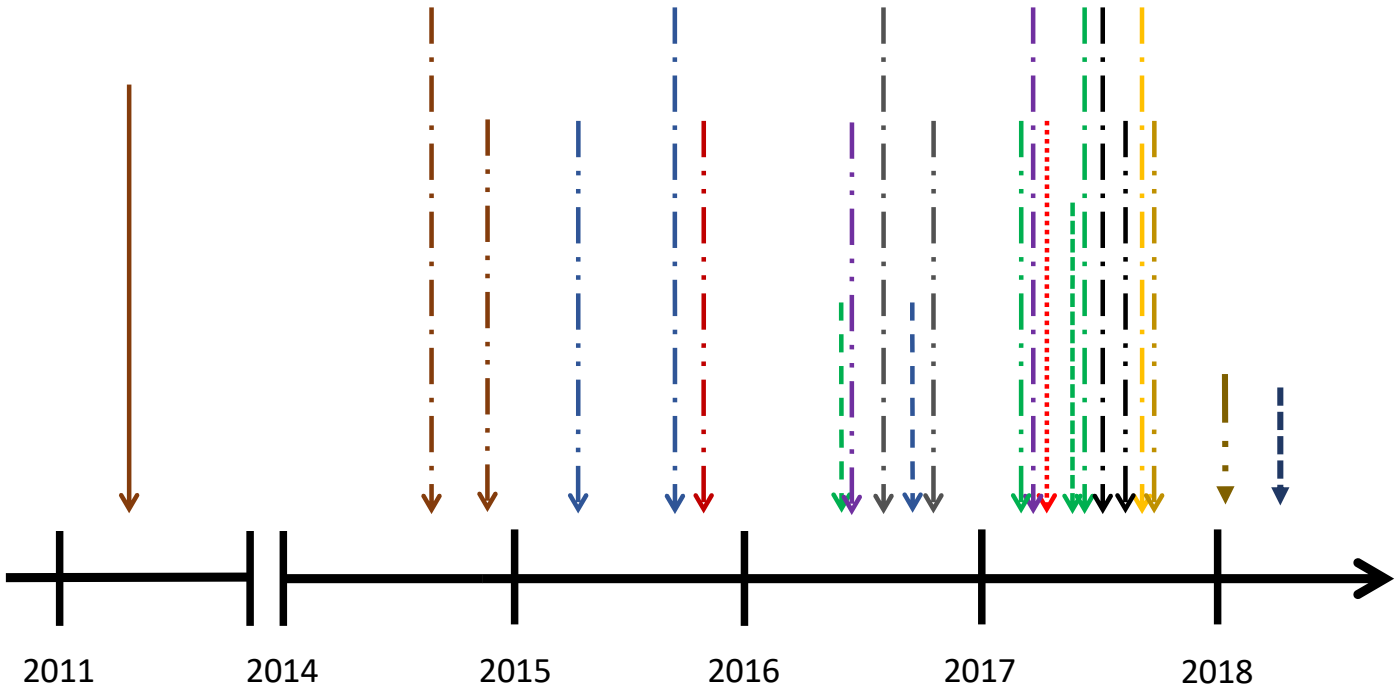
A potentially relevant disclosure

Sanjiv’s espresso

My espresso

A more relevant disclosure:

Immune checkpoint inhibitors and US FDA approvals



Anti-CTLA4

Ipilimumab

Anti-PD-1

Pembrolizumab

Nivolumab

Anti-PD-L1

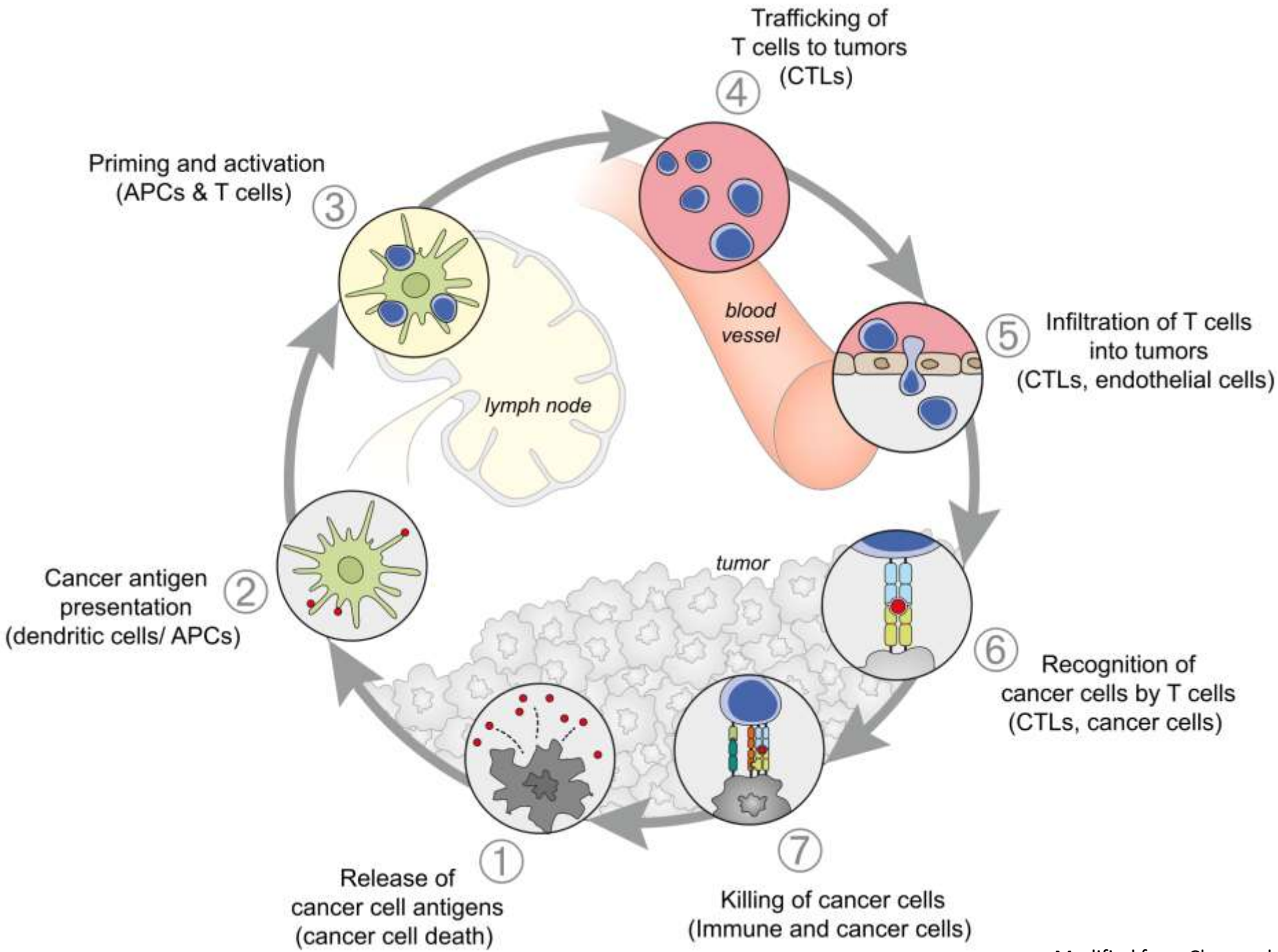
Atezolizumab

Avelumab

Durvalumab

Melanoma
NSCLC
Renal Cell Carcinoma
Urothelial Bladder Cancer
Hodgkin Lymphoma
Head and Neck Squamous Cell Carcinoma
Merkel Cell Carcinoma
MSI Cancers
Gastric Cancer
Hepatocellular Carcinoma

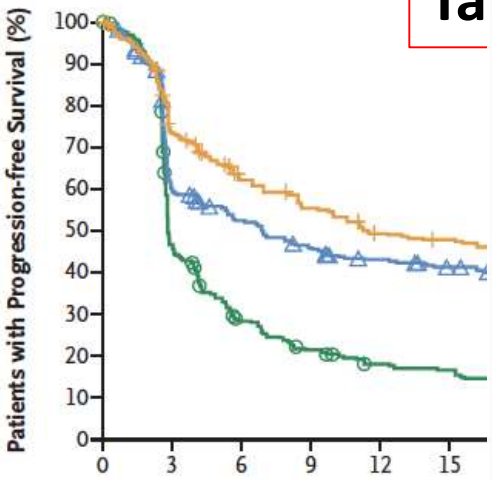
Year	Drugs	Approvals	Disease indications
2011	1	1	1
2014	2	2	1
2015	3	4	3
2016	3	5	4
2017	4	9	6
2018	4	3	3



Modified from Chan and Melman, Immunity 2015

Immunotherapy captures our hearts and minds…

…as it offers the potential of cure.



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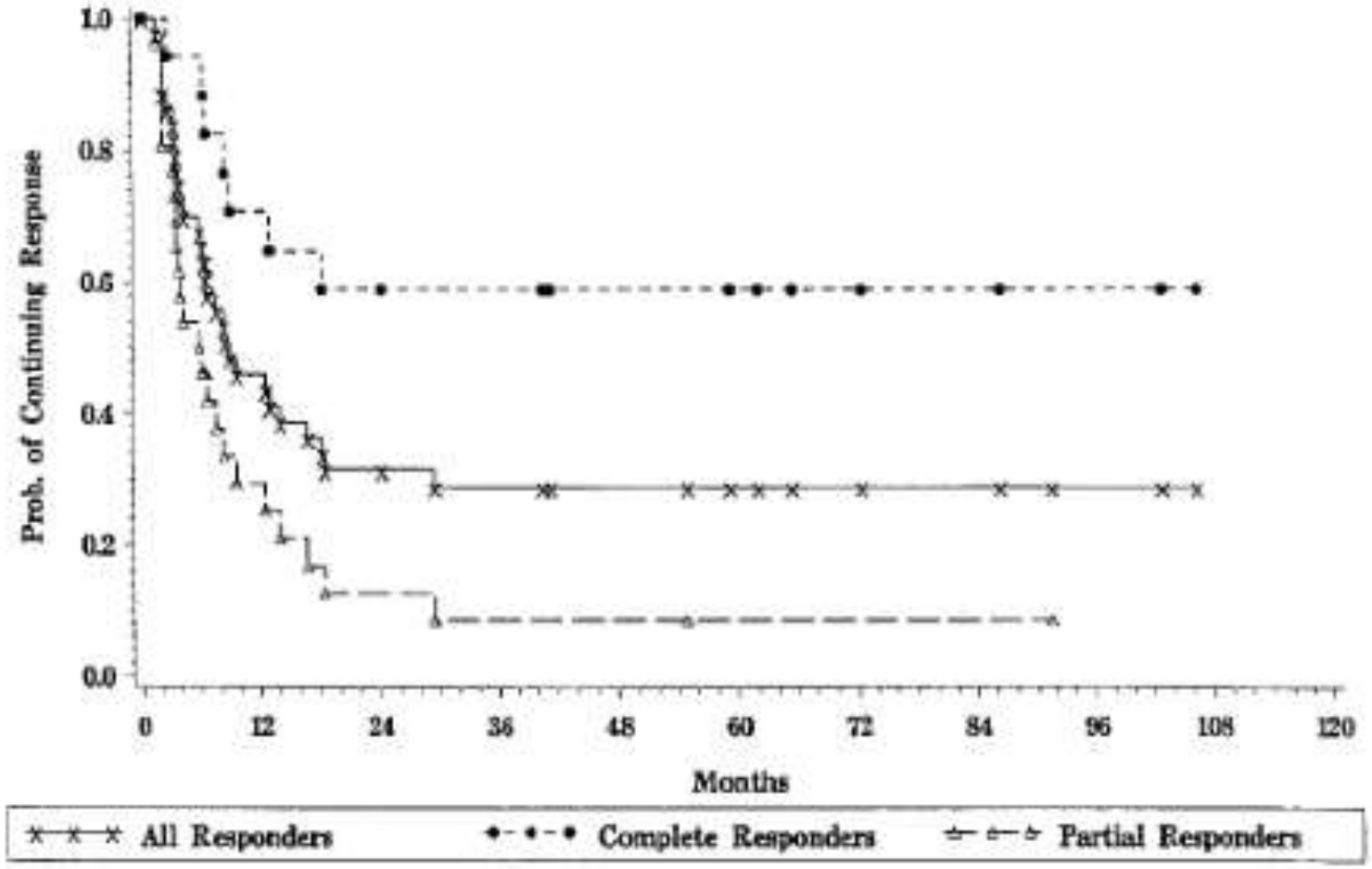
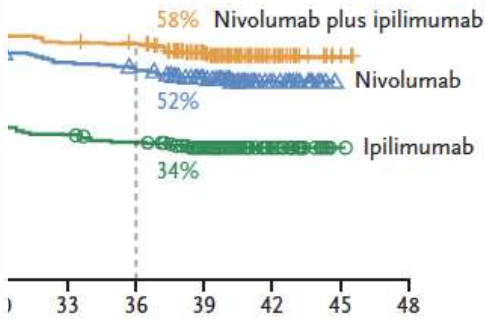


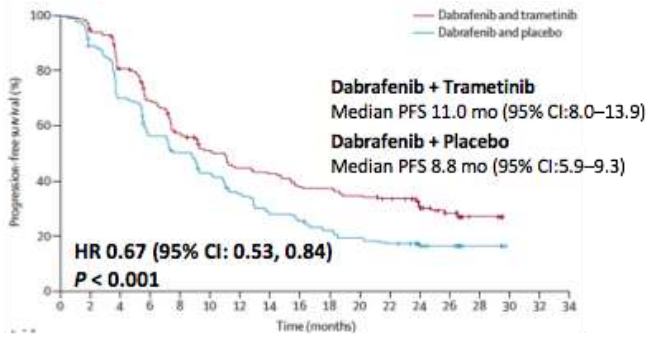
> 3 years!

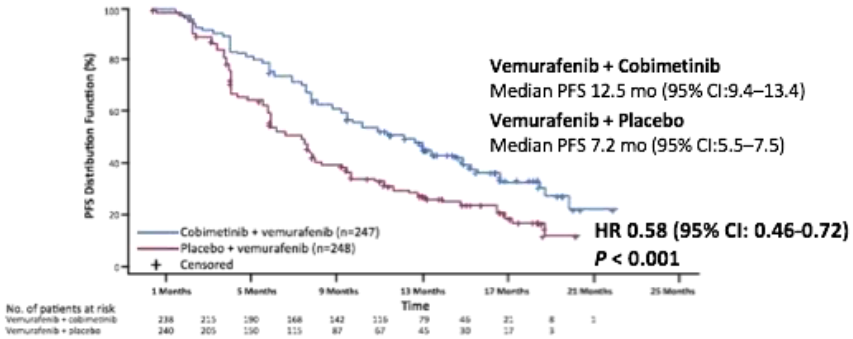


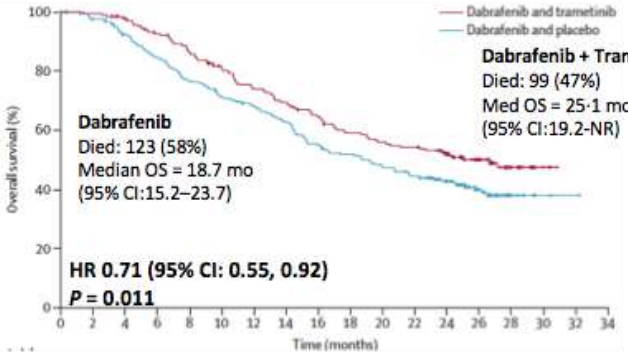
Wolchok et al. NEJM 2017

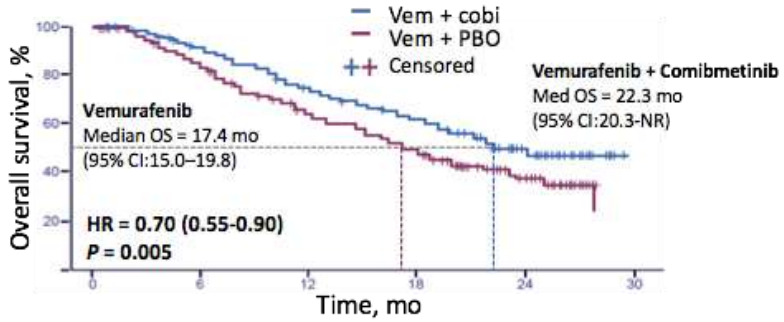
Atkins et al. J Clin Oncol. 1999

Why should we care about BRAF-targeted therapy?

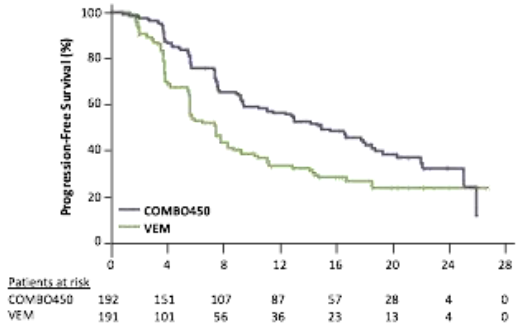








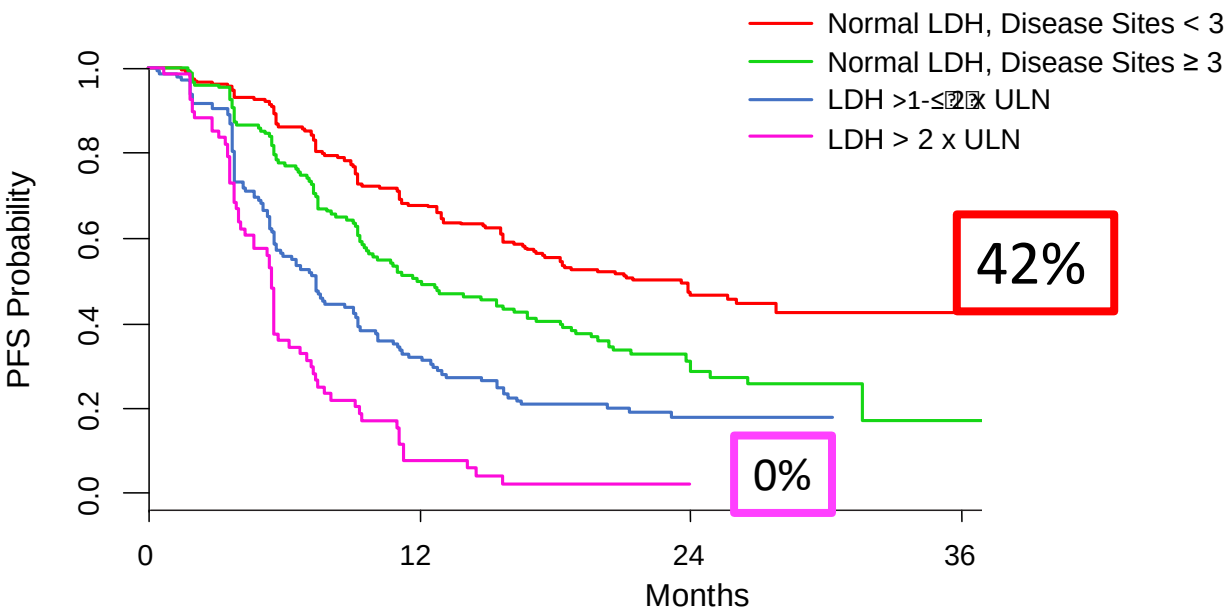
It works!

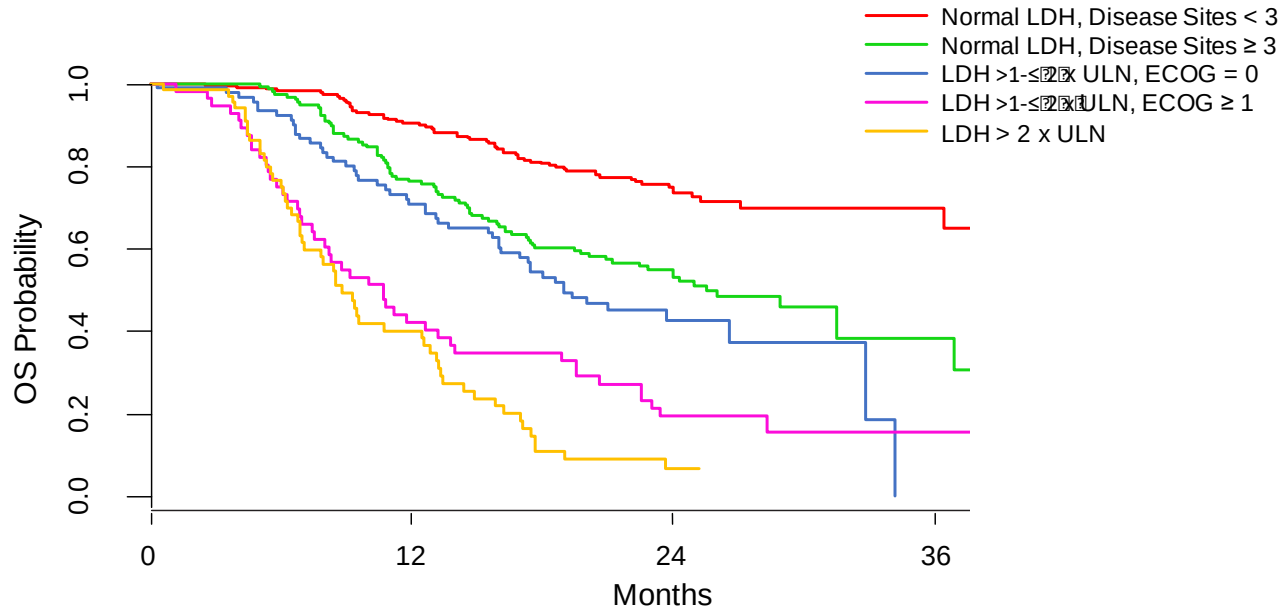


Long et al. NEJM 2014; Long et al. Lancet 2015.

Larkin et al. NEJM 2015; Atkinson et al., SMR 2015.

Dummer et al. Lancet Oncol 2018

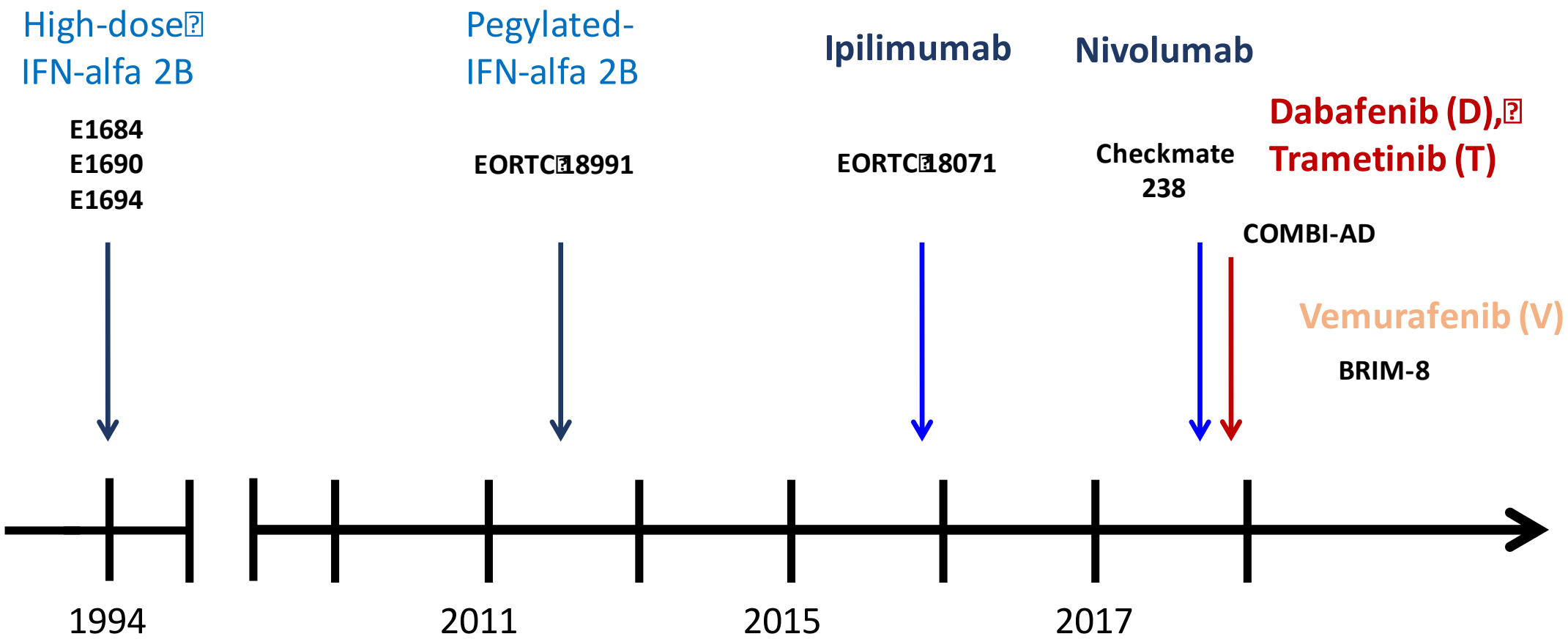




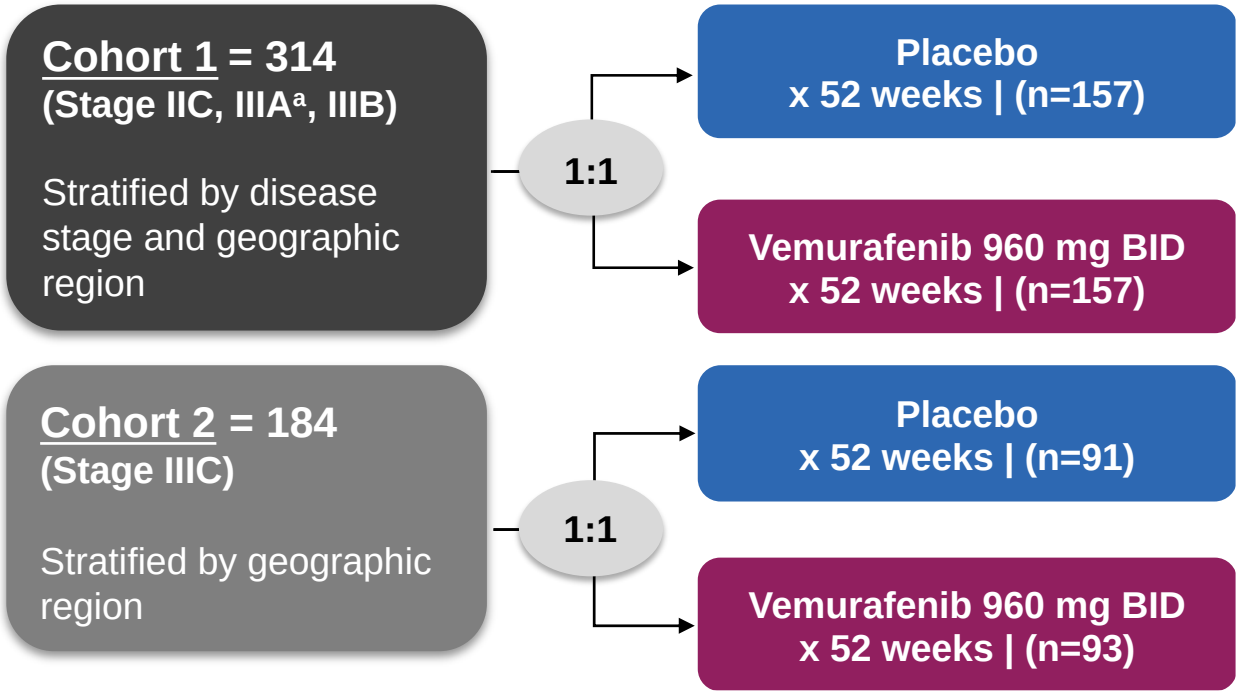
In advanced disease:
Selection of a population of BRAF mutant melanoma patients by clinical factors (LDH, number of tumor sites) can identify patients who have long-term benefit with BRAF/MEK combination.

GV LONG AT SMR 2015
Schadenodorf et al. Eur J Cancer 2017

What about BRAF-targeted therapy in the adjuvant setting?



BRIM8 – Study Design

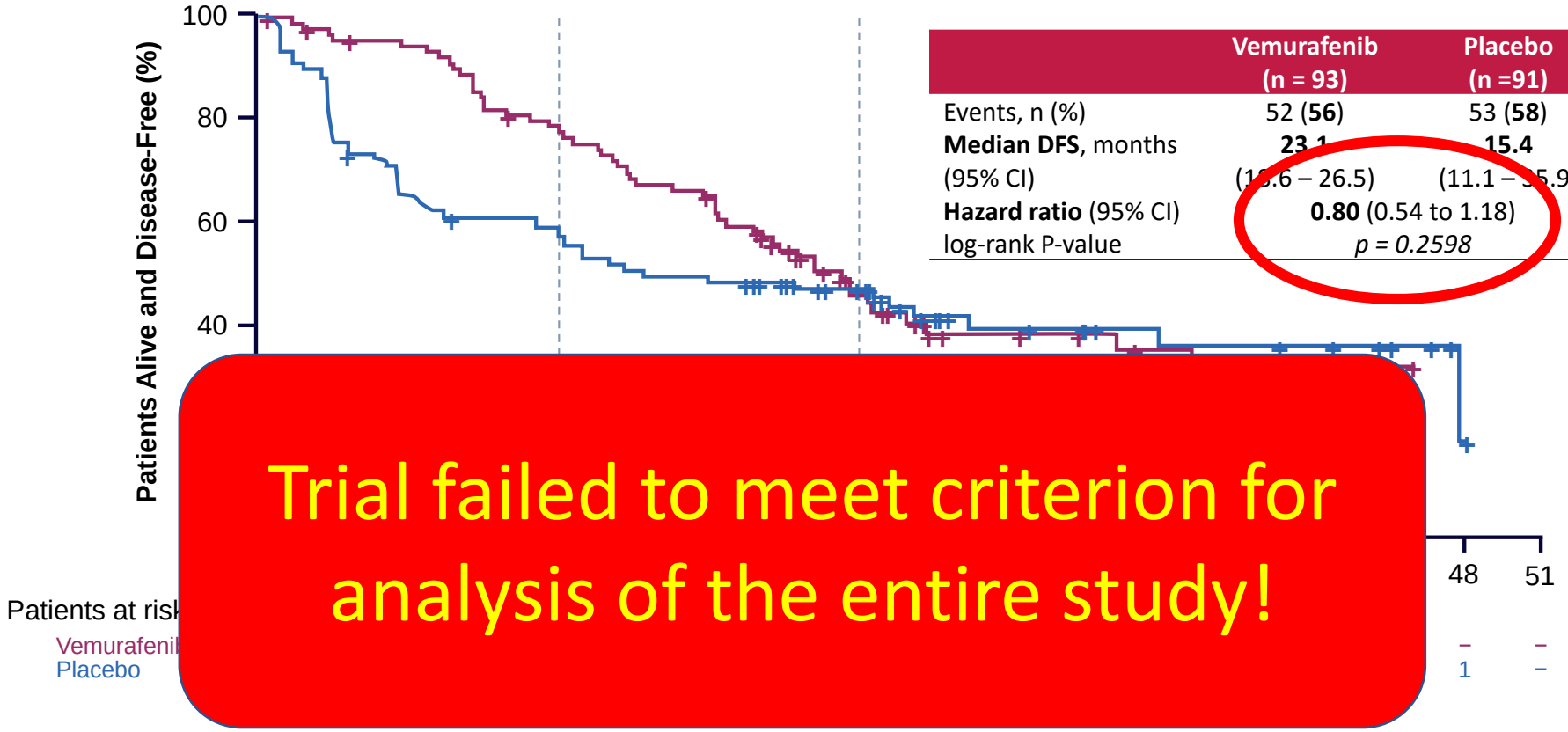


- **Primary endpoint**
  - DFS
- **Secondary endpoints**
  - DMFS
  - OS
  - Safety
  - HRQoL

- **Hierarchical testing of DFS in C2 before C1 was prespecified to maintain an overall Type I error rate <0.05 (two-sided)**
- **Only a *p*-value for C2 of ≤0.05, would provide the opportunity for the analysis of C1 to be considered statistically significant.**

Lewis et al. ESMO 2017

Relapse-Free Survival (Cohort 1 – Stage IIIC)

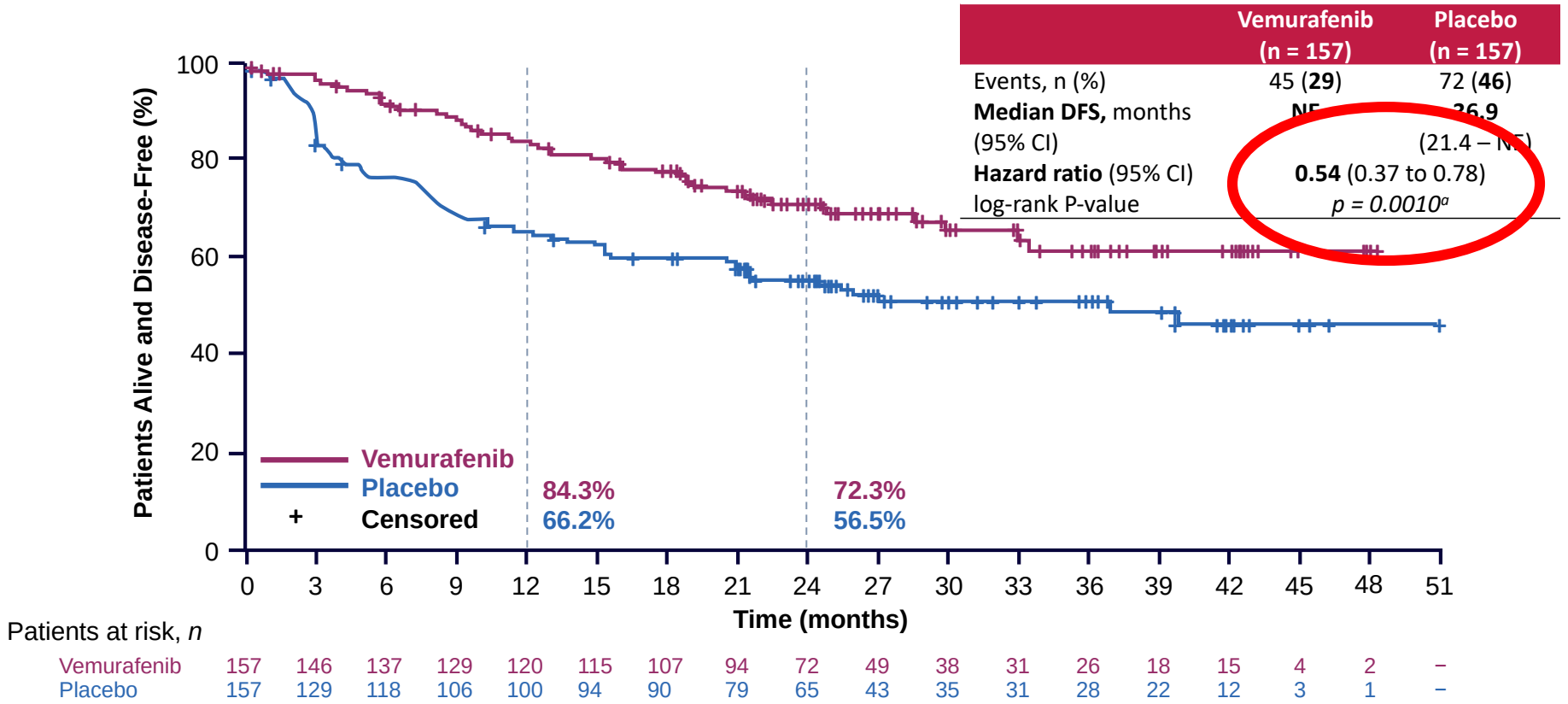


	Vemurafenib (n = 93)	Placebo (n =91)
Events, n (%)	52 (**56**)	53 (**58**)
Median DFS, months	**23.1**	**15.4**
(95% CI)	(15.6 – 26.5)	(11.1 – 35.9)
Hazard ratio (95% CI)	**0.80** (0.54 to 1.18)	
log-rank P-value	*p = 0.2598*	

Trial failed to meet criterion for analysis of the entire study!

Lewis et al. ESMO 2017

Relapse-Free Survival (Cohort 2 – Stage IIC-IIIB)



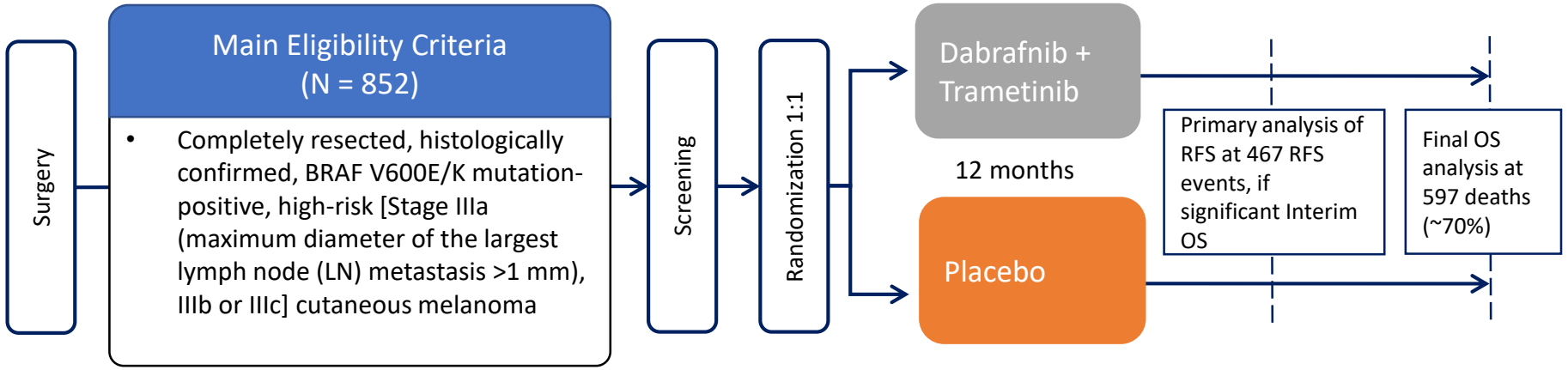
Lewis et al. ESMO 2017

BRIM8 Summary

- Randomized Phase III trial of adjuvant vemurafenib in patients with Stage IIC-IIIC, BRAF mutant melanoma
- Failed to meet its endpoint; due to rapid ”closing of the gap” in the RFS curves after patients stopped therapy
- Encouraging data in patients with Stage IIC-IIIB
- Predictable, reversible toxicity
- 20% discontinuation rate in Vem arm (2% in placebo arm)
- ~20% vs 4+% rate of KA/SCC/BCC, no difference in rate of non-NMSC

COMBI-AD – Study Design

- Phase III randomized double blind study of dabrafenib + trametinib in the adjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection

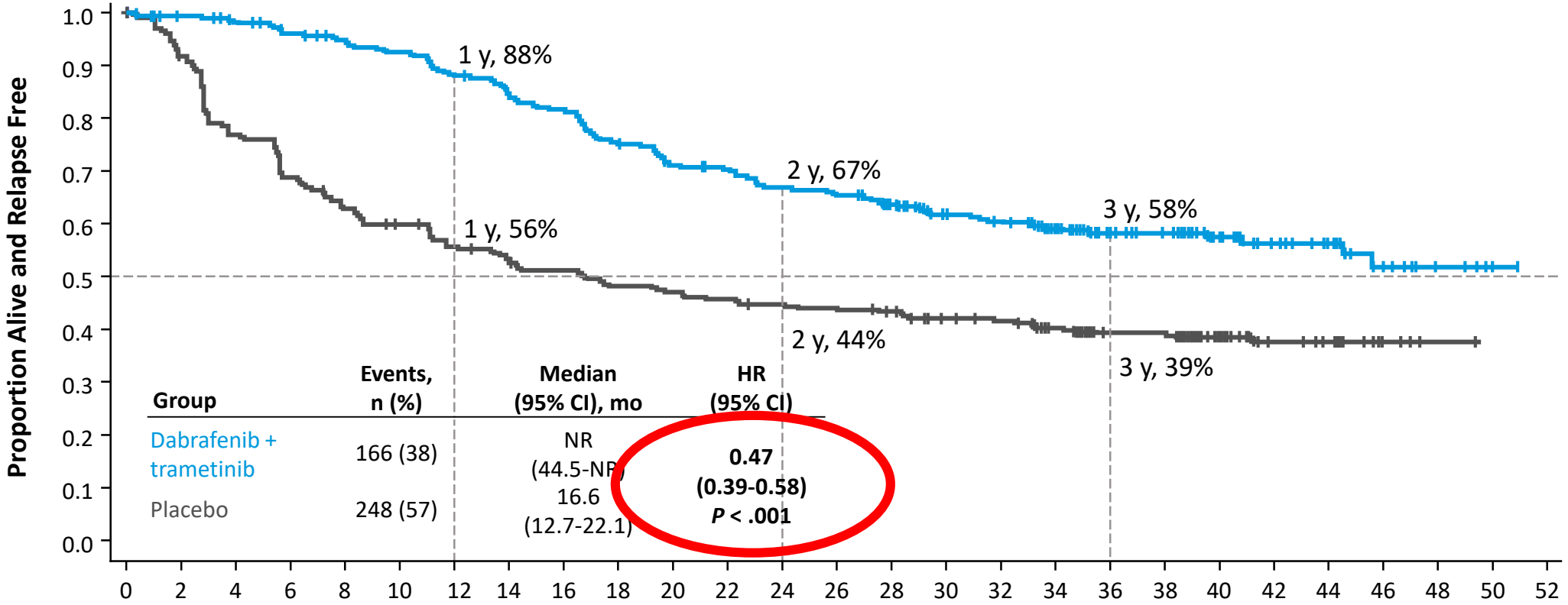


Stratification: BRAF mutation status (V600E, V600K) and stage of disease (IIIa, IIIb, IIIc)
Crossover is not permitted
Primary endpoint: RFS
Secondary endpoints: OS, DMFS, freedom from relapse, safety

- This study is ongoing, but no longer recruiting participants

Hauschild, A et al. Oral presented at ESMO 2017 (Abstract #LBA6PR).

Relapse-Free Survival (Primary Endpoint)

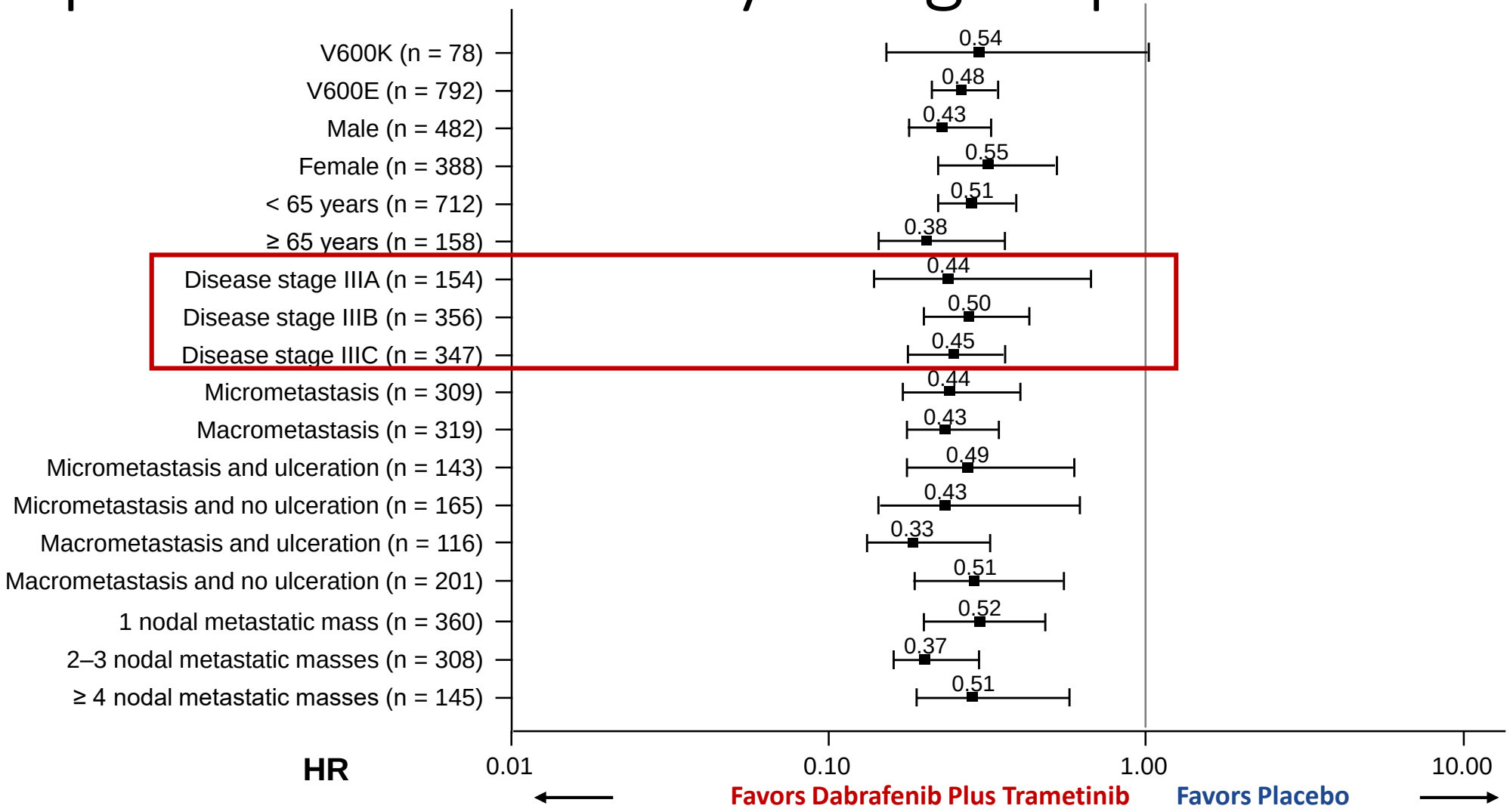


No. at Risk																										
D+T	438	413	405	392	382	373	355	336	325	299	282	276	263	257	233	202	194	147	116	110	66	52	42	19	7	2	0
Placebo	432	387	322	280	263	243	219	203	198	185	178	175	168	166	158	141	138	106	87	86	50	33	30	9	3	0	0

NR, not reached.

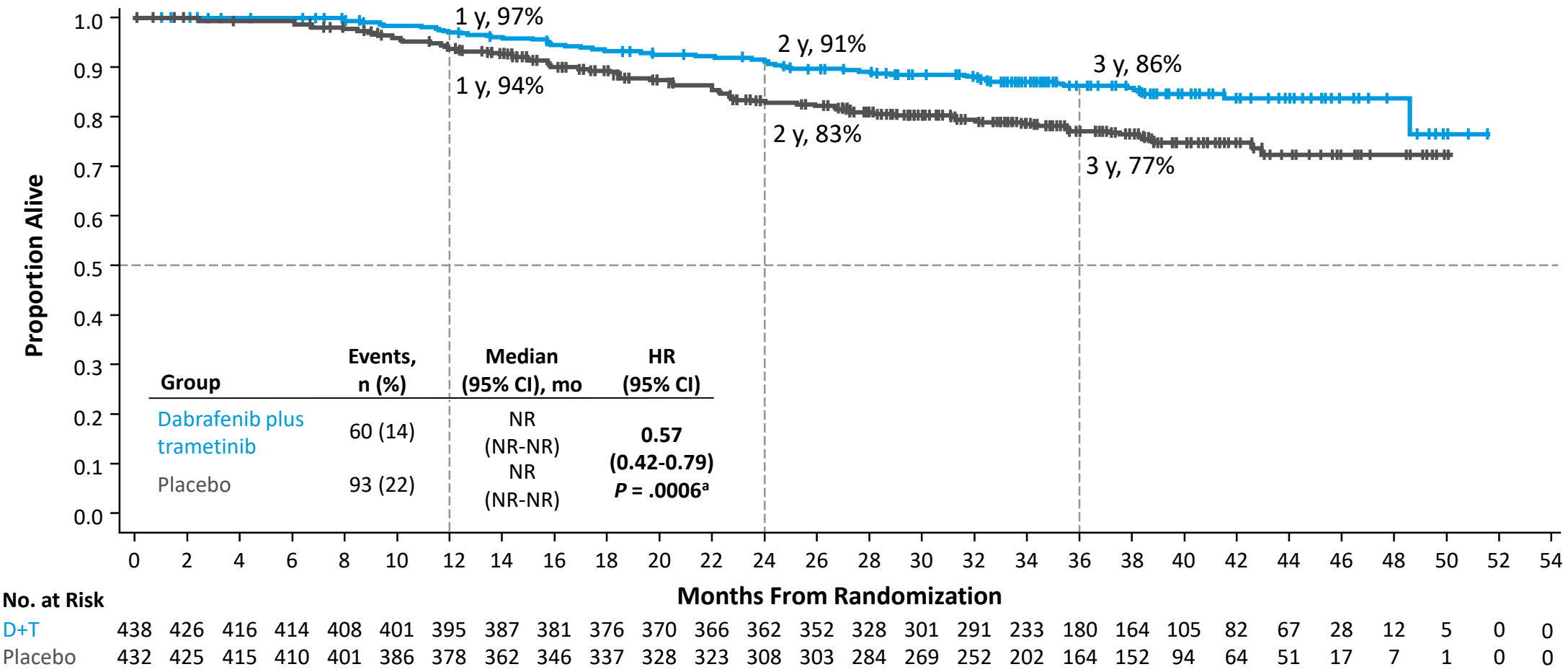
Hauschild, A et al. Oral presented at ESMO 2017 (Abstract #LBA6PR).

Relapse-Free Survival By Subgroup



Hauschild, A et al. Oral presented at ESMO 2017 (Abstract #LBA6PR).

Overall Survival (First Interim Analysis)



[a] Prespecified significance boundary (*P* = .000019)

Hauschild, A et al. Oral presented at ESMO 2017 (Abstract #LBA6PR).

Safety Summary

AE Category, n (%)	Dabrafenib Plus Trametinib (n = 435)	Placebo (n = 432)
Any AE	422 (97)	380 (88)
AEs related to study treatment	398 (91)	272 (63)
Any grade 3/4 AE	180 (41)	61 (14)
Any SAE	155 (36)	44 (10)
SAEs related to study treatment	117 (27)	17 (4)
Fatal AEs related to study drug	0	0
AEs leading to dose interruption	289 (66)	65 (15)
AEs leading to dose reduction	167 (38)	11 (3)
AEs leading to treatment discontinuation[a]	114 (26)	12 (3)

[a] Most common AEs leading to treatment discontinuation in the dabrafenib plus trametinib are were pyrexia (9%) and chills (4%).
AE, adverse event; SAE, serious adverse event.

Hauschild, A et al. Oral presented at ESMO 2017 (Abstract #LBA6PR).

COMBI-AD Summary

- Randomized Phase III trial of adjuvant dab/tram in patients with Stage III, BRAF mutant melanoma
- Met its primary endpoint (RFS, HR 0.47) and secondary endpoint (OS, HR 0.57)
- Improvement maintained in all subgroups with consistent hazard ratios
- Predictable, reversible toxicity
- 26% discontinuation rate in dab/tram arm (3% in placebo arm)
- No significant difference in rate of additional malignancies

Key points (1)

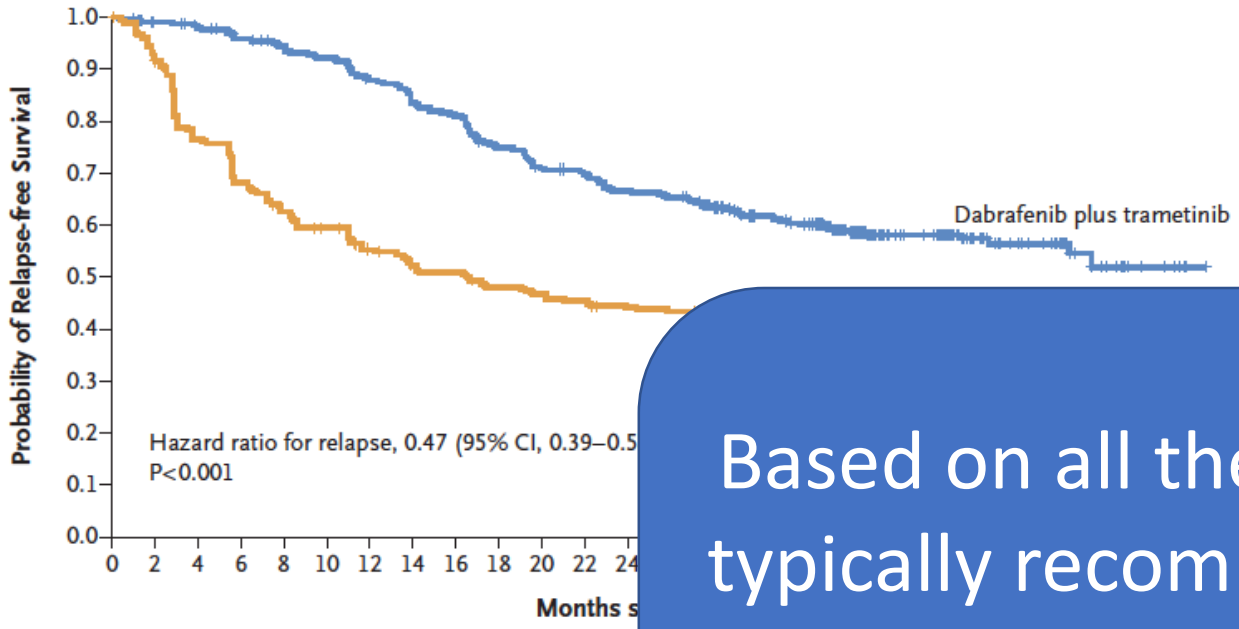
A) Patients with the least amount of disease may be the best group to treat with BRAF targeted therapy.

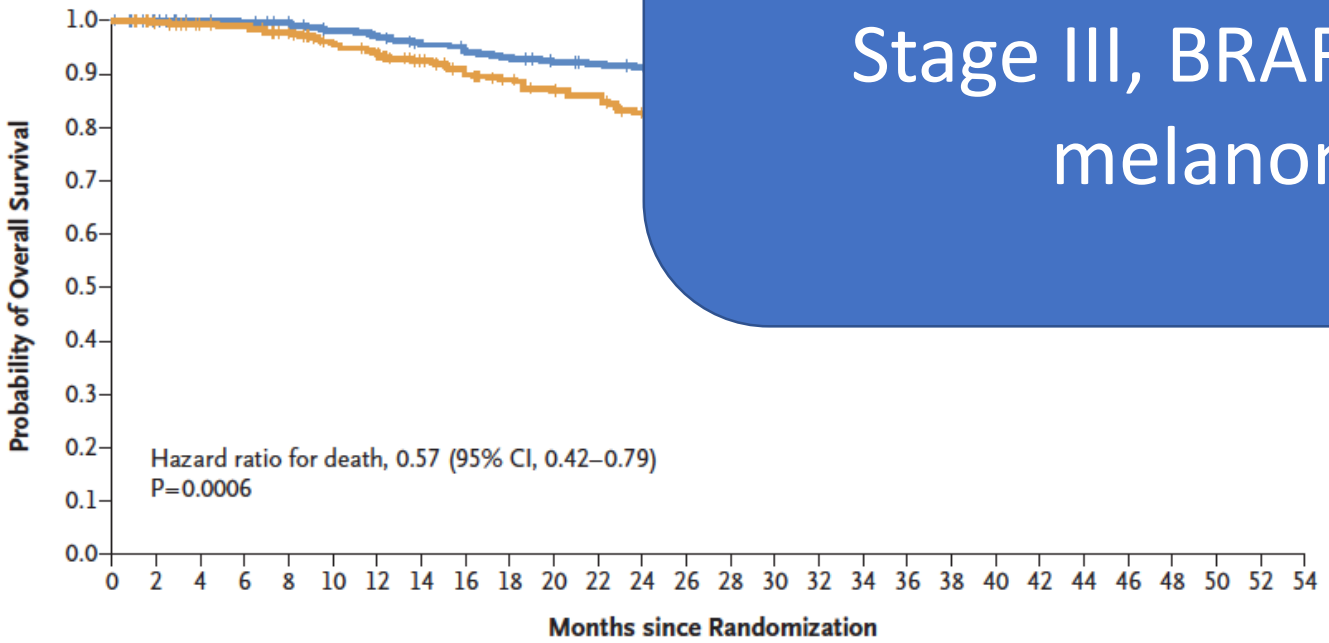
B) BRAF targeted therapy appears to curative in the adjuvant setting and is not in the metastatic setting.

Key points (2)

C) Adjuvant immunotherapy is associated with irreversible side effects in >20% of patients.

D) Adjuvant immunotherapy appears to be curative in the adjuvant setting and metastatic setting.





Based on all these factors, we typically recommend adjuvant BRAF/MEK for patients with Stage III, BRAF mutant melanoma

nt BRAFi/MEKi
associated with
FS and OS and…

use permanent
uch as DM1,
roid, adrenal
insufficiency, etc.

Hauschild, A et al. Oral presented at ESMO 2017 (Abstract #LBA6PR)
Long et al. NEJM 2017

Obrigado!