Randomised Phase II study of BRAF inhibitor dabrafenib vs combination with MEK inhibitor trametinib in BRAF V600 mutant metastatic melanoma

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Disclosures

- G.V. Long: has participated in advisory boards for GlaxoSmithKline, Roche and Bristol-Myers Squibb; has received honoria and research funding from Roche
- J. Sosman: has received research funding from GlaxoSmithKline
- A. Daud: no disclosures
- J. Weber: has participated in advisory boards for and has received honoraria from GlaxoSmithKline
- K. Flaherty: has participated in advisory boards for, acted as compensated consultant for, and has received research funding from GlaxoSmithKline
- J. Infante: has participated in advisory boards for GlaxoSmithKline without compensation
- O. Hamid: has acted as an uncompensated consultant for GlaxoSmithKline; has received honoria and research funding from Bristol-Myers Squibb
- L. Schuchter: has participated in advisory boards for Merck, and has received research funding from Merck, GlaxoSmithKline and Genentech
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- P. Sun: is an employee of GlaxoSmithKline, and owns GlaxoSmithKline stocks and shares
- K.B. Kim: has received research funding from GlaxoSmithKline
- S. Little: is an employee of GlaxoSmithKline, and owns GlaxoSmithKline stocks and shares
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Rationale for Combination

BRAFi (dabrafenib)
- PFS 5.1 mo; RR 53%[1]
- Hyperproliferative skin AEs

MEKi (trametinib)
- OS HR 0.54 v chemo
- PFS 4.8 mo; RR 22%[2]
- Rash AE

Preclinical BRAFi +MEKi
- Delays BRAFi resistance
- ↓ Hyperproliferative skin AE

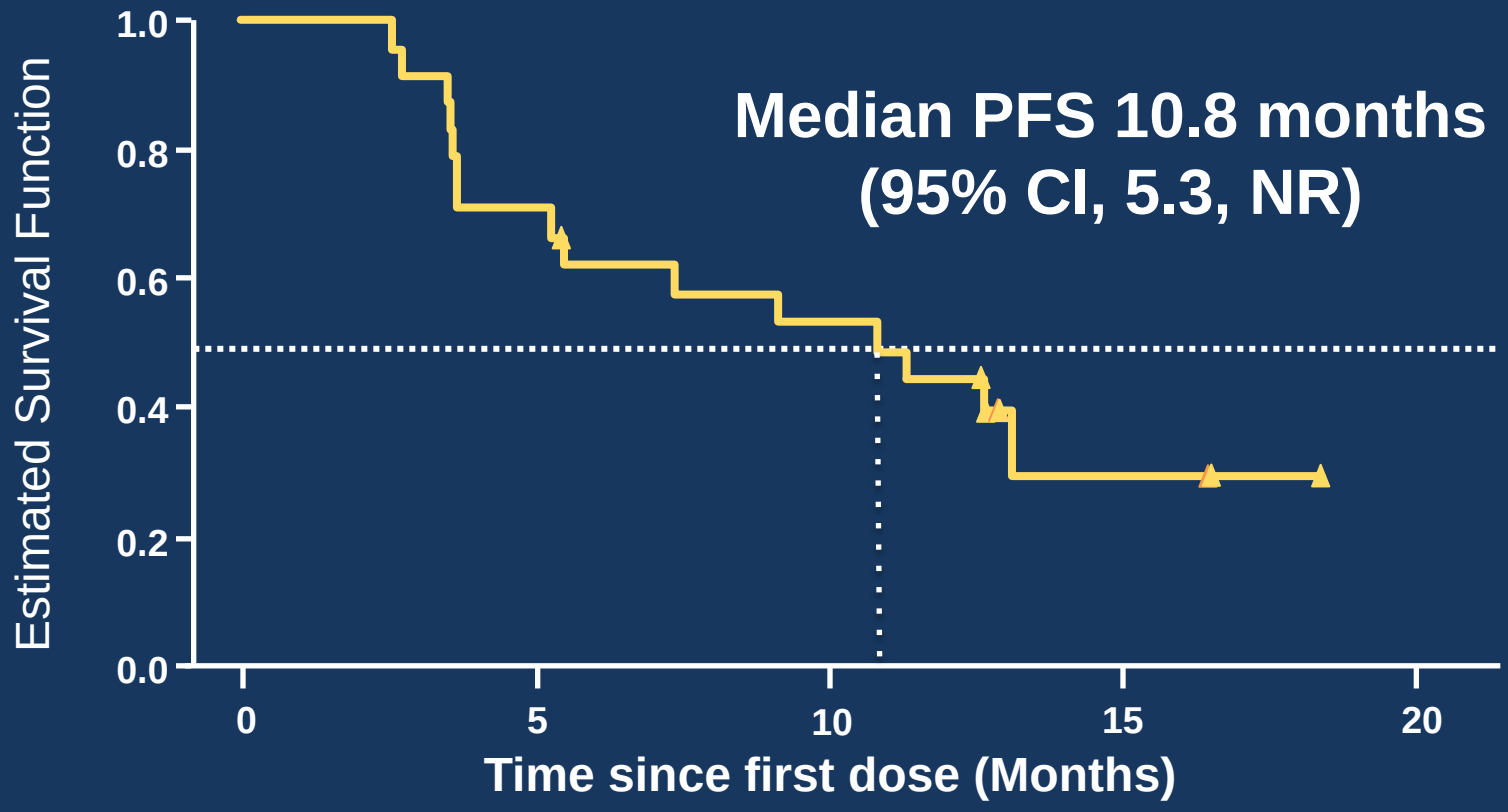
1. Hauschild A, *Lancet* 2012; 2. Flaherty K, *NEJM* 2012

Study Design and Objectives

Part A	Drug–drug interaction	• Trametinib effects on dabrafenib PK
Part B	Dose escalation	• Safety/tolerability • Determine Phase II dose • Steady-state PK • Clinical activity
	Expansion cohorts	
Part C	Randomized Phase II	• PFS, RR and duration of response dab vs dab+ tram • Assess safety/tolerability
Part D	dabrafenib (HPMC) + trametinib	• Safety/tolerability • Characterize PK of dabrafenib HPMC capsules

Progression Free Survival

Part B: BRAFi naïve Combination D+T 150/2



Part C Randomized Phase II Study Design

- BRAF $V600^{E/K}$ metastatic melanoma
- No prior BRAFi or MEKi
- Up to 1 prior treatment
- Treated and stable brain mets

N=162

R A N D O M I Z E

Monotherapy D 150mg BID*
N= 54

Combination D+T
150mg BID/1mg QD
N= 54

Combination D+T
150mg BID/2mg QD
N= 54

*cross over to Combination D+T 150/2 after progression allowed

Objectives

- PFS, ORR, duration of response, rate of cuSCC
- OS, safety

Patient Characteristics

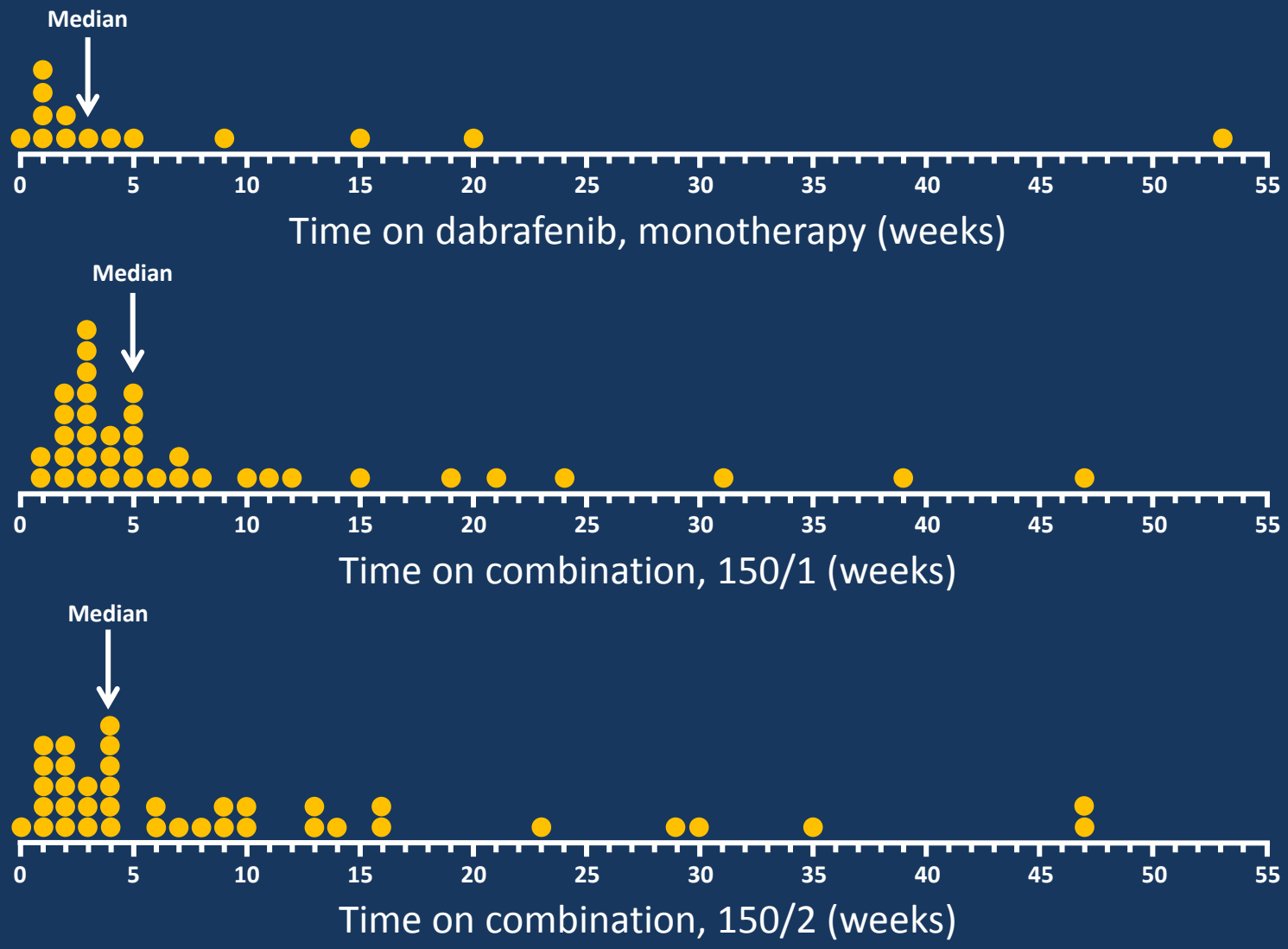
	Monotherapy D (n=54)	Combination D+T 150/1 (n=54)	Combination D+T 150/2 (n=54)
Age, Median (range)	49.5 (18-82)	49 (23-85)	57.5 (27-79)
Male	29 (54)	30 (56)	34 (63)
ECOG PS 0	34 (63)	38 (70)	35 (65)
1	20 (37)	16 (30)	19 (35)
BRAF mutation status			
V600E	45 (83)	45 (83)	47 (87)
V600K	9 (17)	9 (17)	7 (13)
Stage IV M1c	37 (69)	33 (61)	38 (70)
LDH > ULN	27 (50)	25 (46)	22 (41)
History of Brain Mets	4 (7)	7 (13)	2 (4)
Prior Immunotherapy	8 (15)	16 (30)	13 (24)
Prior Chemotherapy	12 (22)	15 (28)	7 (13)

Treatment-Related AEs ≥ 20% (All Grades)

	Monotherapy D (n=53*)	Combination D+T 150/1 (n=54)	Combination D+T 150/2 (n=55*)
Pyrexia†	12 (23)	34 (63)	37 (67)
Chills	9 (17)	22 (41)	28 (51)
Night Sweats	3 (6)	8 (15)	12 (22)
Fatigue	18 (34)	25 (46)	25 (45)
Arthralgia	14 (26)	22 (41)	14 (25)
Myalgia	9 (17)	11 (20)	11 (20)
Vomiting	6 (11)	15 (28)	19 (35)
Nausea	9 (17)	18 (33)	18 (33)
Diarrhea	12 (23)	8 (15)	17 (31)
Alopecia	16 (30)	2 (4)	3 (5)
Peripheral Edema	4 (8)	9 (17)	11 (20)

† pyrexia = temperature ≥ 38.5 degrees Celsius
*Mono D (n=53) - 1 patient in this arm received Combination D+T 150/2 (n=55) due to a dispensing error

Time to First Pyrexia



Treatment Related Grade 3-4 AEs (≥ 5%)

	Monotherapy D (n=53)	Combination D+T 150/1 (n=54)	Combination D+T 150/2 (n=55)
	Grade 3	**Grade 3**	**Grade 3**
Pyrexia	0	5 (9)	3 (5)
Fatigue	3 (6)	1 (2)	2 (4)
Acute renal failure	0	0	3 (5)
Hyponatremia	0	4 (7)	4 (7)
↑γ-glutamyltransferase	0	6 (11)	2 (4)
↑ Alkaline phosphatase	0	3 (6)	0
Anemia	0	3 (6)	2 (4)
Lymphopenia	0	3 (6)	3 (5)
Neutropenia*	1 (2)	1 (2)	3 (5)
Pulmonary embolism	0	1 (2)	2 (4)
Back pain	1 (2)	0	3 (5)

4 deaths, not treatment related - all in Dab + Tram

*Grade 4 AEs: 3 (5%) neutropenia in 150/2

BRAFi and MEKi Associated Adverse Events

	Monotherapy D (n=53)	Combination D+T 150/1 (n=54)	Combination D+T 150/2 (n=55)
Skin papilloma	8 (15)	4 (7)	2 (4)
Hyperkeratosis	16 (30)	3 (6)	5 (9)
Squamous cell carcinoma/ keratoacanthoma	10 (19)	1 (2) p=0.004	4 (7) p=0.09
Acneiform rash	2 (4)	6 (11)	9 (16)
↓ Ejection Fraction	0	2 (4)	5 (9)
Chorioretinopathy	0	0	1 (2)

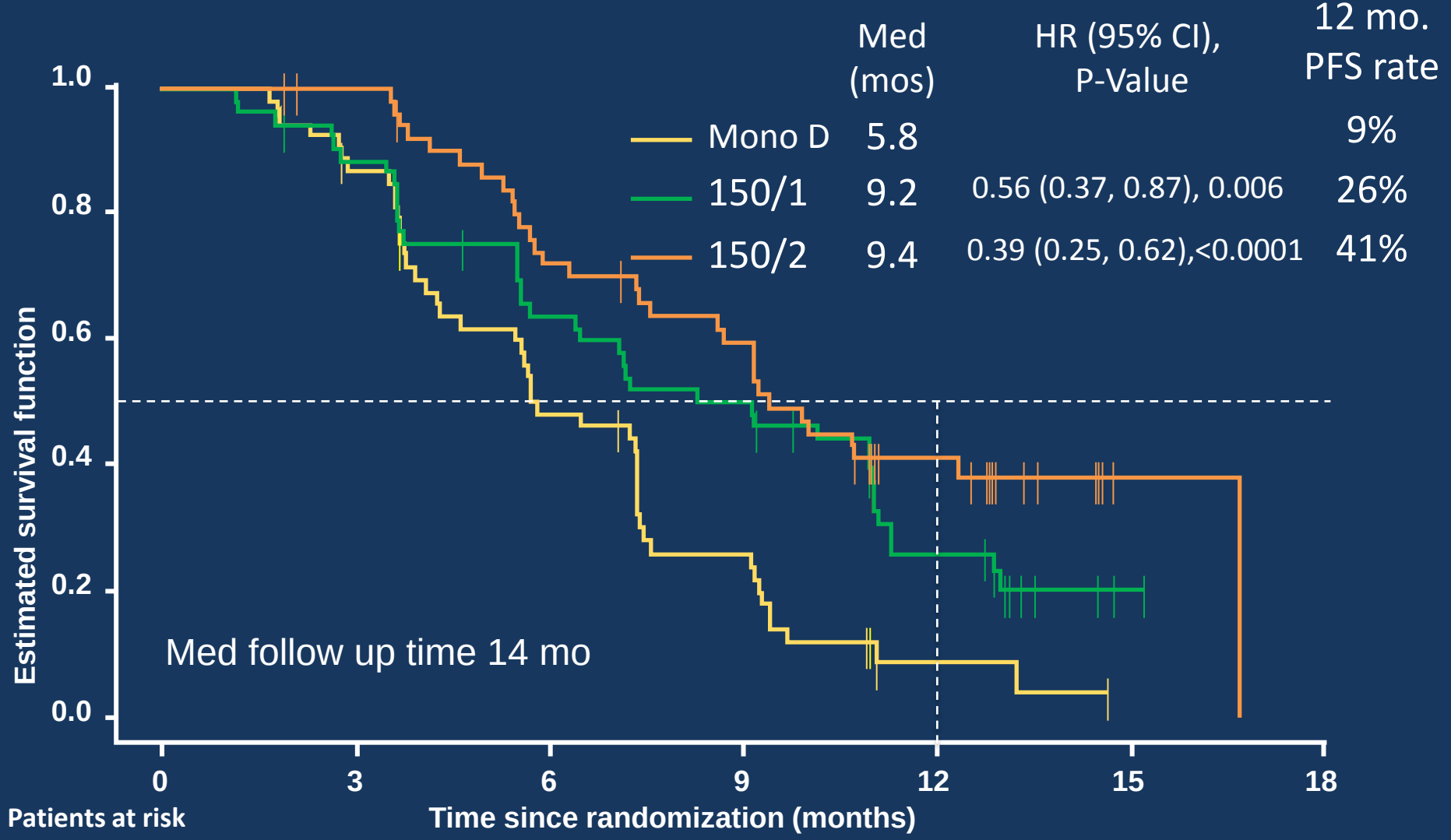
*Skin toxicities include multiple terms
No cases of RVO

Confirmed Response Rate

	Mono D (N=54)	Combination D+T 150/1 (N=54)*	Combination D+T 150/2 (N=54)
CR	2 (4)	3 (6)	5 (9)
PR	27 (50)	24 (44)	36 (67)
SD	22 (41)	24 (44)	13 (24)
PD	3 (6)	2 (4)	0
Response Rate†	29 (54%)	27 (50%) p=0.77	41 (76%) p=0.026
Duration of Response Months (95% CI)	5.6 (4.5, 7.4)	9.5 (7.4, NA)	10.5 (7.4, 14.9)

*1 patient in 150/1 group was not evaluable

Progression-Free Survival



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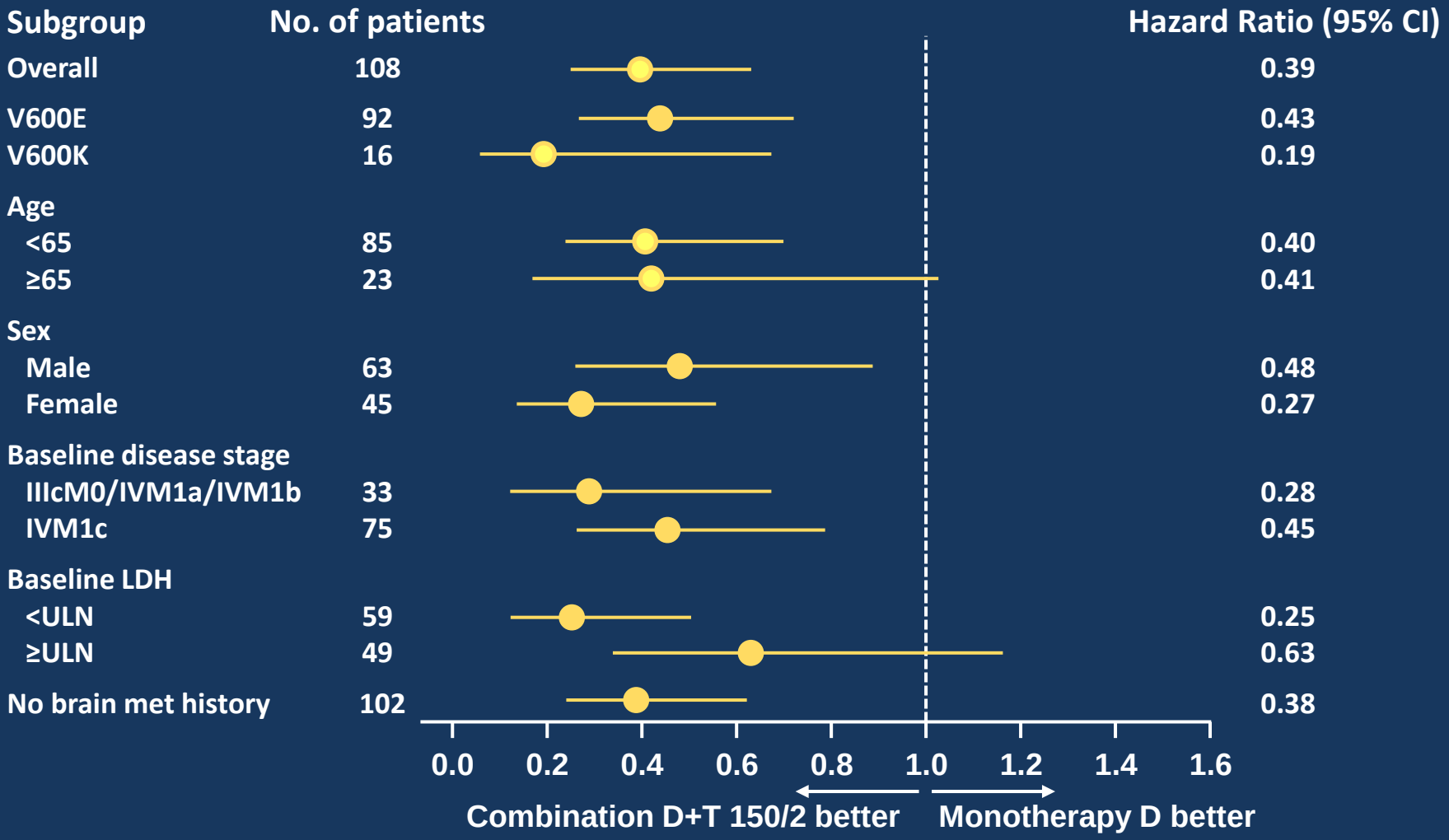
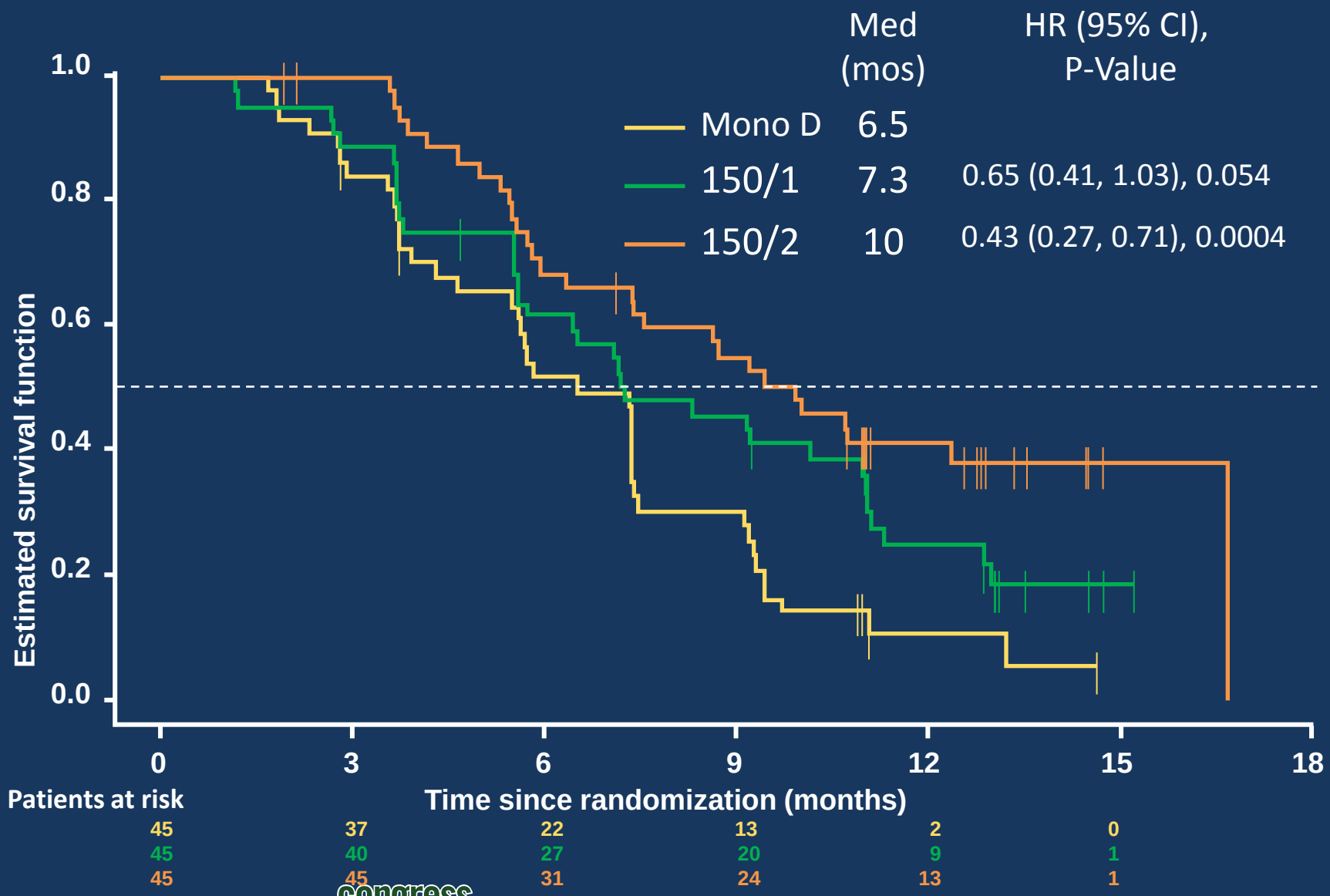
PFS Subgroup Analyses

Combination D+T 150/2 vs Monotherapy D



Progression-Free Survival (V600E)



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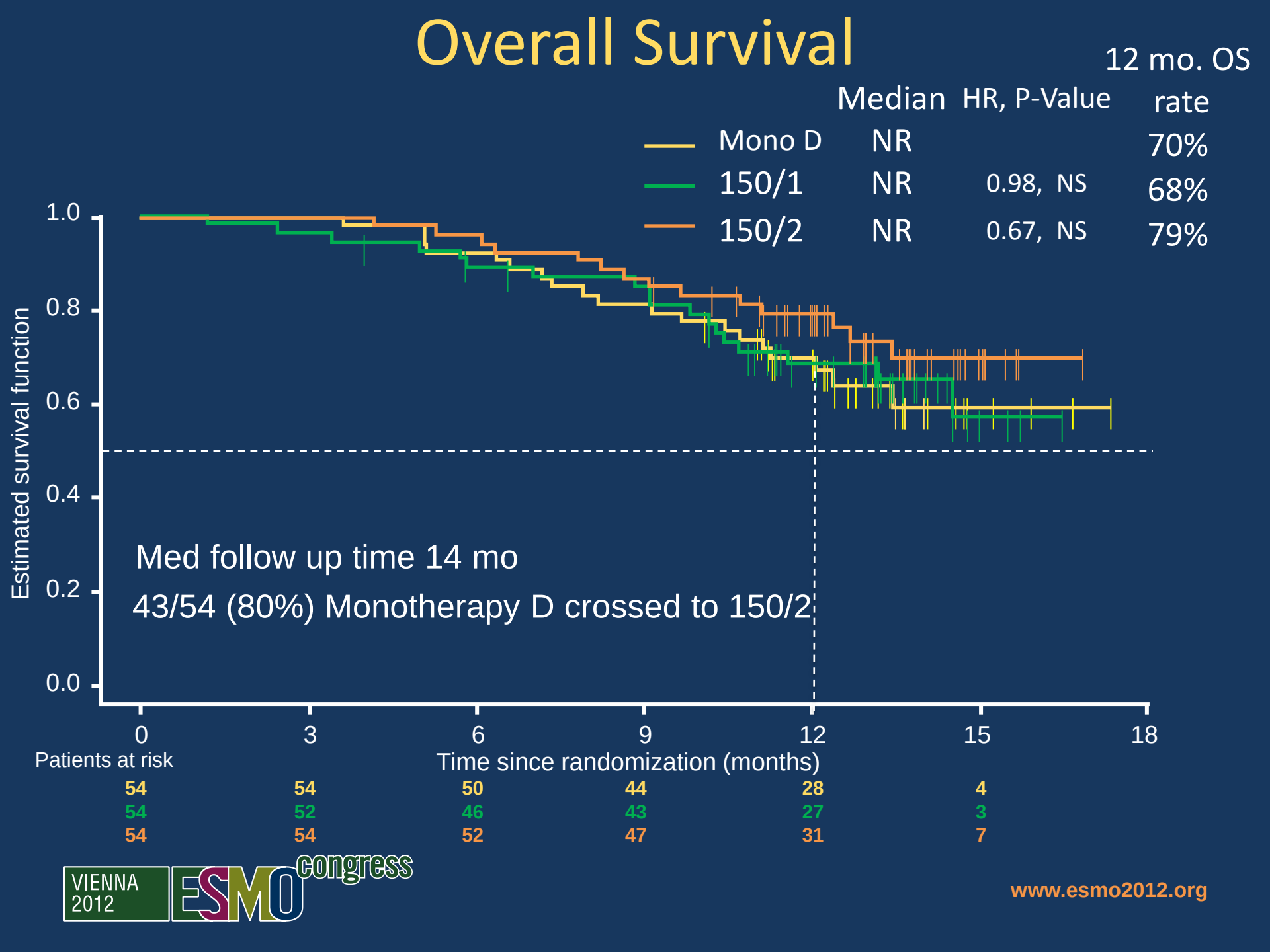
Overall Survival



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Conclusions

- This is the 1st kinase-kinase combination to:
  - Show enhanced anti-tumour activity over the single agent
  - Reduce specific oncogenic toxicities, with biological rationale
- Combined dabrafenib and trametinib prolongs PFS and ORR over dabrafenib alone in $BRAF^{V600}$ metastatic melanoma:
  - Med PFS 9.4 mo vs 5.8 mo; HR 0.39; $p<0.0001$
  - ORR 76% vs 54%; $p=0.026$
- Combined dabrafenib and trametinib safety profile was tolerable and manageable:
  - ↓cuSCC events
  - ↑ pyrexia, neutropenia and GI toxicities
- Two phase III studies (COMBI-d and COMBI-v) are ongoing

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