Efficacy and Safety of Dabrafenib Plus Trametinib in Patients With Radioactive Iodine-Refractory *BRAF* V600-Mutant Differentiated Thyroid Cancer

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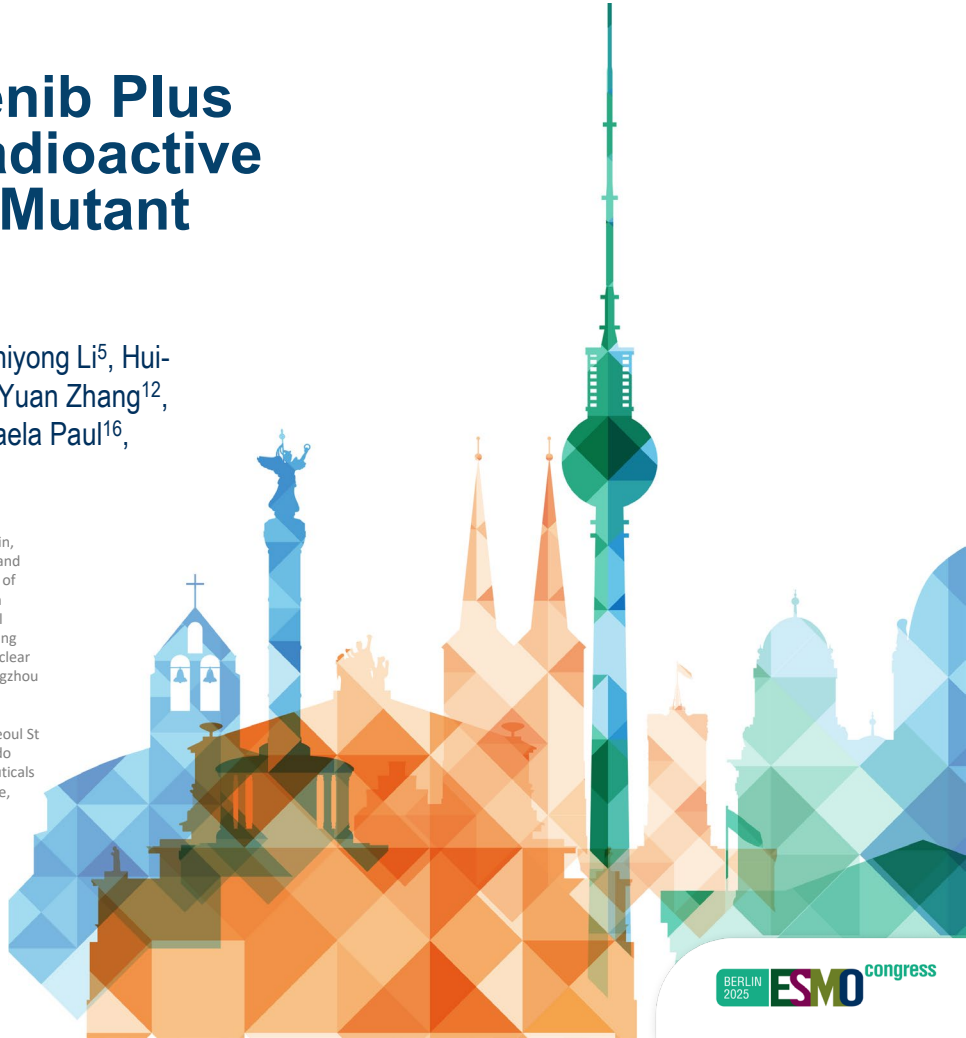

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DECLARATION OF INTERESTS

Dr. Lori J. Wirth received consulting fees from Eisai, Inc, Coherus BioSciences, AbbVie Inc, Bicara Therapeutics, Fore Biotherapeutics, Leo Pharma, Pyxis, Tubulis, Merck, Novartis.

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Treatment Landscape

- Lenvatinib and sorafenib are recommended as the first-line[1,2] and cabozantinib as a second-line treatment of RAI-refractory DTC.[3,4,5]
- While first-line treatment is often effective in RAI-refractory DTC, treatment failure due to disease progression or intolerable treatment-related AEs is common.[6,7]
- Hence, there is a need for more effective therapies with acceptable toxicity.

Clinical Trial	Treatment Type	Treatment	PFS	ORR	OS	Common TEAEs
DECISION[1]	First-line	Sorafenib (n=207) vs placebo (n=210)	10.8 vs. 5.8 months HR: 0·59 (95% CI: 0·45–0·76) P<0.0001	12.2% vs. 0.5% P<0.0001	Not reached HR: 0·80 (95% CI: 0·54–1·19) P=0·14	Hand–foot skin reaction (76.3%) Diarrhea (68.4%)
SELECT[2]	First-line	Lenvatinib (n=261) vs placebo (n=131)	18.3 vs. 3.6 months HR: 0.21 (99% CI: 0.14–0.31) P<0.001	64.8% vs. 1.5% P<0.001	Not reached HR: 0·73 (95% CI: 0·50–1·07) P=0·10	Hypertension (67.8%) Diarrhea (59.4%)
COSMIC-311[3]	Second-line	Cabozantinib (n=170) vs placebo (n=88)	11.0 vs. 1.9 months HR: 0.22 (96% CI: 0.15–0.32) P<0.0001	11% vs. 0% P=0.0003	19.4 months vs. NE HR: 0·76 (95% CI: 0.45–1·31) P-value not calculated	Diarrhea (62%) Palmar–plantar erythrodysesthesia (47%)

AE, adverse event; CI, confidence interval; DTC, differentiated thyroid cancer; HR, hazard ratio; PFS, progression-free survival; ORR, overall response rate; OS, overall survival; RAI, radioiodine-refractory; TEAE, treatment emergent adverse events' NE, not estimable; vs., versus.

1. Brose MS, et al. *Lancet.* 2014;384(9940):319–328. **2.** Schlumberger M, et al. *N Engl J Med* 2015;372:621-30. **3**. Brose MS, et al. *Cancer*. 2022;128(24):4203-4212. **4**. Duke ES, et al. *Clin Cancer Res*. 2022;28(19):4173-4177. **5**. News release. *Ipsen*. May 3, 2022. https://www.ipsen.com/press-releases/european-commission-approves-cabometyx-as-a-second-line-treatment-for-people-living-with-radioactive-iodine-refractory-differentiated-thyroid-cancer. 6. Enokida T, Tahara M. Cancers (Basel). 2021 Nov 4;13(21):5536. 7. Hamidi S, et al. *Front Endocrinol (Lausanne)*. 2023;14:1176731.

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Rationale

- Dabrafenib plus trametinib combination therapy has previously demonstrated robust antitumor activity in several *BRAF* V600E-driven cancers, including non–small cell lung cancer,[1] adjuvant melanoma,[2] glioma[3,4,5] and anaplastic thyroid cancer.[6]
- A phase 2 study recently showed the clinical benefit dabrafenib plus trametinib *BRAF*-positive RAI-refractory DTC.[7]
- Currently, there is no phase 3 study specifically for previously-treated *BRAF* V600E mutation-positive DTC.
- Here, we present the primary analysis from an ongoing phase 3 study evaluating the clinical benefit of dabrafenib plus trametinib in previously treated adult patients with locally advanced/metastatic, RAI-refractory *BRAF* V600E mutation–positive DTC.

DTC, differentiated thyroid cancer; RAI, radioiodine-refractory.

1. Planchard D, et al. *J Thorac Oncol*. 2022;17(1):103-115. **2**. Long GV, et al. N Engl J Med. 2024;391(18):1709-1720. **3**. Bouffet E, et al. *N Engl J Med*. 2023;389(12):1108-1120. **4**. Hargrave DR, et al. *J Clin Oncol*. 2023;41(33):5174-5183. 5. Wen PY, et al. *Lancet Oncology*, 2022;23(1)53-64. 6. Subbiah V, et al. *Ann Oncol*. 2022 Apr;33(4):406-415. **7**. Busaidy NL, et al. *Thyroid*. 2022;32(10):1184-1192.

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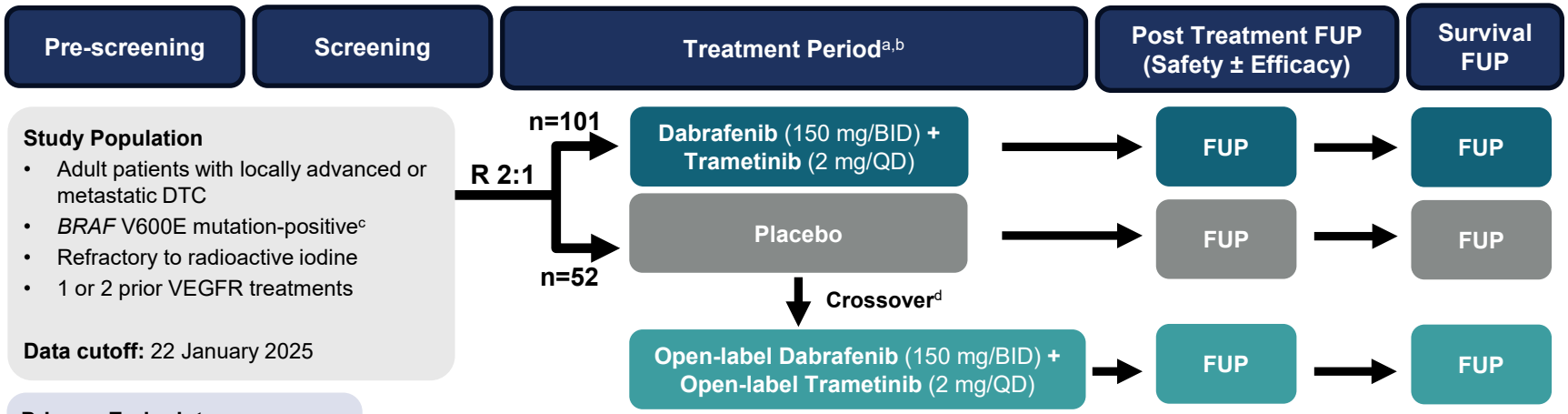
Study Design and Methods



[a]Until RECIST 1.1 PD by BIRC or unacceptable toxicity. [b]Treatment beyond RECIST PD is permittable. [c]As per Novartis-designated central laboratory result. [d]Crossover at BIRC confirmed PD upon investigator request during treatment or post-treatment FUP, as long as they have not initiated new anti-neoplastic therapy.

BID, twice-a-day; BIRC, Blinded Independent Central Review; DTC, differentiated thyroid cancer; FUP, follow-up period; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; QD, once-a-day; VEGFR, vascular endothelial growth factor receptor.

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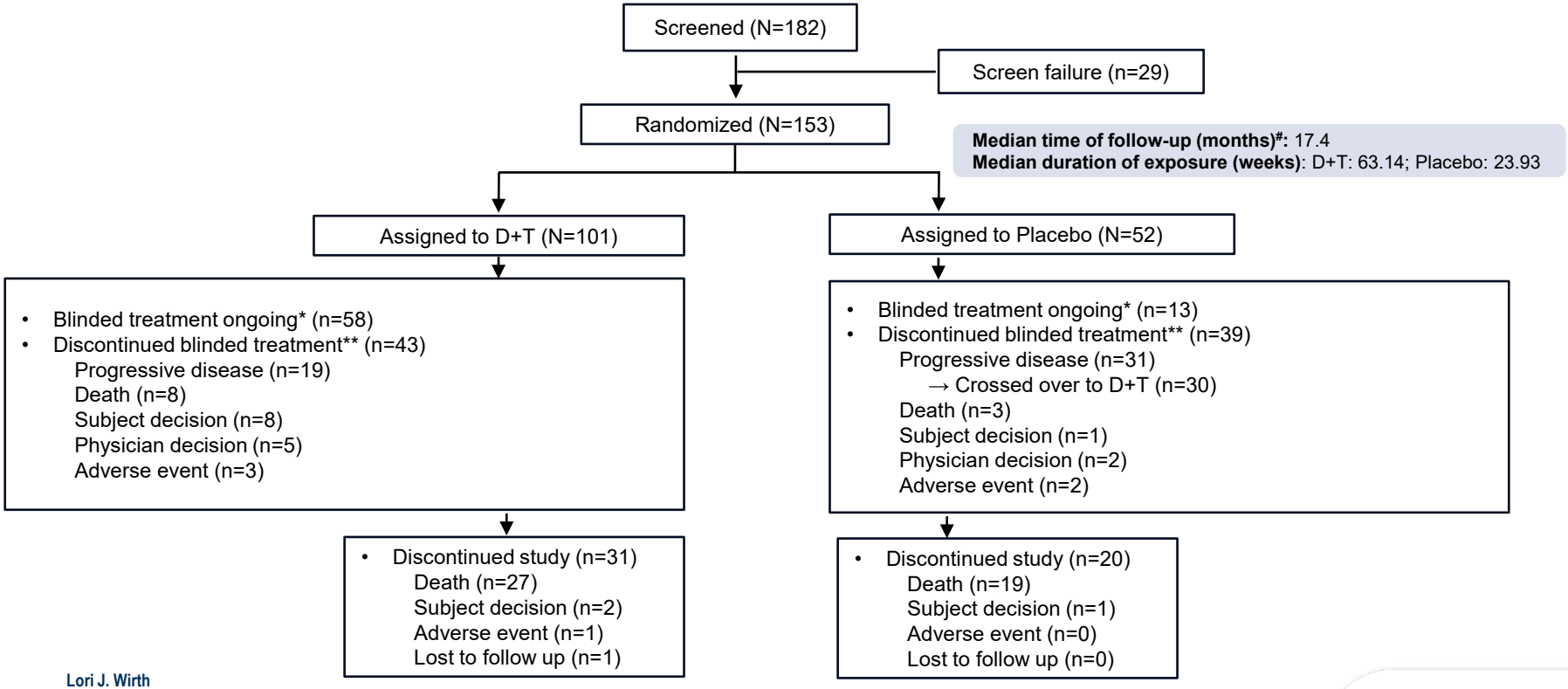
Patient Disposition



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*Blinded treatment still ongoing at the time of the data cut-off. **Treatment discontinuation reason for blinded treatment.
#Time from randomization to either study discontinuation or data cut-off, whichever comes first.
D+T, dabrafenib plus trametinib.

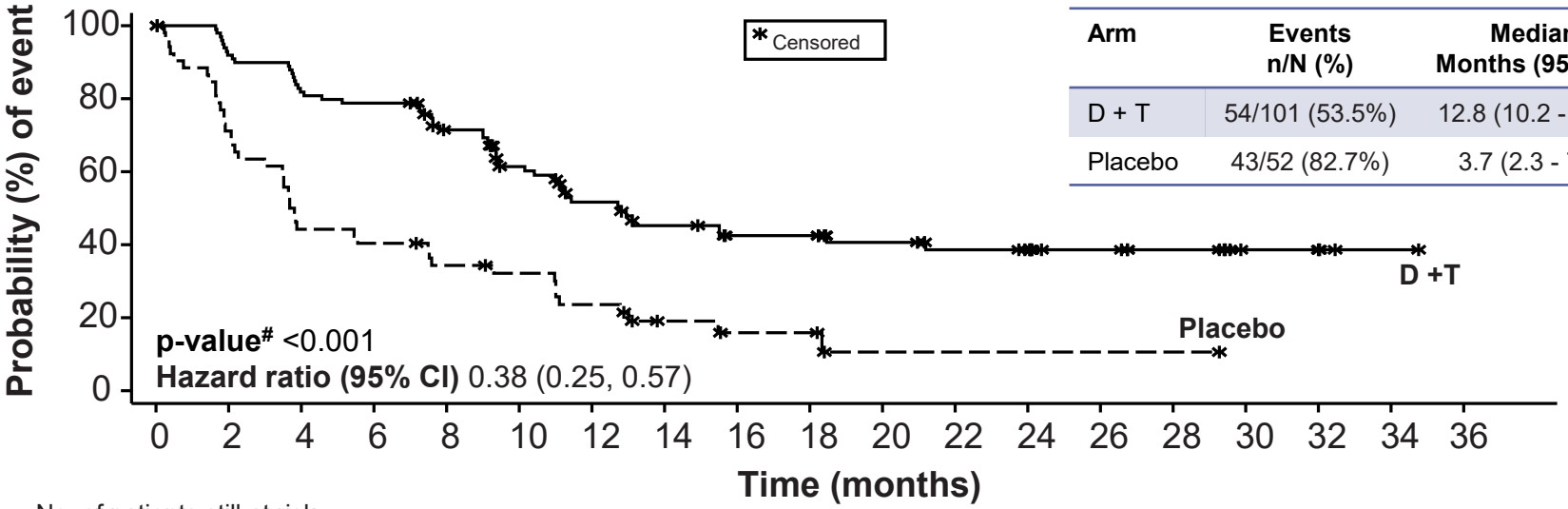
Baseline Characteristics

	Dabrafenib plus Trametinib (N=101)	Placebo (N=52)
Age (years, mean ± SD)	63.1 ± 10.28	61.5 ± 9.90
Female, n (%)	47 (46.5)	33 (63.5)
Race, n (%)		
White	9 (8.9)	9 (17.3)
Black or African American	1 (1.0)	2 (3.8)
Asian	90 (89.1)	41 (78.8)
Multiple	1 (1.0)	0
ECOG performance status, n (%)		
0	52 (51.5)	25 (48.1)
1	48 (47.5)	24 (46.2)
2	1 (1.0)	3 (5.8)
Prior VEGFR targeted therapy, n (%)		
1	79 (78.2)	40 (76.9)
2	22 (21.8)	12 (23.1)
Lenvatinib, n (%)		
Yes	32 (31.7)	16 (30.8)
No	69 (68.3)	36 (69.2)
Centrally confirmed V600E, n (%)		
V600E	101 (100.0)	52 (100.0)

Lori J. Wirth ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; VEGFR, vascular endothelial growth factor receptor.

PFS – Overall Population

Significantly longer PFS for dabrafenib plus trametinib group over placebo



Arm	Events n/N (%)	Median Months (95% CI)
D + T	54/101 (53.5%)	12.8 (10.2 - 21.2)
Placebo	43/52 (82.7%)	3.7 (2.3 - 7.5)

No. of patients still at risk

D + T	101	91	81	78	66	52	41	34	29	29	22	19	17	12	9	4	3	1	0
Placebo	52	37	23	21	17	15	11	6	4	4	1	1	1	1	1	0	0	0	0

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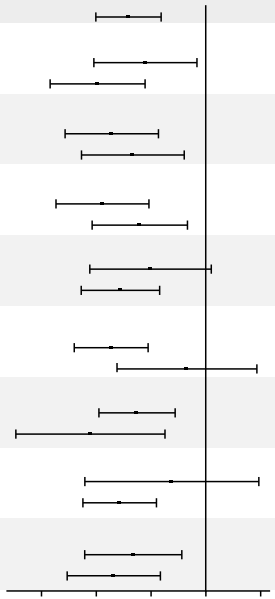
#One-sided p-value obtained from log-rank test stratified based on the randomization stratification factors.
CI, confidence interval; D + T, dabrafenib plus trametinib: PFS, progression-free survival.

PFS Across Key Prespecified Subgroups

Consistent PFS benefit with dabrafenib plus trametinib across all the subgroups

Subgroup	Hazard Ratio [95% CI]	Dabrafenib + Trametinib Events n/N (%)	Placebo Events n/N (%)
All Subjects	0.38 (0.25, 0.57)	54/101 (53.5)	43/52 (82.7)
Gender			
Male (N=73)	0.47 (0.24, 0.89)	32/54 (59.3)	14/19 (73.7)
Female (N=80)	0.25 (0.14, 0.46)	22/47 (46.8)	29/33 (87.9)
Age			
<65 years (N=81)	0.30 (0.17, 0.55)	24/50 (48.0)	26/31 (83.9)
>=65 years (N=72)	0.40 (0.21, 0.76)	30/51 (58.8)	17/21 (81.0)
Region			
China (N=76)	0.27 (0.15, 0.49)	31/53 (58.5)	21/23 (91.3)
Rest of the world (N=77)	0.43 (0.24, 0.79)	23/48 (47.9)	22/29 (75.9)
Type of prior treatment received			
Lenvatinib (N=47)	0.50 (0.23, 1.07)	17/32 (53.1)	11/15 (73.3)
Others (N=106)	0.34 (0.21, 0.56)	37/69 (53.6)	32/37 (86.5)
No .of VEGFR targeted therapies			
1 (N=120)	0.30 (0.19, 0.48)	40/80 (50.0)	35/40 (87.5)
2 (N=33)	0.79 (0.32, 1.91)	14/21 (66.7)	8/12 (66.7)
Baseline TSH			
<=0.5 (N=112)	0.42 (0.26, 0.68)	40/74 (54.1)	31/38 (81.6)
>0.5 (N=40)	0.23 (0.09, 0.6)	13/26 (50.0)	12/14 (85.7)
Baseline Thyroglobulin			
<=10 (N=31)	0.65 (0.22, 1.95)	13/23 (56.5)	5/8 (62.5)
>10 (N=122)	0.34 (0.21, 0.54)	41/78 (52.6)	38/44 (86.4)
ECOG Performance Status			
0 (N=77)	0.40 (0.22, 0.74)	26/52 (50.0)	19/25 (76.0)
1 and 2 (N=76)	0.31 (0.17, 0.56)	28/49 (57.1)	24/27 (88.9)



n/N = number of events/number of patients in the subgroup.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PFS, progression-free survival; TSH, thyroid stimulating hormone; VEGFR, vascular endothelial growth factor receptor.

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ORR – Overall Population

Significantly higher ORR for dabrafenib plus trametinib group over placebo

	Dabrafenib plus Trametinib (N=101)	Placebo (N=52)
BOR[a], n (%)		
CR	6 (5.9)	1 (1.9)
PR	52 (51.5)	1 (1.9)
SD[b]	30 (29.7)	29 (55.8)
PD	10 (9.9)	15 (28.8)
Not evaluable	2 (2.0)	4 (7.7)
Non-CR/Non-PD	1 (1.0)	2 (3.8)
ORR[c], n (%)	58 (57.4)	2 (3.8)
95% CI	(47.2, 67.2)	(0.5, 13.2)
p-value[d]	<0.001	
Odds ratio for ORR, (95% CI)	29.90, (7.02, 127.39)	
ORR difference (%), (95% CI)	53.36, (42.25, 64.47)	
DCR[e], n (%)	89 (88.1)	33 (63.5)
95% CI	(80.2, 93.7)	(49.0, 76.4)

[a]Best overall response based on BIRC assessment and using RECIST 1.1 , [b]Stable disease was defined as a response where there was neither sufficient tumor shrinkage to qualify for PR or CR, nor an increase in lesions which would have qualified for PD. [c]ORR of confirmed CR/PR. [d]Computed from Cochran Mantel-Haenszel chi-square test stratified based on randomization stratification factors. [e]DCR was calculated as the proportion of patients who achieved a BOR of CR or PR or stable disease, irrespective of the duration of the response / stabilization.
BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

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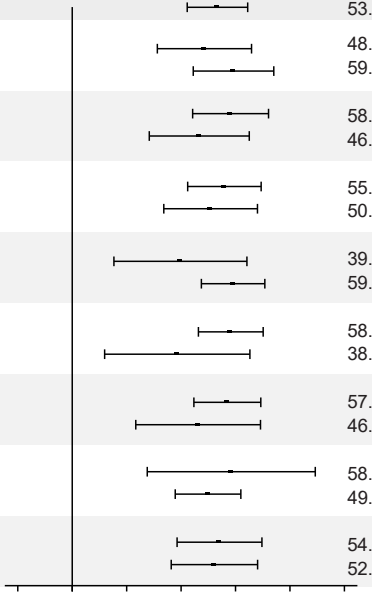
ORR Across Key Prespecified Subgroups

Consistent ORR benefit with dabrafenib plus trametinib across all the subgroups

Subgroup	ORR Difference (%) [95% CI]	Dabrafenib + Trametinib Responders n/N (%)	Placebo Responders n/N (%)
All Subjects	53.36 (42.25, 64.47)	58/101 (57.4)	2/52 (3.8)
Gender			
Male (N=73)	48.58 (31.28, 65.88)	29/54 (53.7)	1/19 (5.3)
Female (N=80)	59.26 (44.47, 74.06)	29/47 (61.7)	1/33 (3.0)
Age			
<65 years (N=81)	58.19 (44.25, 72.12)	29/50 (58.0)	0
>=65 years (N=72)	46.68 (28.31, 65.06)	29/51 (56.9)	2/21 (9.5)
Region			
China (N=76)	55.92 (42.42, 69.42)	30/53 (56.6)	0
Rest of the world (N=77)	50.85 (33.64, 68.06)	28/48 (58.3)	2/29 (6.9)
Type of prior treatment received			
Lenvatinib (N=47)	39.75 (15.32, 64.19)	17/32 (53.1)	2/15 (13.3)
Others (N=106)	59.11 (47.45, 70.77)	41/69 (59.4)	0
No .of VEGFR targeted therapies			
1 (N=120)	58.27 (46.37, 70.16)	48/80 (60.0)	1/40 (2.5)
2 (N=33)	38.60 (11.91, 65.28)	10/21 (47.6)	1/12 (8.3)
Baseline TSH			
<=0.5 (N=112)	57.00 (44.7, 69.29)	44/74 (59.5)	1/38 (2.6)
>0.5 (N=40)	46.26 (23.35, 69.17)	14/26 (53.8)	1/14 (7.1)
Baseline Thyroglobulin			
<=10 (N=31)	58.43 (27.57, 89.3)	17/23 (73.9)	1/8 (12.5)
>10 (N=122)	49.90 (37.85, 61.95)	41/78 (52.6)	1/44 (2.3)
ECOG Performance Status			
0 (N=77)	54.12 (38.53, 69.7)	30/52 (57.7)	1/25 (4.0)
1 and 2 (N=76)	52.25 (36.38, 68.12)	28/49 (57.1)	1/27 (3.7)



n/N = number of events/number of patients in the subgroup.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; TSH, thyroid stimulating hormone; VEGFR, vascular endothelial growth factor receptor.

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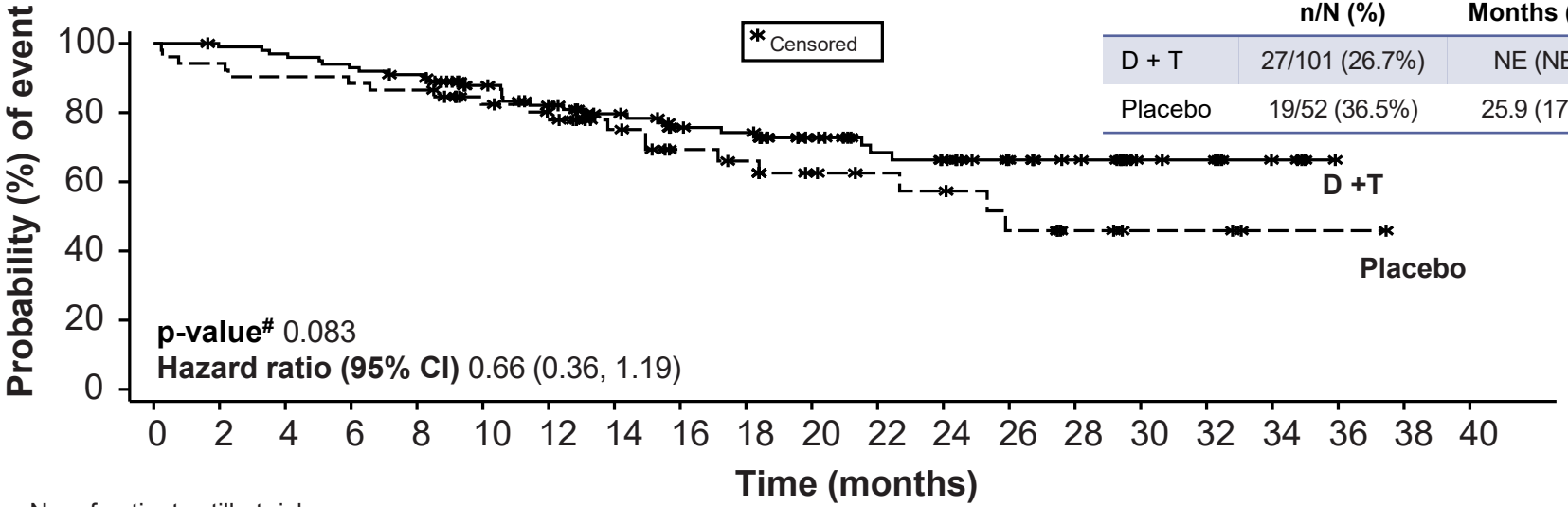
OS – Overall Population

A trend favoring the dabrafenib plus trametinib arm was observed at this OS interim look

Arm	Events n/N (%)	Median Months (95% CI)
D + T	27/101 (26.7%)	NE (NE - NE)
Placebo	19/52 (36.5%)	25.9 (17.1 - NE)



No. of patients still at risk

D + T	101	99	97	93	90	78	69	62	53	51	39	32	29	22	18	9	8	4	0	0	0
Placebo	52	49	47	46	45	38	35	27	21	19	14	12	11	8	5	3	3	1	1	0	0

#One-sided p-value obtained from log-rank test stratified based on the randomization stratification factors.
CI, confidence interval; D + T, dabrafenib plus trametinib; NE, not evaluable;: OS; overall survival.

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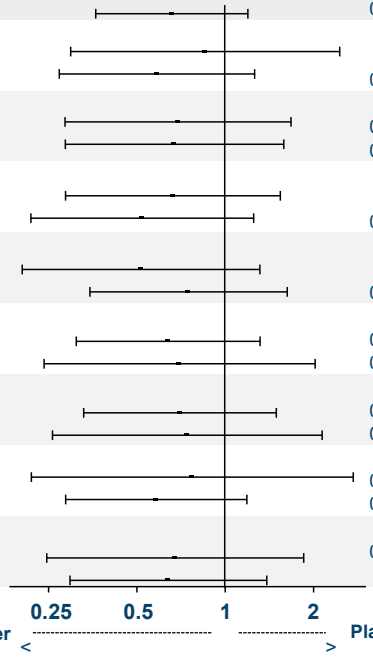
OS Across Key Prespecified Subgroups

Consistent OS benefit with dabrafenib plus trametinib across all the subgroups

Subgroup	Hazard Ratio [95% CI]	Dabrafenib + Trametinib Events n/N (%)	Placebo Events n/N (%)
All Subjects	0.66 (0.36, 1.19)	27/101 (26.7)	19/52 (36.5)
Gender			
Male (N=73)	0.85 (0.3, 2.46)	14/54 (25.9)	5/19 (26.3)
Female (N=80)	0.59 (0.27, 1.26)	13/47 (27.7)	14/33 (42.4)
Age			
<65 years (N=81)	0.69 (0.28, 1.68)	12/50 (24.0)	10/31 (32.3)
>=65 years (N=72)	0.67 (0.29, 1.58)	15/51 (29.4)	9/21 (42.9)
Region			
China (N=76)	0.66 (0.29, 1.54	15/53 (28.3)	9/23 (39.1)
Rest of the world (N=77)	0.52 (0.22, 1.25)	12/48 (25.0)	10/29 (34.5)
Type of prior treatment received			
Lenvatinib (N=47)	0.52 (0.2, 1.31)	11/32 (34.4)	8/15 (53.3)
Others (N=106)	0.75 (0.35, 1.63)	16/69 (23.2)	11/37 (29.7)
No .of VEGFR targeted therapies			
1 (N=120)	0.64 (0.31, 1.31)	18/80 (22.5)	13/40 (32.5)
2 (N=33)	0.70 (0.24, 2.02)	9/21 (42.9)	6/12 (50.0)
Baseline TSH			
<=0.5 (N=112)	0.70 (0.33, 1.49)	17/74 (23.0)	12/38 (31.6)
>0.5 (N=40)	0.74 (0.26, 2.14)	9/26 (34.6)	7/14 (50.0)
Baseline Thyroglobulin			
<=10 (N=31)	0.77 (0.22, 2.73)	10/23 (43.5)	4/8 (50.0)
>10 (N=122)	0.58 (0.29, 1.19)	17/78 (21.8)	15/44 (34.1)
ECOG Performance Status			
0 (N=77)	0.68 (0.25, 1.85)	12/52 (23.1)	7/25 (28.0)
1 and 2 (N=76)	0.64 (0.3, 1.39)	15/49 (30.6)	12/27 (44.4)



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n/N = number of events/number of patients in the subgroup.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; TSH, thyroid stimulating hormone; VEGFR, vascular endothelial growth factor receptor.

Safety (1/2)

In this patient population, no new safety signals were observed

n (%)	Dabrafenib plus Trametinib (N=101)		Placebo (N=52)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Most common adverse events*				
Pyrexia	48 (47.5)	4 (4.0)	5 (9.6)	0
Anemia	45 (44.6)	4 (4.0)	5 (9.6)	0
Urinary tract infection	32 (31.7)	1 (1.0)	4 (7.7)	0
Hyperglycaemia	26 (25.7)	4 (4.0)	3 (5.8)	0
Neutrophil count decreased	26 (25.7)	4 (4.0)	2 (3.8)	0
Rash	26 (25.7)	1 (1.0)	2 (3.8)	0
White blood cell count decreased	26 (25.7)	4 (4.0)	5 (9.6)	0
Hypoalbuminaemia	25 (24.8)	1 (1.0)	3 (5.8)	0
Chills	23 (22.8)	0	1 (1.9)	0
Lipase increased	23 (22.8)	7 (6.9)	2 (3.8)	0
Aspartate aminotransferase increased	22 (21.8)	0	3 (5.8)	0
Weight decreased	22 (21.8)	0	7 (13.5)	0

*≥20% in either arm

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Safety (2/2)

In this patient population, no new safety signals were observed

n (%)	Dabrafenib plus Trametinib (N=101)		Placebo (N=52)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
AEs leading to discontinuation	8 (7.9)	2 (2.0)	3 (5.8)	2 (3.8)
Treatment-related	6 (5.9)	2 (2.0)	1 (1.9)	0
Most common serious adverse events*				
Pneumonia	8 (7.9)	6 (5.9)	1 (1.9)	1 (1.9)
Pleural effusion	1 (1.0)	1 (1.0)	3 (5.8)	2 (3.8)
Pyrexia	4 (4.0)	0	0	0
Most common treatment-related serious adverse events**				
Pyrexia	3 (3.0)	0	0	0
Decreased ejection fraction	2 (2.0)	0	0	0
Detachment of retinal pigment epithelium	2 (2.0)	0	0	0

*≥4% in either arm
**≥2% in either arm

Conclusions

- In this phase 3 study, dabrafenib plus trametinib demonstrated a significantly longer PFS (12.8 months vs. 3.7 months; p<0·001; HR [95% CI]: 0.38 [0.25, 0.57]) and higher ORR (57.4% vs. 3.8%; p<0·001) as compared to placebo
- Median OS was not reached in the dabrafenib plus trametinib arm and was 25.9 months in the placebo arm, with a trend favouring dabrafenib plus trametinib (p=0.083; HR [95% CI]: 0.66 [0.36, 1.19])
- PFS, ORR and OS showed consistent benefit with dabrafenib plus trametinib over placebo across all the subgroups
- Safety results were generally consistent with the well-established safety profile of dabrafenib plus trametinib

These results support the use of dabrafenib plus trametinib in patients with previously-treated locally advanced/metastatic, RAI-refractory *BRAF* V600E mutation–positive DTC

CI, confidence interval; DTC, differentiated thyroid cancer; HR, hazard ratio; RAI, radioiodine; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; vs, versus.

Lori J. Wirth

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