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Phase 1 study of WNT974 in combination with spartalizumab in patients with cutaneous melanoma

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Declaration of interests

Speaker: Dr. Paolo Ascierto

Consulting or Advisory Role: Bristol-Myers Squibb, Roche/Genentech, Merck Sharp & Dohme, Novartis, Merck Serono, Pierre Fabre, AstraZeneca, Sun Pharma, Sanofi, Idera, Ultimovacs, Sandoz, Immunocore, 4SC, Italfarmaco, Nektar, Boehringer Ingelheim, Eisai, Regeneron, Daiichi Sankyo, Pfizer, OncoSec, Nouscom, Lunaphore, Seattle Genetics, ITeos Therapeutics, Medicenna, Bio-Al Health, ValoTx, Replimune, Bayer, Erasca Inc, Philogen, BioNTech SE, Anaveon

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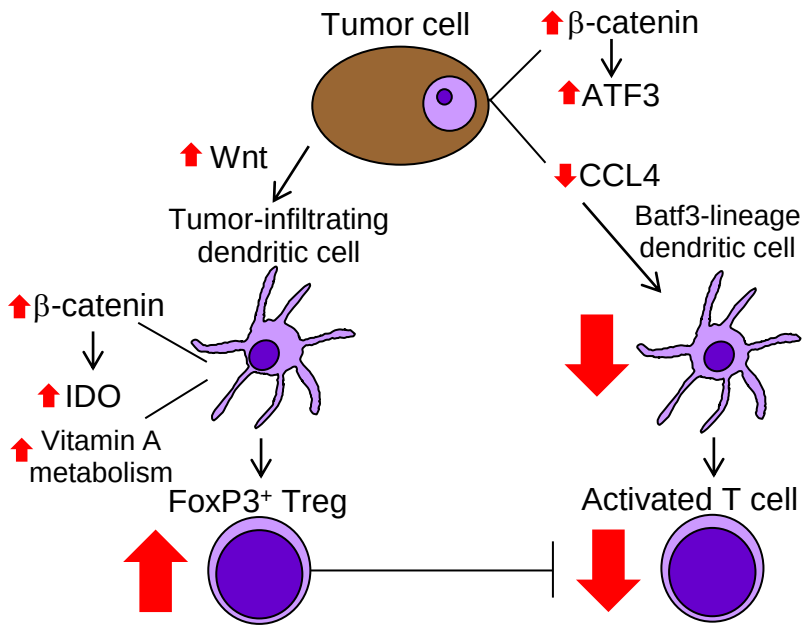
Background

- Wnt/β-catenin signaling has been linked to T-cell exclusion in melanoma, a feature associated with primary resistance to immunotherapy[1-2]
- WNT974, an inhibitor of Porcupine, which mediates post-translational modification of all Wnt ligands, has shown evidence of Wnt pathway inhibition in patients [3,4]
- Dysregulated Wnt/β-catenin signaling has been associated with lack of T cells in tumour microenvironment and failure of immunotherapy[5,6]
- We hypothesized that WNT974 + spartalizumab may lead to clinical benefit in patients with advanced melanoma resistant to anti-PD-1 therapy[7]

Wnt/β-catenin and immune modulation[8]

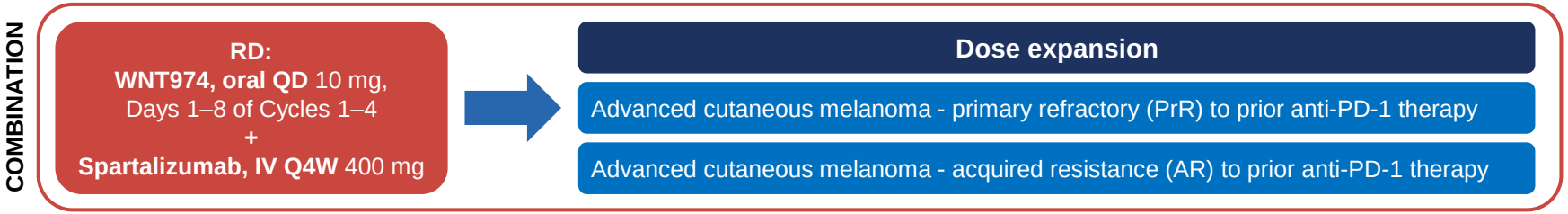


Based on Spranger S *et al. Nature* 2015; Holtzhausen A *et al. Cancer Immunol Res* 2015.

PD-1, programmed death-1.

1. Zhan T et al. *Oncogene*. 2017;36:1461-1473; **2.** Polakis P et al. *Perspect Biol*. 2012;4:a008052; **3.** Rodon J et al. *Br J Cancer*. 2021;125:28-37; **4.** Janku F et al. *Cancer Res.* 2020;80(16_Supplement):CT034; **5.** Spranger S et al. *Nature.* 2015;523:231-235; **6.** Grasso CS et al. *Cancer Discov.* 2018;8:730-749; **7.** Ji RR et al. *Cancer Immunol. Immunother*. 2012;61:1019–1031; **8.** Janku et al. Cancer Res (2020) 80 (16_Supplement): CT034.4

Phase 1, multicentre combination dose expansion study design and methods



Key eligibility criteria for WNT974 + spartalizumab

- Advanced cutaneous melanoma that was either:
  - PrR to prior anti-PD-1 therapy (best response of progressive disease or SD for ≤4 months, or disease recurrence within the first 6 months of adjuvant anti-PD-1 therapy) or
  - had developed AR to prior anti-PD-1 therapy (progressive disease following response or SD for >4 months)
- Patients with osteoporosis, history of pathological fractures, or recent bone fractures were excluded

Objectives for WNT974 + spartalizumab

Primary: To determine the MTD/RD

Secondary: To characterize safety and tolerability, PK, pharmacodynamic response, and antitumor activity

Here, we report on 38 patients treated in the combination dose expansion part of the study, plus 4 patients with PrR cutaneous melanoma treated at the RD in the dose escalation part

IV, intravenous; PK, pharmacokinetics; PD-1, programmed death-1; Q4W, every 4 weeks; QD, once daily; RD, recommended dose; SD, stable disease.

Baseline patient characteristics and disposition

Baseline patient characteristics	WNT974 + spartalizumab PrR N=28	WNT974 + spartalizumab AR N=14	WNT974 + spartalizumab All patients N=42
Age (median), years	57.5 (29–82)	63.0 (48–80)	58.0 (29–82)
Male, n (%)	20 (71.4)	7 (50.0)	27 (64.3)
Race, n (%),			
Caucasian	27 (96.4)	13 (92.9)	40 (95.2)
Missing	1 (3.6)	1 (7.1)	2 (4.8)
WHO PS, n (%)			
0	21 (75.0)	8 (57.1)	29 (69.0)
1	7 (25.0)	6 (42.9)	13 (31.0)
Prior therapy, n (%)	28 (100)	14 (100)	42 (100)
Median number of therapies, n (range)	3.0 (1–5)	3.5 (2–9)	3.0 (1–9)
Primary reason for treatment discontinuation			
AE(s)*	1 (3.6)	1 (7.1)	2 (4.8)
Administrative**	5 (17.9)	0	5 (11.9)
Death#	1 (3.6)	0	1 (2.4)
Disease progression	21 (75.0)	13 (92.9)	34 (81.0)

AE, adverse event; AR, acquired resistance; PrR, primary refractory
*AEs: PrR: bleeding brain metastases, AR: immune-mediated gastritis; **One pt discontinued due to clinical progression, and 4 pts were receiving study treatment and were transferred to a rollover protocol to continue treatment under that study; #not attributed to study treatment

WNT974 + spartalizumab treatment was well tolerated

TRAEs reported in ≥10% of patients		
	WNT974 + spartalizumab N=42	
	Any grade	Grade 3/4
Overall*	**31 (73.8)**	**6 (14.3)**
Nausea	10 (23.8)	0
Alopecia	8 (19.0)	0
ALT increased	7 (16.7)	0
Dysgeusia	7 (16.7)	0
Pruritus	7 (16.7)	0
Asthenia	6 (14.3)	0
Diarrhoea	6 (14.3)	0
Lipase increased	6 (14.3)	4 (9.5)
Myalgia	5 (11.9)	0

- MTD was not established
- TEAEs were reported in 40 patients, with grade 3/4 AEs reported in 15 (35.7%)
- The majority of AEs were Grade 1/2; no Grade 5 AEs were reported
- No dose reductions were reported either for WNT974 or spartalizumab
- One treatment-related SAE (immune-mediated gastritis) was reported
- Bone toxicity: Fracture and pathological fracture were reported in 1 patient each; both were Grade 2 and not attributed to study treatment

*A subject with multiple severity grades for a PT is only counted under the maximum grade. Only TRAEs occurring during treatment or within 30 days of the last dose of study medication are reported.

ALT, alanine aminotransferase; MTD, maximum tolerated dose; PT, preferred term; TEAEs, treatment-emergent adverse event; TRAEs, treatment-related adverse events.

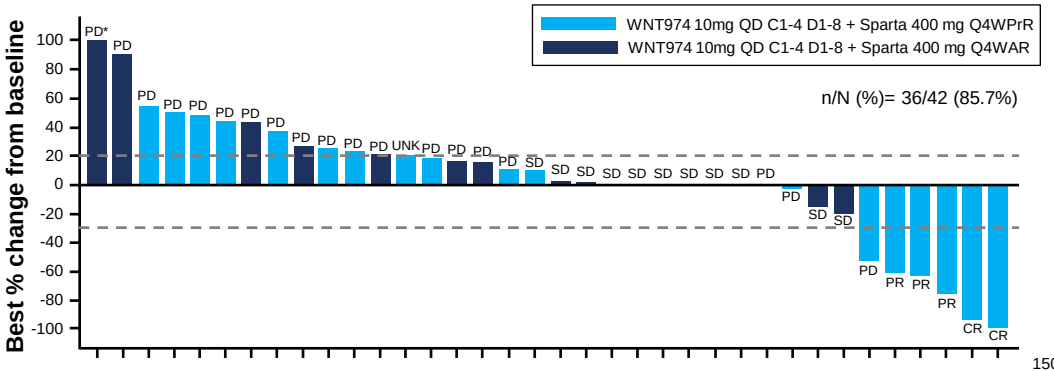
Confirmed responses were reported only in the PrR group

Best overall response per RECIST v1.1, investigator assessment	WNT974 + spartalizumab PrR N=28	WNT974 + spartalizumab AR N=14	WNT974 + spartalizumab All patients N=42
Best overall response, n (%)			
Complete response (CR)	2 (7.1)	0 (0.0)	2 (4.8)
Partial response (PR)	3 (10.7)	0 (0.0)	3 (7.1)
Non-CR/Non-PD	0 (0.0)	0 (0.0)	0 (0.0)
Stable disease (SD)	5 (17.9)	6 (42.9)	11 (26.2)
Progressive disease (PD)	13 (46.4)	8 (57.1)	21 (50.0)
Unknown	5 (17.9)	0 (0.0)	5 (11.9)
Overall response rate (ORR) (CR or PR), n (%) [95% CI]	5 (17.9) [6.1–36.9]	0 (0.0) [0.0–23.2]	5 (11.9) [4.0–25.6]
Disease control rate (DCR) (CR or PR or SD), n (%) [95% CI]	10 (35.7) [18.6–55.9]	6 (42.9) [17.7–71.1]	16 (38.1) [23.6–54.4]

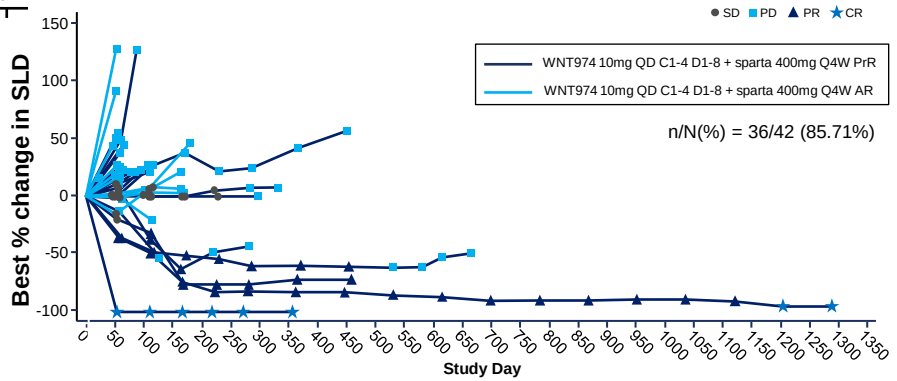
AR, acquired resistance; PrR, primary refractory; RD, recommended dose; RECIST, Response Evaluation Criteria In Solid Tumors.

Durable responses were observed in a subset of patients with PrR disease

Best percent change from baseline in sum of target lesion diameters*



Percentage change in sum of target lesion diameters over time*



- Median duration of response (90% CI) was 15.44 months (3.55, NE) for all patients

*Six out of 42 patients are not included in these plots due to missing post-baseline assessments

CR, Complete response; CI, confidence interval; NE, not estimable; PrR, primary refractory; PD, progressive disease; PR, partial response; QD, once daily; RD, recommended dose; SLD, sum of longest diameter; SD, stable disease .

Conclusions

- WNT974 in combination with spartalizumab was well tolerated and demonstrated preliminary anti-tumor activity in patients with advanced cutaneous melanoma that had progressed on prior anti-PD-1–based therapy
- Objective responses were only observed in patients whose tumors had been primary refractory to prior anti-PD-1 therapy, suggesting that this clinical feature may predict benefit from the combination
- Biomarker analyses to identify additional predictive markers of response and resistance to study treatment are ongoing

PD-1, programmed death-1

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https://bit.ly/Paolo1081MO