

IO102-IO103 cancer vaccine plus pembrolizumab for first line advanced melanoma: primary results from a randomized phase 3 trial (IOB-013/KN-D18)

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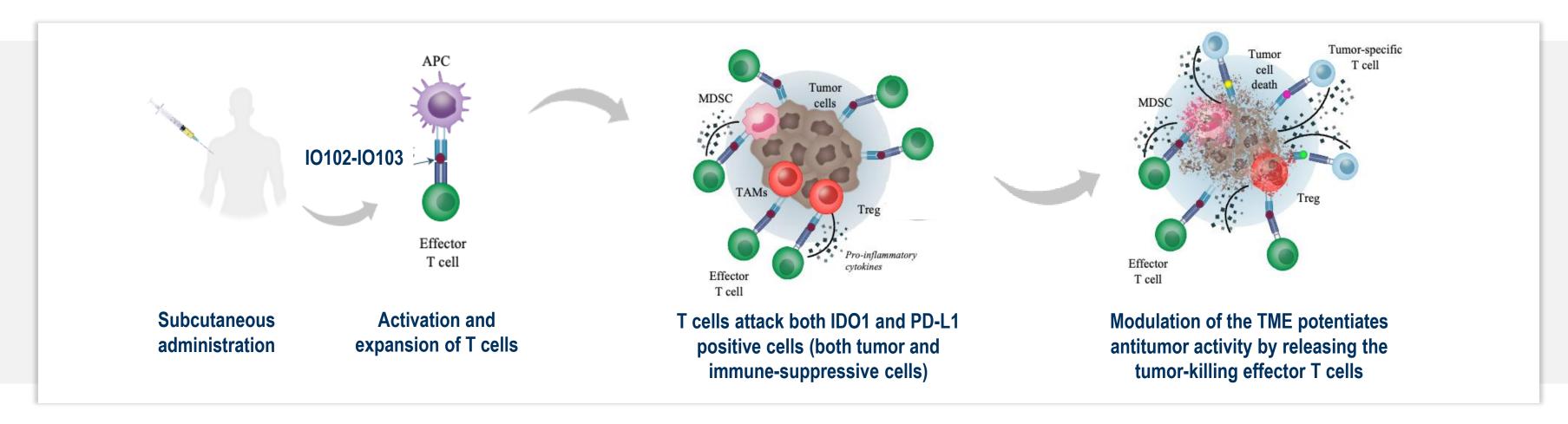


Declaration of interests

J.C. Hassel reports speaker honoraria from BMS, Delcath, Immunocore, MSD, Novartis, Pierre Fabre, Sanofi and Sun Pharma, and honoraria for advisory board participation from Onkowissen and Sun Pharma

IO102-IO103 immune-modulatory, off-the-shelf cancer vaccine

 A unique investigational immune-modulatory cancer vaccine targeting IDO1 and PD-L1 positive tumor cells and immuno-suppressive cells within the tumor microenvironment



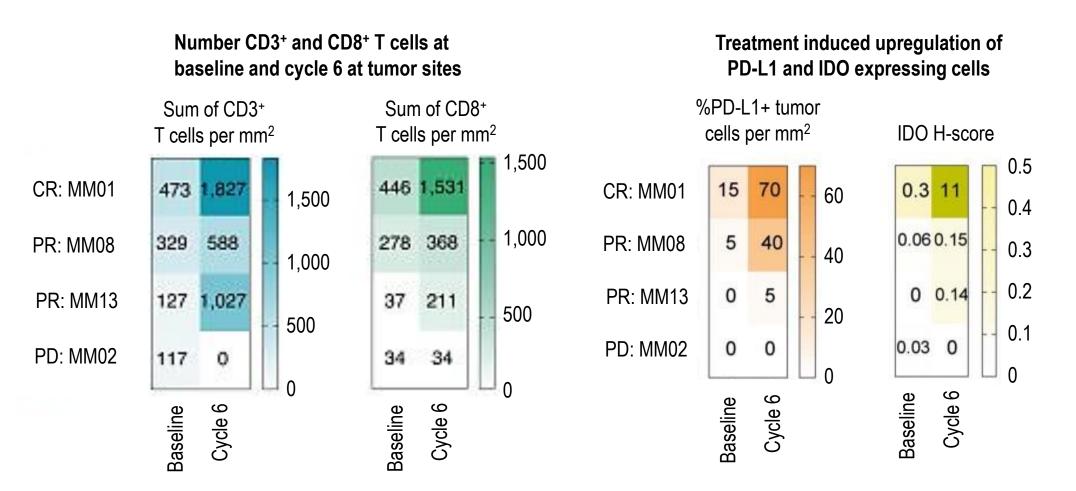
• This phase 3 trial was conducted based on the phase 1/2 trial of 30 patients with anti-PD-1 treatment-naïve metastatic melanoma, where combination with nivolumab demonstrated encouraging clinical activity without additional significant systemic toxicity^{1,2}



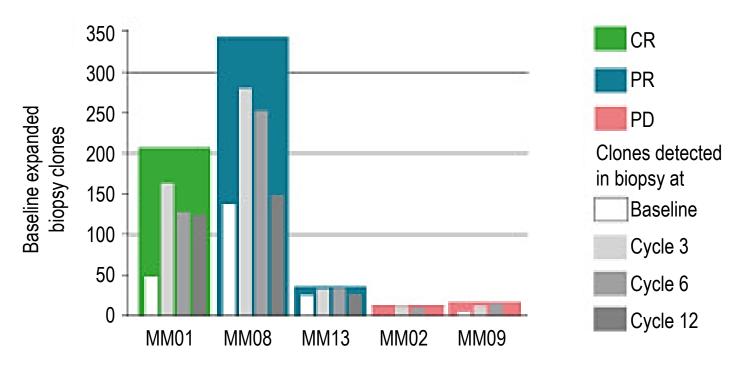
Effects of IO102-IO103 in the TME

Translational data from phase 1/2 study¹

- 1. Evidence of T cells infiltration at tumor sites
- 2. Increase of PD-L1 and IDO expressing cells on both immune and tumor cells
- 3. Evidence of T cell clonal expansion in the tumor



Baseline expanded biopsy clones also detected in the periphery



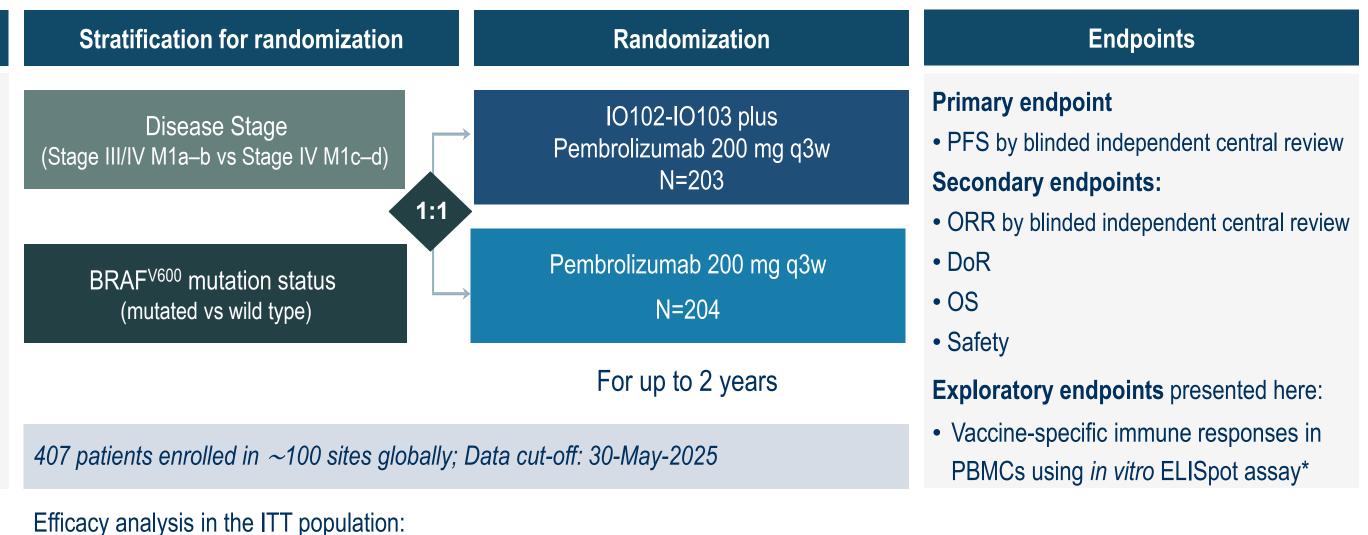
IOB-013/KN-D18: Trial design

Global, randomized, phase 3 trial

Eligibility criteria Untreated advanced melanoma Unresectable stage III Metastatic stage IV

- Measurable disease (RECIST 1.1)
- ECOG performance status 0–1
- Neoadjuvant / adjuvant therapy allowed if last dose was >6 months prior start of study treatment
- Stable CNS disease allowed

ClinicalTrials.gov: NCT05155254



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- Stratified log-rank test with PD-L1 status and disease stage as the stratification factors

- HR and 95% CI estimated by Cox proportional hazards model and tested at a two-sided 0.045

Study planned to enroll 380 patients, powered for 89%, based on assumed hazard ratio 0.65

*Preliminary data; AE, adverse event; BICR, blinded independent central review; BRAF, proto-oncogene *B-Raf*; CI, confidence internal; CNS, central nervous system; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; ELISpot, enzyme-linked immunospot; HR, hazard ratio; ITT, intention-to-treat; N, number; ORR, objective response rate; OS, overall survival; PBMCs, peripheral blood mononuclear cells; PFS, progression-free survival; q3w, once every 3 weeks; RECIST, response evaluation criteria in solid tumors; SAE, serious adverse event.



Baseline characteristics

	IO102-IO103 plus pembrolizumab (n=203)	Pembrolizumab (n=204)
Median age (range), years	71.0 (59.0–78.0)	69.0 (60.0–78.0)
Age groups, n (%)		
<65 years	78 (38.4)	77 (37.7)
≥65 to <75 years	49 (24.1)	56 (27.5)
≥75 years	76 (37.4)	71 (34.8)
Male sex, n (%)	136 (67.0)	120 (58.8)
Melanoma subtype, n (%)		
Cutaneous	176 (86.2)	174 (85.3)
Mucosal	4 (2.0)	11 (5.4)
Acral	7 (3.4)	3 (1.5)
Unknown primary melanoma or other	16 (7.9)	16 (7.8)
PD-L1 , n (%)*		
Positive (≥1%)	129 (63.5)	127 (62.3)
Negative (<1%)	67 (33.0)	63 (30.9)
Not available	7 (3.4)	14 (6.9)
BRAF ^{V600} mutation status**, n (%)		
Mutated	84 (41.4)	83 (40.7)
Wild type	119 (58.6)	121 (59.3)

	IO102-IO103 plus pembrolizumab (n=203)	Pembrolizumab (n=204)			
Baseline metastatic stage, n (%)					
M0	26 (12.8)	22 (10.8)			
M1a	34 (16.7)	40 (19.6)			
M1b	60 (29.6)	61 (29.9)			
M1c	76 (37.4)	75 (36.8)			
M1d	7 (3.4)	6 (2.9)			
LDH level, n (%)					
≤ULN	133 (65.5)	131 (64.2)			
>ULN	70 (34.5)	72 (35.3)			
>2×ULN	14 (6.9)	13 (6.4)			
Baseline tumor burden, median (Q1, Q3) – mm	51.5 (28.0, 84.5)	46.0 (30.0, 76.0)			
Liver metastases, n (%)					
Yes	42 (20.7)	37 (18.1)			
ECOG performance status, n (%)					
0	149 (73.4)	159 (77.9)			
1	54 (26.6)	45 (22.1)			
Prior melanoma neoadjuvant/adjuvant therapy, n (%)					
Anti PD-1	15 (7.4)	21 (10.3)			
BRAF/MEK inhibitors	9 (4.4)	3 (1.5)			
Hormonal therapy, other biological or targeted therapies	5 (2.5)	11 (5.4)			
No prior systemic treatment	175 (86.2)	171 (83.8)			

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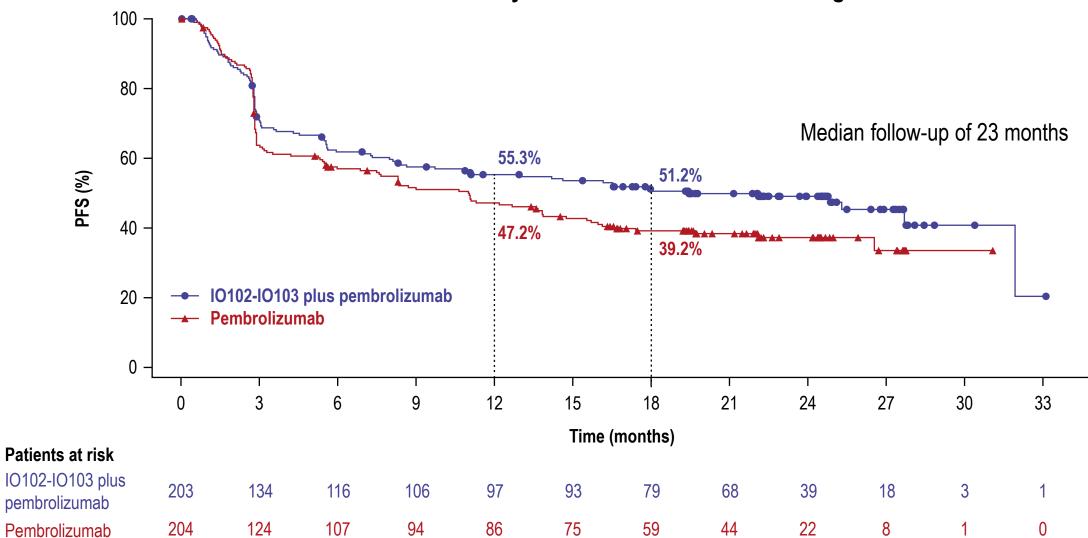
*PD-L1 expression in tumor tissue (archival or acquired at screening) was assessed at a central laboratory by immunohistochemistry with clone 22C3; based on the MEL Score approach as per Duad et al. J Clin Oncol 2016" using a ratio of tumor and associated immune cells expressing membranous PD-L1 at any intensity (weak, moderate, or strong staining), relative to all viable tumor cells. Positive PD-L1 reflects a MEL score of 2 or greater (e.g. of greater than or equal to 1% of PD-L1 cells as calculated above). **BRAF mutation status per stratification; BRAF, proto-oncogene *B-Raf*; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MEL, melanoma; MEK, mitogen-activated protein kinase; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; Q, quartile; ULN, upper limit of normal.



Primary endpoint: PFS

Blinded independent central review

Kaplan–Meier estimate of PFS in ITT determined by BICR per RECISTv1.1 and stratified by PD-L1 status and disease stage



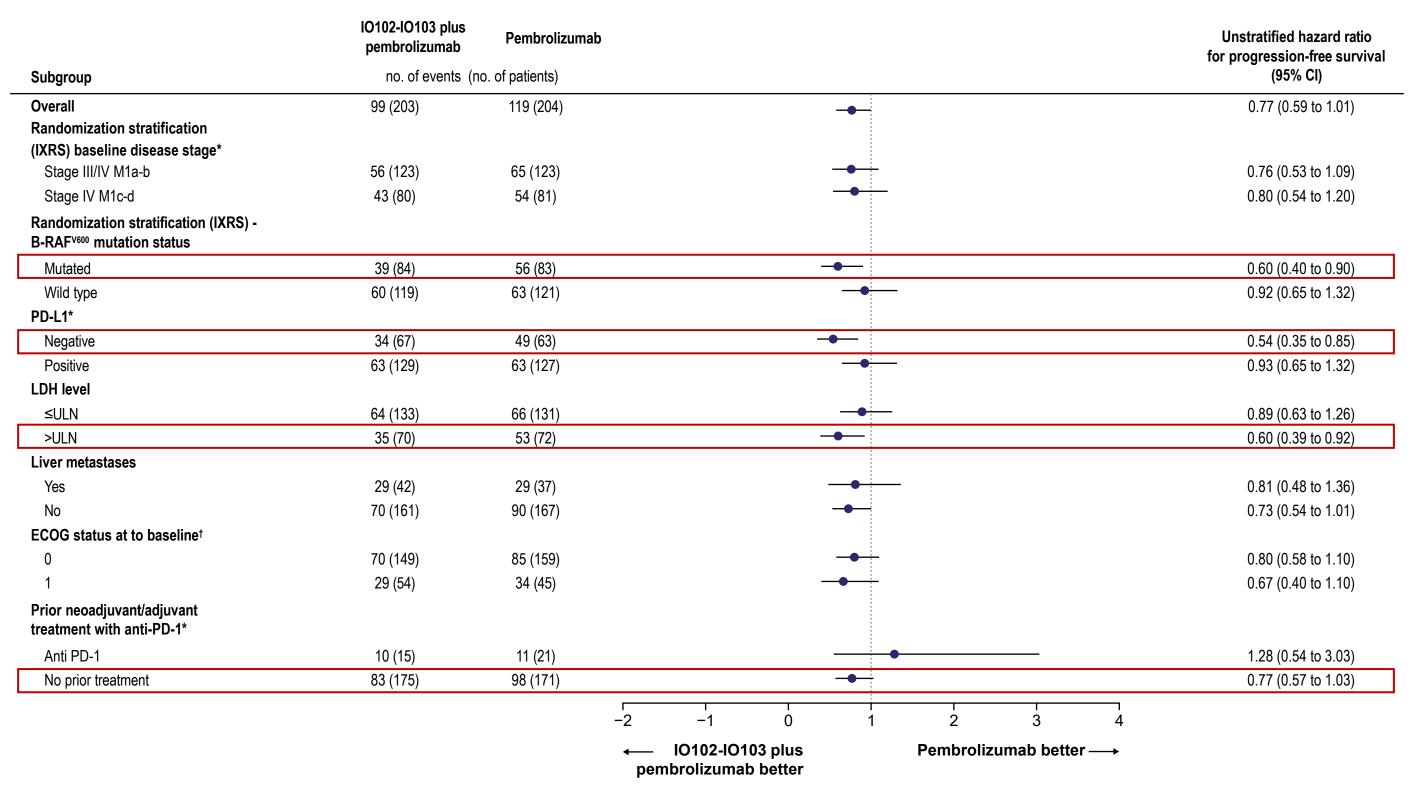
	IO102-IO103 plus pembrolizumab N=203	Pembrolizumab N=204	
Events	99	119	
PFS, months, median (95% CI)	19.4 (9.7 to NR)	11.0 (6.0 to 14.8)	
HR (95% CI)	0.77 (0.58 to 1.00)		
Log-rank P	0.0558		

^{*}Statistical significance threshold for this study was p=0.045.





Subgroups: PFS per blinded independent central review



Improvement in PFS favored the combination across subgroups

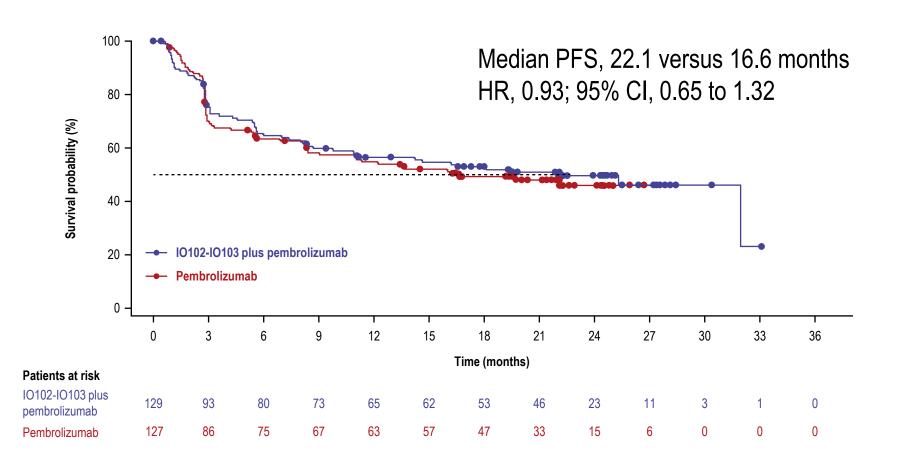
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*Median PFS and hazard ratio are not reported if fewer than five events occur in either treatment arm within a sub-group. B-RAF, proto-oncogene *B-Raf*; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IXRS, interactive extreme response system; LDH, lactate dehydrogenase; No, number; PD-L1, programmed death ligand 1; PFS, progression-free survival; ULN, upper limit of normal.



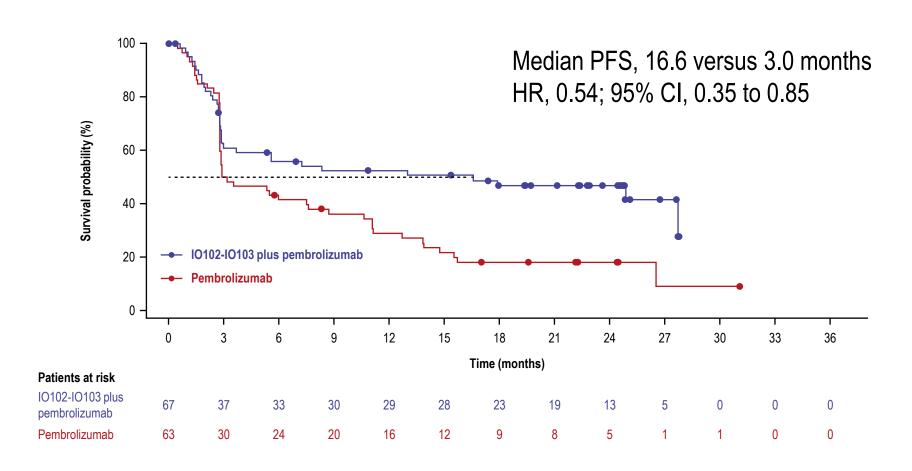
Pre-specified analysis: PFS per PD-L1 status*

PD-L1 positive tumors



ORR, 47.3% in IO102-IO13 plus pembrolizumab vs 48.8% in pembrolizumab

PD-L1 negative tumors



ORR, 43.3% in IO102-IO13 plus pembrolizumab vs 25.4% in pembrolizumab



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*PD-L1 expression in tumor tissue was assessed at a central laboratory by IHC with clone 22C3; based on the MEL Score approach as per Duad et al. J Clin Oncol 2016 using a ratio of tumor and associated immune cells expressing membranous PD-L1 at any intensity (weak, moderate, or strong staining), relative to all viable tumor cells. Positive PD-L1 reflects a MEL score of 2 or greater (e.g. of greater than or equal to 1% of PD-L1 cells as calculated above).

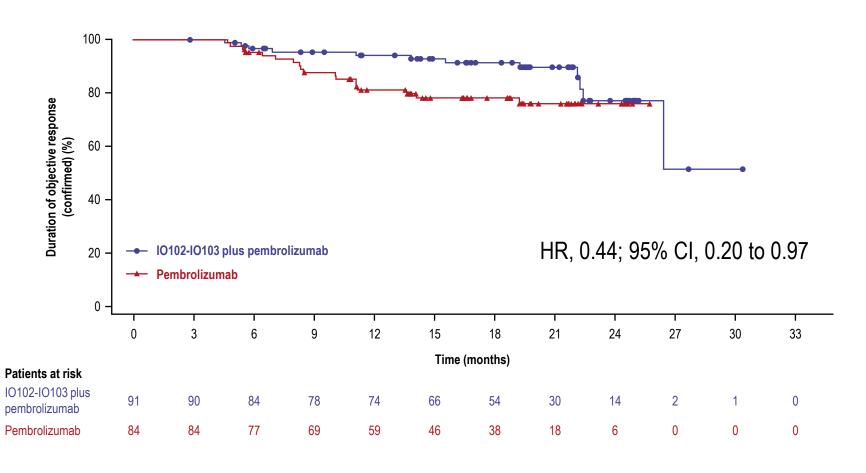


Secondary endpoints: ORR and duration of response

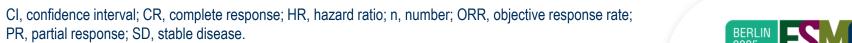
Blinded independent central review

	IO102-IO103 plus pembrolizumab N=203	Pembrolizumab N=204
ORR, n (%)	91 (44.8%)	84 (41.2%)
CR, n (%)	34 (16.7%)	37 (18.1%)
PR, n (%)	57 (28.1%)	47 (23.0%)
SD, n %)	38 (18.7%)	36 (17.6%)

Kaplan–Meier estimate of duration of confirmed objective response



Due to insufficient follow-up beyond 18 months, the curve drop at 24-month is likely due to small sample size at risk.



Summary of adverse events

	IO102-IO103 plus pembrolizumab, N=200		Pembrolizumab, N=198	
	Any grade, n (%)	Grade 3–4, n (%)	Any grade, n (%)	Grade 3–4, n (%)
Any AEs*	194 (97.0)	75 (37.5)	187 (94.4)	69 (34.8)
AE leading to discontinuation of study treatment	31 (15.5)	15 (7.5)	31 (15.7)	13 (6.6)
Serious AEs	64 (32.0)	44 (22.0)	64 (32.3)	39 (19.7)
Treatment-related AEs	171 (85.5)	29 (14.5)	161 (81.3)	31 (15.6)
Treatment-related serious AE	19 (9.5)	13 (6.5)	25 (12.6)	15 (7.6)
Immune-mediated AEs	68 (34.0)	17 (8.5)	76 (38.4)	18 (9.1)
Investigator assessed immune-related AE not included in the immune-mediated AE definition	102 (51.0)	13 (6.5)	99 (50.0)	15 (7.6)
Injection-site reaction (grouped term)	112 (56.0)	1 (0.5)	_	_

^{*}The AEs leading to death among patients who received IO102-IO103 plus pembrolizumab (n=4) or pembrolizumab (n=5) were considered not related to the study treatment by the investigators Safety analyses conducted on all randomized patients who received ≥1 dose of assigned trial medication; AEs classified by the MedDRA version 28.0 and graded by CTCAE version 5.0 Treatment-related AE: events possibly or probably related to either IO102-IO103 or Pembrolizumab Immune-mediated AE defined by KEYTRUDA adverse events of special interest list version 28.0 Immune-related events based on the investigator assessment

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AE, adverse event; CTCAE, common terminology criteria for adverse events; MedDRA, medical dictionary for medical regulatory activities; N, number.

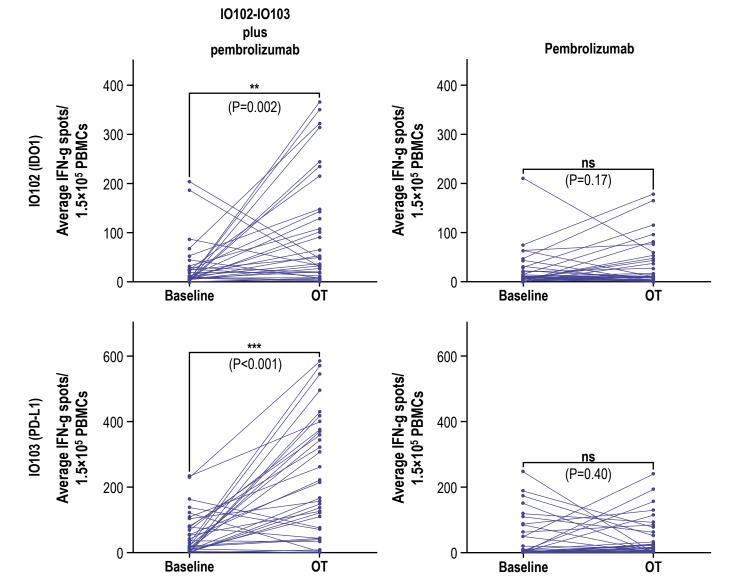
Treatment-related AEs occurring in at least 10% of the patients in any treatment group

	IO102-IO103 plus pembrolizumab, N=200		Pembrolizumab, N=198	
	Any grade, n (%)	Grade 3–4, n (%)	Any grade, n (%)	Grade 3–4, n (%)
Pruritus	42 (21.0)	0	40 (20.2)	1 (0.5)
Fatigue	40 (20.0)	1 (0.5)	37 (18.7)	0
Injection-site swelling	31 (15.5)	0	_	_
Diarrhea	29 (14.5)	0	26 (13.1)	3 (1.5)
Asthenia	27 (13.5)	2 (1.0)	24 (12.1)	0
Injection-site pruritus	26 (13.0)	0	_	_
Arthralgia	25 (12.5)	0	27 (13.6)	1 (0.5)
Injection-site granuloma	25 (12.5)	1 (0.5)	_	_
Injection-site pain	25 (12.5)	0	_	_
Rash	23 (11.5)	1 (0.5)	18 (9.1)	2 (1.0)
Vitiligo	23 (11.5)	0	27 (13.6)	0
Injection-site erythema	20 (10.0)	0	_	_
Hypothyroidism	16 (8.0)	0	21 (10.6)	0



10102-10103 vaccine-specific immune responses

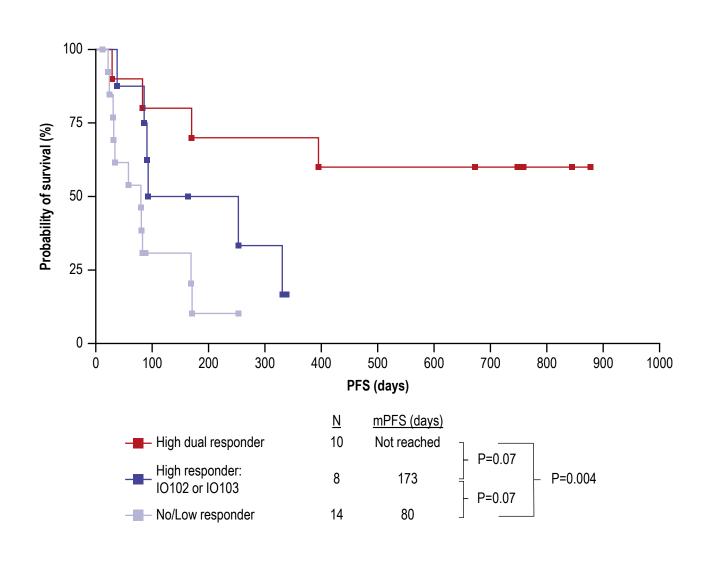
Vaccine-specific immune responses assessed by IFN-y ELISpot assay PBMCs were isolated from patients at baseline, week 10, and end of treatment



Average normalized spot count for up to n=68 patients (for which results were available at time of publication)

IDO1- and PD-L1-specific T cell responses are expanded in the vaccinated arm and not in the pembrolizumab arm

Preliminary correlation between vaccine-specific immune response and clinical response



Exploratory analysis of PFS for patients in the IO102-IO103 plus pembrolizumab arm according to level of response to peptides by ELISpot. Interim data analysis from 32 patients are included



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Statistically significant (P<0.01). *Statistically significant (P<0.001). ELISpot, enzyme-linked immunoSpot; IDO1, indoleamine 2,3-dioxygenase; IFN-γ, interferon gamma; neg, negative; ns, not significant; OT, on treatment; mPFS median progression free survival; PBMC, peripheral blood mononuclear cell; PD-L1, programmed death-ligand 1; PFS, progression free survival; pos, positive.



Key findings and conclusions

- IO102-IO103 plus pembrolizumab showed a median PFS of 19.4 months versus 11.0 months with pembrolizumab alone (HR, 0.77; 95% CI, 0.58 to 1.00; P=0.0558)
 - The primary endpoint of PFS narrowly missed statistical significance threshold of P≤0.045
- Improvement in PFS favored the combination across subgroups
- Profound effect in the subgroup of PD-L1 negative tumors (mPFS: 16.6 versus 3.0 months) (HR, 0.54; 95% CI, 0.35 to 0.85)
- IO102-IO103 + pembrolizumab was well tolerated, without added systemic toxicity to the known safety of pembrolizumab. Vaccine-related injection site reactions were mostly grade 1/2 events
- These data support the potential benefit of an immune-modulatory cancer vaccine in combination with pembrolizumab in patients with untreated advanced melanoma





Thank you!

Thank you to those who have made this trial possible:

- The patients and their families
- The investigators and all the site staff
- IO Biotech team

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This trial (ClinicalTrials.gov NCT05155254) was sponsored by IO Biotech ApS; pembrolizumab drug supply was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, US



Immune-modulatory cancer vaccines are a distinct from traditional cancer vaccines

IO102-IO103 is an investigational, immune modulatory, off-the-shelf, therapeutic cancer vaccine^{1,2}

	Immune-modulatory vaccine ³	Neoantigen vaccine ⁴	Cancer vaccine ^{5,6}
Antigen	Immune regulatory target	Neoantigen	Tumor-associatedCancer-testisTissue-specific
Examples	IDO1, PD-L1 , Arg1, TGFβ	Diverse targets	MUC1, MAGE, gp-100
Targets suppressive immune cells?	Yes Treg Suppressive myeloid cell M2 macrophages	No	No
Targets tumor?	Yes	Yes	Yes
Off-the-shelf/personalized	Off-the-shelf	Personalized	Off-the-shelf



IO102-IO103 is an investigational, immune-modulatory, off-the-shelf cancer vaccine^{1,2}

PREPARATION^{3,4}



85 µg IO102

21-amino-acid peptide from IDO1

Montanide ISA-51 as an adjuvant



85 µg IO103

19-amino-acid peptide from PD-L1

Montanide ISA-51 as an adjuvant

Immediately before injection, each peptide is emulsified with the adjuvant montanide ISA-51

SUBCUTANEOUS ADMINISTRATION⁵

IO102 and IO103 are administered as separate subcutaneous injections

Injections should be around 5 cm apart in the same arm per visit

Rotate injections at each visit

Alternative areas for injection can be considered if needed





IOB-013/KN-D18: Statistical plan

Sample size calculation

- A minimum of 380 patients were required to observe 226 events for 89% power based on assumed hazard ration of 0.65, with type I error controlled at 0.045
- An interim analysis of ORR was planned with an alpha allocation of 0.005

Efficacy analysis

- Conducted in the intention-to-treat population
- Used a stratified log-rank test with PD-L1 status and disease stage as the stratification factors
- HR and 95% CI were estimated by Cox proportional hazards model

Safety analysis

- Conducted on all randomized patients who received ≥1 dose of assigned trial medication
- AEs classified by the MedDRA version 28.0 and graded by CTCAE version 5.0

PD-L1 assessment

- PD-L1 expression in tumor tissue (archival or acquired at screening) was assessed at a central laboratory by IHC with clone 22C3 Dako Agilent PharmDx and scored for positivity according to manufacturer's insert. The MEL score was calculated using a ratio of tumor and associated immune cells within tumor nests expressing membranous PD-L1 at any intensity, relative to all viable tumor cells. Positive PD-L1 reflects a MEL score of ≥2 or greater (e.g. of ≥1% of PD-L1 cells as calculated above)
- For six patients where no specimen was available for central testing, local test results were provided for determining PD-L1 positivity

Exploratory analysis presented here

 Vaccine-specific immune responses in PBMCs at baseline, week 10 and end of treatment using in vitro ELISpot assay





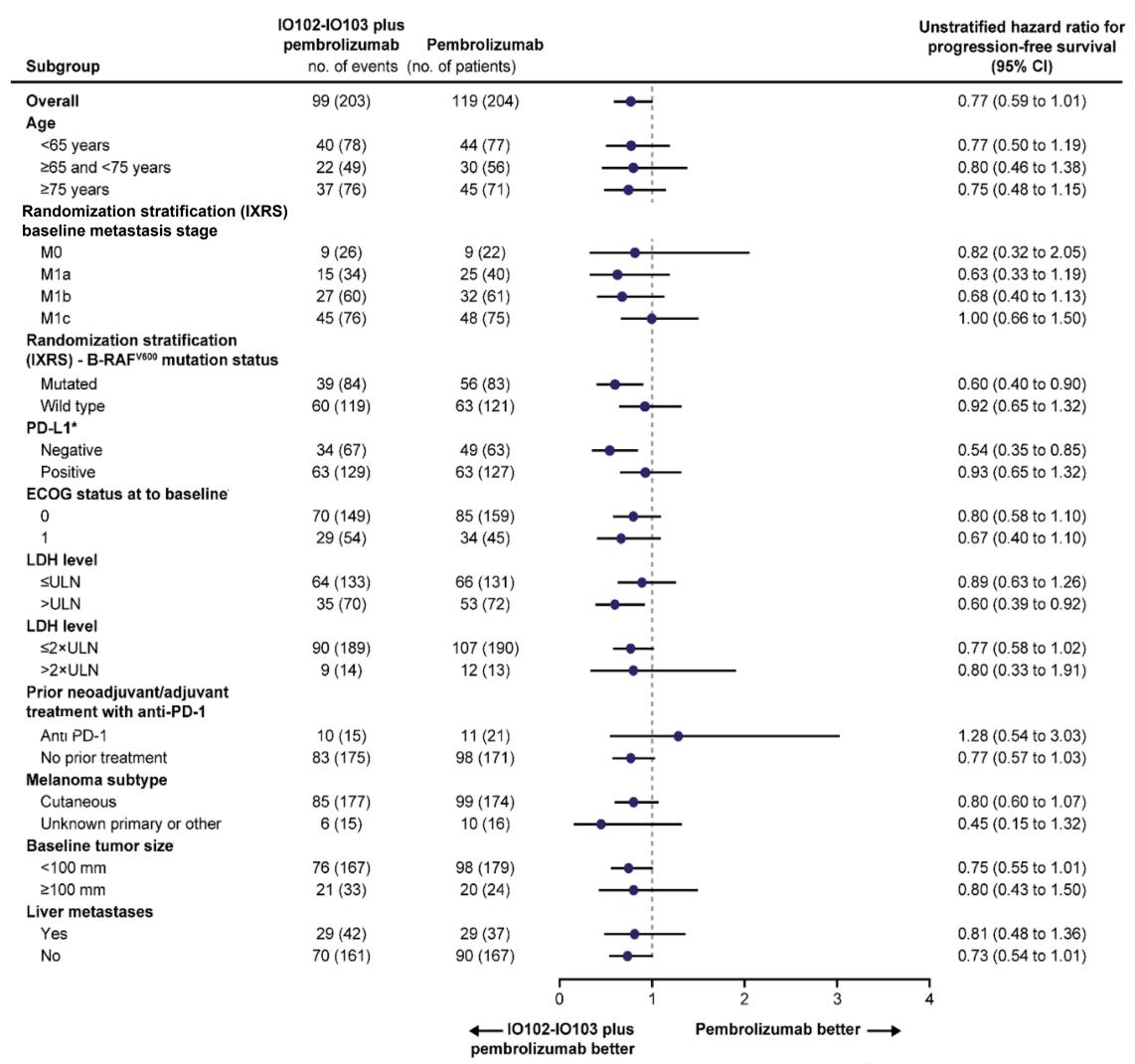
Forest plot for PFS determined by blinded independent central review

*PD-L1 expression in tumor tissue was assessed at a central laboratory by IHC with clone 22C3; based on the MEL Score approach as per Duad et al. J Clin Oncol 2016 using a ratio of tumor and associated immune cells expressing membranous PD-L1 at any intensity (weak, moderate, or strong staining), relative to all viable tumor cells. Positive PD-L1 reflects a MEL score of 2 or greater (e.g. of greater than or equal to 1% of PD-L1 cells as calculated above).

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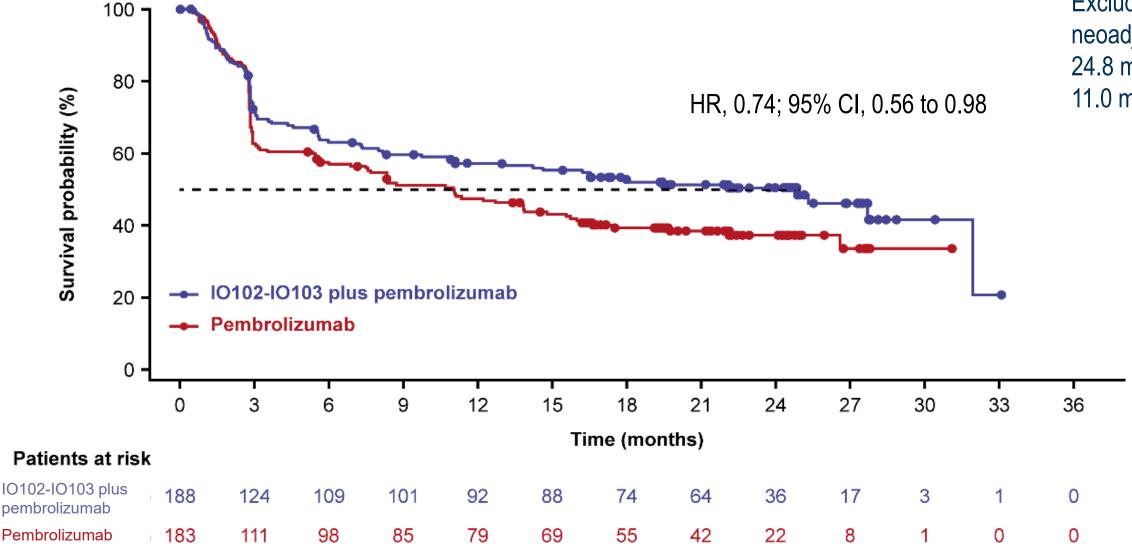
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Post-hoc analysis: PFS for patients with no prior (neo-)adjuvant anti-PD-1 therapy



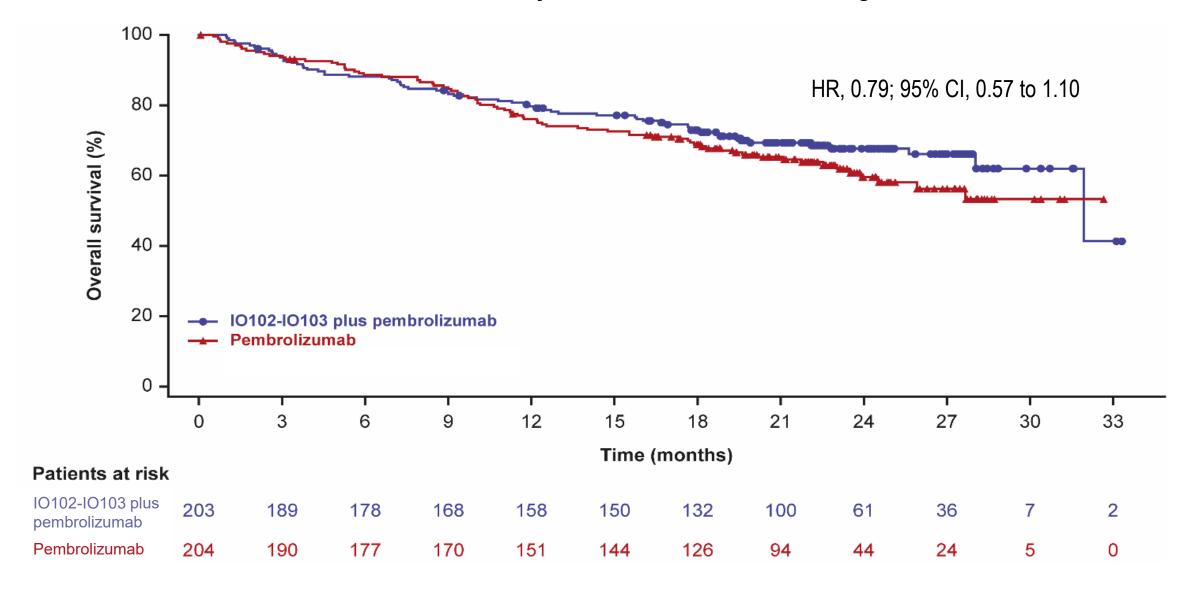


Excluding patients with prior anti-PD-1 therapy as neoadjuvant/adjuvant therapy, median PFS was 24.8 months with IO102-IO103 plus pembrolizumab versus 11.0 months with pembrolizumab alone



Secondary endpoint: Overall survival

Kaplan-Meier estimate of OS in ITT and stratified by PD-L1 status and disease stage



Median follow-up of 23 months

Endpoint not mature