

INTerpath-001: Phase 3 Study of the mRNA-Based Individualized Neoantigen Therapy (INT) Intismeran Autogene plus Pembrolizumab vs Pembrolizumab Alone for Adjuvant Treatment of Resected Stage IIB-IV Melanoma

Georgina V. Long; Muhammad A. Khattak; Helen J. Gogas; Dirk Schadendorf; Ana Arance; Matteo S. Carlino; Piotr Rutkowski; Gareth Rivalland; Antoni Ribas; Janice M. Mehnert; Patrick A. Ott; Reinhard Dummer; Paola Queirolo; Christoffer Gebhardt; Laureen S. Ojalvo; Jinchun Zhang; Dmitri O. Grebennik; Mizuho Fukunaga-Kalabis; Paolo A. Ascierto; Michele Del Vecchio on behalf of the INTerpath-001 Investigators

Declaration of Interests

Georgina V. Long

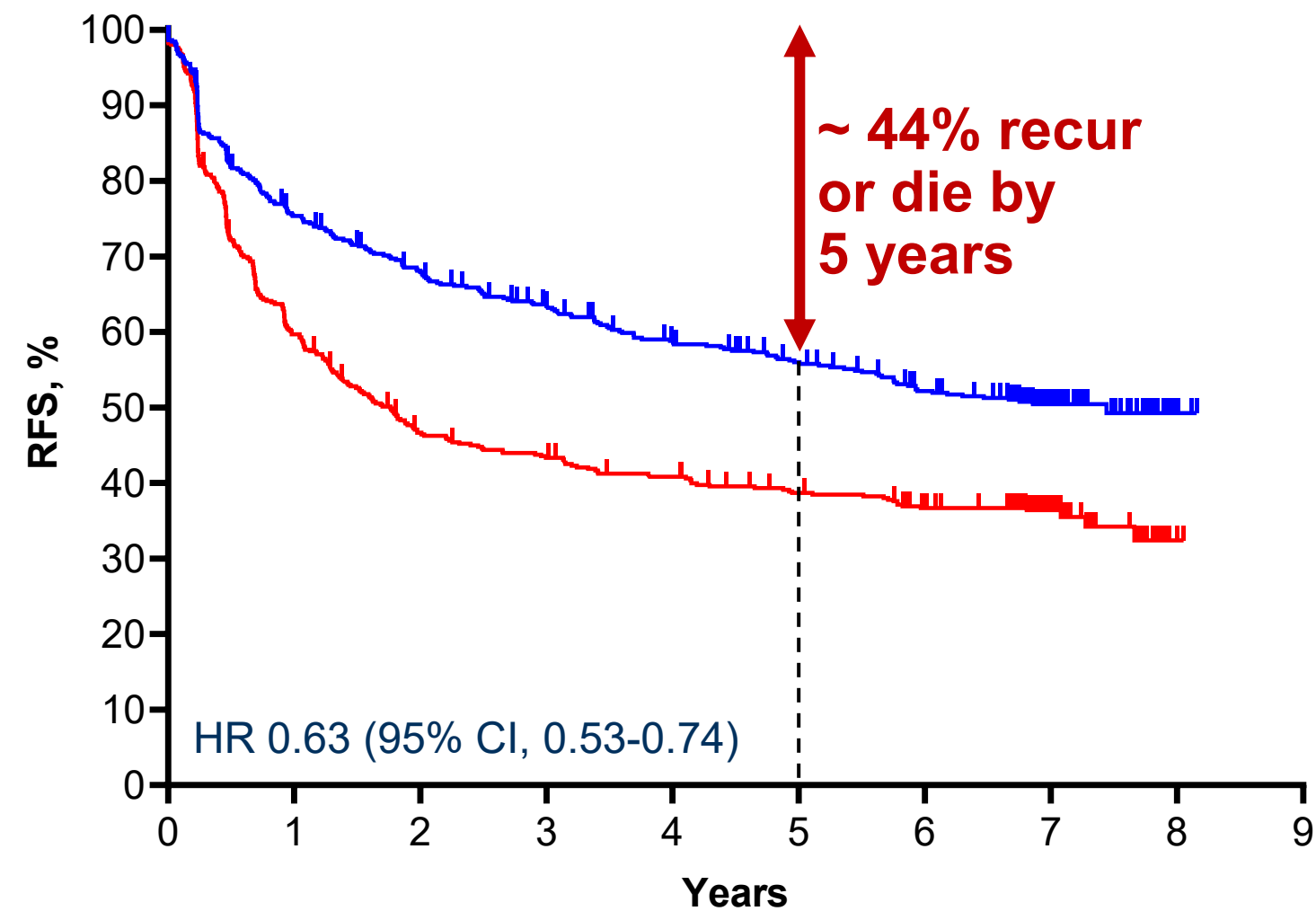
- Consultant advisor: BioNTech, Boehringer Ingelheim, Bristol Myers Squibb, Byondis B.V., Evaxion, Fortiva Biologics, GI Innovation, Immunocore, Innovent Biologics USA, Iovance Biotherapeutics, Jazz Pharmaceuticals, MSD, Replimune, Regeneron, Scancell, Strand Therapeutics
- Principal investigator: more than 60 clinical trials

All Authors

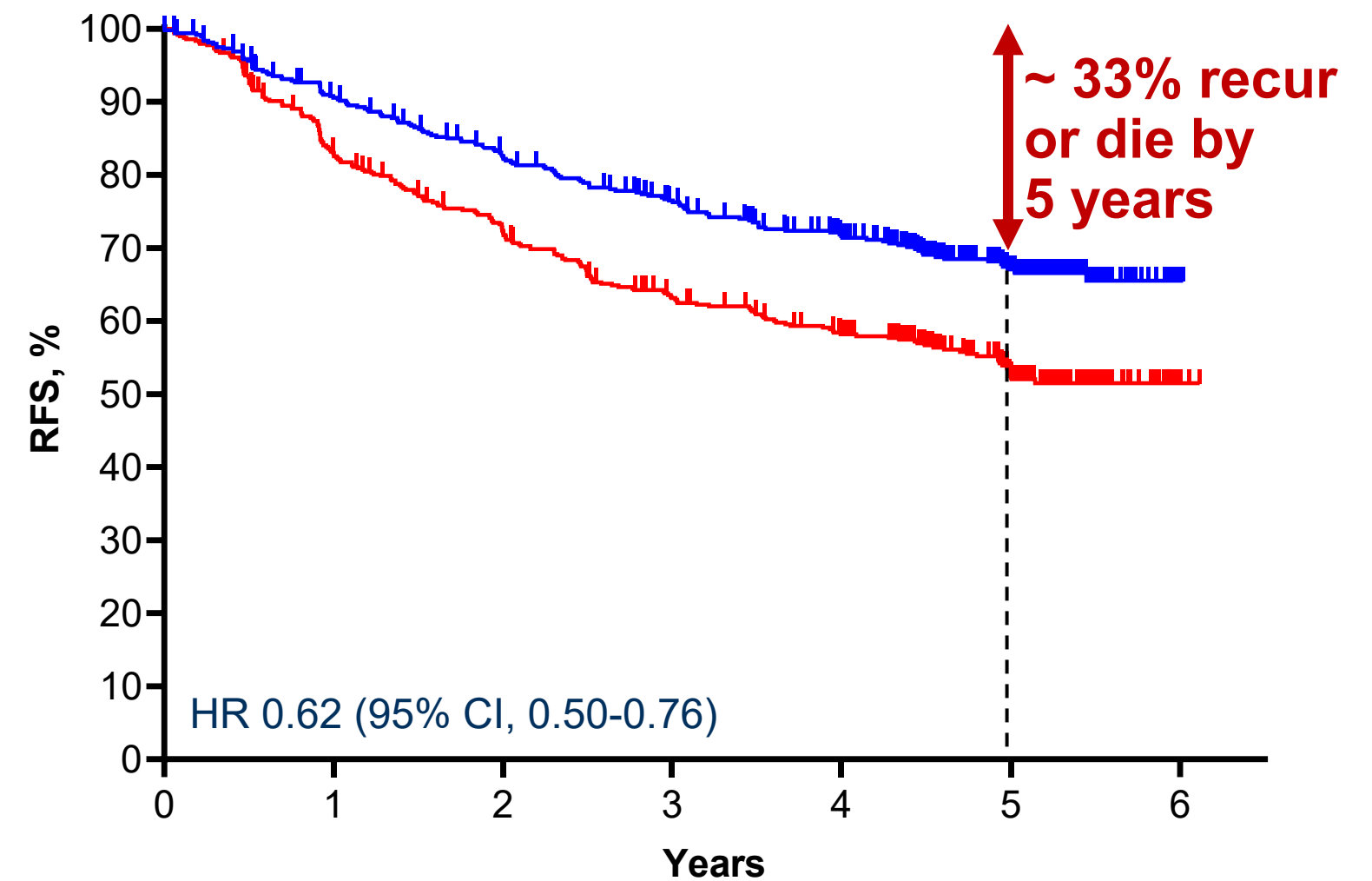
- Funding to institution to support conduct of INTerapth-001: Merck Sharp & Dohme, LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) and Moderna, Inc., Cambridge, MA, USA
- Medical writing and editorial support for this presentation: Provided by Melanie Leiby of MSD

Despite RFS and DMFS benefit for adjuvant PD-1 inhibition in phase 3 melanoma trials, many patients have recurrence¹⁻¹⁰

EORTC-1325/KEYNOTE-054¹
Pembrolizumab vs placebo, stage III



KEYNOTE-716²
Pembrolizumab vs placebo, stage IIB/IIC



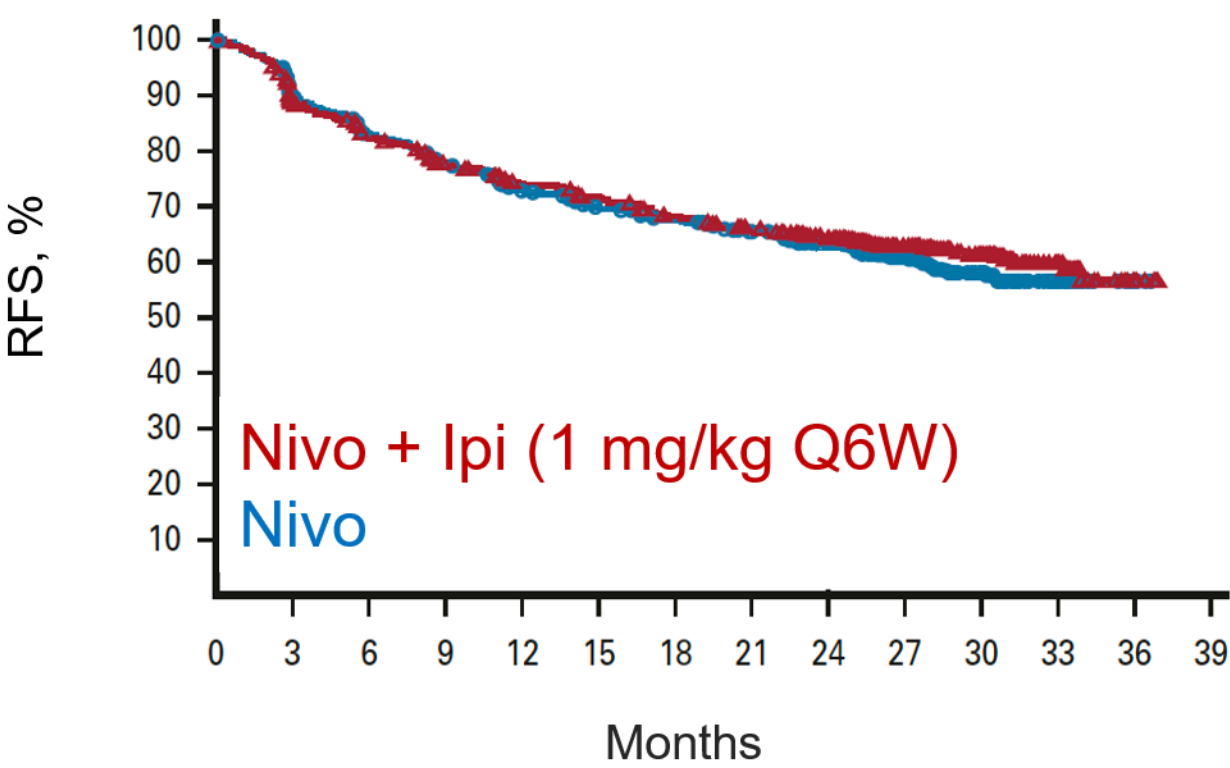
¹Eggermont AMM et al. *Eur J Cancer* 2024;211:114327. ²Luke JJ et al. *Ann Oncol* 2025;36:abstr 1611P. ³Eggermont AMM et al. *N Engl J Med* 2018;378:1789–1801. ⁴Eggermont AMM et al. *Lancet Oncol* 2021;22:643–54. ⁵Luke JJ et al. *Lancet* 2022;399:1718–29. ⁶Long GV et al. *Lancet Oncol* 2022;23:1378–88. ⁷Weber J et al. *N Engl J Med* 2027;377:1824–35. ⁸Ascierto PA et al. *Lancet Oncol* 2020;21:1465–77. ⁹Kirkwood JM et al. *Nat Med* 2023;29:2835–43. ¹⁰Ascierto PA et al. *N Engl J Med* 2026;394:333–42.

Dual checkpoint blockade in the adjuvant setting has failed to improve efficacy while increasing toxicity in phase 3 trials

CheckMate 915¹

RFS: HR 0.92 P = 0.269

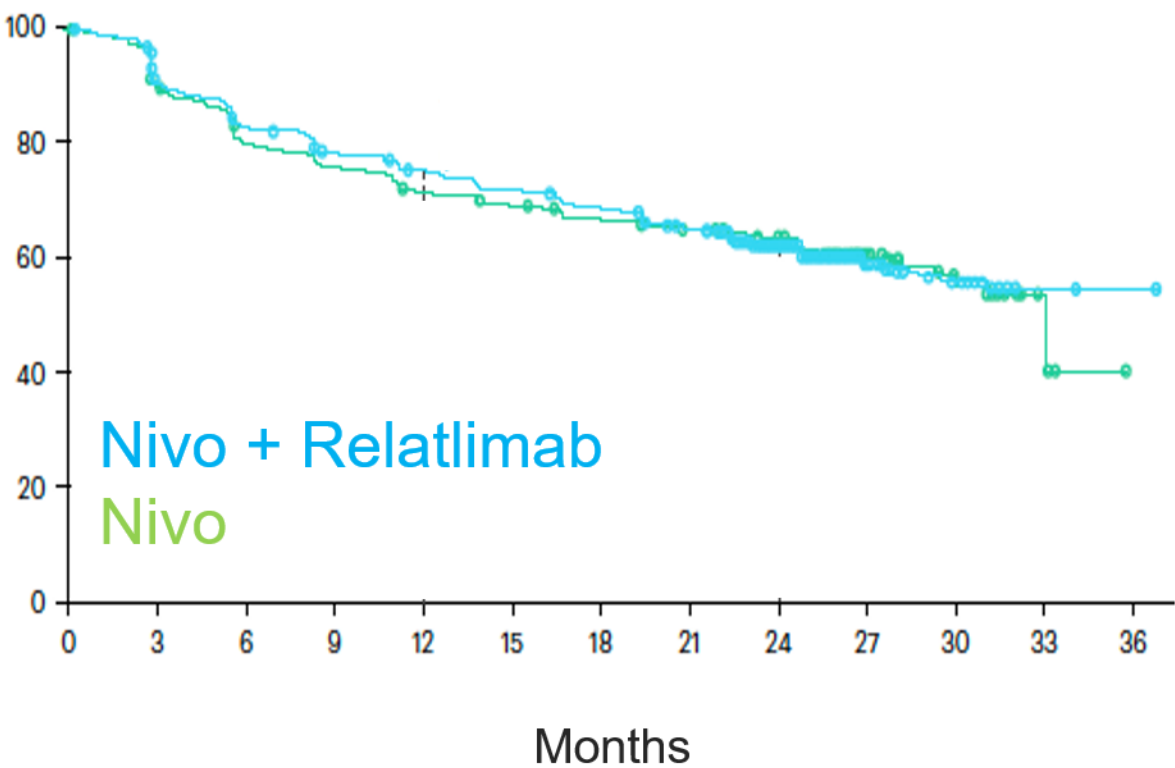
Grade 3-4 TRAEs: 32.6% vs 12.8%



RELATIVITY-098²

RFS: HR 1.01 P = 0.928

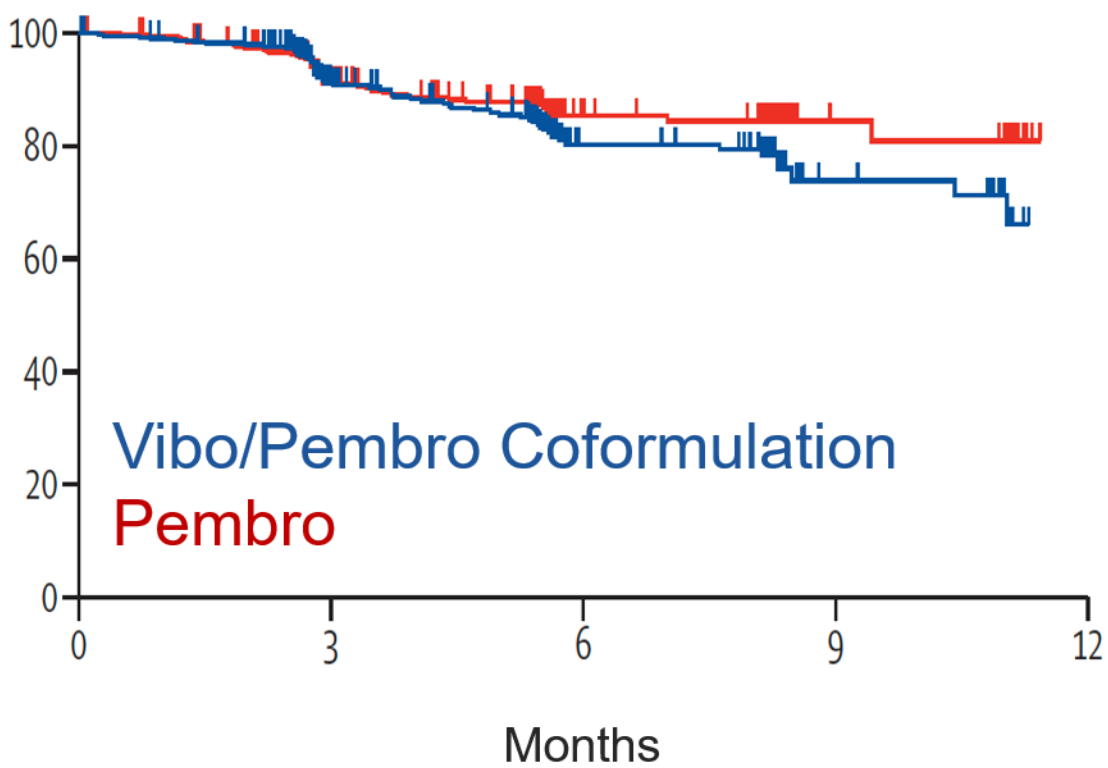
Grade 3-4 TRAEs: 19.0% vs 8.4%



KEYVIBE-010³

RFS: HR 1.25 (95% CI 0.9-1.8)

Grade 3-5 TRAEs: 16% vs 7%



¹Weber JS et al. *J Clin Oncol* 2023;41:517–27. ²Long GV et al. *Nat Med* 2025;31:4301–9. ³Dummer R et al. *Lancet Oncol* 2026;27:327–39.

Science enables individualized therapeutic cancer vaccines

Neoantigen discovery

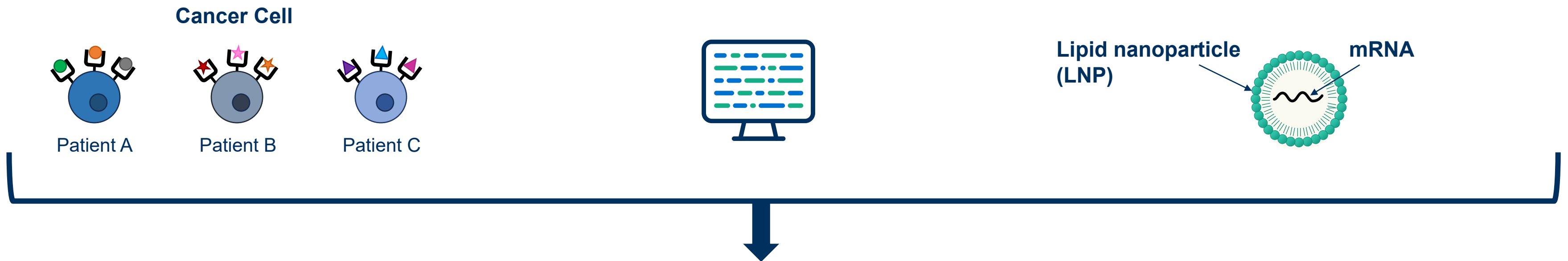
- Tumor-specific mutations
- Potential for enhanced immunogenicity

Neoantigen selection

- NGS identifies tumor mutations
- Computational prediction of HLA presentation and ranking

The mRNA platform

- Multiple antigens per mRNA
- Robust CD8+ and CD4+ T cell responses
- Rapid, individualized manufacturing



Intismeran autogene, a type of individualized neoantigen therapy (INT)

- Composed of an mRNA encoding up to 34 neoantigens encapsulated in LNP
- Specific to each patient's tumor mutanome and HLA type

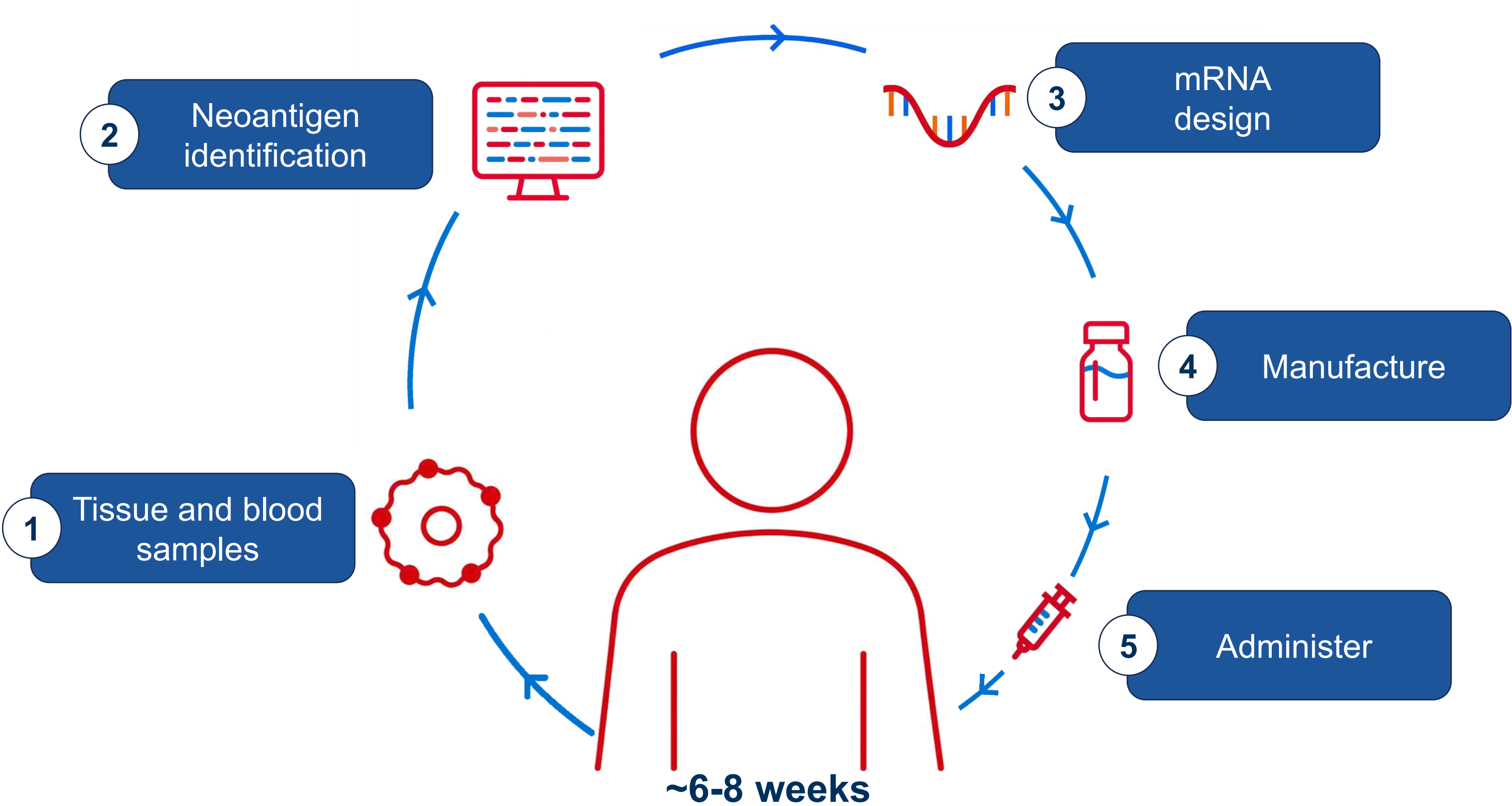
HLA, human leukocyte antigen; mRNA, messenger RNA; NGS, next-generation sequencing.

Ascierto PA, Melero I. *J Immunother Cancer* 2025;13:e013766. Zaidi N et al. *Nat Rev Cancer* 2025;25:517–33. Haanen JB et al. *Nat Med* 2026;32:828-40. Weber JS et al. *Lancet* 2024;403:632–44. Ojalvo LS et al. *JCO Oncol Adv* 2026;3:e2500206.

Presented by: Georgina V. Long, Melanoma Institute Australia

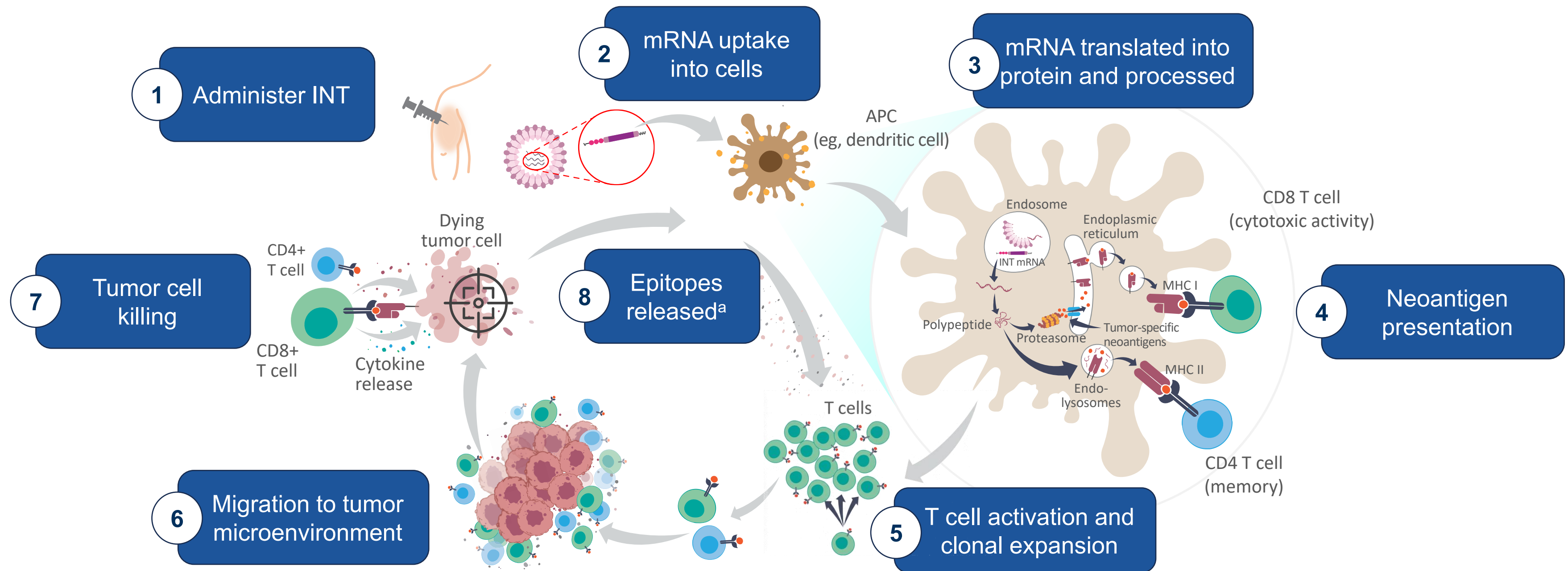
Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Standardized intismeran workflow



Intismeran mechanism of action

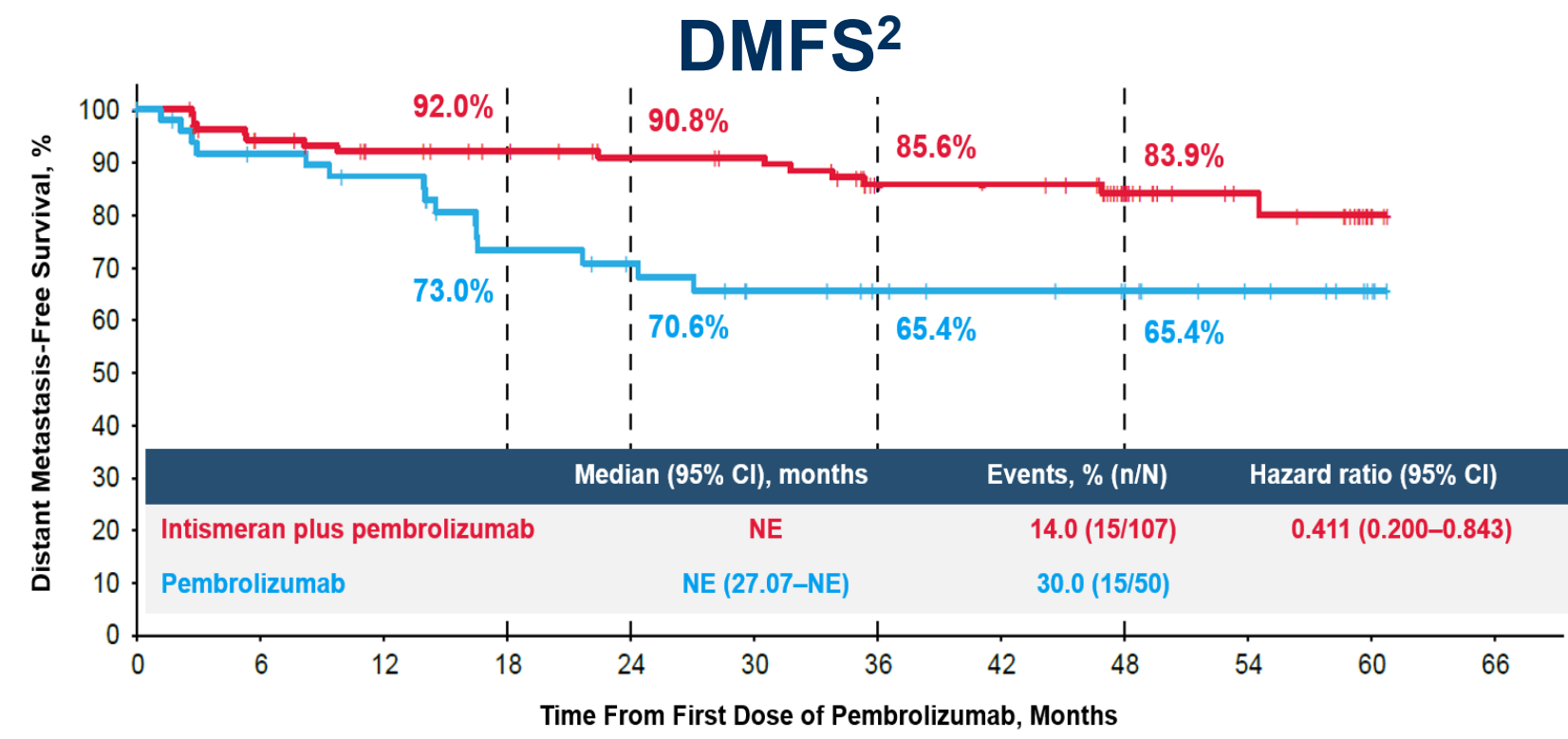
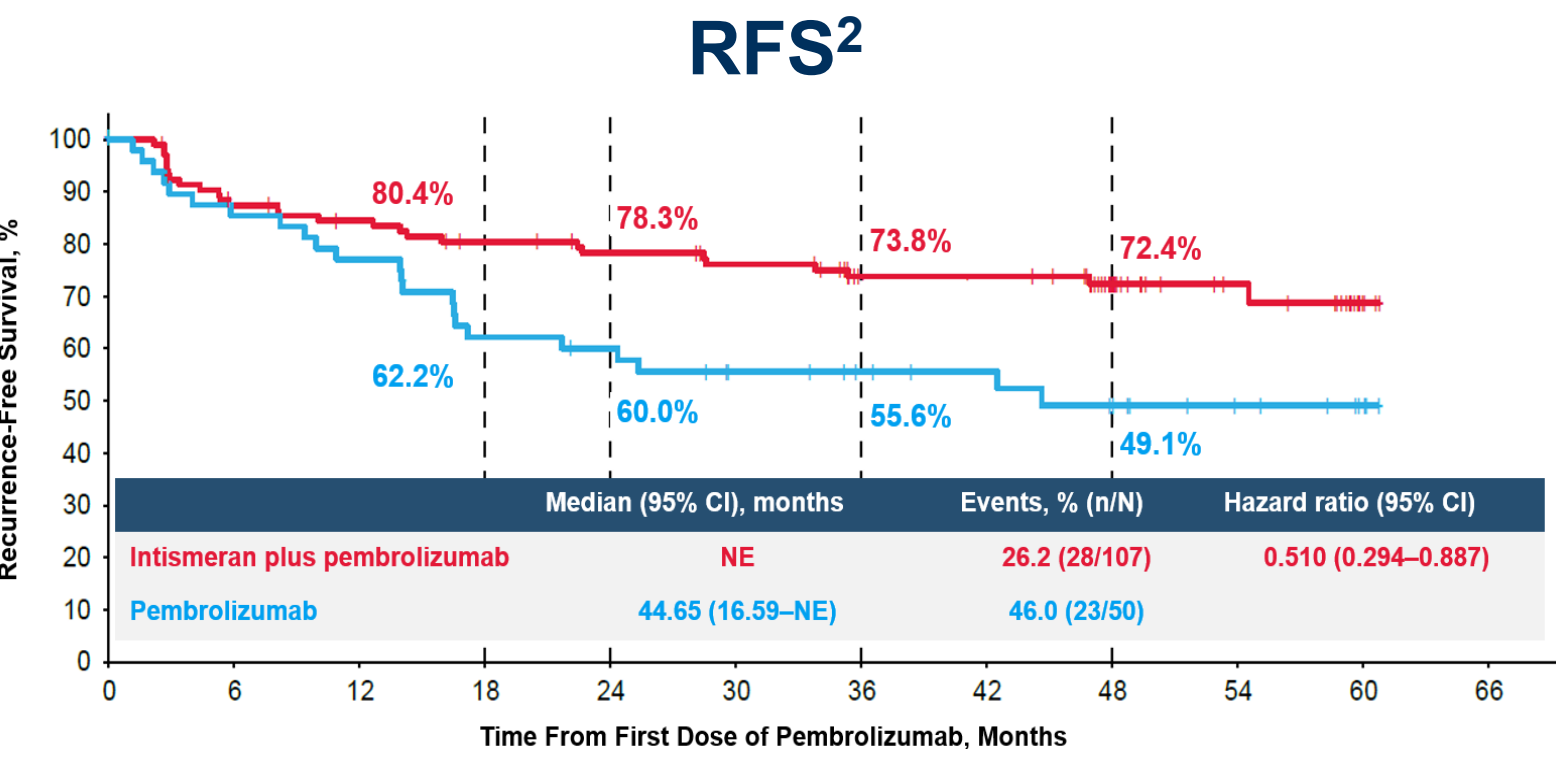
- Intismeran is designed to **strengthen existing** and **create new** T cell responses¹⁻³
- Pembrolizumab **blocks PD-1** to enhance T-cell activity, complementing intismeran's MOA



^aHypothetical mechanism of action.

¹Weber JS et al. *Lancet* 2024;403:632–44. ²Ojalvo LS et al. *JCO Oncol Adv* 2026;3:e2500206. ³Gainor JF, et al. *Cancer Discov*. 2024;14(11):2209-2223

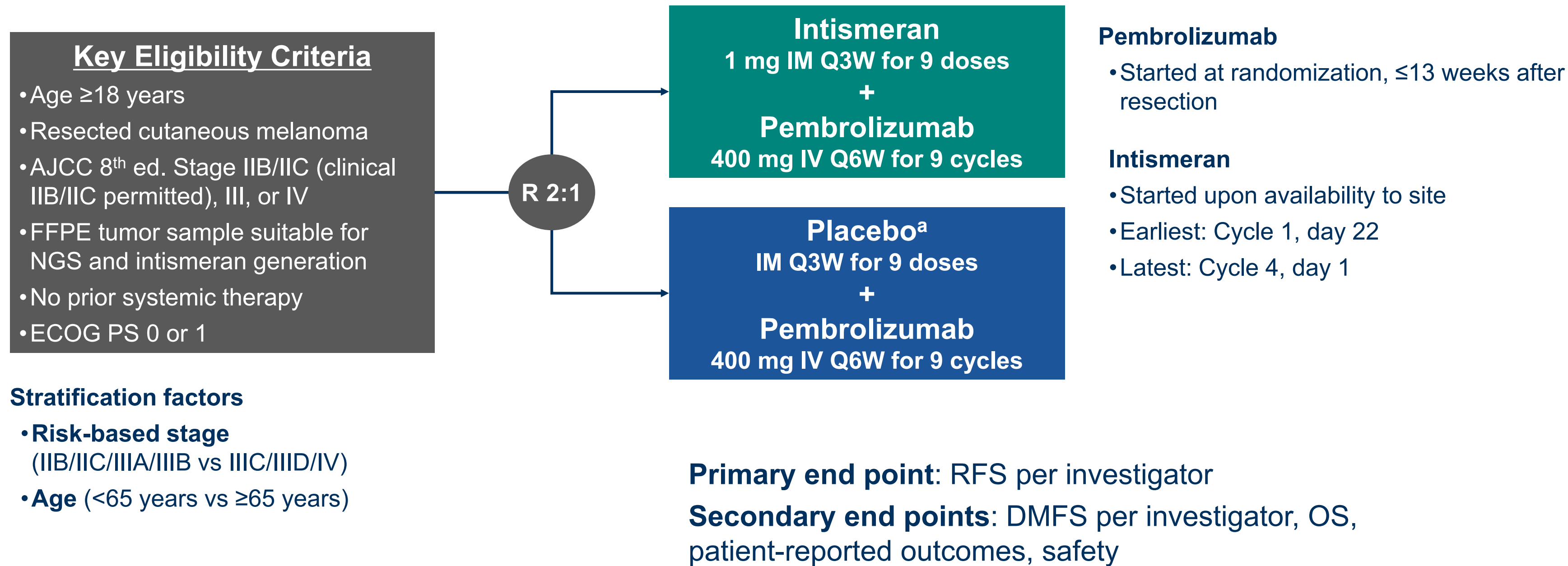
KEYNOTE-942: Phase 2b trial of pembrolizumab ± intismeran: Proof of concept in stage IIIB–IV resected melanoma



- Intismeran + pembrolizumab significantly improved RFS and DMFS and had a tolerable safety profile¹
 - Clinical benefit durable at 5 years²
- Intismeran-induced immune responses are associated with clinical outcomes²
 - Greater sustained expansion of novel T-cell clonotypes was associated with lack of recurrence^{2,3}
- Novel T-cell clonotypes were mapped to intismeran-encoded neoantigens and functionally validated³

¹Weber JS et al. *Lancet* 2024;403:632–44. ²Khattak A et al. *J Clin Oncol* 2026;44:2482–9. ³Sullivan RJ et al. *J Clin Oncol* 2026;44:abstr 9564.

INTerpath-001: Randomized, Double-Blind, Phase 3 Trial



^aNormal saline or dextrose. Placebo was started at random to maintain the blind.
ClinicalTrials.gov identifier: NCT05933577.

Key Statistical Considerations

Statistical methods

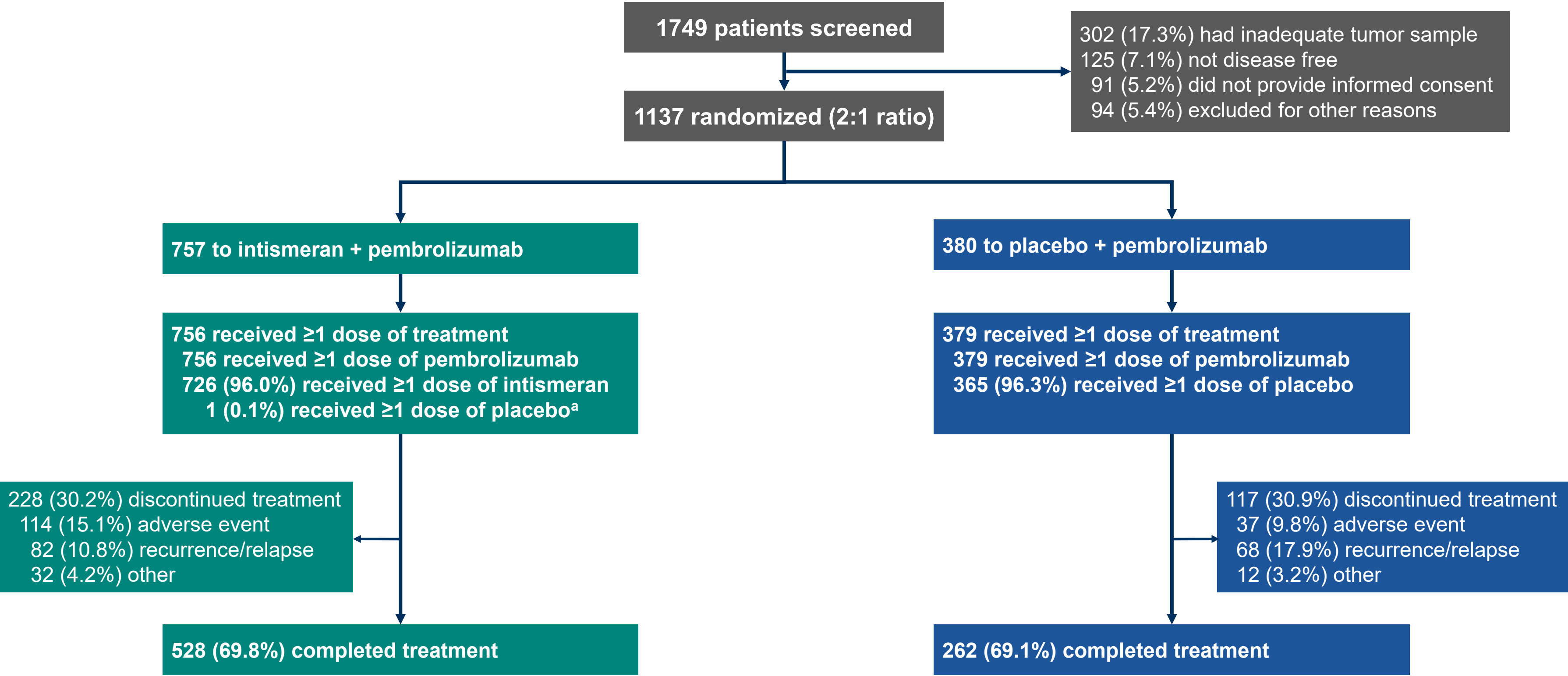
- Hierarchical testing^a: order of RFS → DMFS → OS
- Between-group treatment differences: stratified log-rank test^b
- Magnitude of treatment differences
 - Primary method: HR (95% CI) based on stratified Cox regression model^b in ITT population
 - Sensitivity analysis 1: unstratified piecewise HRs (95% CIs) in ITT population
 - Sensitivity analysis 2: HR (95% CI) based on stratified Cox regression model^b in mITT population^c

Interim analysis 1 (IA1)

- Timing: after ~240 RFS events and ≥18 months after last patient randomized
- Data cutoff date: June 30, 2026
 - Median follow-up^d: 24.6 months (range, 18.2–34.5)

^aThe overall type I error was strongly controlled at one-sided 0.025 across RFS, DMFS, and OS. All alpha was initially allocated to RFS; alpha was transferred to DMFS and OS only if the preceding end point was significant. ^bRandomization stratification factors applied to all stratified analyses. ^cModified ITT (mITT) population included all randomized patients who received intismeran or placebo as planned. ^dDefined as time from randomization to the data cutoff date.

Treatment Disposition and Exposure



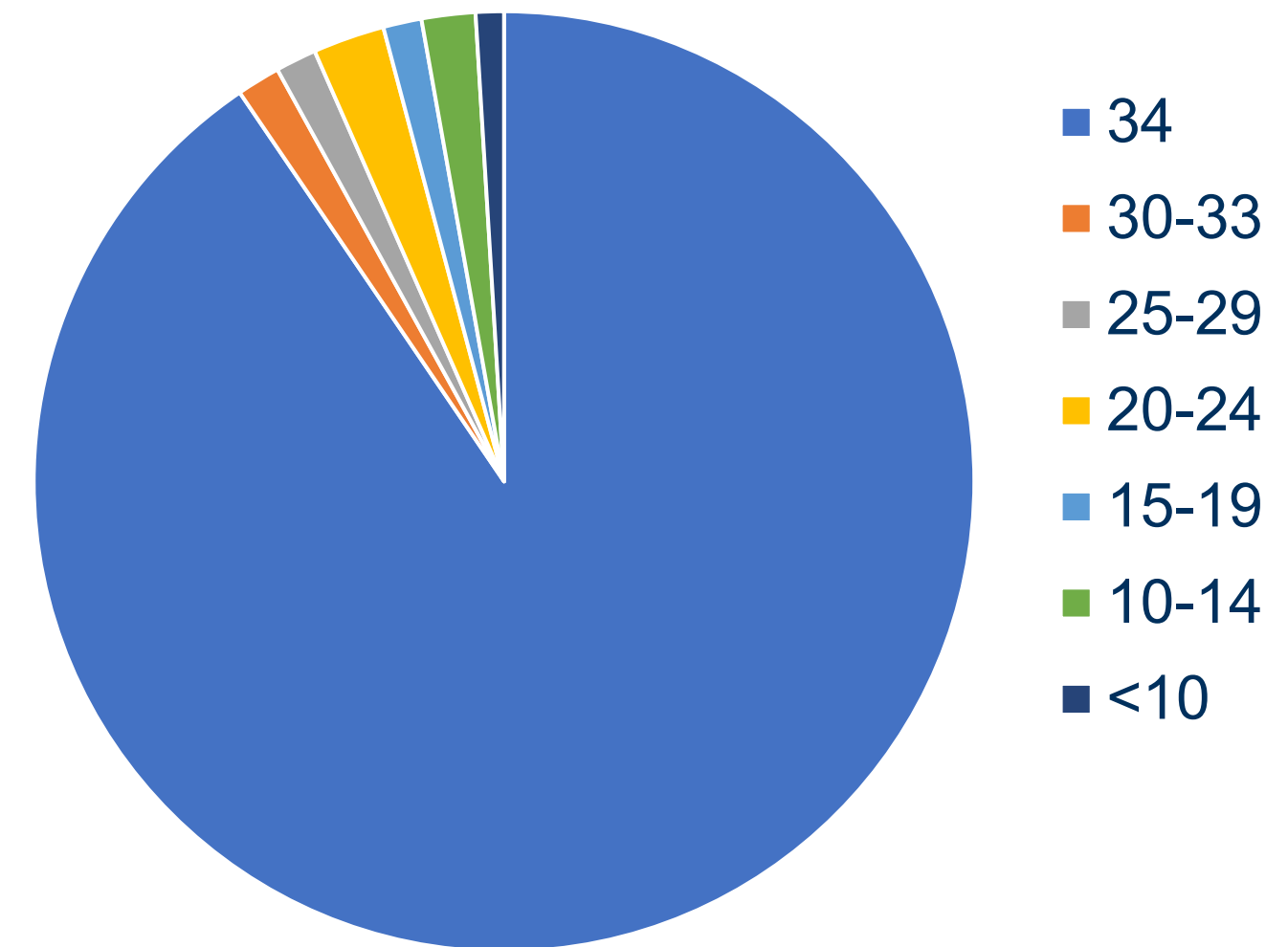
^aThe patient for whom intismeran could not be manufactured received placebo to maintain the blind.

Intismeran Design, Manufacture,^a and Exposure

- 91% of the 1137 randomized patients had the maximum 34 neoantigens identified for intismeran design
- >99% of the 757 patients in the intismeran + pembrolizumab arm had their intismeran successfully manufactured
- Median time to first intismeran dose was 64 days
- Median number of intismeran doses was 9^b

No. neoantigens in each intismeran

Median: 34 (range, 7–34)



^aIntismeran was designed for all randomized patients. The manufacturing workflow was initiated when it was known that a patient was randomized to the intismeran + pembrolizumab arm.

^bThe median number of placebo administrations and pembrolizumab cycles was also 9.

Baseline Characteristics

	Intismeran + pembrolizumab (N = 757)	Placebo + pembrolizumab (N = 380)		Intismeran + pembrolizumab (N = 757)	Placebo + pembrolizumab (N = 380)
Age, median (range)	61.0 y (18–89)	61.5 y (18–88)	ECOG PS 0, n (%)	697 (92.1)	350 (92.1)
Male sex, n (%)	456 (60.2)	227 (59.7%)	Risk-based disease stage, n (%)		
Race, n (%)			IIB/IIC/IIIA/IIIB	441 (58.3)	230 (60.5)
Asian	15 (2.0)	13 (3.4)	IIIC/IIID/IV	316 (41.7)	150 (39.5)
Multiple	5 (0.7)	4 (1.1)	Overall disease stage, n (%)		
White	696 (91.9)	337 (88.7)	IIA	1 (0.1) ^c	0
Other	10 (1.3) ^a	4 (1.1) ^b	IIB	155 (20.5)	73 (19.2)
Missing	31 (4.1)	22 (5.8)	IIC	92 (12.2)	42 (11.1)
Geographic region, n (%)			IIIA	50 (6.6)	32 (8.4)
Australia	89 (11.8)	39 (10.3)	IIIB	143 (18.9)	83 (21.8)
Europe	415 (54.8)	209 (55.0)	IIIC	245 (32.4)	118 (31.1)
Latin America	45 (5.9)	22 (5.8)	IIID	10 (1.3)	4 (1.1)
United States	84 (11.1)	35 (9.2)	IV	61 (8.1)	28 (7.4)
Rest of world	124 (16.4)	75 (19.7)			

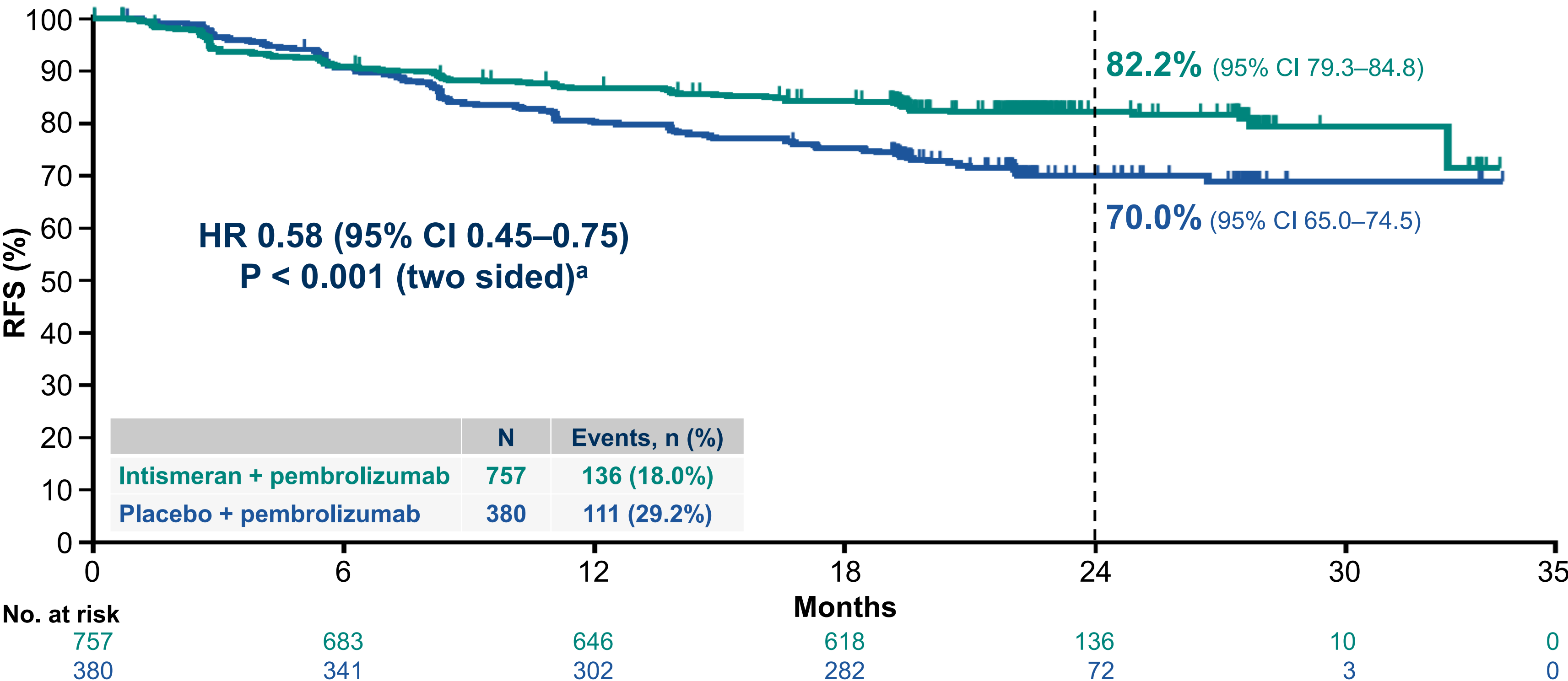
^aIncludes American Indian or Alaska Native (n = 5), Black or African American (n = 3), and Native Hawaiian or other Pacific Islander (n = 2). ^bIncludes American Indian or Alaska Native (n = 3) and Black or African American (n = 1). ^cProtocol deviation.

ITT population: all randomized patients according to the arm to which they were assigned. Data cutoff date: June 30, 2026 (median study follow-up, 24.6 mo).

Presented by: Georgina V. Long, Melanoma Institute Australia

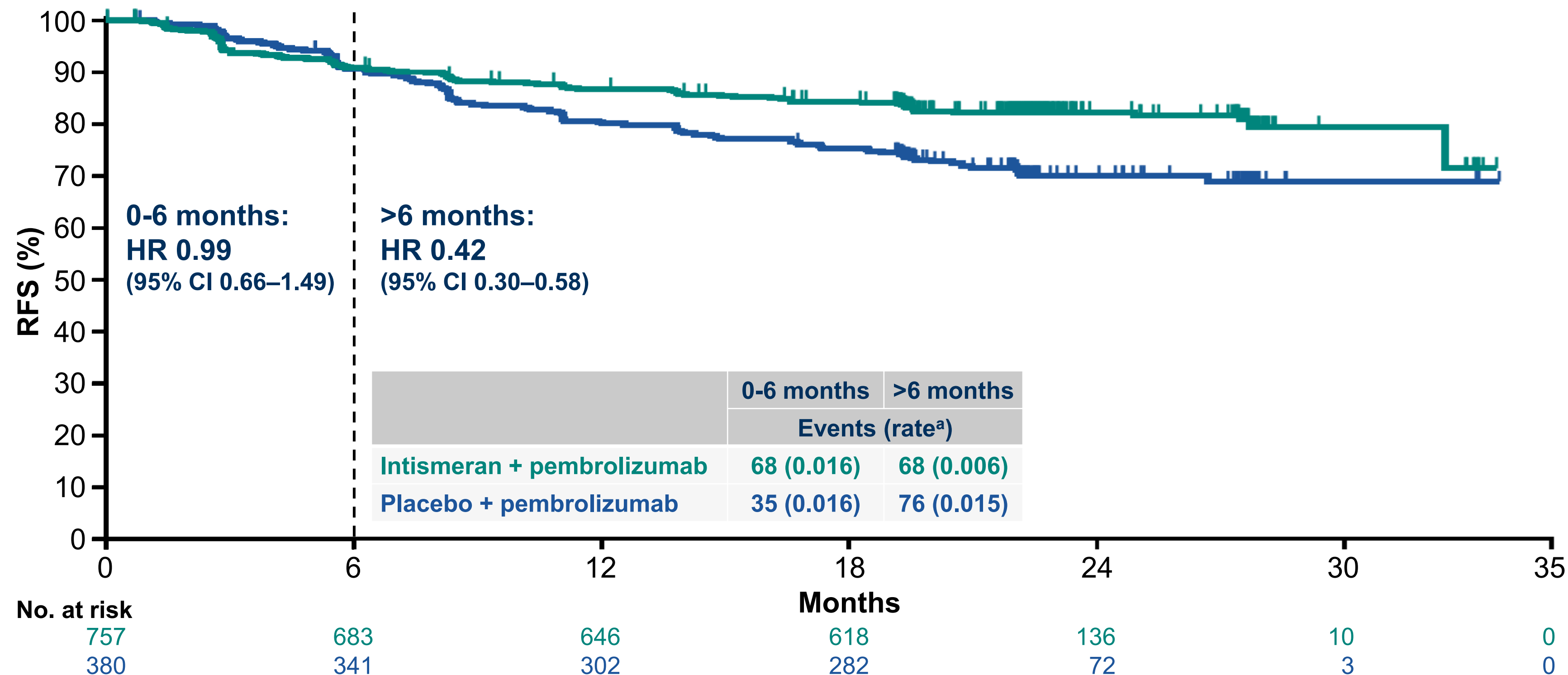
Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

RFS Primary Analysis: ITT



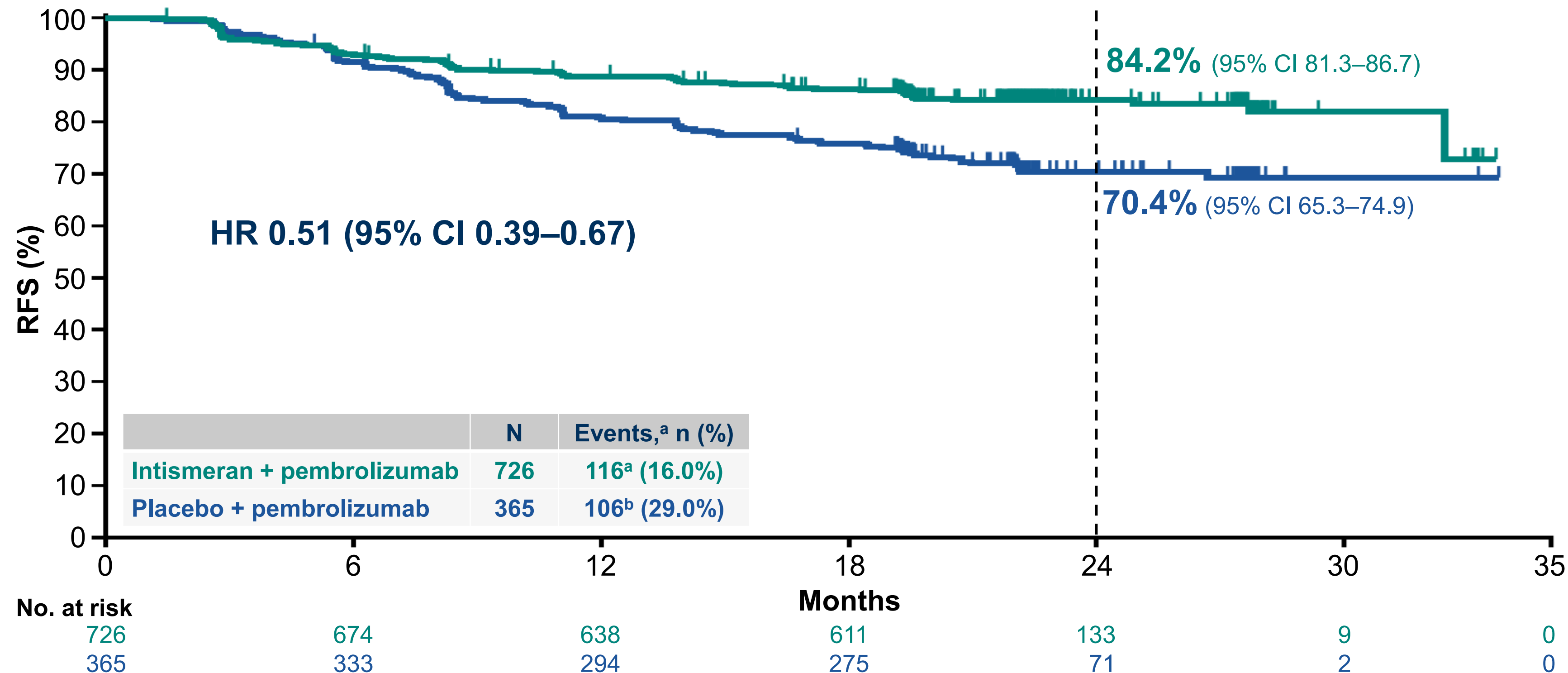
^aMultiplicity-adjusted significance level: two-sided 0.024692.
ITT: all randomized patients according to the arm to which they were assigned.
RFS: time from randomization to the first occurrence of any recurrence or death from any cause. Data cutoff date: June 30, 2026 (median study follow-up, 24.6 mo).

RFS Sensitivity Analysis: Piecewise Hazard Ratios, ITT



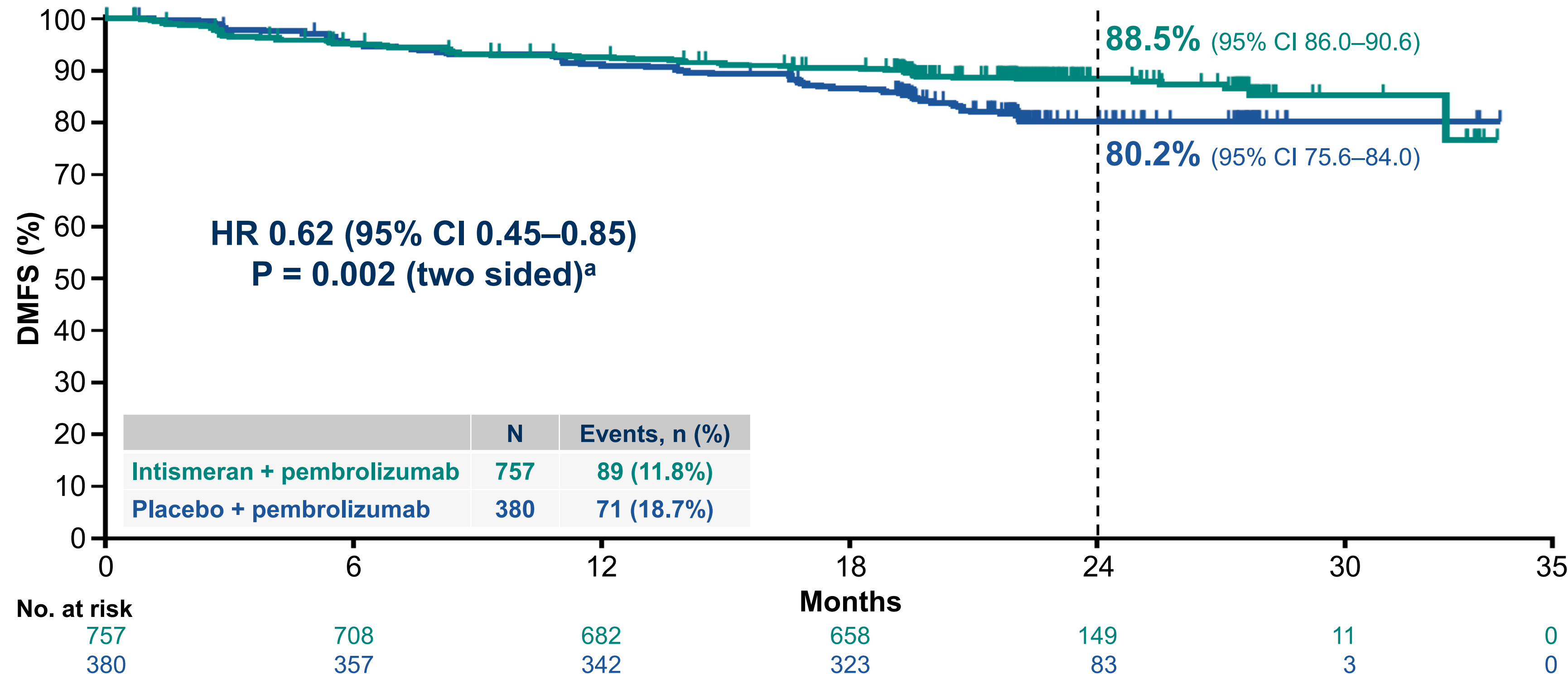
^aRate calculated as no. of events divided by person-time in each interval. ITT: all randomized patients according to the arm to which they were assigned.
RFS: time from randomization to the first occurrence of any recurrence or death from any cause. Data cutoff date: June 30, 2026 (median study follow-up, 24.6 mo).

RFS Sensitivity Analysis: mITT



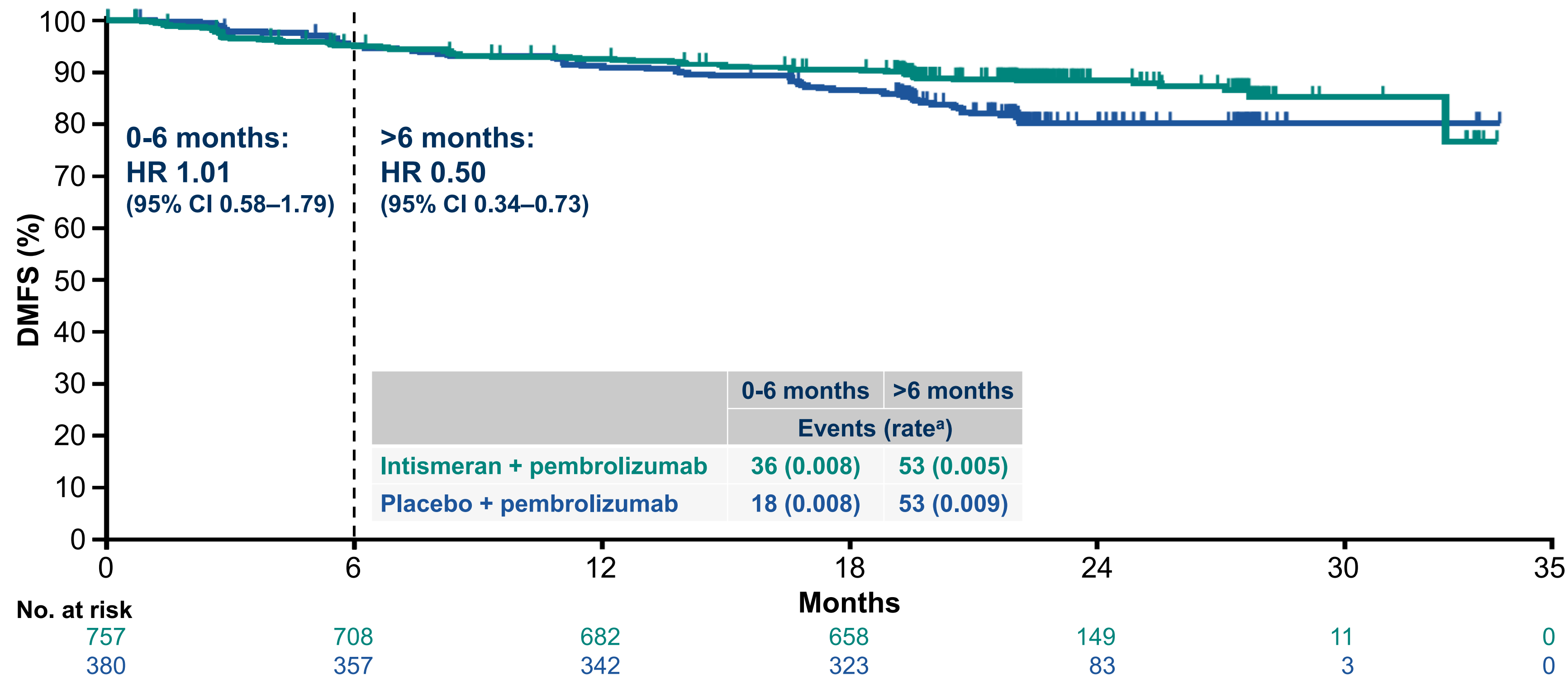
^a31 patients in the intismeran + pembrolizumab arm were excluded from the mITT population due to AEs (n=13), recurrence (n=10), or other reason (n=8). RFS events occurred in 20 (64.5%) of the 31 patients who did not receive intismeran as planned. ^b15 patients in the placebo + pembrolizumab arm were excluded from the mITT population due to AEs (n=5), recurrence (n=4), or other reason (n=6). RFS events occurred in 5 (33.3%) of 15 patients who did not receive placebo as planned. mITT: all randomized patients who received intismeran or placebo as assigned. RFS: time from randomization to the first occurrence of any recurrence or death from any cause. Data cutoff date: June 30, 2026 (median study follow-up, 24.6 mo).

DMFS Primary Analysis: ITT



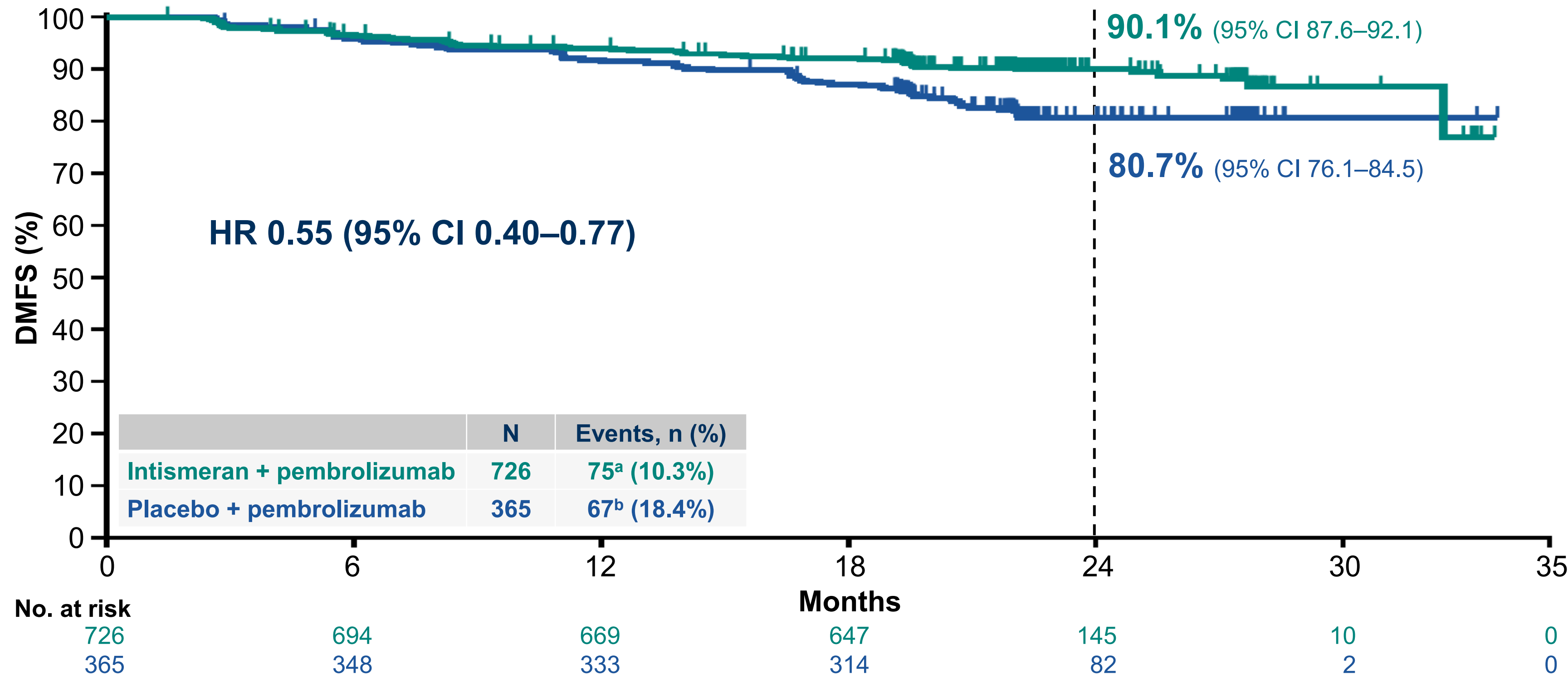
^aMultiplicity-adjusted significance level: two-sided 0.01608.
ITT: all randomized patients according to the arm to which they were assigned.
DMFS: time from randomization to first occurrence of distant metastasis or death from any cause. Data cutoff date: June 30, 2026 (median study follow-up, 24.6 mo).

DMFS Sensitivity Analysis, Piecewise Hazard Ratios, ITT



^aRate calculated as no. of events divided by person-time in each interval. ITT: all randomized patients according to the arm to which they were assigned.
DMFS: time from randomization to first occurrence of distant metastasis or death from any cause. Data cutoff date: June 30, 2026 (median study follow-up, 24.6 mo).

DMFS Sensitivity Analysis: mITT



^aDMFS events occurred in 14 (45.2%) of 31 patients who did not receive intismeran. ^bDMFS events occurred in 4 (26.7%) of 15 patients who did not receive placebo as planned.

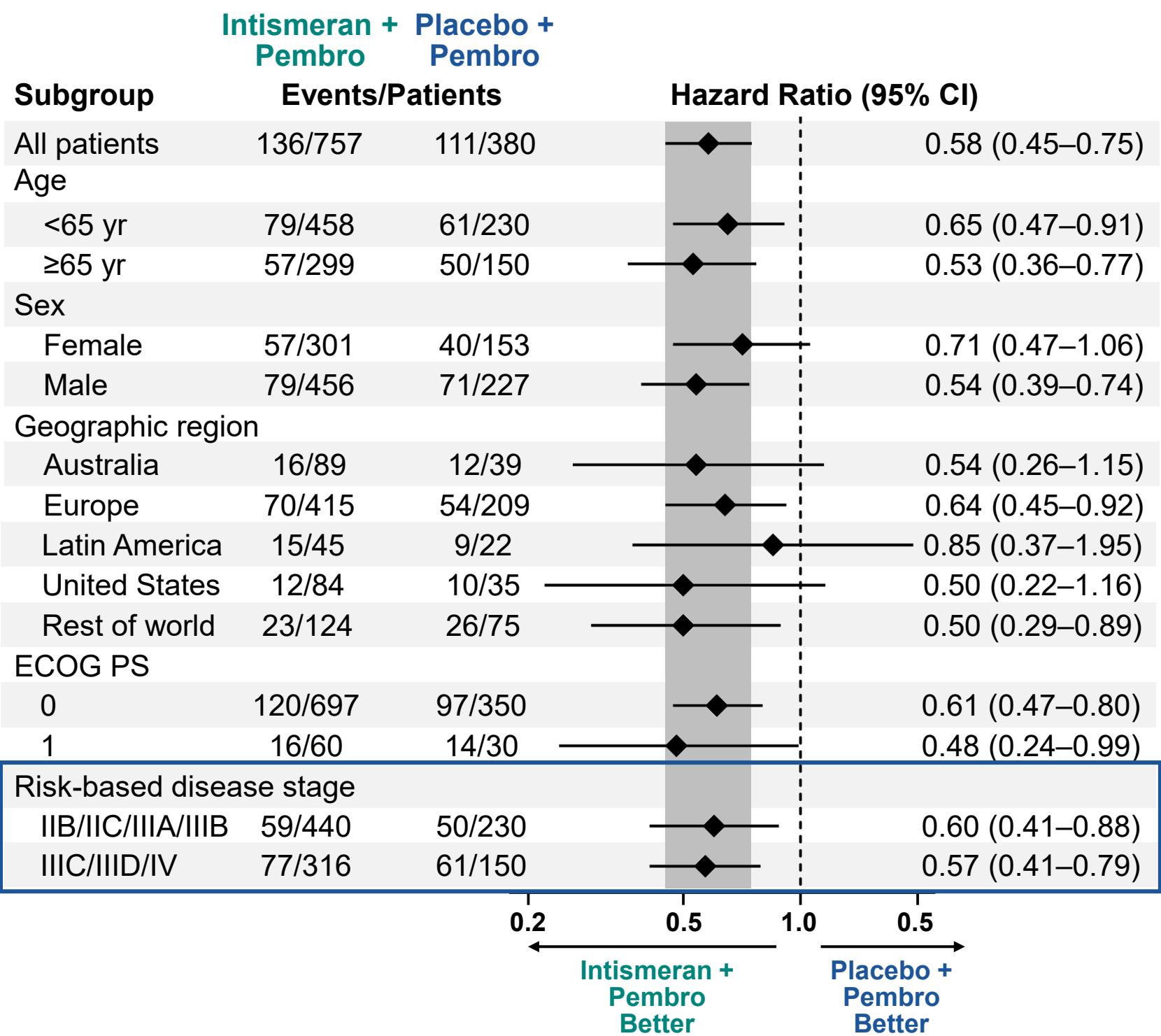
mITT: all randomized patients who received intismeran or placebo as assigned.

DMFS: time from randomization to first occurrence of distant metastasis or death from any cause. Data cutoff date: June 30, 2026 (median study follow-up, 24.6 mo).

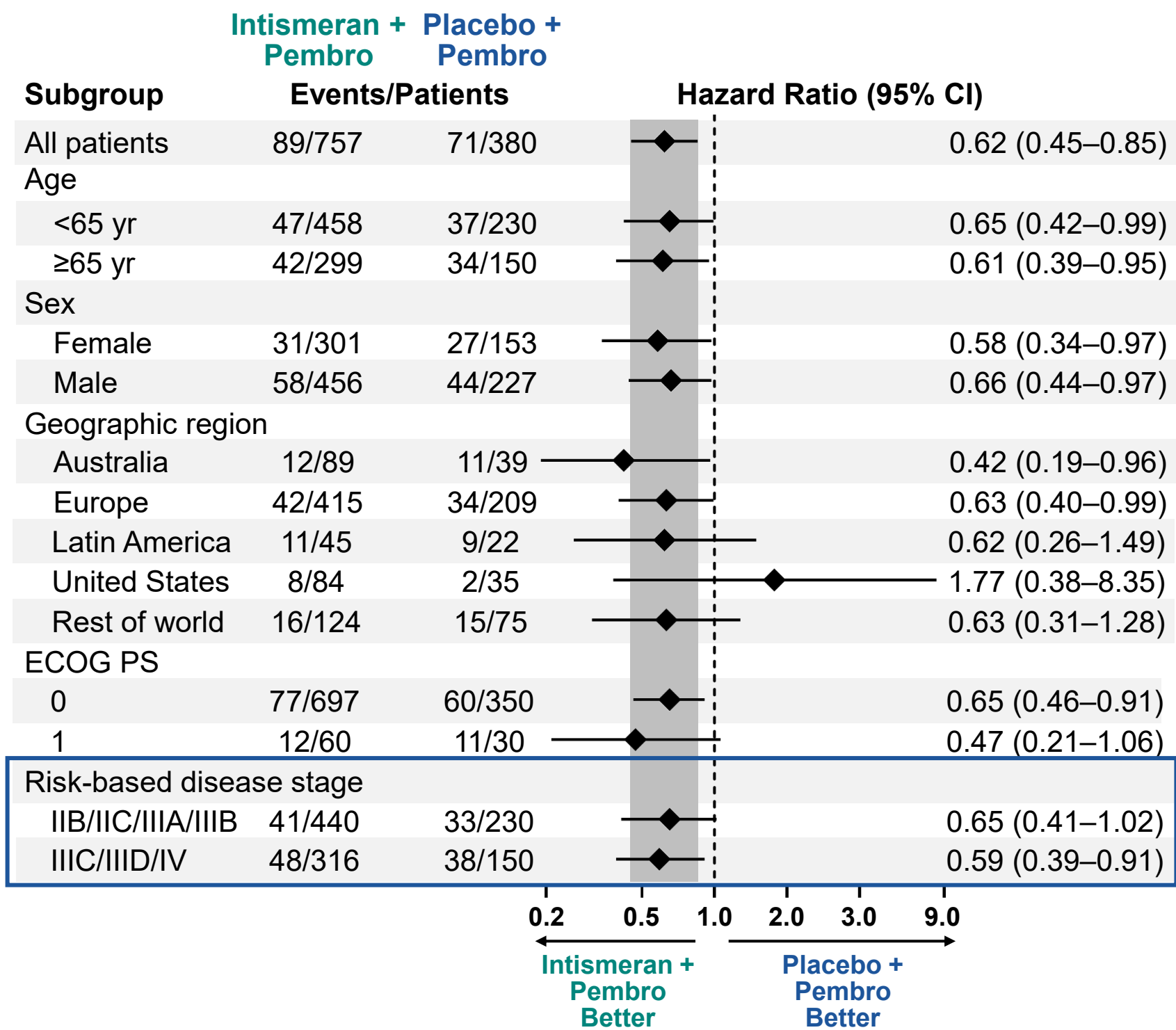
Efficacy in Prespecified Subgroups

RFS and DMFS benefits observed in most subgroups

Recurrence-Free Survival



Distant Metastasis-Free Survival



ITT: all randomized patients according to the arm to which they were assigned. Data cutoff date: June 30, 2026 (median study follow-up, 24.6 mo).

Presented by: Georgina V. Long, Melanoma Institute Australia

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Adverse Event Summary

	All-Cause AEs		Treatment-Related AEs	
	Intismeran + Pembrolizumab (N = 755)	Placebo + Pembrolizumab (N = 380)	Intismeran + Pembrolizumab (N = 755)	Placebo + Pembrolizumab (N = 380)
Any grade	742 (98.3)	366 (96.3)	723 (95.8)	342 (90.0)
Grade 3-5	178 (23.6)	77 (20.3)	107 (14.2)	51 (13.4)
Serious	133 (17.6)	60 (15.8)	74 (9.8)	42 (11.1)
Led to discontinuation of any drug	125 (16.6)	36 (9.5)	106 (14.0)	33 (8.7)
Discontinuation of pembrolizumab	115 (15.2)	36 (9.5)	97 (12.8)	33 (8.7)
Discontinuation of intismeran or placebo	66 (8.7)	21 (5.5)	54 (7.2)	19 (5.0)
Discontinuation of both drugs simultaneously	49 (6.5)	20 (5.3)	39 (5.2)	18 (4.7)
Led to death (none related to intismeran)	8 (1.1)	0	2 (0.3)	0

Grade 5 AEs

- 5 of the deaths occurred **before** the first dose of intismeran^a; 2 were attributed to pembrolizumab
- 3 of the deaths occurred **after** the first dose of intismeran^b; none attributed to treatment

^aOf the 5 events, 2 were attributed to pembrolizumab (muscular weakness, myocarditis, and myositis in 1 patient and myasthenia gravis in 1 patient); the remaining deaths were due to cardiac failure (n=1), road traffic accident (n=1), and sudden death (n=1).

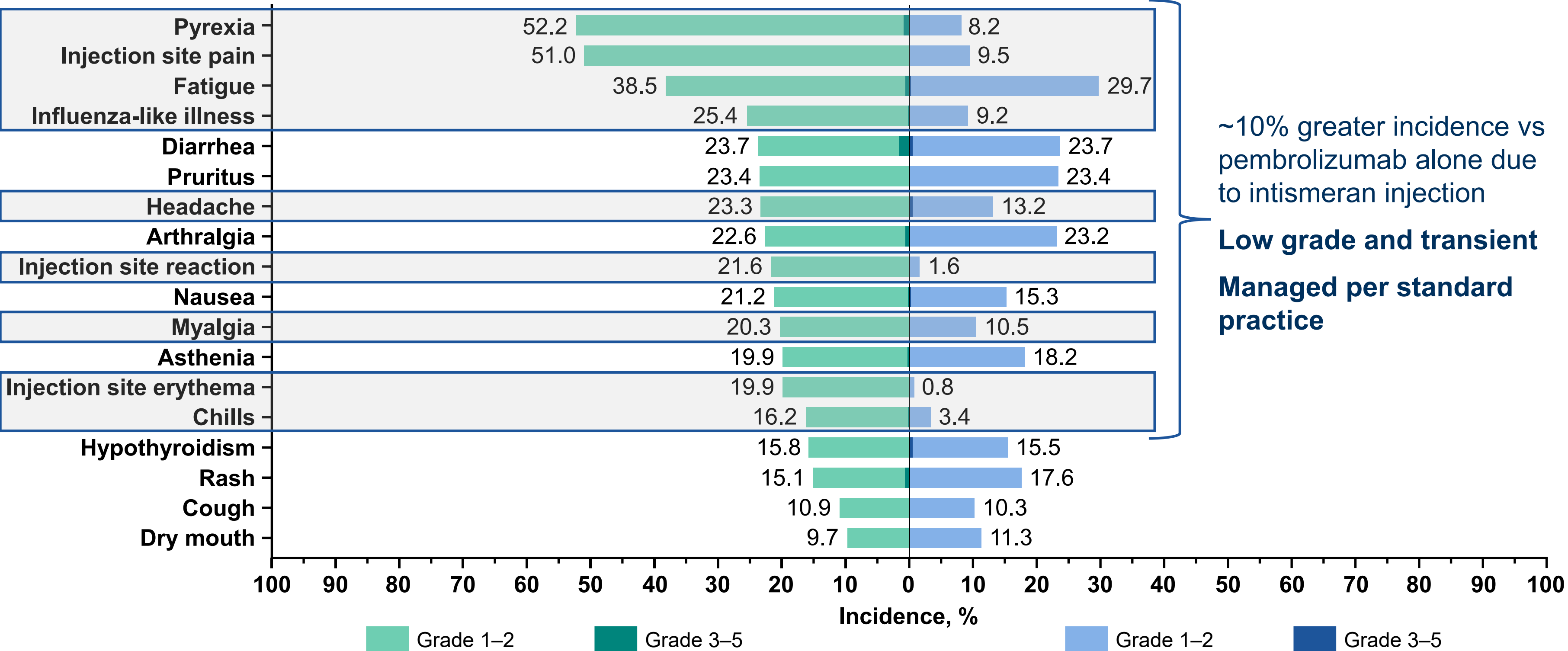
^bOf the 3 events, none were attributed to study treatment (acute myocardial infarction (n=1), aspiration pneumonia (n=1), and sudden cardiac death (n=1)).

As-treated population: all randomized patients who received at ≥1 dose of study treatment. Data cutoff date: June 30, 2026 (median study follow-up, 24.6 mo).

All-Cause AEs, Incidence $\geq 10\%$

Intismeran + Pembrolizumab (N = 755)

Placebo + Pembrolizumab (N = 380)



As-treated population: all randomized patients who received at ≥ 1 dose of study treatment. Data cutoff date: June 30, 2026 (median study follow-up, 24.6 mo).

Presented by: Georgina V. Long, Melanoma Institute Australia

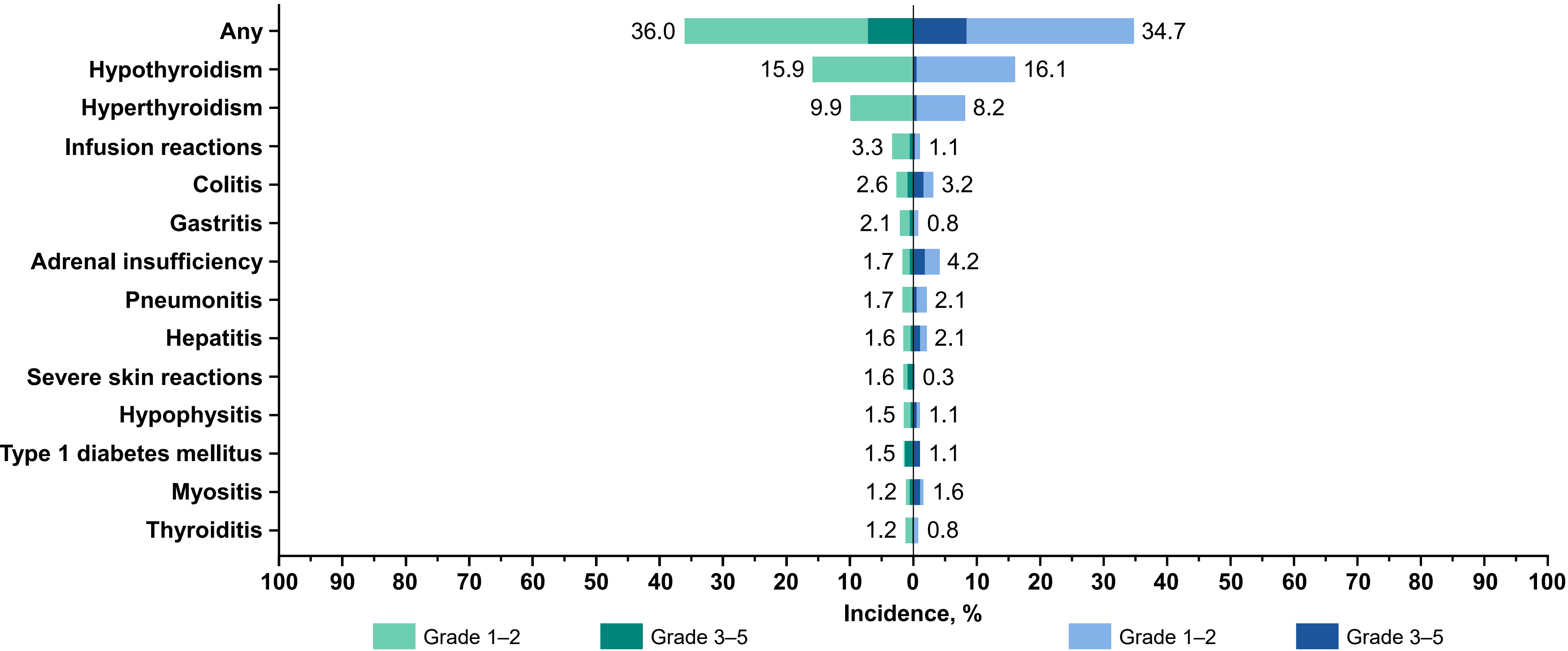
Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

AEs of Interest for Pembrolizumab, Incidence $\geq 1\%$

Intismeran did not potentiate pembrolizumab-associated AEs

Intismeran + Pembrolizumab (N = 755)

Placebo + Pembrolizumab (N = 380)



As-treated population: all randomized patients who received at ≥ 1 dose of study treatment. Data cutoff date: June 30, 2026 (median study follow-up, 24.6 mo).

Presented by: Georgina V. Long, Melanoma Institute Australia

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Summary and Conclusions

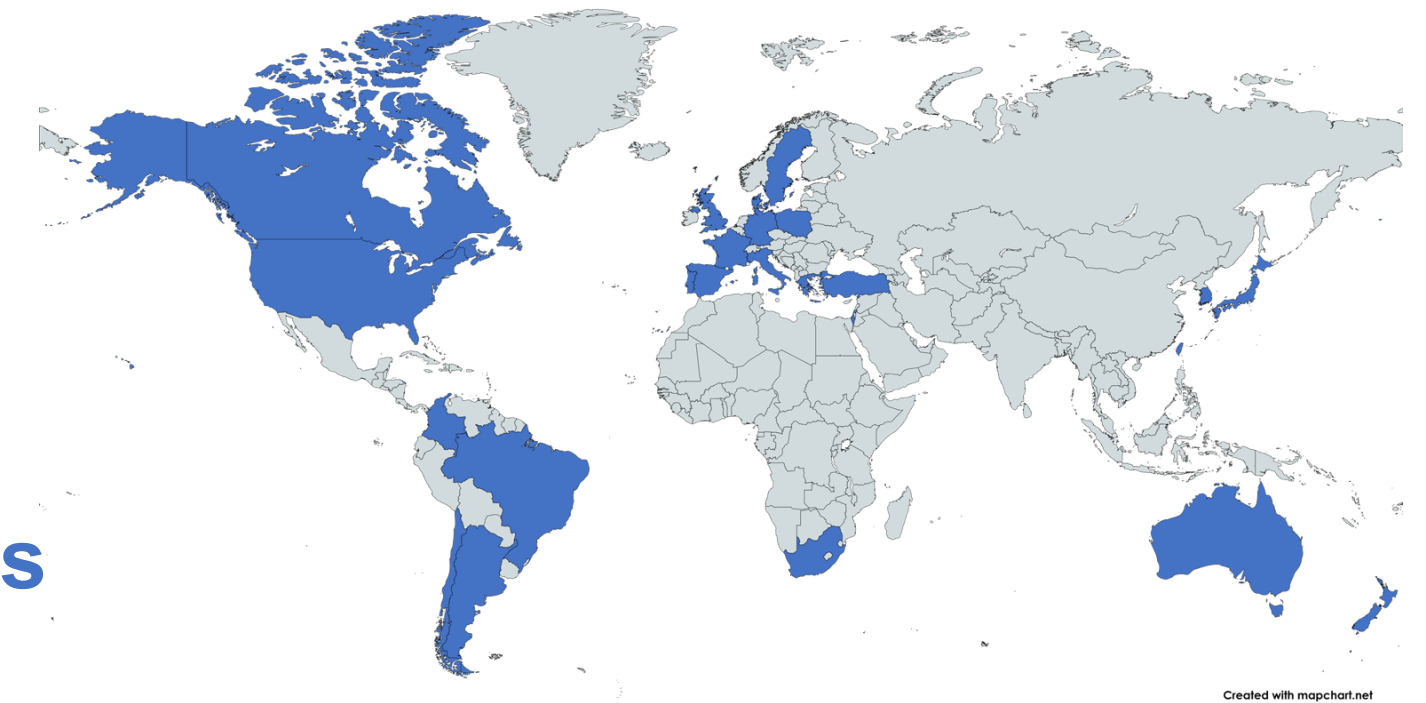
- INTerpath-001 met both the primary RFS and key secondary DMFS endpoints
 - Intismeran + pembrolizumab reduced the risk of recurrence or death by 42% and the risk of distant metastasis or death by 38% compared with placebo + pembrolizumab
 - In a sensitivity analysis, intismeran + pembrolizumab reduced the risk of recurrence or death by 58% after month 6
 - Benefit was observed in most prespecified subgroups, including risk-based disease stages
 - OS was immature and did not meet prespecified significance boundary^a; follow-up is ongoing
- Safety was generally consistent with previous experience, with no potentiation of pembrolizumab-associated AEs with the combination
- Intismeran was reliably delivered at a global scale
- Ongoing phase 2 and 3 trials are evaluating intismeran for bladder cancer, melanoma, NSCLC, and RCC in the neoadjuvant, adjuvant, or metastatic settings
- INTerpath-001 sets a new benchmark for adjuvant therapy in melanoma and establishes intismeran as a landmark advance in personalized cancer medicine

^aThe hazard ratio for OS was 0.77 (95% CI, 0.45–1.31); two-sided P = 0.33.

Acknowledgments

PATIENTS AND THEIR FAMILIES

Investigators and site personnel from 157 global sites



The members of the Independent Data and Safety Monitoring Committee

Dr. Jeffrey S. Weber (1952–2024) for contributions to the INTerpath-001 design, and the enrolment and care of patients

All current and former personnel of MSD and Moderna who supported the study, particularly Stephan Anami, Claudia Del Vino, Li Fan, Jia Guo, Giulia Indellicati, Clemens Krepler, Tejaskumar Mehta, Kristen Pesci, Nivetha Ramachandran, Lili Zhu

Contact Dr. Georgina Long at georgina.long@sydney.edu.au for questions or comments



To Download a Copy
of Today's Presentation



Visit <https://bit.ly/4gKuQsZ>



To Download a Plain Language
Summary of Today's Presentation



Visit <https://bit.ly/3Vx8Jz2>

Copies of this presentation obtained through QR, AR, and/or text key codes are for personal use only and may not be reproduced without written permission of the authors. Requesting this content will immediately download the requested content to your device. This presentation is intended as an educational resource and is for the exchange of scientific data to clinical investigators and health care professionals.

Presented by: Georgina V. Long, Melanoma Institute Australia

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.



ORIGINAL ARTICLE

Intismeran Autogene plus Pembrolizumab for Resected Stage IIB–IV Melanoma

Georgina V. Long, M.D., Ph.D.,¹⁻⁴ Muhammad A. Khattak, M.D., Ph.D.,^{5,6}
Helen J. Gogas, M.D.,⁷ Dirk Schadendorf, M.D.,⁸ Ana Arance, M.D., Ph.D.,^{9,10}
Matteo S. Carlino, M.D., Ph.D.,^{1,2,11,12} Piotr Rutkowski, M.D., Ph.D.,¹³
Gareth Rivalland, M.D.,^{14,15} Antoni Ribas, M.D., Ph.D.,¹⁶
Janice M. Mehnert, M.D.,¹⁷ Patrick A. Ott, M.D., Ph.D.,^{18,19}
Reinhard Dummer, M.D.,²⁰ Paola Queirolo, M.D.,^{21,22}
Christoffer Gebhardt, M.D.,^{23,24} Caroline Dutriaux, M.D.,^{25,26}
Carlos Rojas, M.D.,^{27,28} Yuanbin Chen, M.D., Ph.D.,^{29,30} Lisa M. Tachiki, M.D.,^{31,32}
Ronnie Shapira-Frommer, M.D.,³³ Oliver Bechter, M.D.,³⁴
Ryan J. Sullivan, M.D.,^{19,35} Alexander M. M. Eggermont, M.D., Ph.D.,³⁶⁻³⁹
Laureen S. Ojalvo, M.D., Ph.D.,⁴⁰ Michelle Brown, M.D., Ph.D.,⁴⁰
Jinchun Zhang, Ph.D.,⁴¹ Dmitri O. Grebennik, M.D.,⁴¹
Mizuho Fukunaga-Kalabis, M.D., Ph.D.,⁴¹ Paolo A. Ascierto, M.D.,^{42,43} and
Michele Del Vecchio, M.D.,⁴⁴ for the INTerpath-001 Investigators*

In press. Currently planned for publication on November 11, 2026.