Multiple Myeloma Updates

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Disclosure of Conflicts of Interest

Nasreen Vohra, MD, FACS, FSSO has the following financial relationship to disclose:

Advisory Board – Castle Biosciences

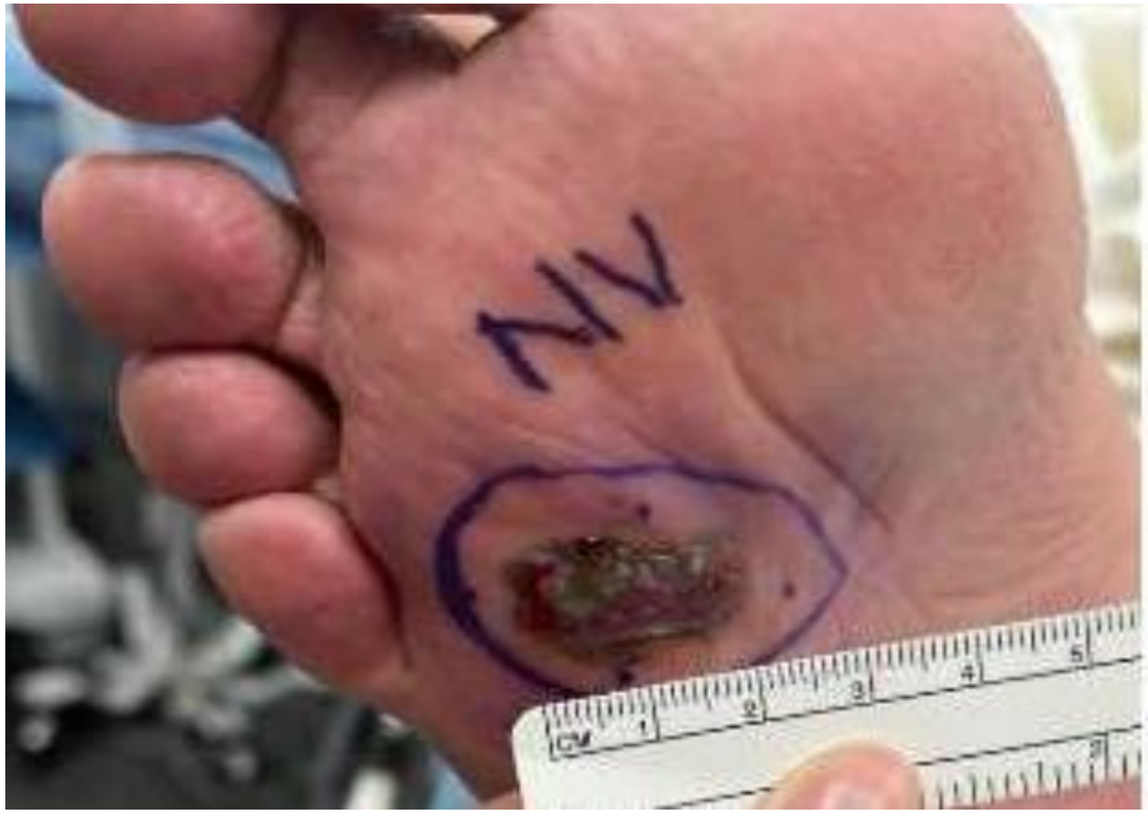
Case – Plantar Foot Melanoma

- 70 y/o male with a non-healing wound on the plantar foot

- Breslow thickness 4 mm
- Ulcerated
- 2 mitoses/mm2

- No palpable adenopathy

- Wide excision of melanoma – 2cm margin
- Sentinel lymph node dissection



- pT3b pN2a
- Post-op staging negative for distant disease

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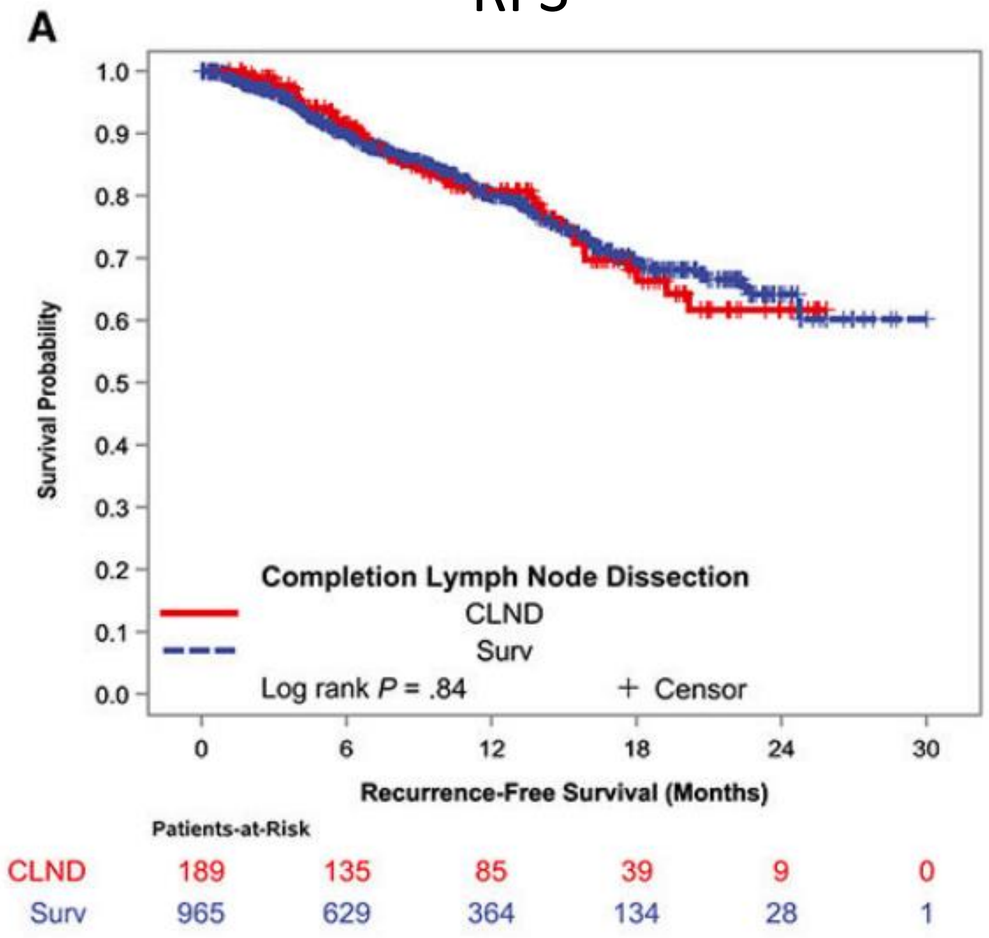
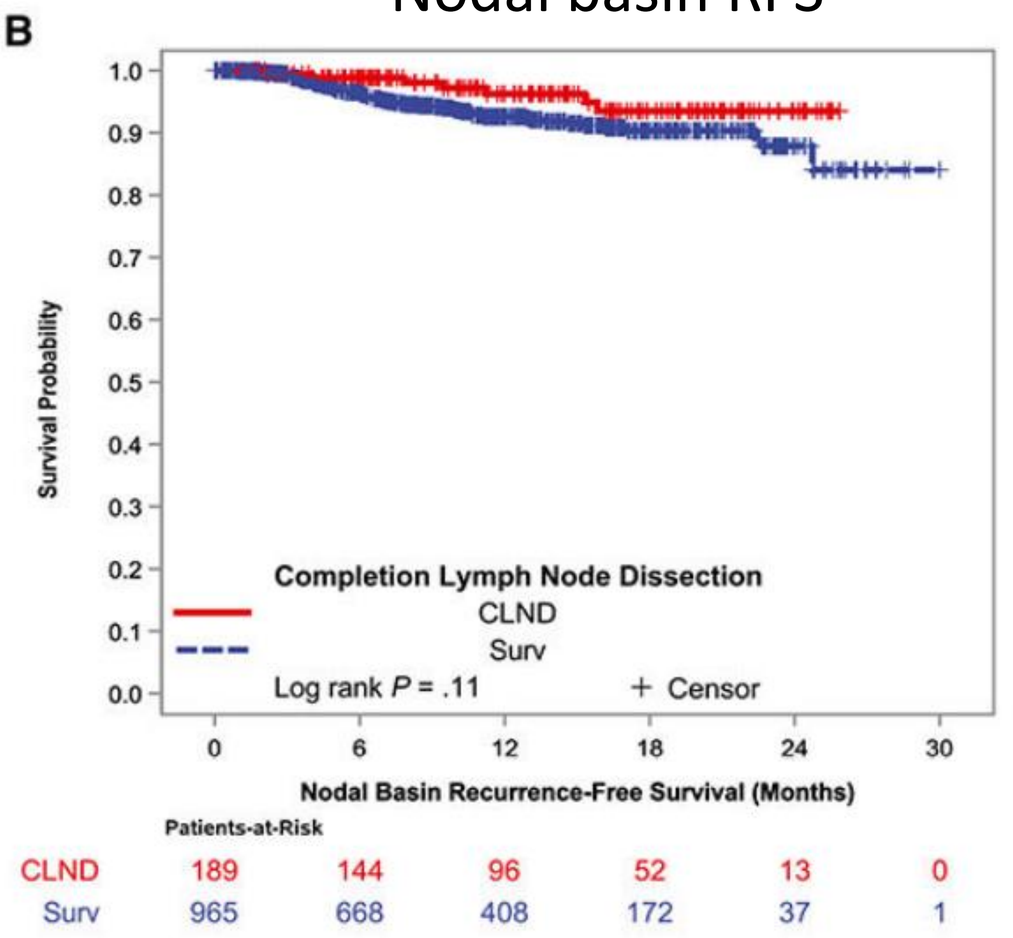
Management of the Nodal Basin – Post MSLT-2/DeCOG-SLT Era

RFS



Nodal basin RFS



Cancer 2021July 01; 127(13):2251-2261

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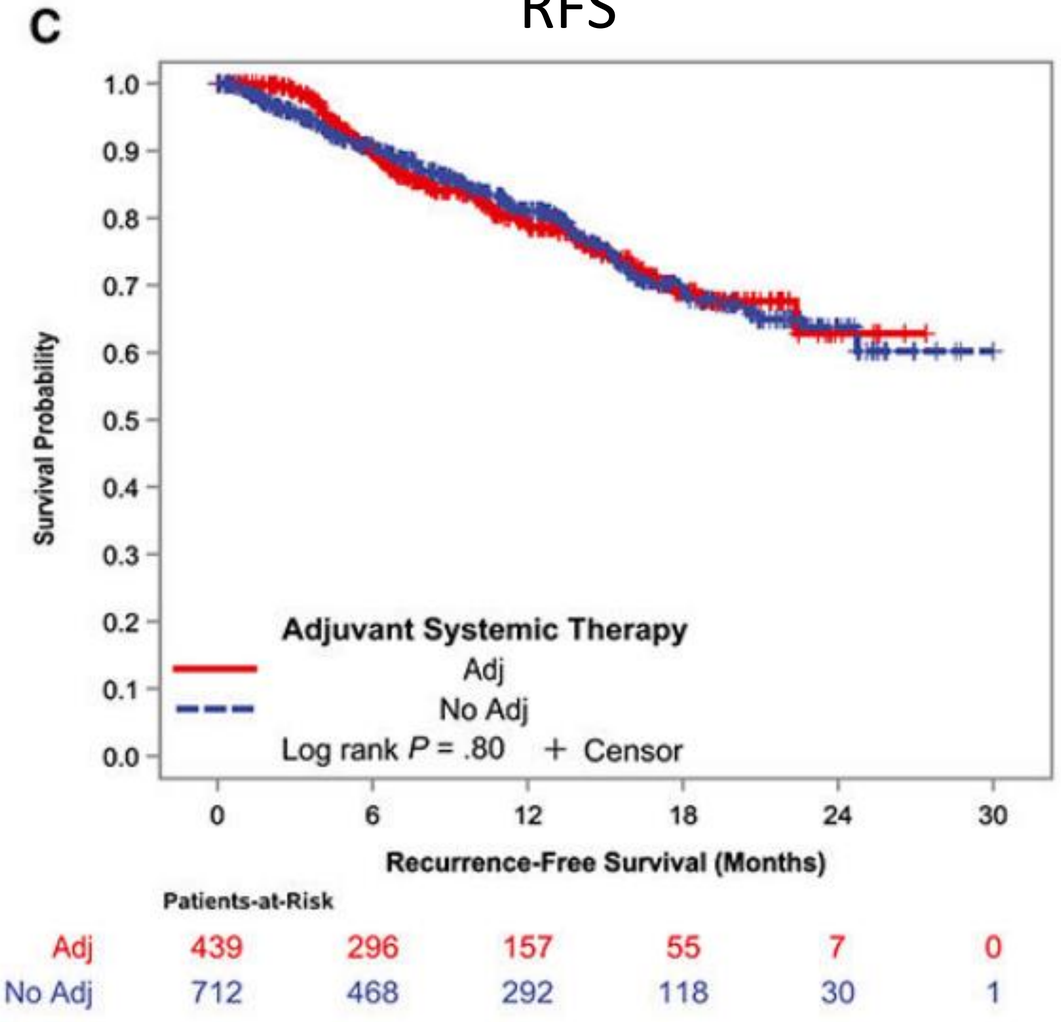
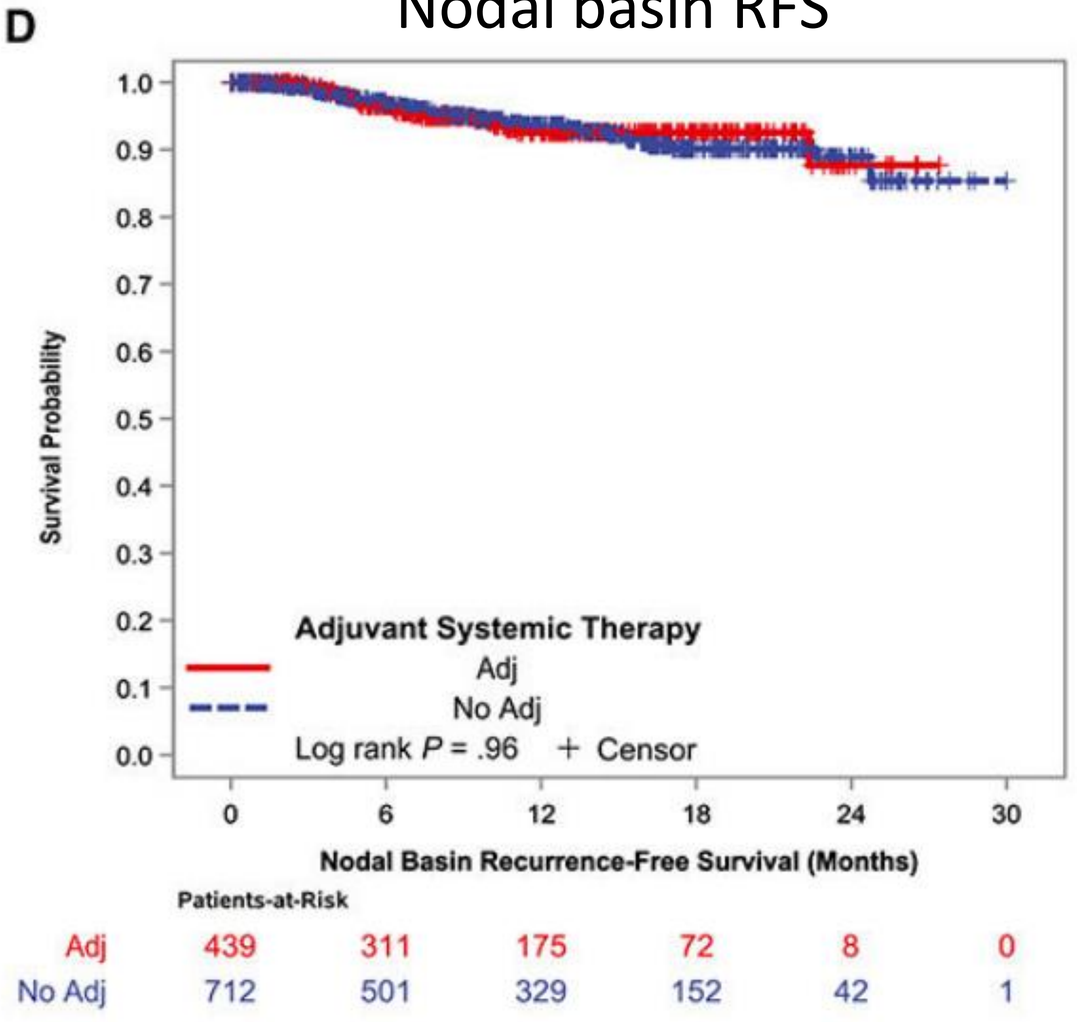


Nodal basin RFS



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Case– Plantar Foot Melanoma – Adjuvant therapy

- 70 y/o male with a non-healing wound on the plantar foot

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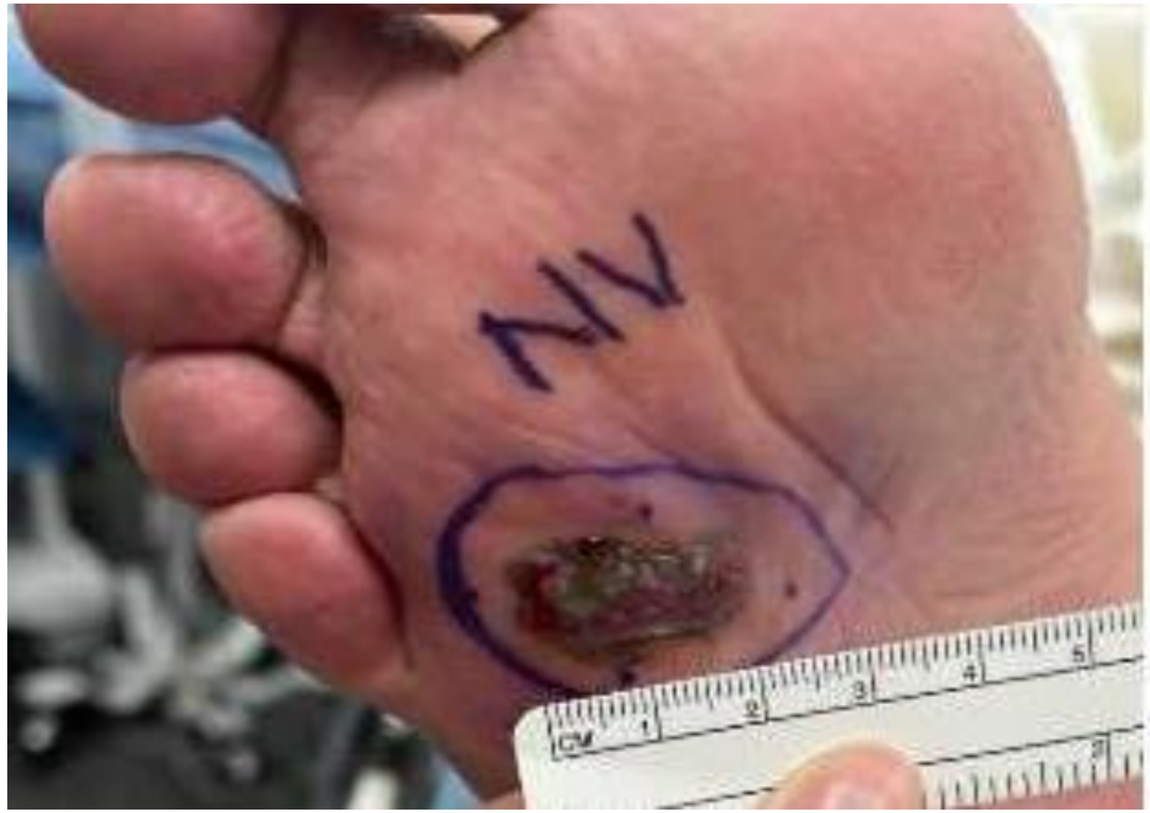
- Wide excision of melanoma – 2cm margin
- Sentinel lymph node dissection



- pT3b pN2a
- Post-op staging negative for distant disease

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Adjuvant therapy

- First line therapy ?
- Combination or Monotherapy?
- Discuss adjuvant immunotherapy data

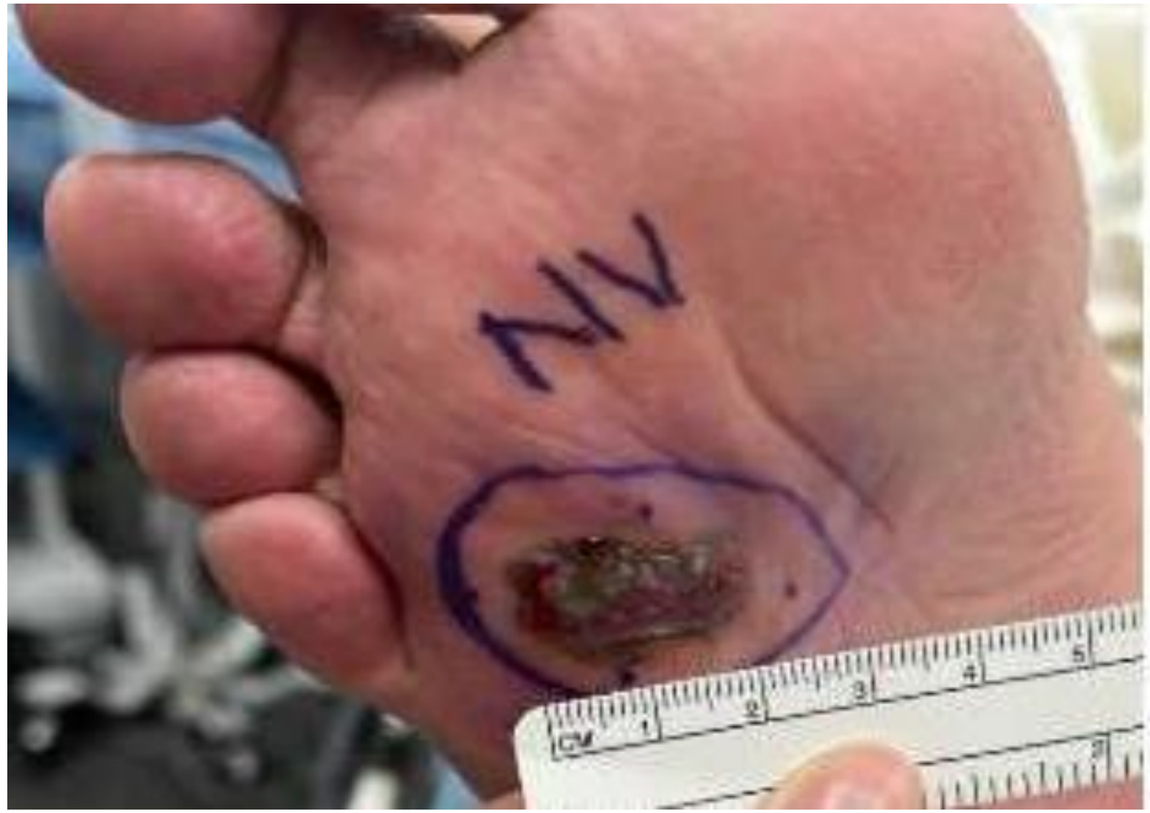
Case – Plantar Foot Melanoma – recurrent nodal disease

- 70 y/o male with a non-healing wound on the plantar foot

- Breslow thickness 4 mm
- Ulcerated
- 2 mitoses/mm2

- No palpable adenopathy

- Wide excision of melanoma – 2cm margin
- Sentinel lymph node dissection

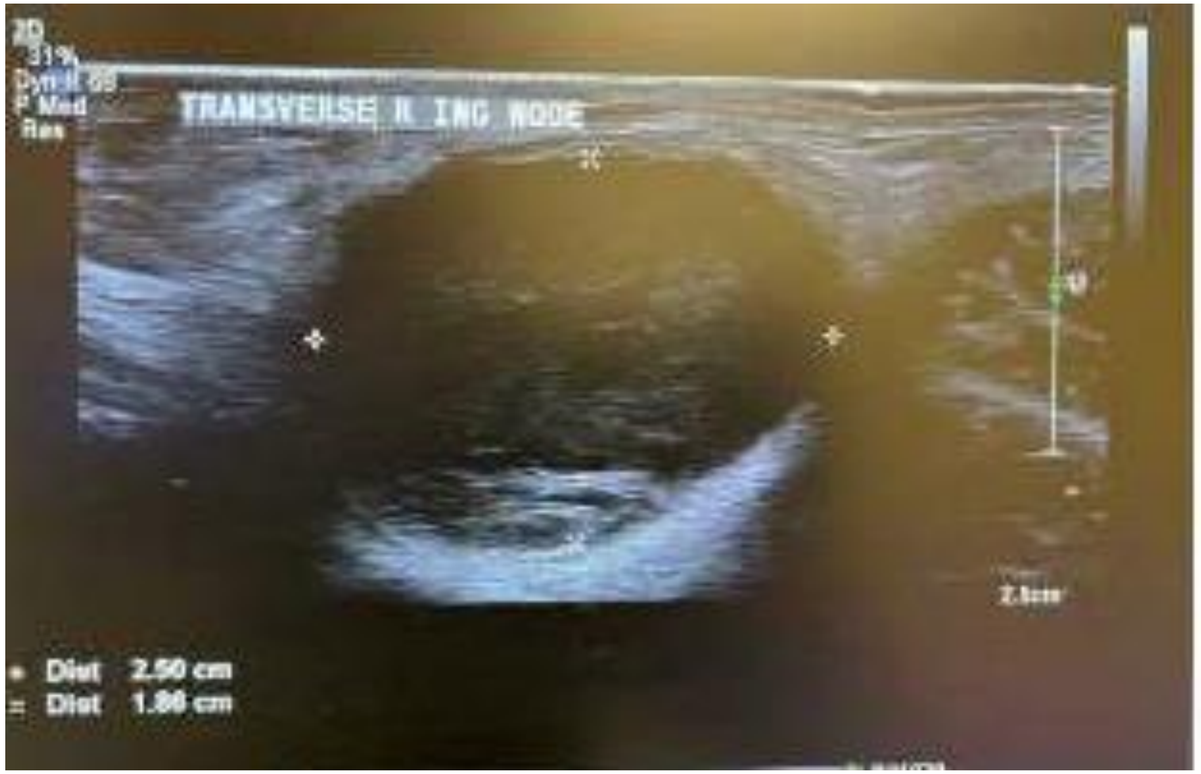


- pT3b pN2a
- Post-op staging negative for distant disease

Recurrent disease post immunotherapy

- Adjuvant pembrolizumab
- Towards completion noted to have a palpable node in the inguinal basin
- FNA positive
- PET – no distant disease

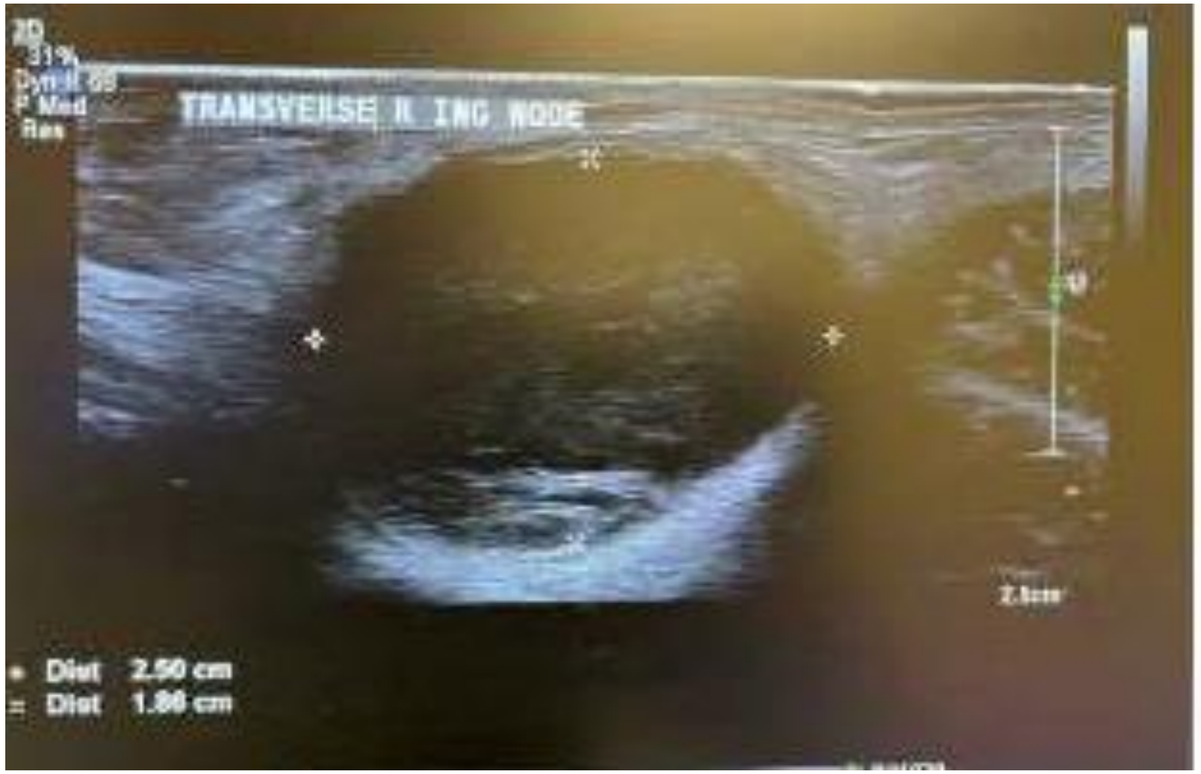
Ultrasound of inguinal node



Recurrent disease post immunotherapy

- Received Adjuvant pembrolizumab
- Discuss RELATIVITY 020

Ultrasound of inguinal node

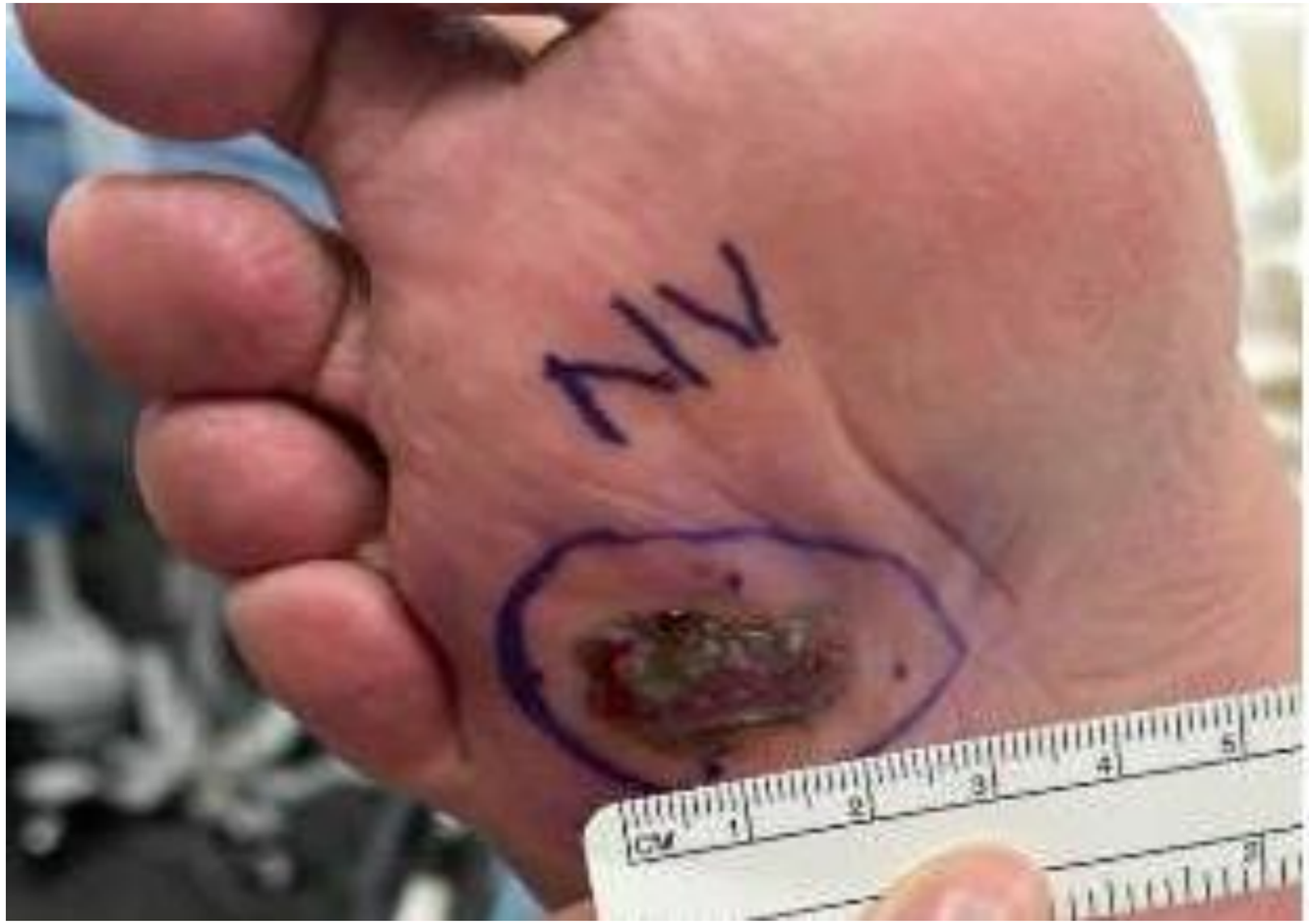


PRADO study – Surgical Management of nodal basin

Phase 2 study of personalized response directed surgery and adjuvant therapy after neoadjuvant ipilimumab and nivolumab in clinical stage III setting

Case –Plantar foot melanoma – advanced disease

DISCUSS RELATIVITY 047



What's new in 2022 ?

Combination Therapy in Advanced Melanoma

Shift in Treatment Strategy

- Default to combination therapy for most ?
- Who should get monotherapy ?

Original Article

Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma

Hussein A. Tawbi, M.D., Ph.D., Dirk Schadendorf, M.D., Evan J. Lipson, M.D., Paolo A. Ascierto, M.D., Luis Matamala, M.D., Erika Castillo Gutiérrez, M.D., Piotr Rutkowski, M.D., Ph.D., Helen J. Gogas, M.D., Christopher D. Lao, M.D., M.P.H., Juliana Janoski De Menezes, M.D., Stéphane Dalle, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean-Jacques Grob, M.D., Shivani Srivastava, M.D., Mena Abaskharoun, Pharm.D., Melissa Hamilton, M.P.H., Sarah Keidel, M.B., Ch.B., Katy L. Simonsen, Ph.D., Anne Marie Sobiesk, Ph.D., Bin Li, Ph.D., F. Stephen Hodi, M.D., Georgina V. Long, M.D., Ph.D., for the RELATIVITY-047 Investigators

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RESEARCH SUMMARY

Relatlimab and Nivolumab vs. Nivolumab in Untreated Advanced Melanoma

Tawbi HA et al. DOI: 10.1056/NEJMoa2109970

CLINICAL PROBLEM

Lymphocyte-activation gene 3 (LAG-3) and programmed-death 1 (PD-1) are immune checkpoints that contribute to tumor-mediated T-cell exhaustion. In an early study, relatlimab — a new human LAG-3–blocking antibody — combined with the PD-1 inhibitor nivolumab elicited durable objective responses in patients with previously treated melanoma. Whether the drug combination benefits patients who have not been treated previously needs investigation.

CLINICAL TRIAL

Design: A phase 2–3, global, double-blind, randomized trial compared relatlimab plus nivolumab with nivolumab alone (standard care) in patients with previously untreated metastatic or unresectable melanoma.

Intervention: 714 patients 12 years of age or older were randomly assigned to receive either relatlimab–nivolumab or nivolumab, administered as a single intravenous infusion every 4 weeks. The primary end point was progression-free survival.

RESULTS

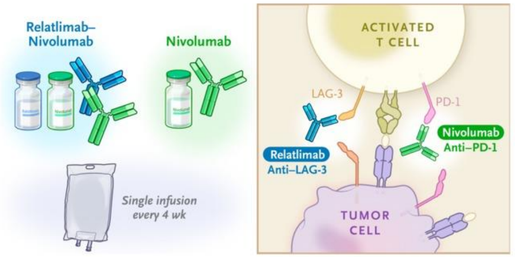
Efficacy: Progression-free survival with relatlimab–nivolumab was superior to that with nivolumab alone. Combination therapy prolonged progression-free survival regardless of tumor burden, lactate dehydrogenase (LDH) level, and other key prognostic indicators.

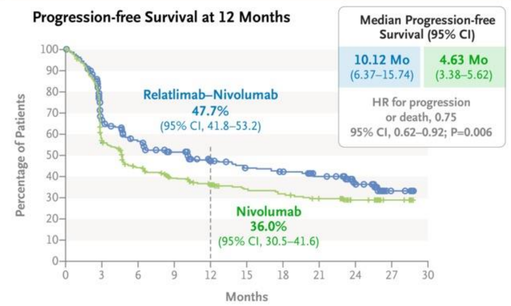
Safety: Grade 3 or 4 treatment-related adverse events occurred in 18.9% of patients in the relatlimab–nivolumab group and 9.7% of patients in the nivolumab group. These adverse events included increased levels of lipase, alanine aminotransferase, and aspartate aminotransferase, as well as fatigue.

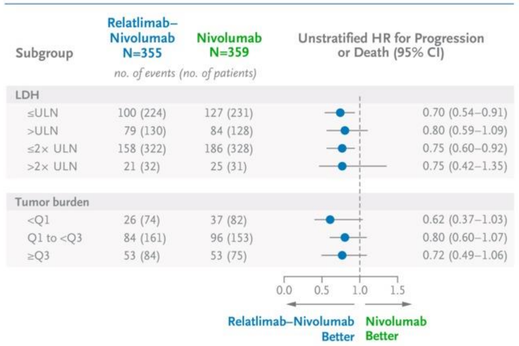
LIMITATIONS AND REMAINING QUESTIONS

- Data are still being collected regarding overall survival and objective response in the two treatment groups.
- Additional studies of the efficacy of relatlimab–nivolumab among patients frequently excluded from clinical melanoma trials (e.g., those with untreated brain metastases) are needed.

Links: Full Article | NEJM Quick Take







CONCLUSIONS

The combination of relatlimab, a human LAG-3–blocking antibody, and nivolumab, a PD-1 inhibitor, was superior to nivolumab alone with respect to progression-free survival among patients with previously untreated, advanced melanoma.

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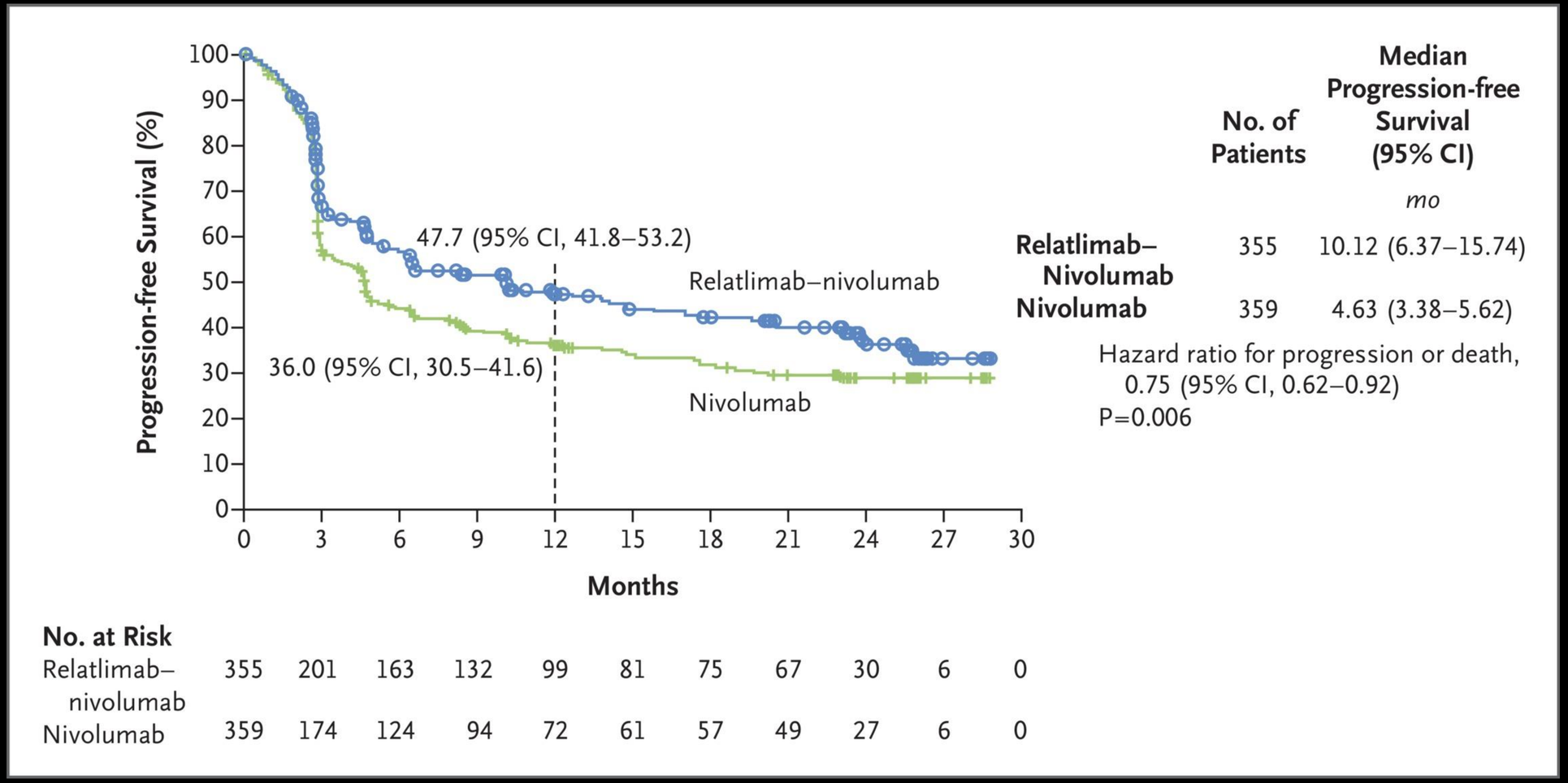
Progression-free Survival



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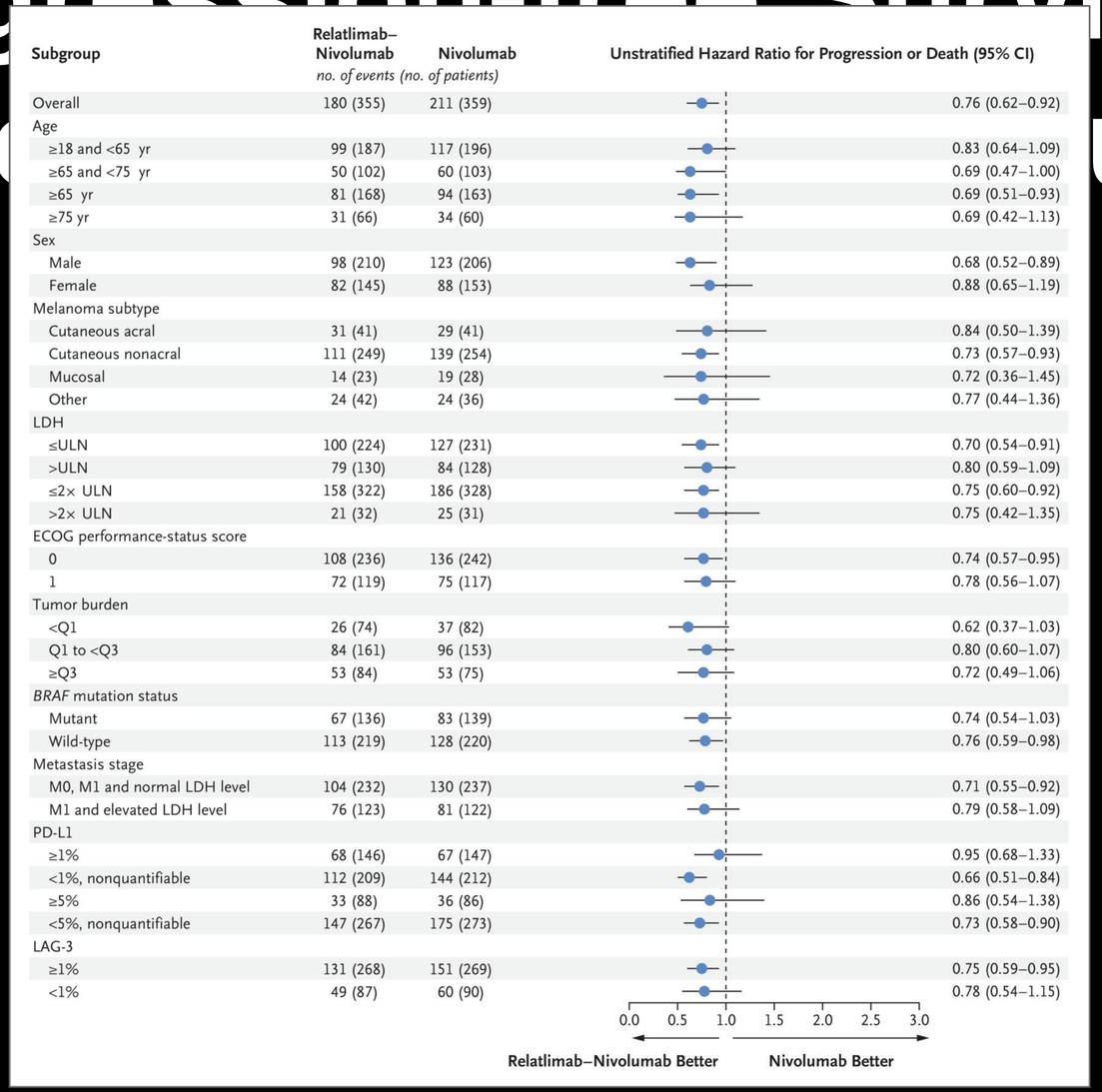
Progression-free Survival, Acc up



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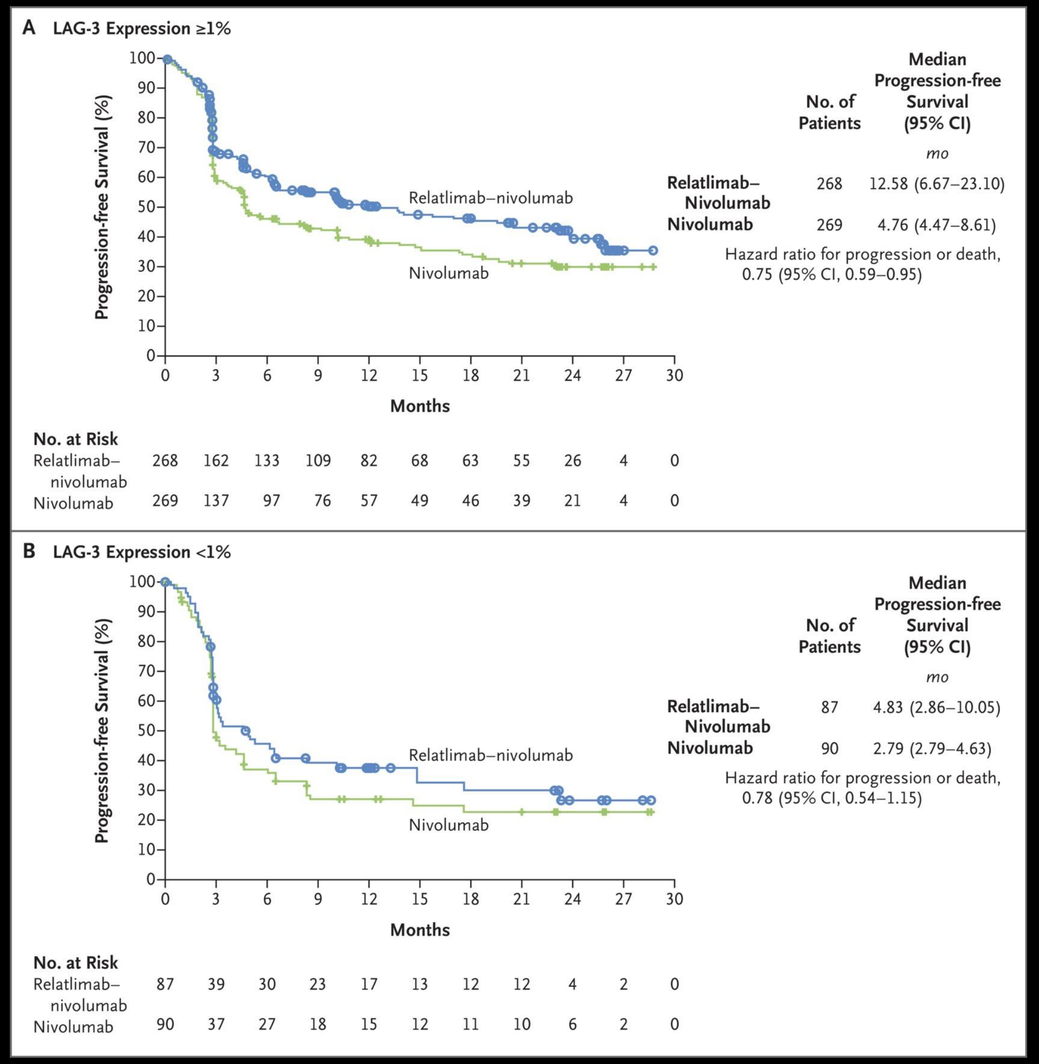
Progression-free Survival, According to LAG-3 Expression.



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Patient Demographics and Disease Characteristics at Baseline.

Table 1. Patient Demographics and Disease Characteristics at Baseline.*

Characteristic	Relatlimab–Nivolumab (N=355)	Nivolumab (N=359)	Total (N=714)
Median age (range) — yr	63.0 (20–94)	62.0 (21–90)	63.0 (20–94)
Female sex — no. (%)	145 (40.8)	153 (42.6)	298 (41.7)
Previous systemic therapy — no. (%)			
Adjuvant	31 (8.7)	26 (7.2)	57 (8.0)
Neoadjuvant	2 (0.6)	1 (0.3)	3 (0.4)
Unknown or other	0	2 (0.6)	2 (0.3)
Metastasis stage — no. (%)†			
M0	35 (9.9)	23 (6.4)	58 (8.1)
M1a or b	162 (45.6)	195 (54.3)	357 (50.0)
M1c	151 (42.5)	127 (35.4)	278 (38.9)
M1d	6 (1.7)	11 (3.1)	17 (2.4)
Melanoma subtype classification — no. (%)			
Cutaneous acral	41 (11.5)	41 (11.4)	82 (11.5)
Cutaneous nonacral	249 (70.1)	254 (70.8)	503 (70.4)
Mucosal	23 (6.5)	28 (7.8)	51 (7.1)
Other	42 (11.8)	36 (10.0)	78 (10.9)
ECOG performance status — no. (%)‡			
0	236 (66.5)	242 (67.4)	478 (66.9)
1	119 (33.5)	117 (32.6)	236 (33.1)
LDH level — no. (%)			
> ULN	130 (36.6)	128 (35.7)	258 (36.1)
>2× ULN	32 (9.0)	31 (8.6)	63 (8.8)
Median tumor burden (range) — mm§	59.0 (10–317)	54.5 (10–548)	
Sites with ≥1 lesion — no. (%)¶			
1	127 (35.8)	158 (44.0)	285 (39.9)
2	111 (31.3)	102 (28.4)	213 (29.8)
≥3	112 (31.5)	87 (24.2)	199 (27.9)
Stratification factors — no. (%)			
LAG-3 expression			
≥1%	268 (75.5)	269 (74.9)	537 (75.2)
<1%	87 (24.5)	90 (25.1)	177 (24.8)
PD-L1 expression			
≥1%	146 (41.1)	147 (40.9)	293 (41.0)
<1%	209 (58.9)	212 (59.1)	421 (59.0)
BRAF mutation status			
Patients with *BRAF* mutations	136 (38.3)	139 (38.7)	275 (38.5)
Patients without *BRAF* mutations	219 (61.7)	220 (61.3)	439 (61.5)
Metastasis stage with LDH level			
M0, M1 and normal LDH level	232 (65.4)	237 (66.0)	469 (65.7)
M1 and elevated LDH level	123 (34.6)	122 (34.0)	245 (34.3)

* LAG-3 denotes lymphocyte-activation gene 3, LDH lactate dehydrogenase, PD-L1 programmed death ligand 1, and ULN upper limit of the normal range.
† Metastasis stages are defined according to the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*, 8th edition.[13]
‡ The Eastern Cooperative Oncology Group (ECOG) performance status is assessed on a 5-point scale, with 0 indicating no performance restrictions and higher scores indicating greater disability.
§ Measurements shown are the sums of the reference diameters of the target lesions.
¶ Included are both target and nontarget lesions.

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Summary of Adverse Events.

Table 2. Summary of Adverse Events.

Adverse Event	Relatlimab–Nivolumab (N=355)		Nivolumab (N=359)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
	number of events (percent)			
Any adverse event	345 (97.2)	143 (40.3)	339 (94.4)	120 (33.4)
Treatment-related adverse event	288 (81.1)	67 (18.9)	251 (69.9)	35 (9.7)
Led to discontinuation of treatment	52 (14.6)	30 (8.5)	24 (6.7)	11 (3.1)
Treatment-related adverse event in ≥10% of patients in the relatlimab–nivolumab group				
Pruritus	83 (23.4)	0	57 (15.9)	2 (0.6)
Fatigue	82 (23.1)	4 (1.1)	46 (12.8)	1 (0.3)
Rash	55 (15.5)	3 (0.8)	43 (12.0)	2 (0.6)
Arthralgia	51 (14.4)	3 (0.8)	26 (7.2)	1 (0.3)
Hypothyroidism	51 (14.4)	0	43 (12.0)	0
Diarrhea	48 (13.5)	3 (0.8)	33 (9.2)	2 (0.6)
Vitiligo	37 (10.4)	0	35 (9.7)	0
Immune-mediated adverse event*				
Hypothyroidism or thyroiditis	64 (18.0)	0	50 (13.9)	0
Rash	33 (9.3)	2 (0.6)	24 (6.7)	5 (1.4)
Diarrhea or colitis	24 (6.8)	4 (1.1)	11 (3.1)	5 (1.4)
Hyperthyroidism	22 (6.2)	0	24 (6.7)	0
Hepatitis	20 (5.6)	14 (3.9)	9 (2.5)	4 (1.1)
Adrenal insufficiency	15 (4.2)	5 (1.4)	3 (0.8)	0
Pneumonitis	13 (3.7)	2 (0.6)	6 (1.7)	2 (0.6)
Hypophysitis	9 (2.5)	1 (0.3)	3 (0.8)	1 (0.3)
Nephritis and renal dysfunction	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)
Hypersensitivity	4 (1.1)	0	4 (1.1)	0

* Immune-mediated adverse events included adverse events of any grade that occurred in at least 1% of patients in the relatlimab–nivolumab group, that were considered by investigators to be potentially immune-mediated, and that met the following criteria: occurred within 100 days after the last dose (regardless of causality) and were treated with immune-modulating medication with no clear alternate cause or had an immune-mediated component.

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What's on the horizon?

Combination Therapy in Advanced Melanoma

- Combination therapy (IO + other)
- Intralesional therapy
- Adoptive therapy
- Vaccines

Conclusions

Combination Therapy in Advanced Melanoma

- Combination therapy (IO + other)
- Intralesional therapy
- Adoptive therapy
- Vaccines