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Erstlinientherapie des Melanoms: Eine für alle?

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13.10.2024

Interessenerklärung

Honorare für Vorträge/Beratungstätigkeit ausbezahlt an meine Institution durch : BMS, MSD, Merck, Ipsen, Roche, Pfizer, Novartis, Janssen, Sanofi

Therapielandschaft des metastasierten Melanoms 2024

Optimale Sequenz?

BRAF Wildtyp

BRAF Mutant

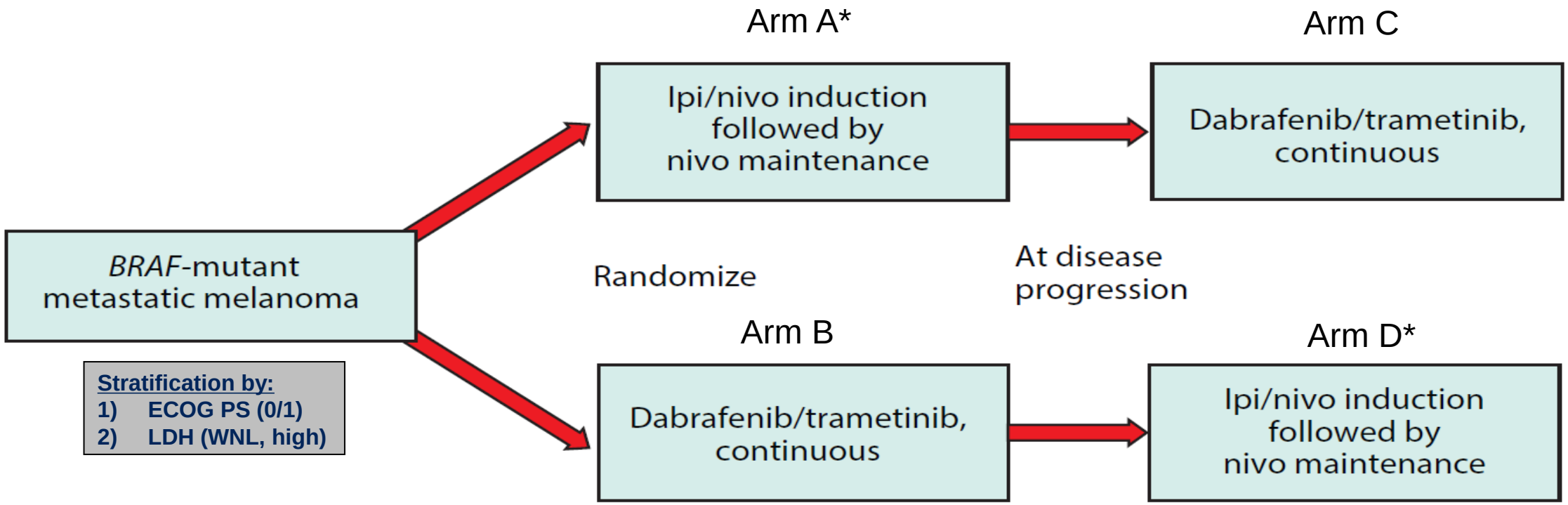
- **Anti-PD1**
(Pembrolizumab / Nivolumab)
- **Anti-PD1 + Anti-CTLA**
(Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg : Checkmate 067)
(Nivolumab 3mg /kg+ Ipilimumab 1mg/kg: Checkmate 511)
Anti-PD1 +Anti-Lag 3
(Nivolumab 480 mg + Relatlimab 160 mg)
- **T-VEC**

Monotherapie oder Kombinationstherapie?

- **BRAFi/MEKi**
  - Vemurafenib + Cobimetinib
  - Dabrafenib + Trametinib
  - Encorafenib + Binimetinib

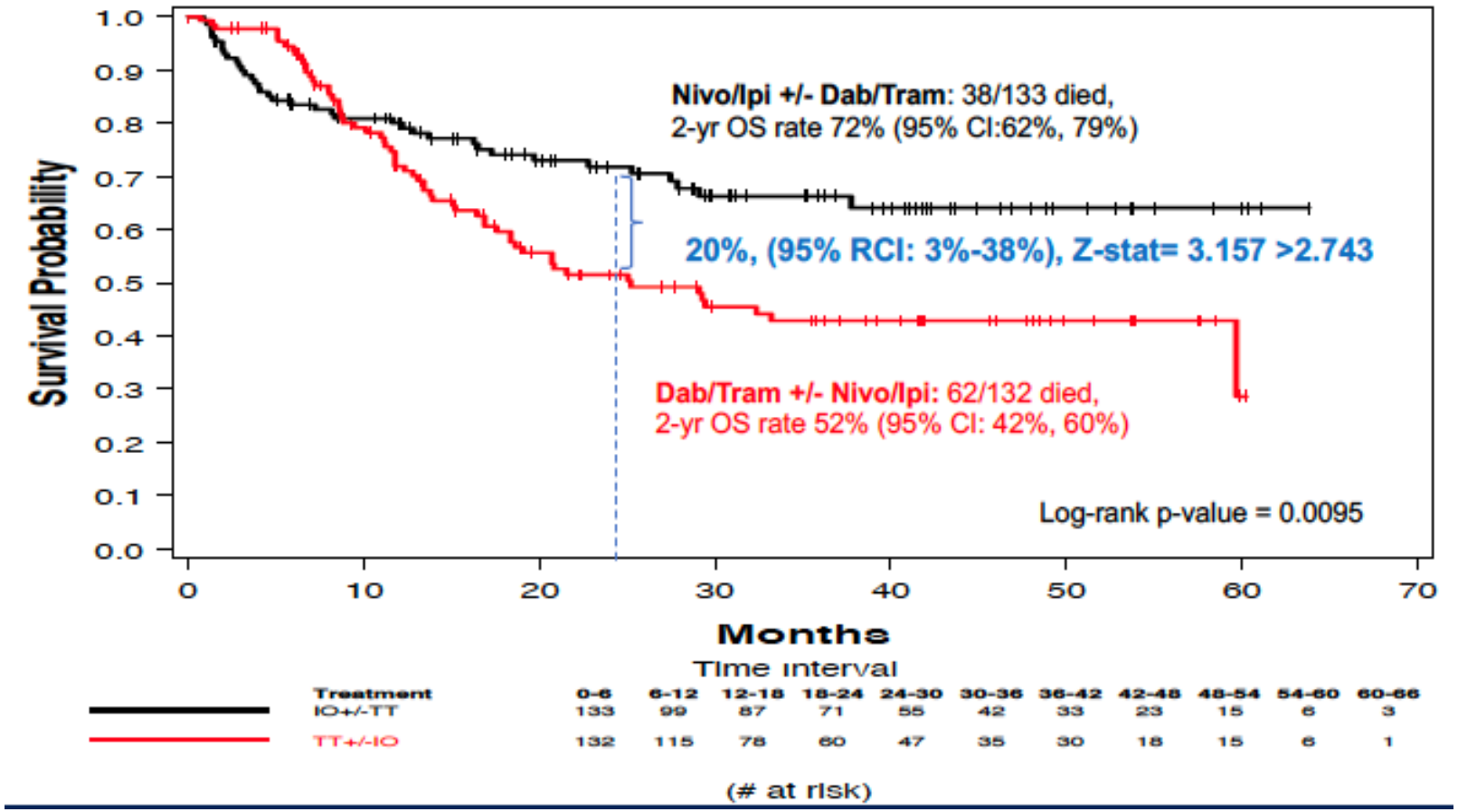
- **BRAFi/MEKi + Anti-PD-L1**
  - Vemurafenib + Cobimetinib + Atezolizumab

Optimale Sequenz- DREAMseq Studie



*Nivo/Ipi Induction = 12 wks; nivo maintenance = 72 wks

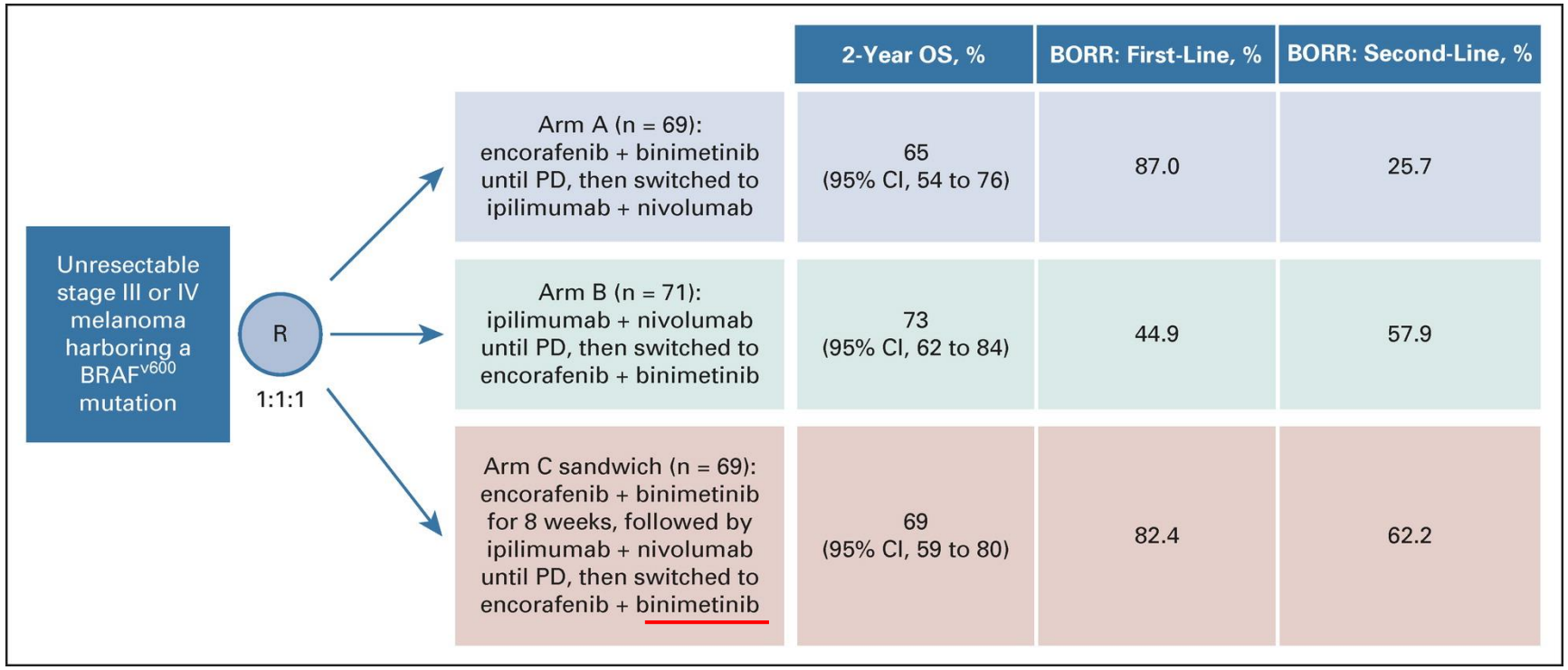
Optimale Sequenz- DREAMseq Studie



Immuntherapie ist erste Wahl!

Atkins M et al JCO 2022

Optimale Sequenz- SECOMBIT Studie



	2-Year OS, %	BORR: First-Line, %	BORR: Second-Line, %
Arm A (n = 69): encorafenib + binimetinib until PD, then switched to ipilimumab + nivolumab	65 (95% CI, 54 to 76)	87.0	25.7
Arm B (n = 71): ipilimumab + nivolumab until PD, then switched to encorafenib + binimetinib	73 (95% CI, 62 to 84)	44.9	57.9
Arm C sandwich (n = 69): encorafenib + binimetinib for 8 weeks, followed by ipilimumab + nivolumab until PD, then switched to encorafenib + binimetinib	69 (95% CI, 59 to 80)	82.4	62.2

Immuntherapie ist erste Wahl!
“Sandwich”- Strategie ist machbar!

Offene Fragen:
- Braucht es zwingend Ipi-Nivo?
- Welche Dosis Ipi-Nivo? ist Ipi 1/Nivo3 akzeptabel? (EBIN Studie)

Ascierto P et al. JCO 2023

Triple Therapien?

	PFS (months)	ORR (%)	DOR (months)	OS at 24 months (%)	Grade 3-5 Toxicity
KEYNOTE-022					
Dabrafenib + trametinib + pembrolizumab	16.9	63.3	25.1	63	58%
vs	10.7 (HR 0.53)	71.7	12.1	52	25%
Dabrafenib + trametinib + placebo					
IMspire150					
Vemurafenib + cobimetinib + atezolizumab	15.1	66.3	21.0	60.4	48%
vs	10.6 (HR 0.78, $p=0.0249$)	65.0	12.6	53.1	42%
Vemurafenib + cobimetinib + placebo					
COMBI-i					
Dabrafenib + trametinib + spartalizumab vs	16.2	68.5	NR	68	55%
Dabrafenib + trametinib + placebo	12.0 (HR 0.82, $p=0.042$)	64.2	20.7	62	33%

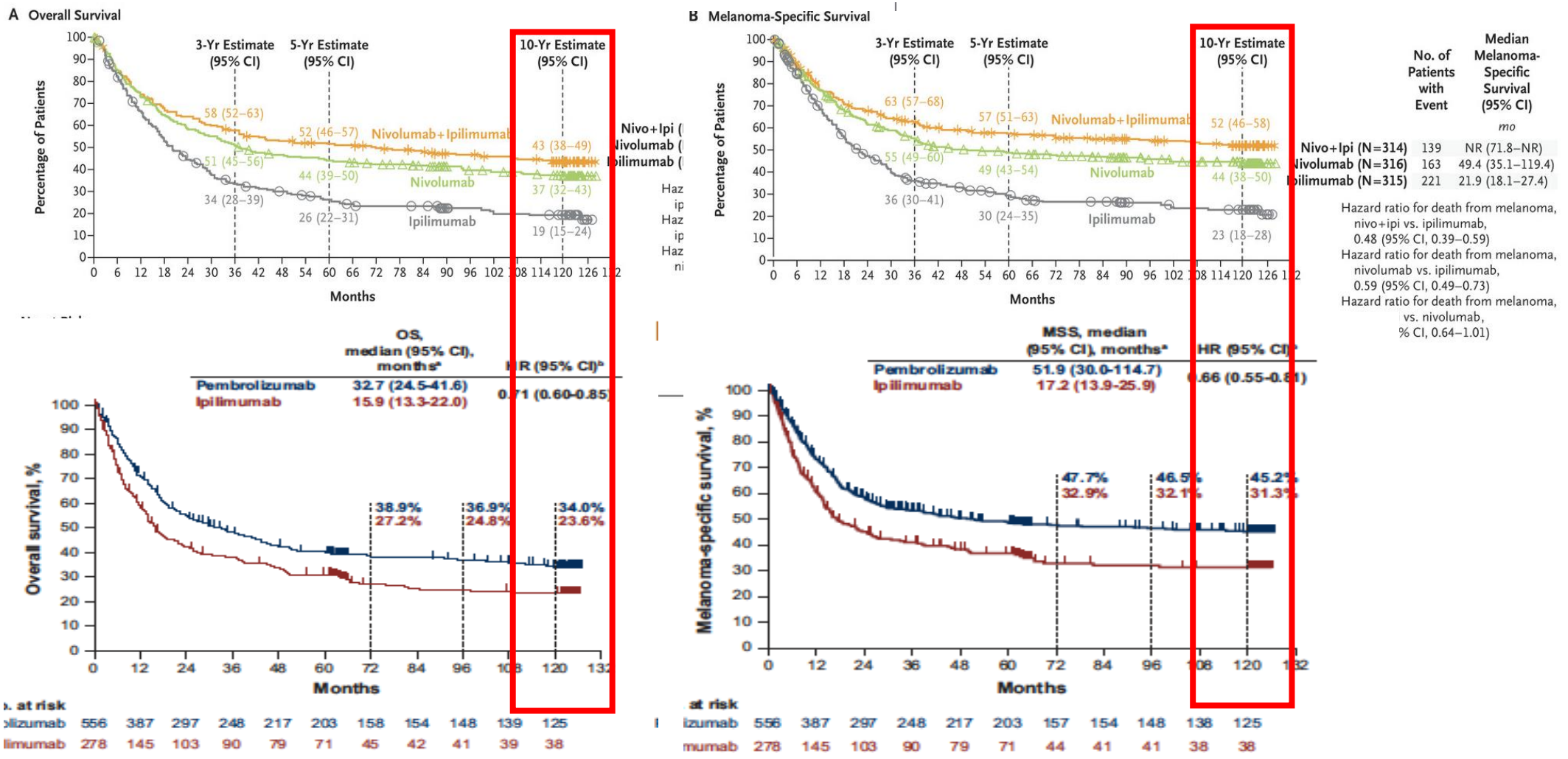
PFS, median progression-free survival (months); *HR*, hazard ratio; *ORR*, objective response rate (%); *DOR*, duration of response (months); *OS*, overall survival (%)

Endpunkt des verbesserten Überlebens PFS/OS nicht erreicht !

STARBOARD Studie: Enco-Bini-Pembro vs Pembro : Resultate ausstehend

Dixon-Douglas J et al. Curr Oncol Rep 2022
Dummer et al. JCO 2022
Ferrucci et al. JITC 2022
Ascierto et al. Lancet Oncol 2023

Kombinationstherapie vs Monotherapie: 10 Jahresüberleben

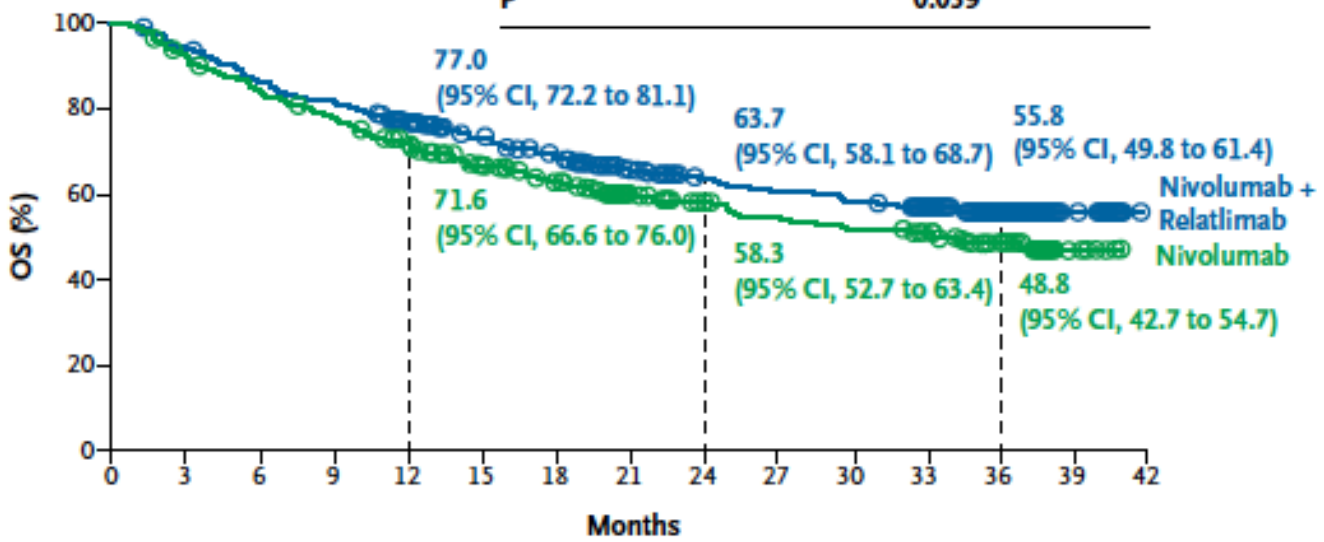


Long GV et al NEJM 2024, Wolchok JD et al NEJM 2024

Kombinationstherapie : Nivolumab-Relatlimab

B

	Nivolumab + Relatlimab (n=355)	Nivolumab (n=359)
Median OS, mo (95% CI)	NR (34.20 to NR)	34.10 (25.23 to NR)
Hazard ratio (95% CI)	0.80 (0.64 to 1.01)	
P	0.059	



No. at risk															
Nivolumab + Relatlimab	355	334	305	287	261	227	203	167	145	139	133	109	50	9	0
Nivolumab	359	329	301	277	240	202	182	155	126	119	113	96	42	8	0

Long GV NEJM Evidence 2023

Indirekter Vergleich Kombination Ipi-Nivo vs Rela-Nivo

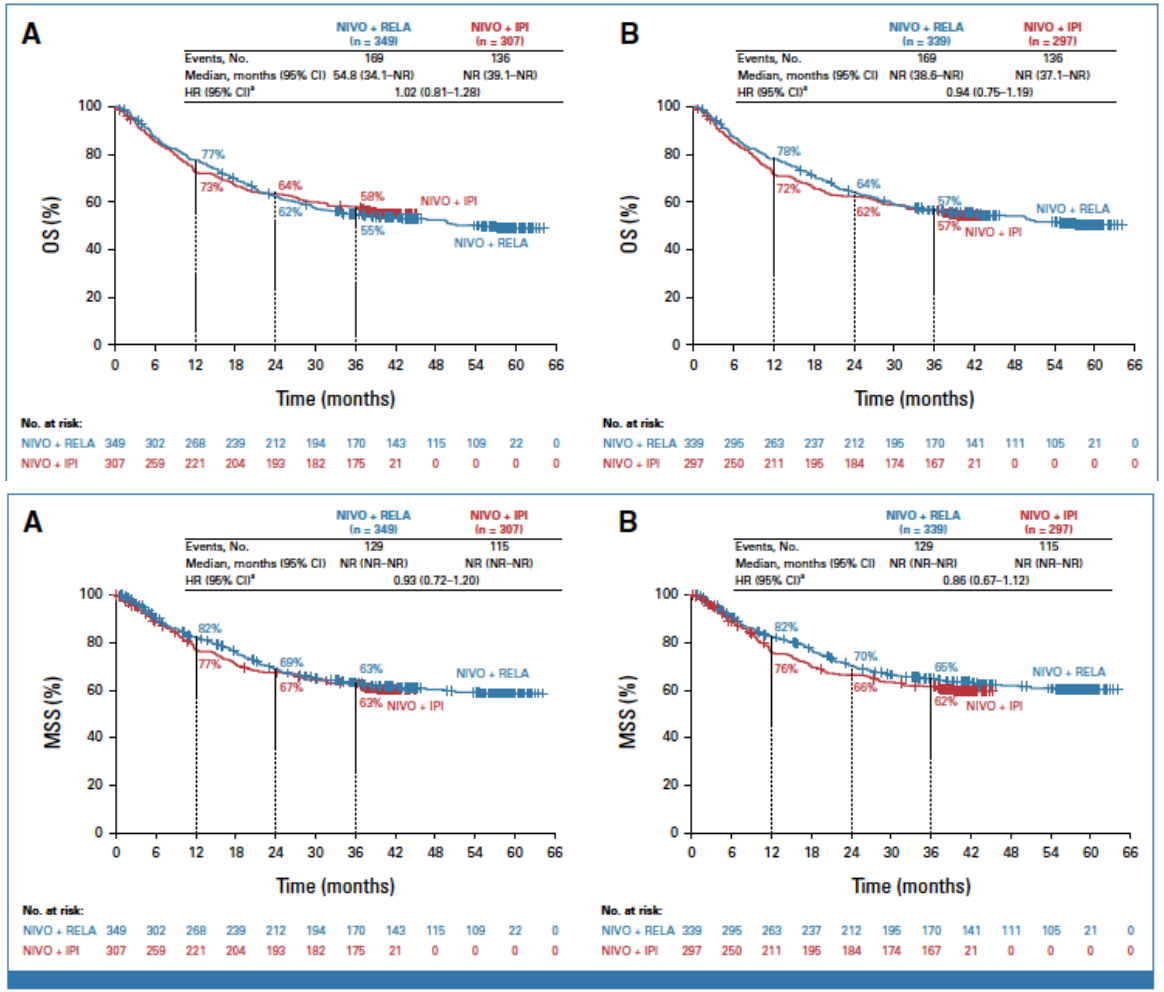


FIG 3. MSS per INV (A) before and (B) after weighting. To align with the follow-up for RELATIVITY-047 (median follow-up, 33.8; minimum follow-up, 33 months), follow-up for CheckMate 067 was truncated (median follow-up, 37 months; minimum follow-up, 36 months). [a]Comparison of NIVO + RELA with NIVO + IPI. HR, hazard ratio; INV, investigator; MSS, melanoma-specific survival; NIVO + IPI, nivolumab plus ipilimumab; NIVO + RELA, nivolumab plus relatlimab; NR, not reached.

Grade 3-4 Toxizität : 61% vs 23%

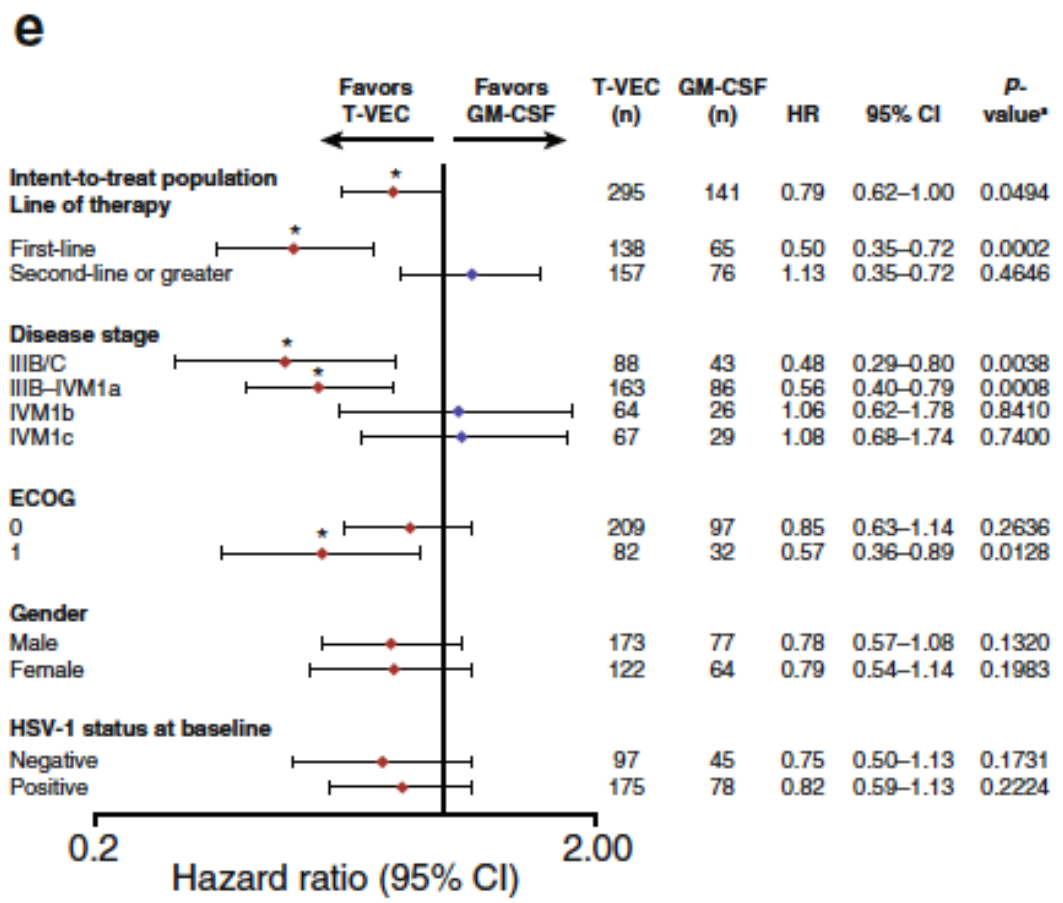
Therapieabbruch wegen Toxizität: 41% vs 17%

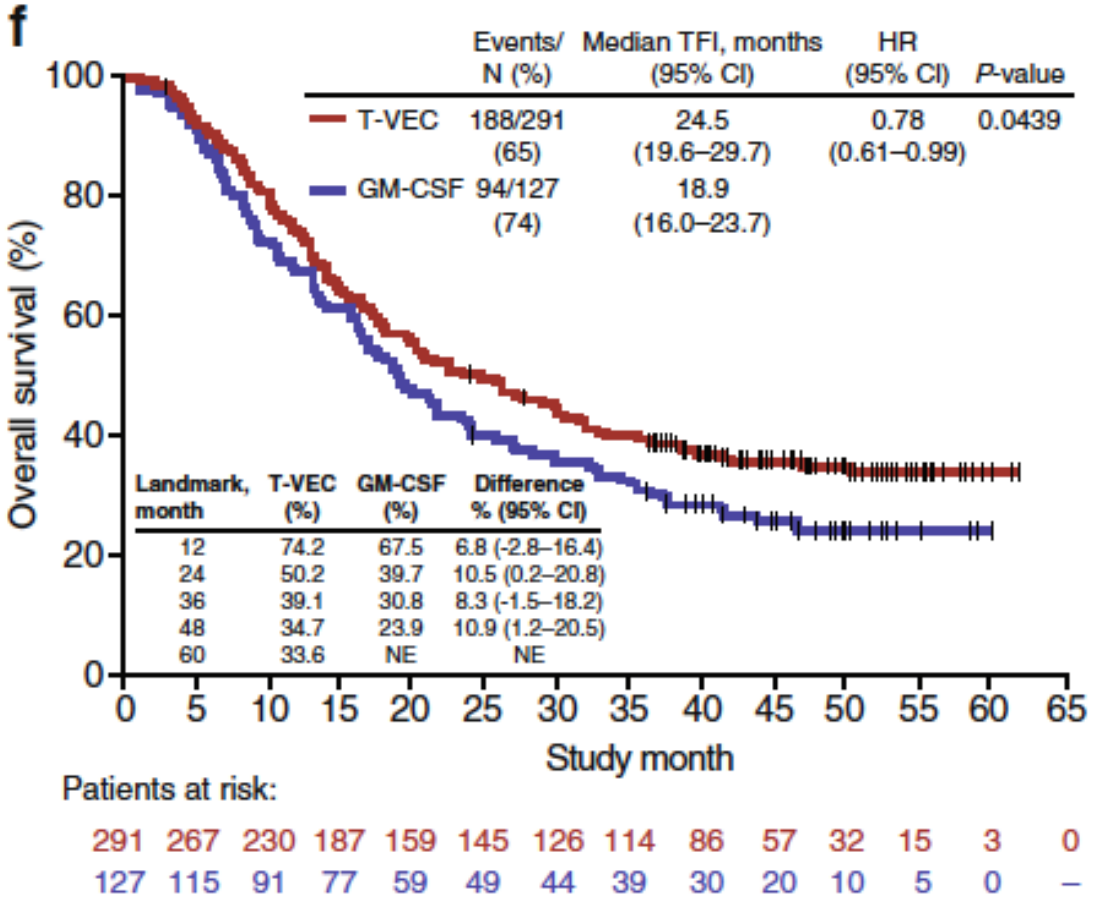
Cave:

- 10 Jahres Follow up ipi-Nivo
- Fehlende Evidenz für Rela-Nivo bei Hirnmetastasen

Long GV et al. JCO 2024

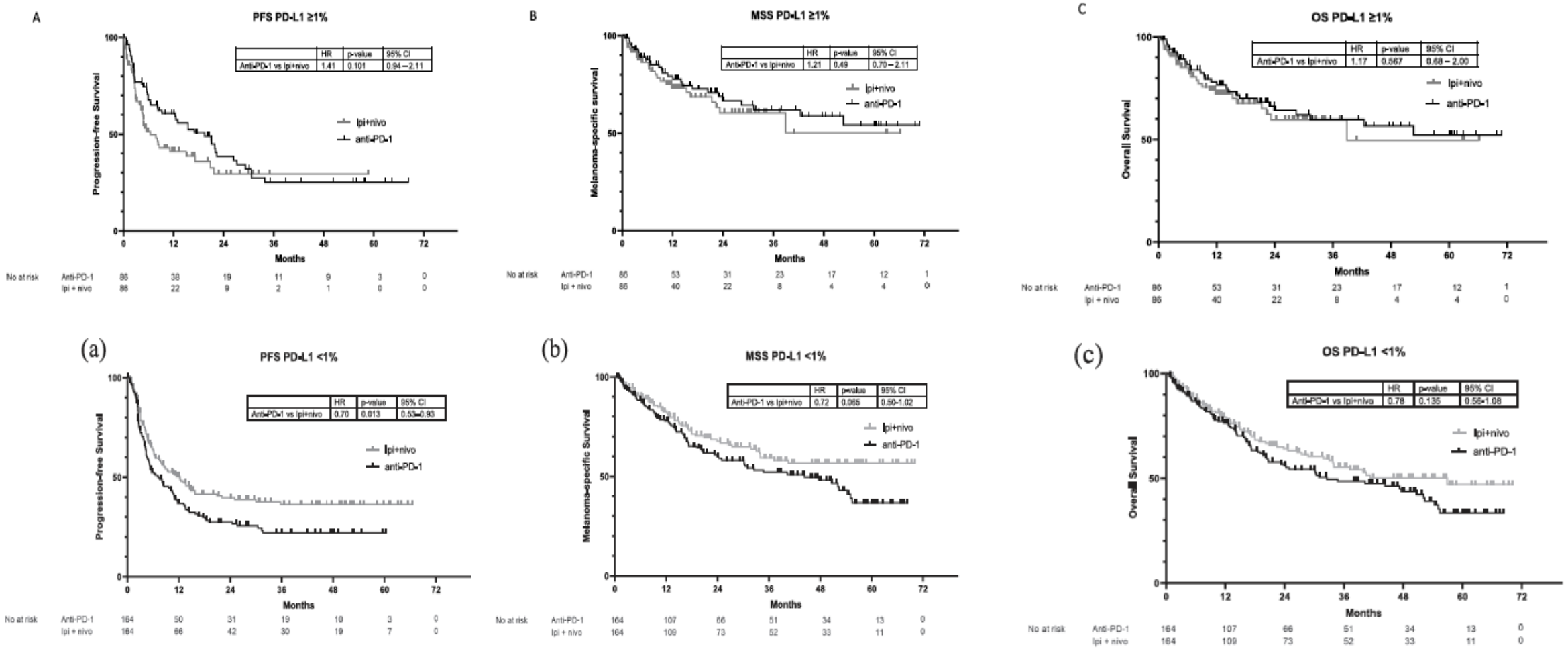
Monotherapie: T-VEC





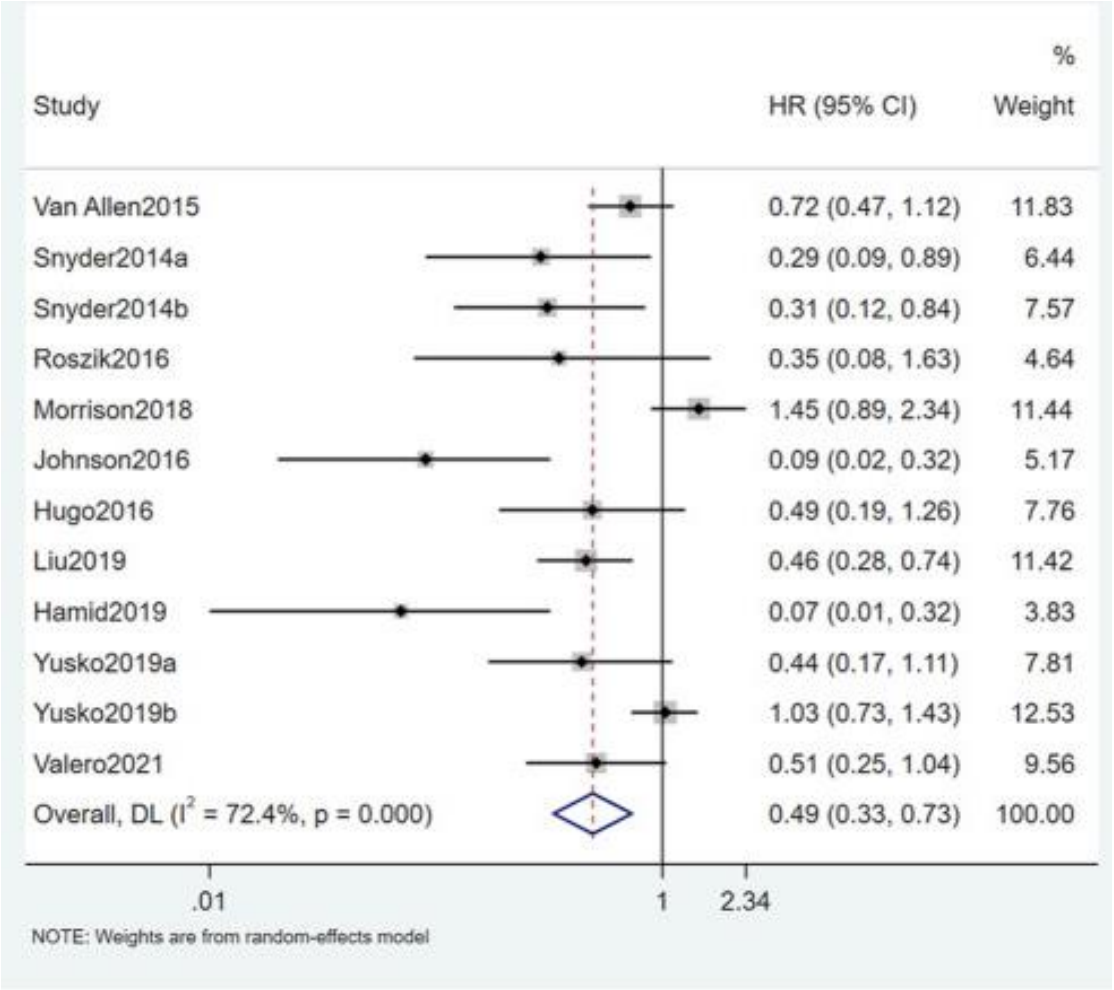
Andtbacka et al JITC 2023

Biomarker –PD L1 ?



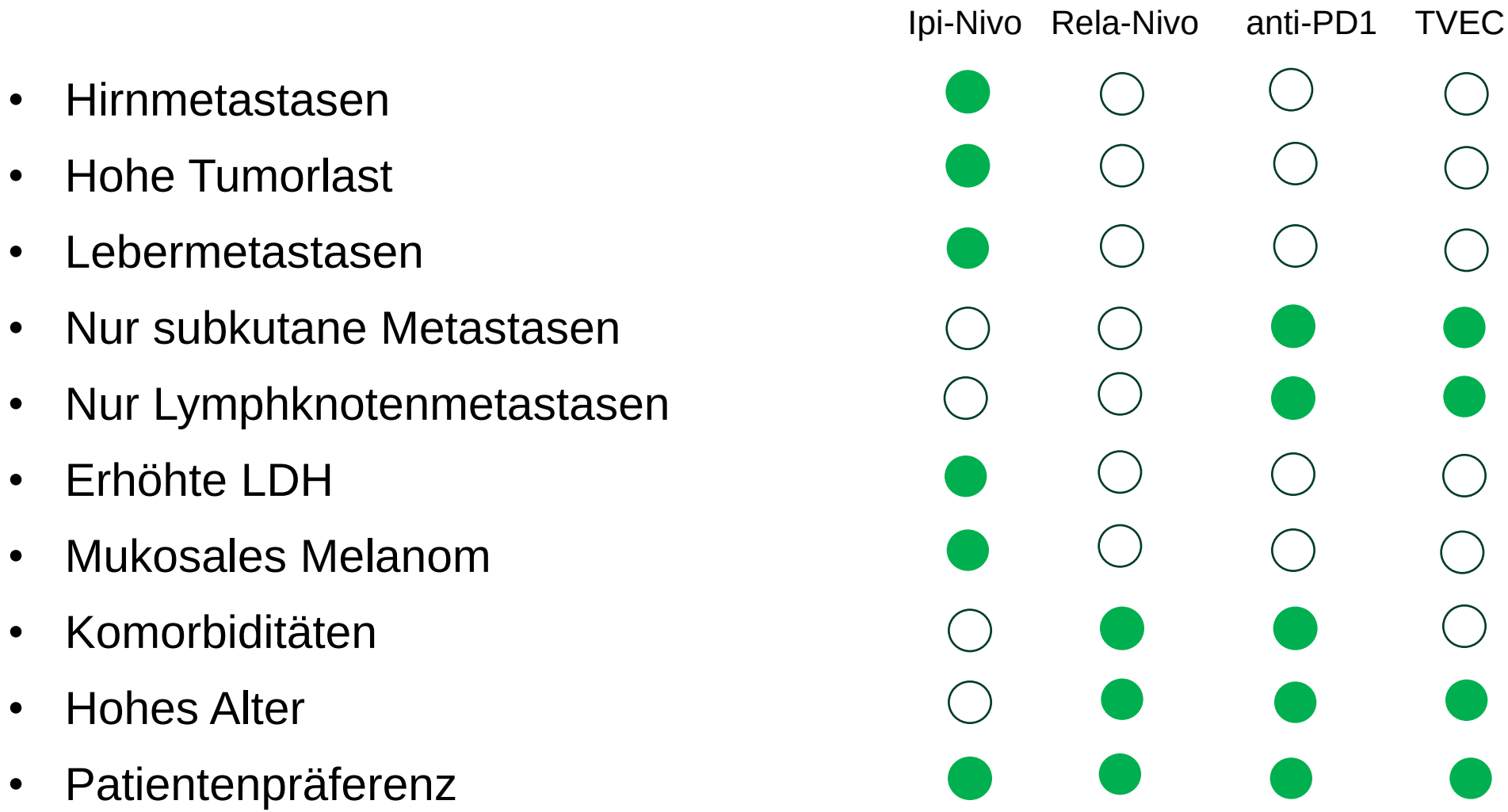
Ellebaek et al. EJC 2024

Biomarker –TMB ?



Ning et al. Front Pharmacol 2022

Patienten- und Tumorcharakteristika zur Entscheidungsfindung



Was ist in der Pipeline?

A Phase 3, Randomized, Double-Blind, Placebo- and Active-Comparator-Controlled Clinical Study of Adjuvant V940 (mRNA-4157) Plus Pembrolizumab Versus Adjuvant Placebo Plus Pembrolizumab in Participants With High-Risk Stage II-IV Melanoma (INTerpath-001)

A phase 3 study (TILVANCE-301) to assess the efficacy and safety of lifileucel, an autologous tumor-infiltrating lymphocyte cell therapy, in combination with pembrolizumab compared with pembrolizumab alone in patients with untreated unresectable or metastatic melanoma.

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Schlussfolgerungen

- 10 Jahresdaten zeigen lang anhaltende Remission mit Immuncheckpointinhibitoren in 40-50% der Patienten
- Für BRAF mutierte Patienten: Erstlinien-Immuntherapie besser als BRAFi/MEKi, 8-12 Wochen BRAF/MEKi bei hoher Tumorlast/symptomatischen Patienten ist sinnvoll
- Patientenselektion für Kombination vs Mono-Immuntherapie beruht auf klinischen Faktoren, keine etablierten Biomarker

→ Welche Therapie für Patienten post-neoadjuvant/adjuvant PD-1/BRAFi/MEKi?

→ Kann die Therapietolerenz verbessert werden?

Vielen Dank für Ihre Aufmerksamkeit!

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