TARGETING LAG-3 IN CANCER: CLINICAL OUTCOMES

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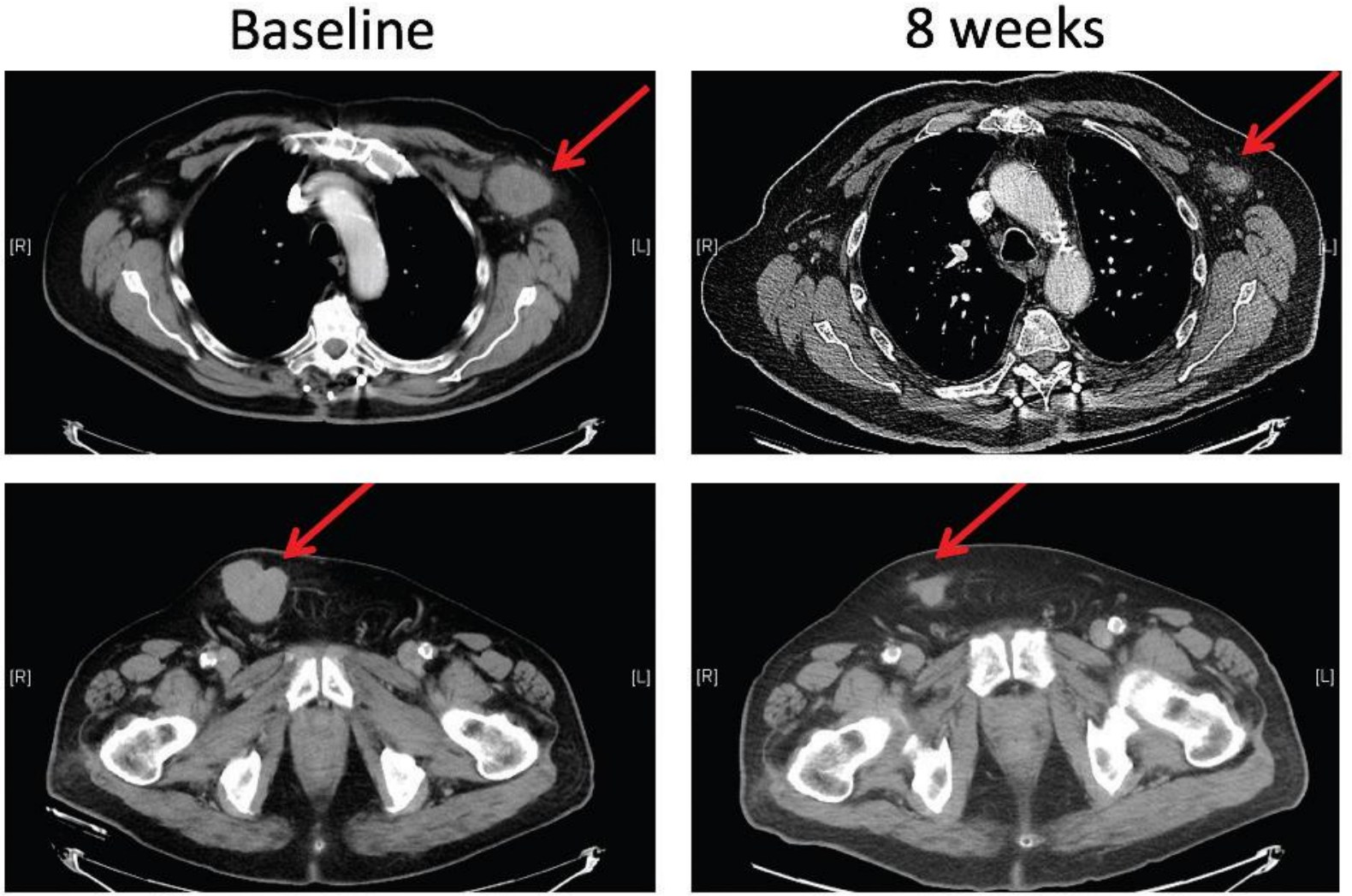
Anti-LAG-3: into the clinic

- Relatlimab (RELA) is a human IgG4 LAG-3-blocking antibody
- 2013: phase 1 studies of RELA alone or plus nivolumab (anti-PD-1)

Lipson et al., SITC Annual Meeting; November 9-13, 2016

Relatlimab in anti-PD-1–refractory NSCLC

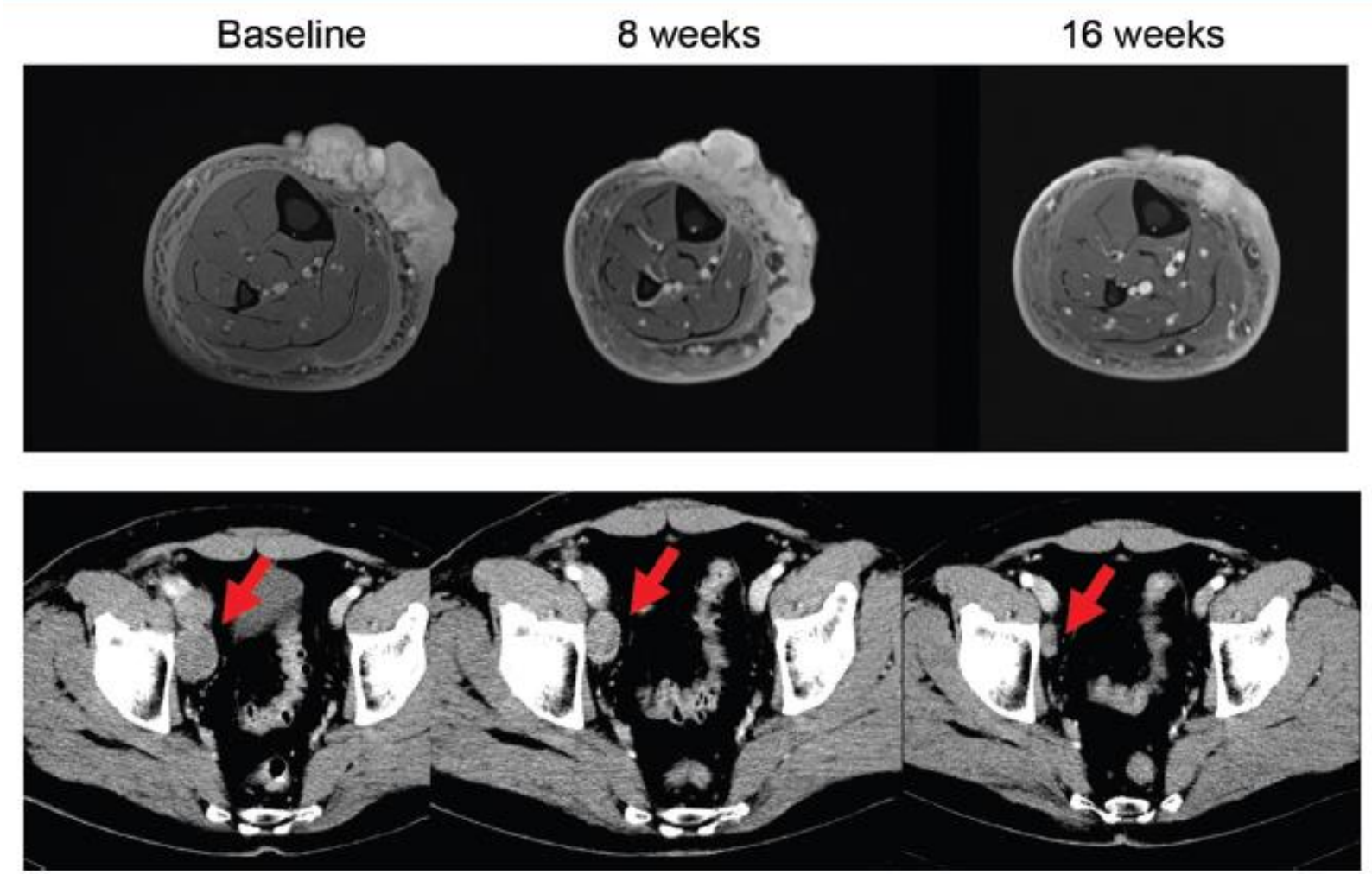
- 67-year-old man with advanced KRAS-mutant lung adenocarcinoma, refractory to nivolumab administered 2 months prior to receiving relatlimab
- Trial Rx: relatlimab 800mg q2w
- Confirmed partial response; duration of response = 2 months



Lipson et al., SITC Annual Meeting; Nov 2016

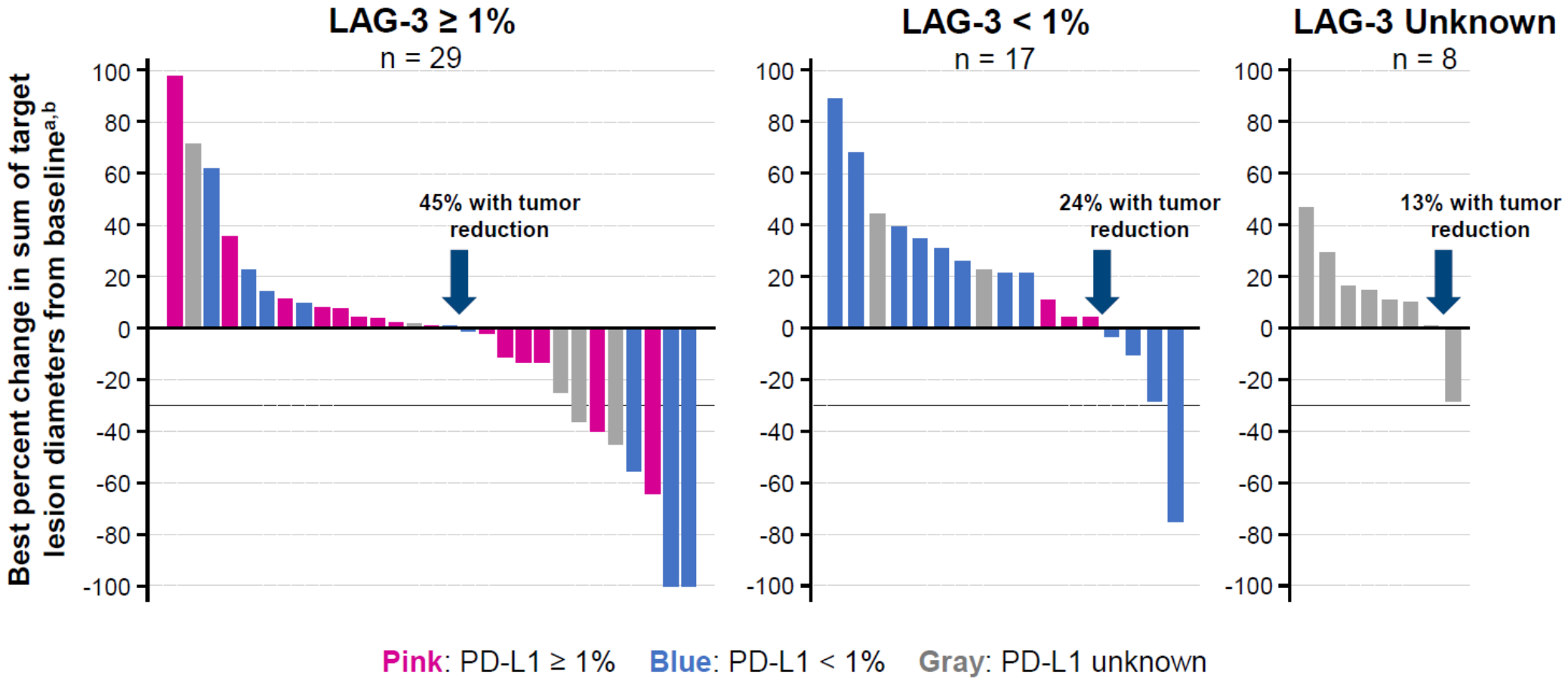
Relatlimab + nivolumab in anti-PD-1–refractory melanoma

- 51 y.o. M w/ advanced BRAF-WT melanoma, refractory to first-line nivolumab (anti-PD-1)
- Trial Rx: relatlimab 80 + nivolumab 240 q2w
- Cutaneous and nodal tumor regressions



Lipson et al., SITC Annual Meeting; Nov 2016

LAG-3 expression in tumor microenvironment may enrich for anti-tumor response



LAG-3 expression (percent of positive cells within invasive margin, tumor, and stroma) evaluated using immunohistochemistry (IHC) assays on formalin-fixed, paraffin-embedded tumor sections. Immune cell LAG-3 expression (≥1% or <1%) determined using mouse antibody clone 17B4. Ascierto et al, ESMO 2017

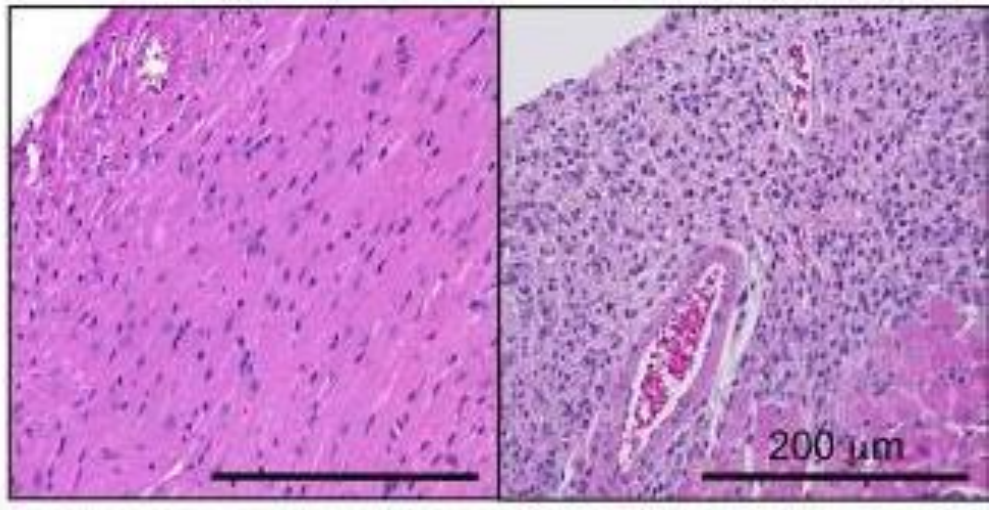
Initial experience with anti-LAG-3 +/- anti-PD-1 (N=122)

- Blocking LAG-3 appears to restore the effector function of exhausted T cells in a heavily pretreated, anti-PD-1 refractory/relapsed population
  - Evidence of clinical benefit observed in ~10-15% of patients with melanoma, other tumor types
- Generally manageable side effect profile among 122 pts
  - One case of fatal myocarditis
- Trial data support further investigation in patients with a variety of tumor types

Autoimmunity associated with LAG-3

- Mice harboring a loss-of-function mutation in the LAG-3 gene were crossed with PD-1 knockout mice, all of whom died of severe myocarditis before 10 weeks of age.[1]
- Histology: massive lymphocytic infiltration into myocardium

Wild type



PD-1 / LAG-3 knockout

1. Okazaki, Honjo, et al., J Exp Med, 2011

RELA + NIVO in the first-line setting

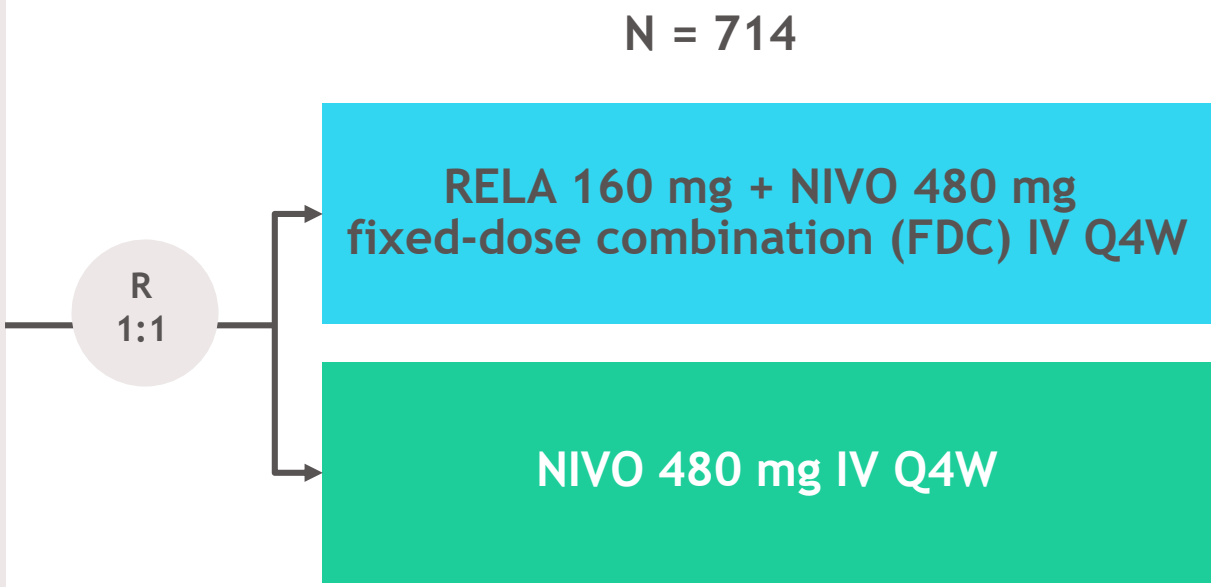
- **RELATIVITY-047** is a global, randomized, double-blind, phase 2/3 study

Key eligibility criteria

- Previously untreated unresectable or metastatic melanoma[a]
- ECOG PS 0–1

Stratification factors

- LAG-3[b]
- PD-L1[c]
- *BRAF*
- AJCC v8 M stage



Primary endpoint

- PFS by BICR[d]

Secondary endpoints

- OS
- ORR by BICR[d]

AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CTLA-4, cytotoxic T lymphocyte antigen-4; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; IV, intravenous; ORR, overall response rate; Q4W, every 4 weeks; R, randomization.
ClinicalTrials.gov: NCT03470922; Lipson E, et al. Poster presentation at ESMO Congress; October 19–23, 2018; Munich, Germany. Abstract 1302TiP.
[a]Prior adjuvant/neoadjuvant treatment permitted (anti-PD-1 or anti-CTLA-4 permitted if at least 6 months between the last dose and recurrence; interferon therapy permitted if the last dose was at least 6 weeks before randomization); [b]LAG-3 expression on immune cells was determined using an analytically validated IHC assay (LabCorp); [c]PD-L1 expression on tumor cells was determined using the validated Agilent/Dako PD-L1 IHC 28-8 pharmDx test; [d]First tumor assessment (RECIST v1.1) performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks. Database lock date: March 9, 2021.

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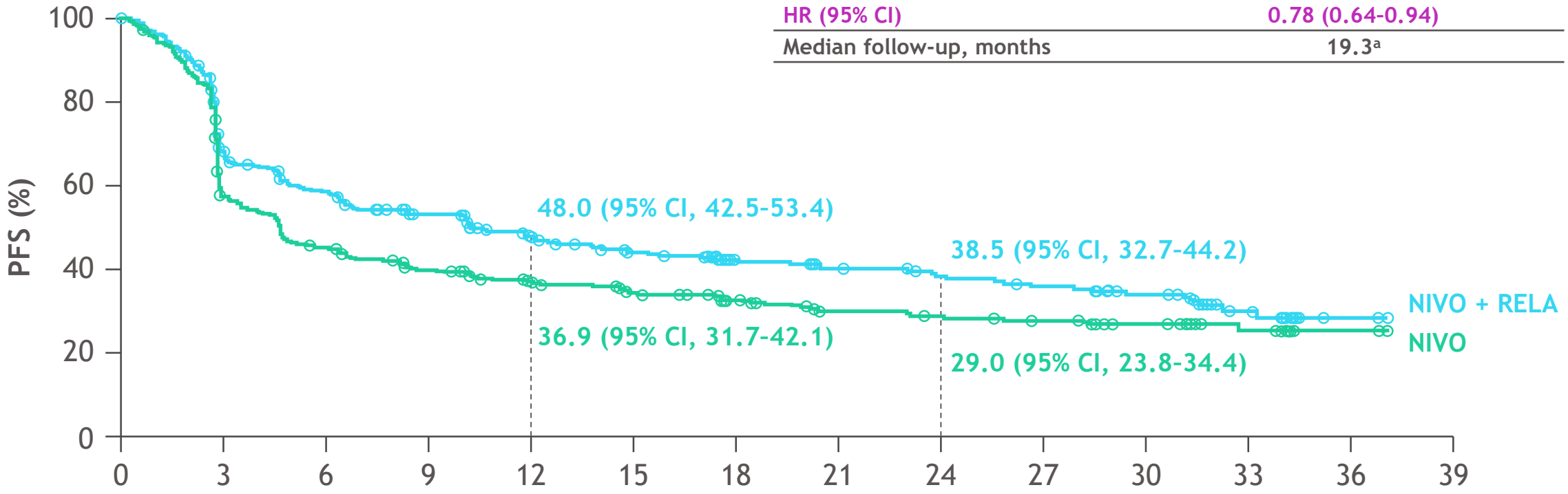
Baseline characteristics

Characteristic		NIVO + RELA (n = 355)	NIVO (n = 359)	Total (N = 714)
Median age, years		63	62	63
Female, n (%)		145 (40.8)	153 (42.6)	298 (41.7)
AJCC v8 M stage, n (%)	M1A	77 (21.7)	107 (29.8)	184 (25.8)
	M1B	85 (23.9)	88 (24.5)	173 (24.2)
	M1C	151 (42.5)	127 (35.4)	278 (38.9)
	M1D	6 (1.7)	11 (3.1)	17 (2.4)
ECOG PS, n (%)	0	236 (66.5)	242 (67.4)	478 (66.9)
	1	119 (33.5)	117 (32.6)	236 (33.1)
Serum LDH level, n (%)	> ULN	130 (36.6)	128 (35.7)	258 (36.1)
	> 2 × ULN	32 (9.0)	31 (8.6)	63 (8.8)
Prior neoadjuvant/adjuvant,[a] n (%)		33 (9.3)	27 (7.5)	60 (8.4)
Tumor burden,[b] median (min-max), mm		59.0 (10–317)	54.5 (10–548)	-
Stratification factor, n (%)				
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	Mutant	136 (38.3)	139 (38.7)	275 (38.5)
	Wild-type	219 (61.7)	220 (61.3)	439 (61.5)
AJCC M stage	M0/M1any[0][c]	232 (65.4)	237 (66.0)	469 (65.7)
	M1any[1][d]	123 (34.6)	122 (34.0)	245 (34.3)

[a]Most common therapy was interferon; [b]Sum of reference diameters of target lesions in mm; [c]AJCC M stage M0/M1any (LDH not elevated); [d]AJCC M stage M1any (elevated LDH).
Tawbi HA, et al. *N Engl J Med* 2022;386:24–34.

Primary endpoint: updated PFS by BICR

	NIVO + RELA (n = 355)	NIVO (n = 359)
Median PFS, months	10.22	4.63
(95% CI)	(6.51–14.75)	(3.48-6.44)
HR (95% CI)	0.78 (0.64-0.94)	
Median follow-up, months	19.3[a]	



No. at risk														
NIVO + RELA	355	223	189	159	130	106	82	70	64	59	48	20	2	0
NIVO	359	192	150	124	98	82	67	52	49	45	33	15	3	0

Statistical model for HR and *P* value: stratified Cox proportional hazard model. Stratified by LAG-3, *BRAF*, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients. Database lock date: October 28, 2021.

[a]Minimum potential follow-up (time from last patient randomized to last patient, last visit) was 8.7 months.

Safety summary

AE, n (%)	NIVO + RELA (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AE	352 (99.2)	154 (43.4)	344 (95.8)	126 (35.1)
TRAE	297 (83.7)	75 (21.1)	260 (72.4)	40 (11.1)
Leading to discontinuation	54 (15.2)	32 (9.0)	26 (7.2)	13 (3.6)
TRAE ≥ 10%				
Pruritus	87 (24.5)	0	59 (16.4)	2 (0.6)
Fatigue	83 (23.4)	5 (1.4)	47 (13.1)	1 (0.3)
Rash	59 (16.6)	3 (0.8)	48 (13.4)	2 (0.6)
Hypothyroidism	55 (15.5)	0	46 (12.8)	0
Arthralgia	53 (14.9)	3 (0.8)	29 (8.1)	1 (0.3)
Diarrhea	53 (14.9)	4 (1.1)	36 (10.0)	2 (0.6)
Vitiligo	45 (12.7)	0	42 (11.7)	0
Treatment-related deaths[a]	4 (1.1)	0	2 (0.6)	0

Includes events reported between first dose and 30 days after last dose of study therapy. Other grade 3–4 TRAEs that were associated with any-grade TRAEs occurring in < 10% of patients not shown. Database lock date: October 28, 2021.
[a]Treatment-related deaths: NIVO + RELA (n = 4) – hemophagocytic lymphohistiocytosis, acute edema of the lung, pneumonitis, and multiorgan failure; NIVO (n = 2) – sepsis and myocarditis, and worsening pneumonia.

Immune-mediated adverse events

Immune-mediated AE category[a], n (%)	RELA + NIVO (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Hypothyroidism/thyroiditis	64 (18.0)	0	50 (13.9)	0
Rash	33 (9.3)	2 (0.6)	24 (6.7)	5 (1.4)
Diarrhea/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

- Additional AE of interest: myocarditis (any grade) occurred in 6 (1.7%) patients with RELA + NIVO and 2 (0.6%) with NIVO. Troponin monitoring was performed for the first 2 months of treatment per protocol

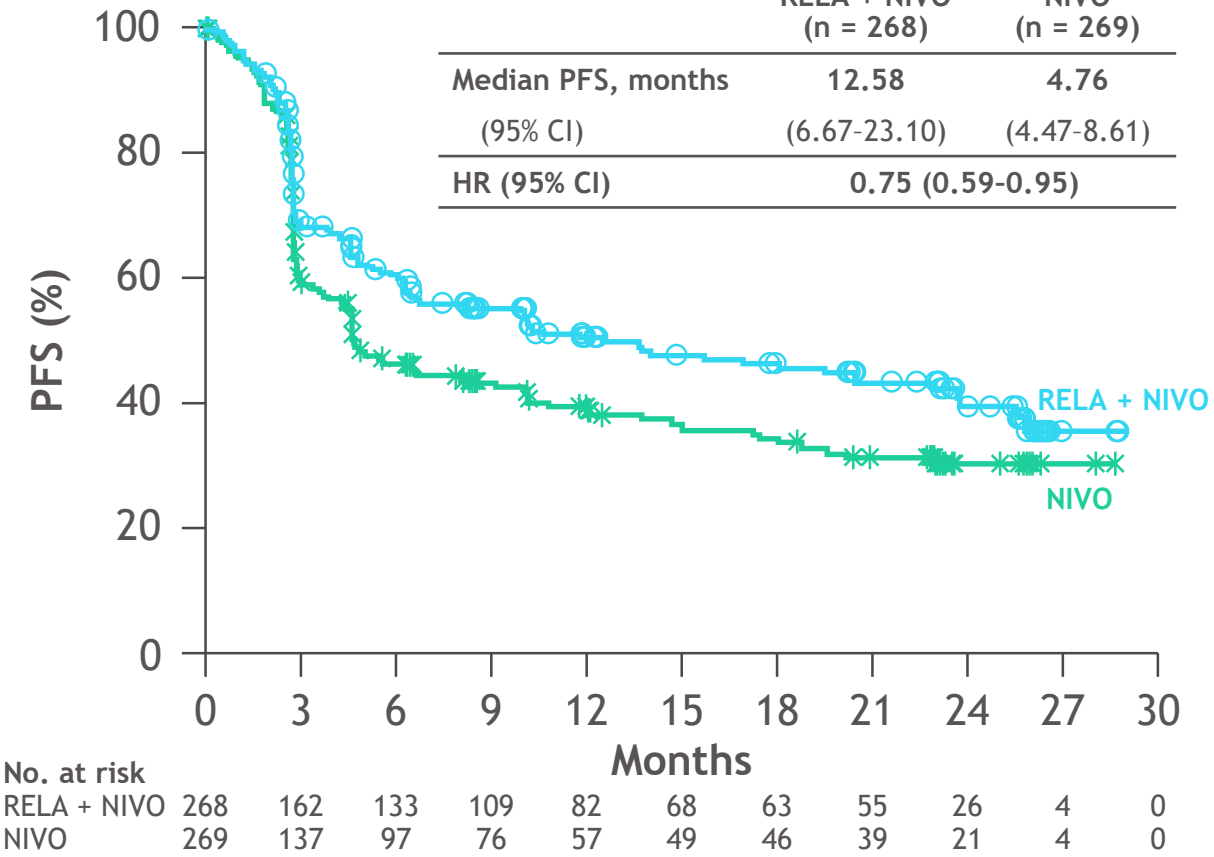
[a]Includes AEs of any grade occurring in ≥ 1% of patients considered by investigators to be potentially immune-mediated that met the following criteria: occurred within 100 days of the last dose, regardless of causality, treated with immune-modulating medication with no clear alternate etiology, or had an immune-mediated component.

PFS by LAG-3 expression

- PFS benefit favored RELA + NIVO FDC regardless of LAG-3 expression status

LAG-3 expression ≥ 1%

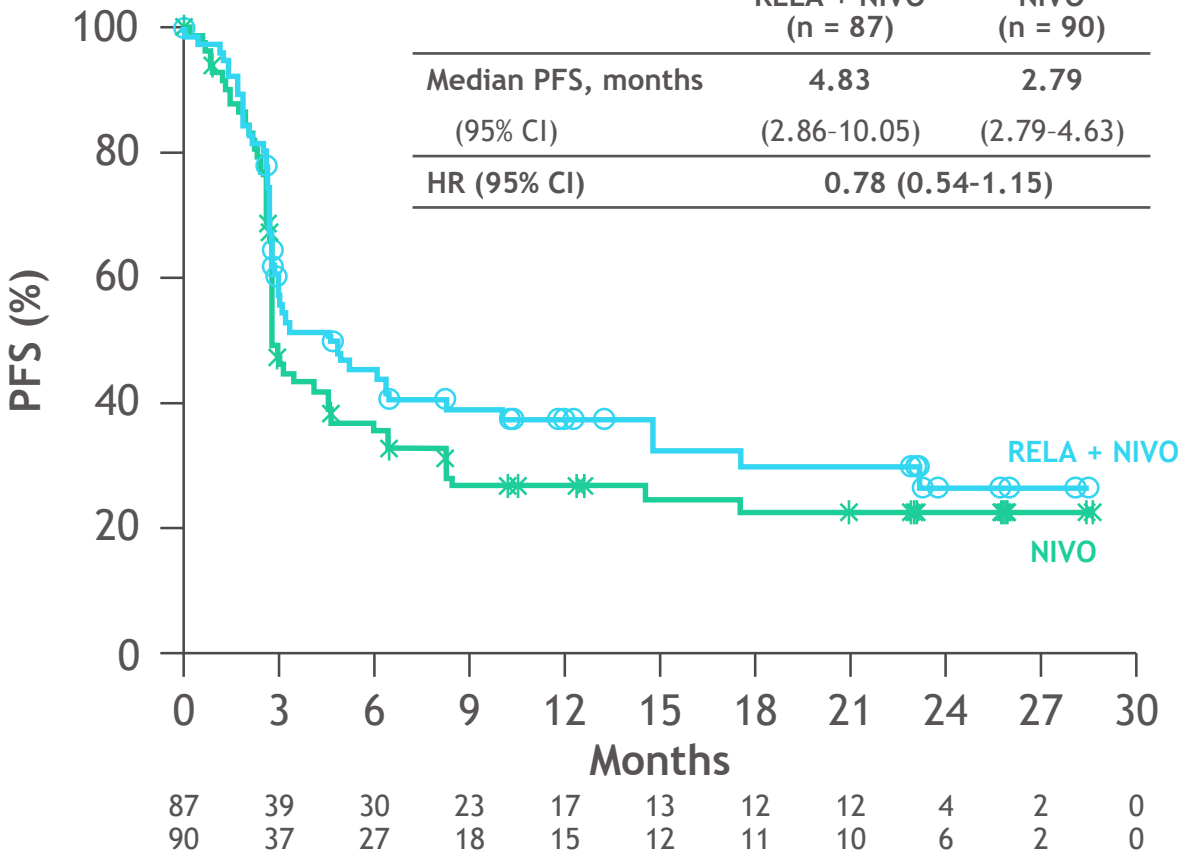
	RELA + NIVO (n = 268)	NIVO (n = 269)
Median PFS, months	12.58	4.76
(95% CI)	(6.67-23.10)	(4.47-8.61)
HR (95% CI)	0.75 (0.59-0.95)	



No. at risk											
RELA + NIVO	268	162	133	109	82	68	63	55	26	4	0
NIVO	269	137	97	76	57	49	46	39	21	4	0

LAG-3 expression < 1%

	RELA + NIVO (n = 87)	NIVO (n = 90)
Median PFS, months	4.83	2.79
(95% CI)	(2.86-10.05)	(2.79-4.63)
HR (95% CI)	0.78 (0.54-1.15)	



	87	39	30	23	17	13	12	12	4	2	0
	90	37	27	18	15	12	11	10	6	2	0

Statistical model for HR: unstratified Cox proportional hazard model.

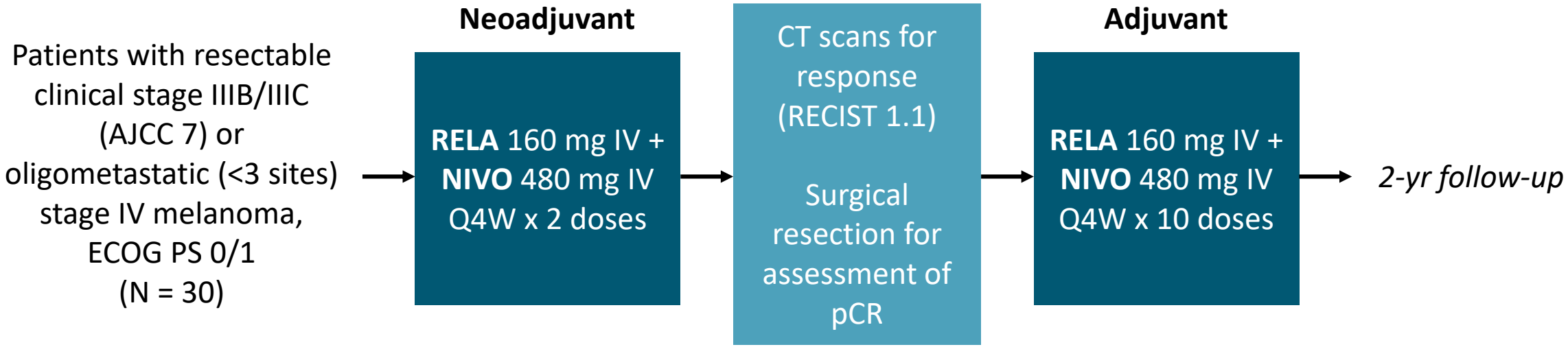
March 2022: FDA approval of relatlimab+nivolumab

"…indicated for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma."

- Line agnostic
- No companion diagnostic (e.g., LAG-3 or PD-L1 expression)

Neoadjuvant Relatlimab + Nivolumab

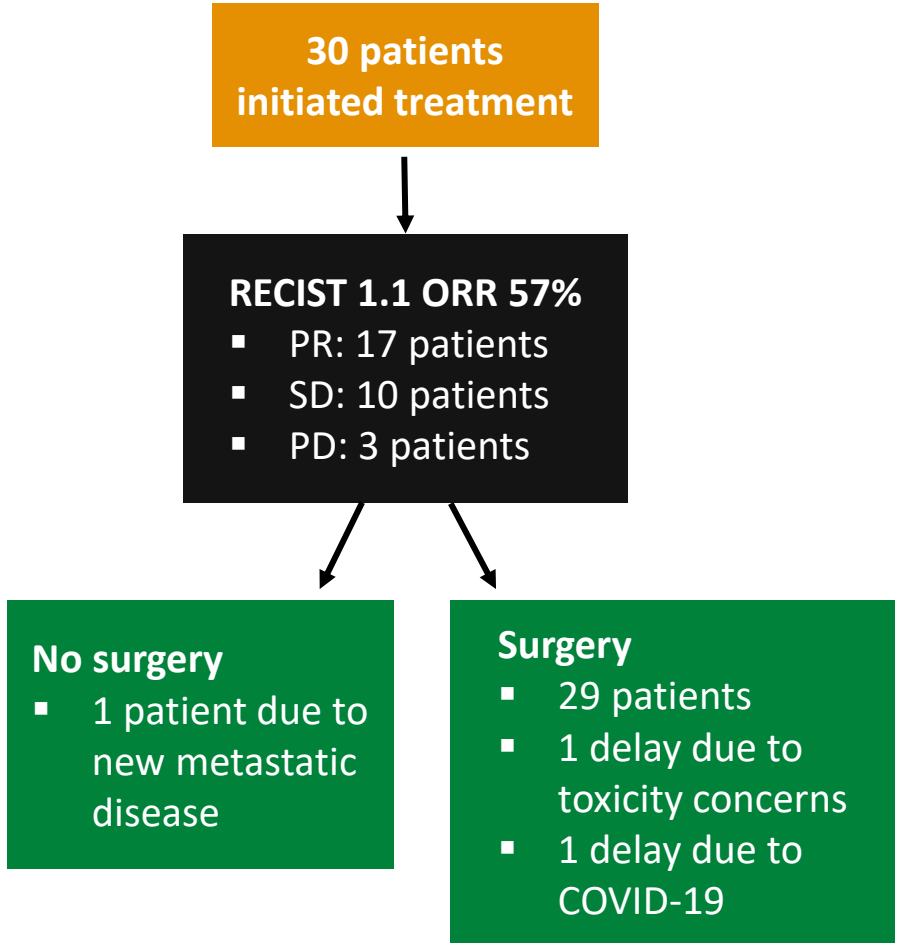
- Investigator-initiated, single-arm phase 2 study



- Primary endpoint: pCR
- Secondary endpoints: ORR, RFS, EFS, OS, safety, mechanisms of response

Amaria. ASCO 2021. Abstr 9502.

Neoadjuvant Relatlimab + Nivolumab for Stage III Melanoma: ORR and pCR

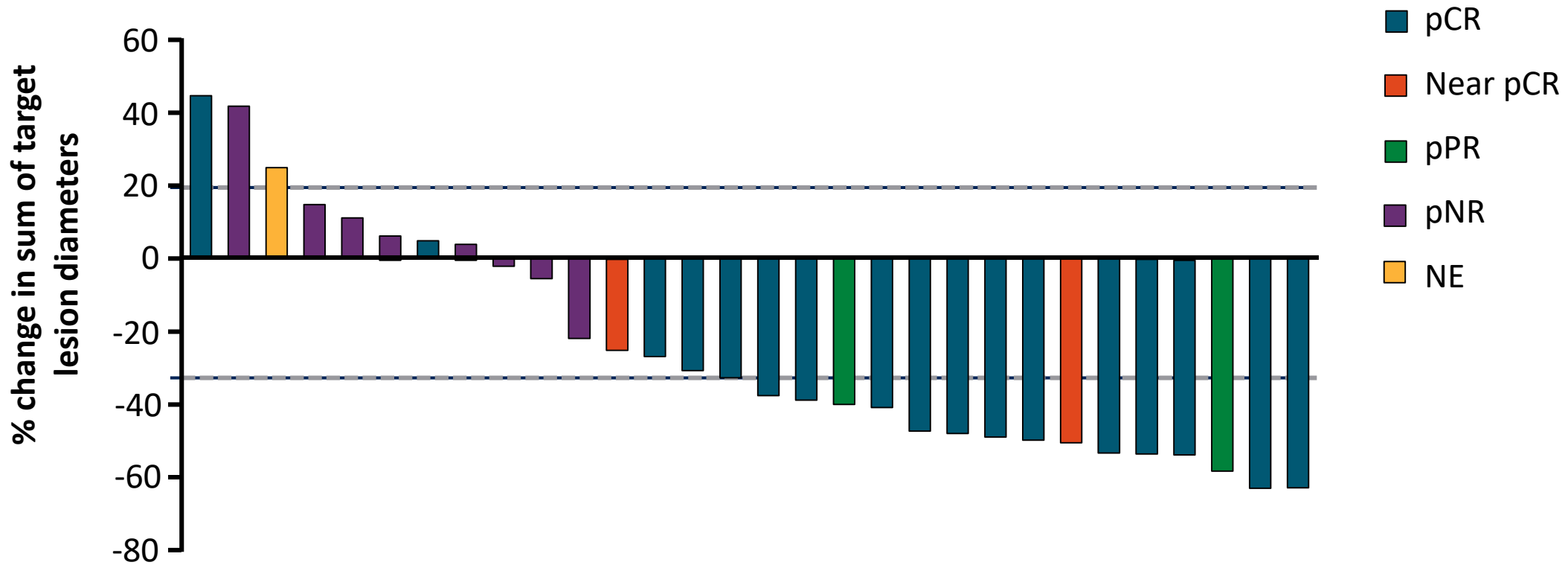


Pathologic Response, n (%)	Total Cohort (N = 29)
pCR	17 (59)
Near pCR	2 (7)
pPR	2 (7)
pNR	8 (27)

- Any pathologic response (pCR + near pCR + pPR): 73%
- Major pathologic response (pCR + near pCR): 66%

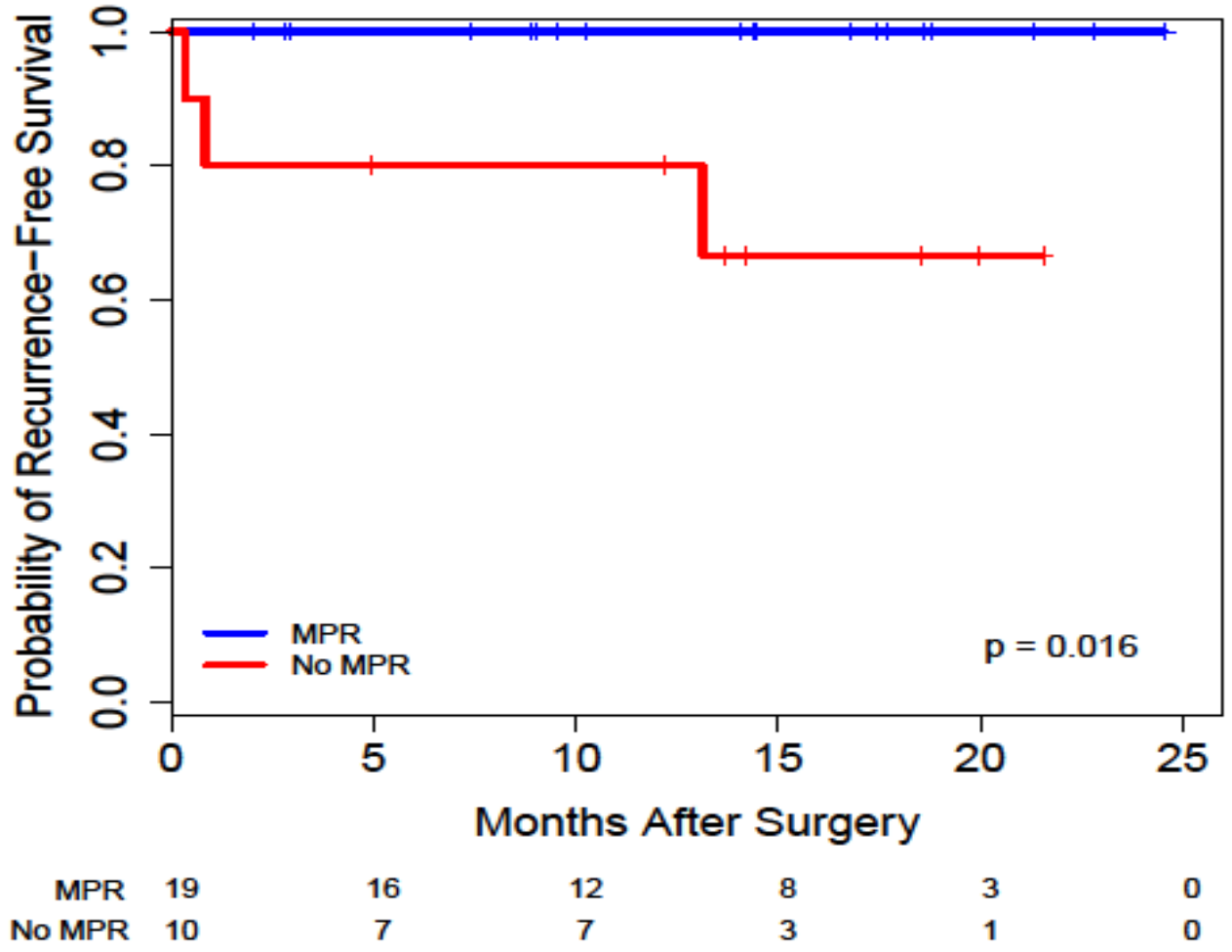
Amaria. ASCO 2021. Abstr 9502.

Neoadjuvant RELA + NIVO: Tumor Responses



Amaria. ASCO 2021. Abstr 9502.

Improved RFS Outcomes for MPR Patients



MPR: pCR + near pCR
Median 16.2 mo follow up

Amaria. ASCO 2021. Abstr 9502.

Select Ongoing Trials of Relatlimab

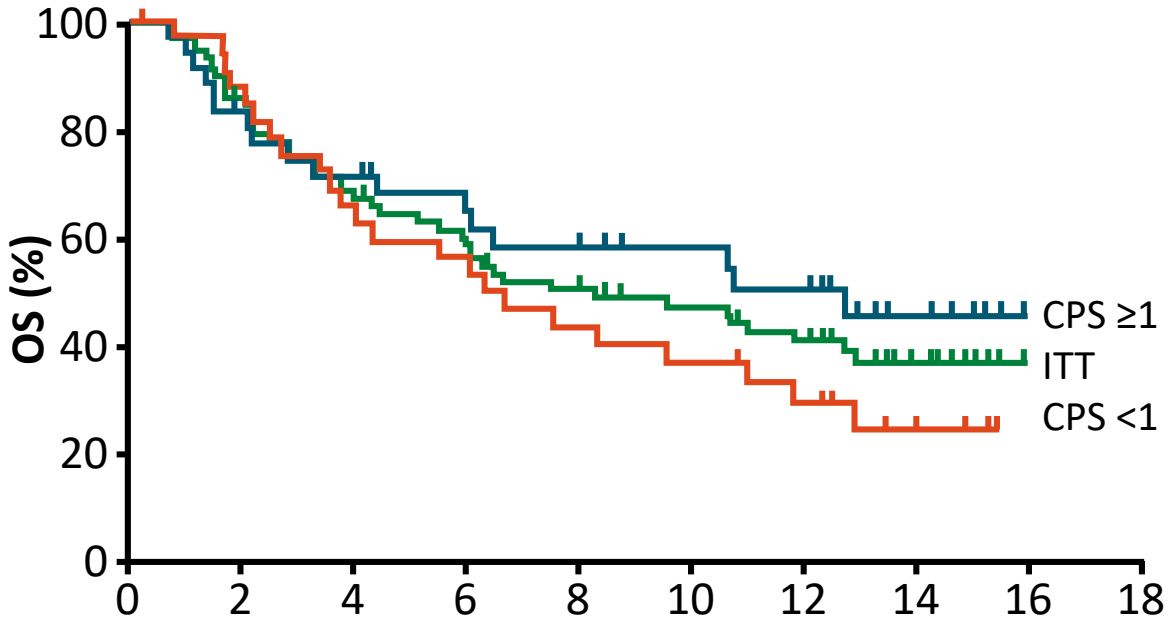
Trial Identifier/Name	Tumor Type	Intervention	Phase
NCT05002569/RELATIVITY-098	Resected melanoma	Adjuvant RELA + NIVO vs NIVO	III
NCT03978611	Melanoma after progression on anti–PD-1	RELA + IPI vs IPI	I/IIa
NCT04552223	Uveal melanoma	RELA + NIVO	II
NCT04095208/CONGRATS	Soft tissue sarcoma	RELA + NIVO, NIVO alone (non-comparative)	II
NCT04658147	Resectable HCC	Perioperative NIVO ± RELA	I
NCT04567615	HCC post TKI therapy	RELA + NIVO vs NIVO	II
NCT04080804	Resectable HNSCC	Neoadjuvant NIVO ± RELA, NIVO/IPI	II
NCT04326257	Recurrent HNSCC post ICI	NIVO ± RELA, NIVO/IPI	II
NCT04623775	Stage IV or recurrent NSCLC	First-line RELA + NIVO + CT vs NIVO + CT	II
NCT03642067	MSS CRC	RELA + NIVO	II

Investigational LAG-3-Targeted Monoclonal Antibodies

Agent	Ongoing Clinical Trials	Trial Identifier
Ieramilimab (LAG-525)	Phase II, melanoma, with spartalizumab	NCT03484923
Favezelimab/ pembrolizumab coformulation (MK-4280A)	Phase III vs SoC in mCRC Phase I/II, NSCLC Phase I/II, ES-SCLC Phase I/II, RCC	NCT05064059 NCT03516981 NCT04938817 NCT04626479, NCT04626518
Fianlimab (REGN3767)	Phase I, advanced cancers ± cemiplimab	NCT03005782
INCAGN-2385	Phase I/II, advanced cancers, with anti–TIM-3 ± anti–PD-1	NCT04370704
Miptenalimab (BI 754111)	Phase I, advanced solid tumors, with anti–PD-1 ± MDM2 inhibitor	NCT03964233
LBL-007	Phase Ib/II, advanced tumors	NCT05102006
Sym022	Phase I, biliary tract carcinoma with anti–PD-1	NCT04641871
Encelimab (GSK-4074386, TSR-033)	Phase I, advanced solid tumors, + anti–PD-1 Phase I, advanced solid tumors + anti–TIM-3	NCT03250832 NCT02817633
IBI110	Phase II, ES-SCLC, + sintilimab Phase I, NSCLC, + sintilimab (neoadjuvant)	NCT05026593 NCT05088967

Favezelimab (MK4280) + Pembrolizumab for Previously Treated Microsatellite Stable mCRC: Phase I Efficacy

- Favezelimab: Humanized IgG4 anti–LAG-3 mAb
- First-in-human study, ± pembrolizumab (N = 100)
- 0% ORR among 20 patients receiving favezelimab monotherapy
- CPS=combined positive score (quantification of PD-L1 expression on tumor cells, lymphocytes, macrophages



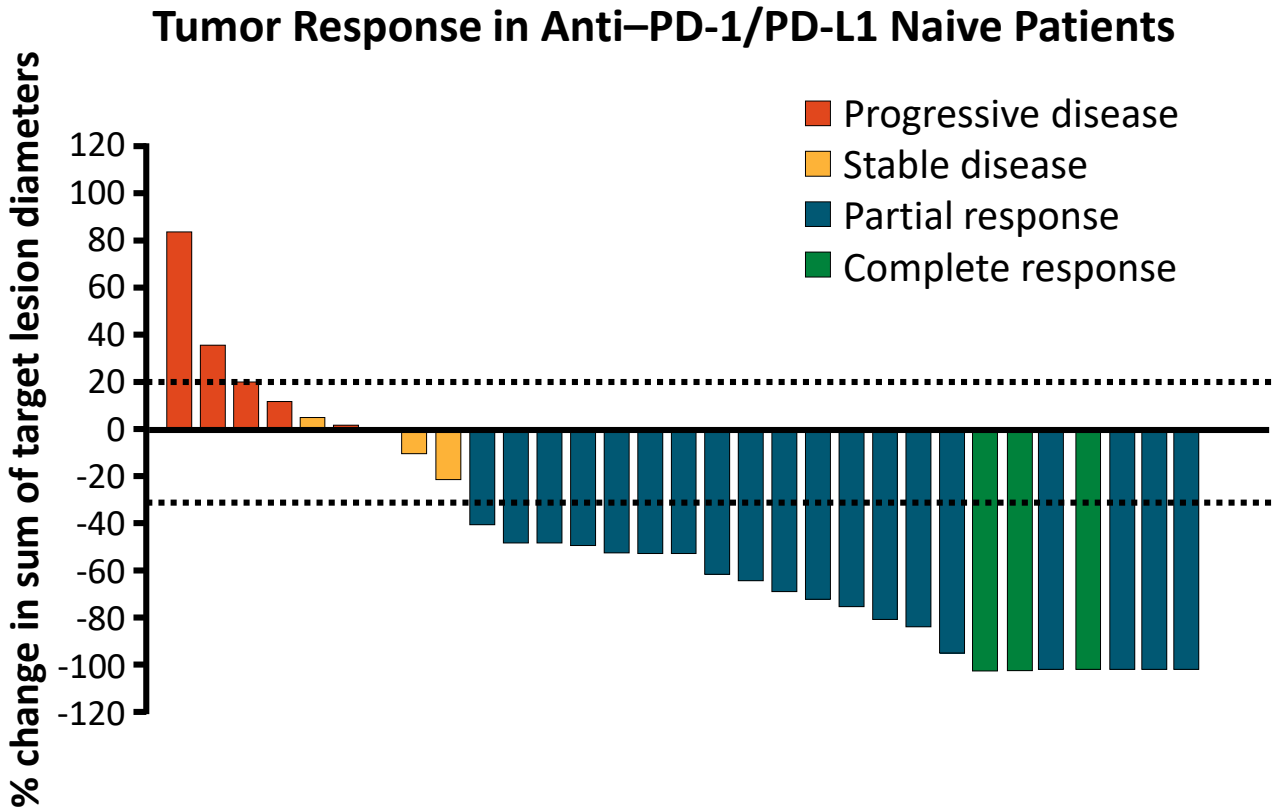
Pt at Risk, n									
CPS ≥1	36	29	24	21	18	15	13	6	0	0
CPS <1	35	28	21	18	13	11	8	3	0	0
Total	80	65	51	43	35	30	25	11	0	0

Lakhani. SITC 2018. Abstr O26. Garralda. ASCO 2021. Abstr 3584.

Fianlimab (fully human IgG4 LAG-3 mAb) + cemiplimab in Advanced Melanoma

Tumor Response to Fianlimab + Cemiplimab, n (%)	Anti–PD-1/PD-L1 Naive (n = 33)	Anti–PD-1/PD-L1 Experienced (n = 15)
ORR*, % (95% CI)	66.7 (48.2-82.0)	13.3 (1.7-40.5)
▪ CR	3 (9.1)	0
▪ PR	19 (57.6)	2 (13.3)
▪ SD	3 (9.1)	4 (26.7)
▪ PD	6 (18.2)	8 (53.3)
▪ NE	2 (6.1)	1 (6.7)
DCR	25 (75.8)	6 (40.0)
mPFS, mo (95% CI)	NR (4.2-NE)	1.4 (1.3-10.7)

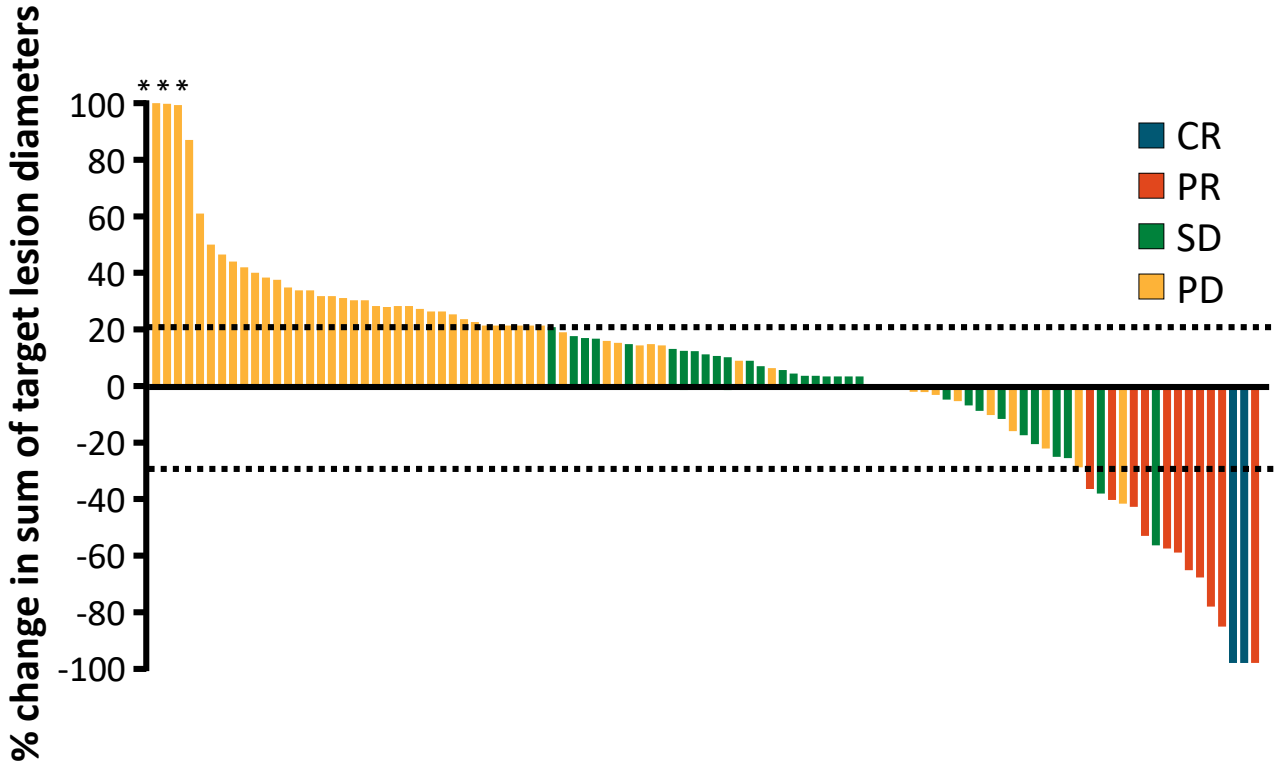
*Investigator-assessed responses per RECIST v1.1.



Hamid. ASCO 2021. Abstr 9515. NCT03005782.

Phase I/II Study of Ieramilimab (anti–LAG-3) ± spartalizumab (anti-PD-1) in Previously Treated Advanced Cancers

Best Overall Response,* n (%)	Phase I Single-Agent Patients (n = 134)	Phase I Combination Patients (n = 121)
ORR, % (90% CI)	0 (0.0-2.2)	10.7 (6.5-16.5)
▪ CR	0	3 (2.5)
▪ PR	0	10 (8.3)
▪ SD	32 (23.9)	35 (28.9)
▪ PD	82 (16.2)	55 (45.5)
▪ NCRNPD	2 (1.5)	1 (0.8)
▪ Unknown	18 (13.4)	17 (14.0)
DCR, % (90% CI)	25.4 (19.3-32.3)	40.5 (33.0-48.4)



*Investigator-assessed per RECIST v1.1.

Schöffski. J Immunother Cancer. 2022;10:e003776.

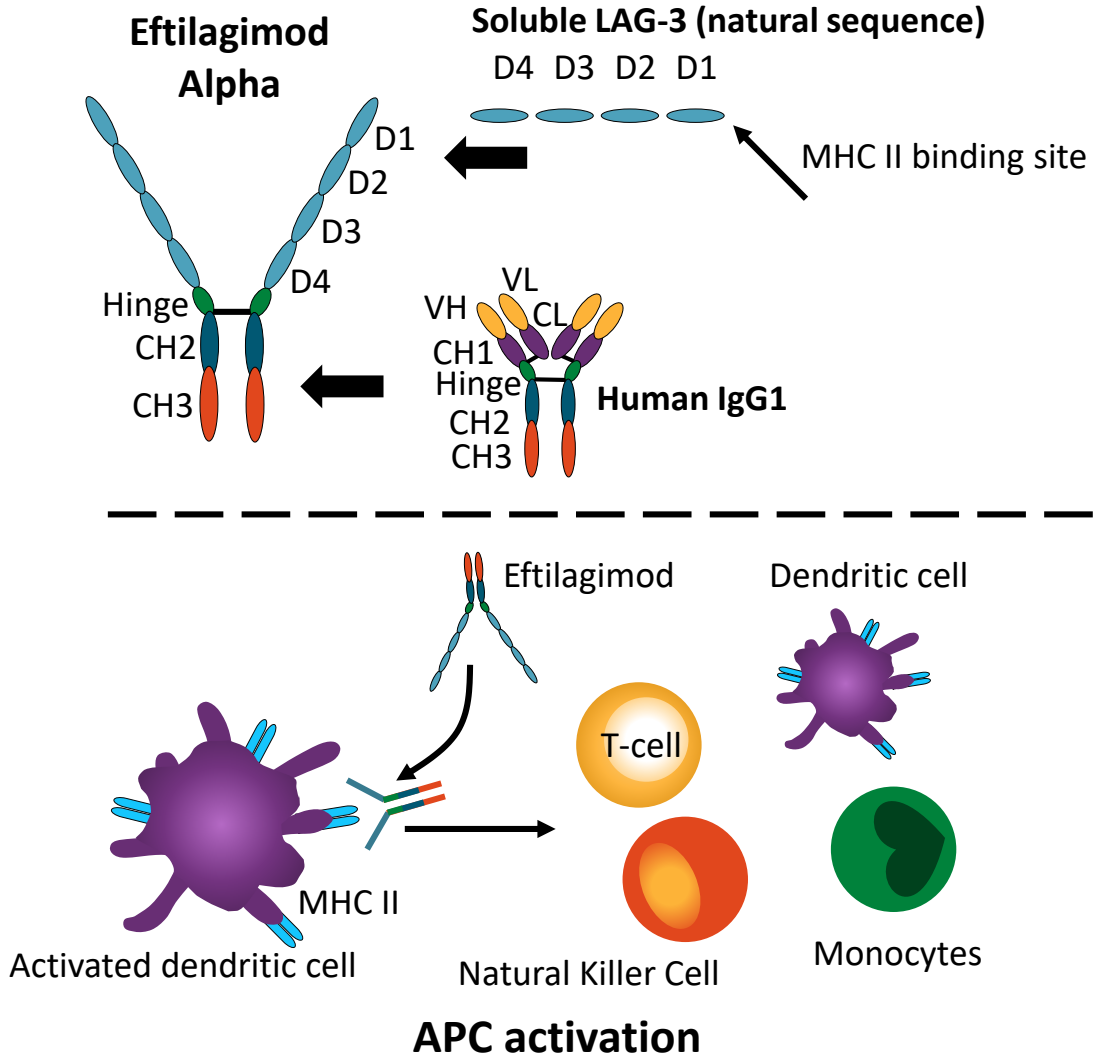
Anti–LAG-3 Bispecific Antibodies in Development

Agent	Targets	Clinical Development	Trial Identifier
Tebotelimab (MDG-013)[1,2]	LAG-3/PD-1	Phase II in HNSCC Phase III; MAHOGANY; gastric/GEJ HER2 with margetuximab	NCT04634825 NCT04082364
EMB-02	LAG-3/PD-1	Phase I/II in solid tumors	NCT04618393
RO-7247669	LAG-3/PD-1	Phase II in esophageal cancer	NCT04785820
RG6139	LAG-3/PD-1	Phase I study in advanced solid tumors	NCT04140500
IBI-323	LAG-3/PD-1	Phase I in adv malignancies	NCT04916119
FS 118[1,3]	LAG-3/PD-L1	Phase I /II in adv malignancies	NCT03440437
Pavunalimab (XmAb-841)	LAG-3/CTLA-4	Phase I w/pembrolizumab in solid tumors	NCT03849469

1. Maruhashi. J ImmunoTher Cancer. 2020;8e001014. 2. Wang. ASH 2020. Abstr 3022. 3. Yap. SITC 2020. Abstr 395.

Eftilagimod Alpha Dimeric Recombinant LAG-3

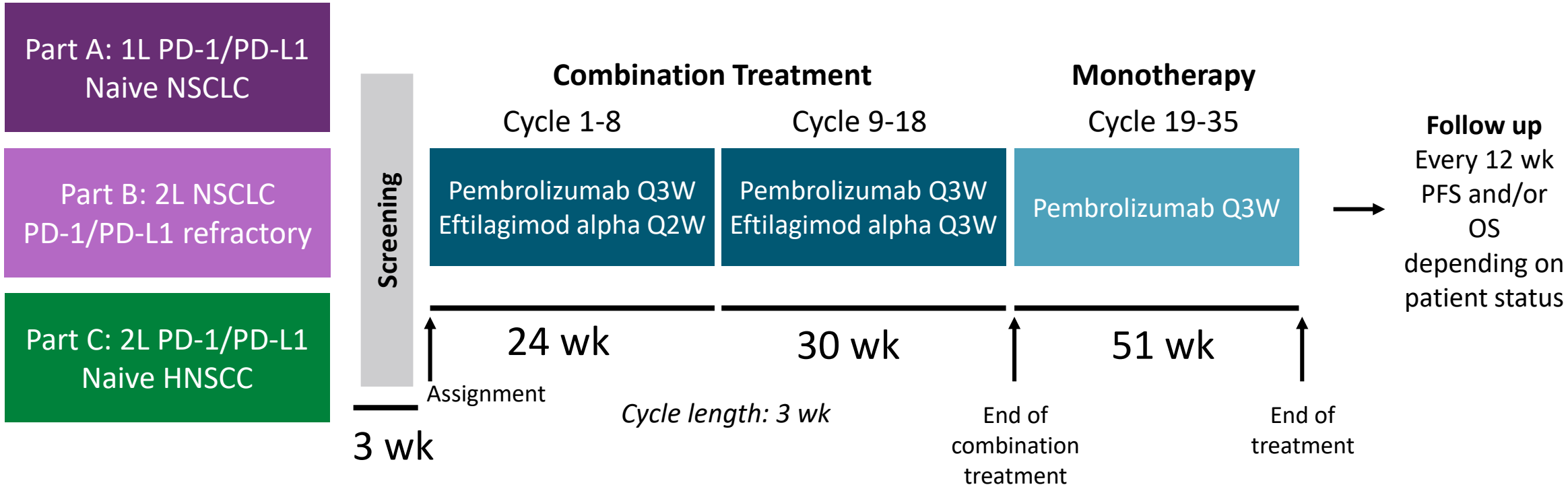
- Recombinant, soluble LAG-3 fusion protein
- Mechanism of action is different from antibodies or bispecific antibodies targeting LAG-3
- MHC class II agonist
  - Binds to MHC class II on APC leading to APC activation
- Activated APCs leads to increased T-cell activation



Felip. ASCO 2020. Abstr 3100. Clay. ASCO 2021. Abstr 9046.

TACTI-002 Trial Eftilagimod Alpha Plus Pembrolizumab in NSCLC or HNSCC

- Non-randomized, parallel assignment, open-label, phase II trial



- **Primary endpoint:** ORR per iRECIST
- **Secondary endpoints:** PFS, OS, PK, biomarker, PD, safety

Felip. ASCO 2020. Abstr 3100. Clay. ASCO 2021. Abstr 9046. NCT03625323.

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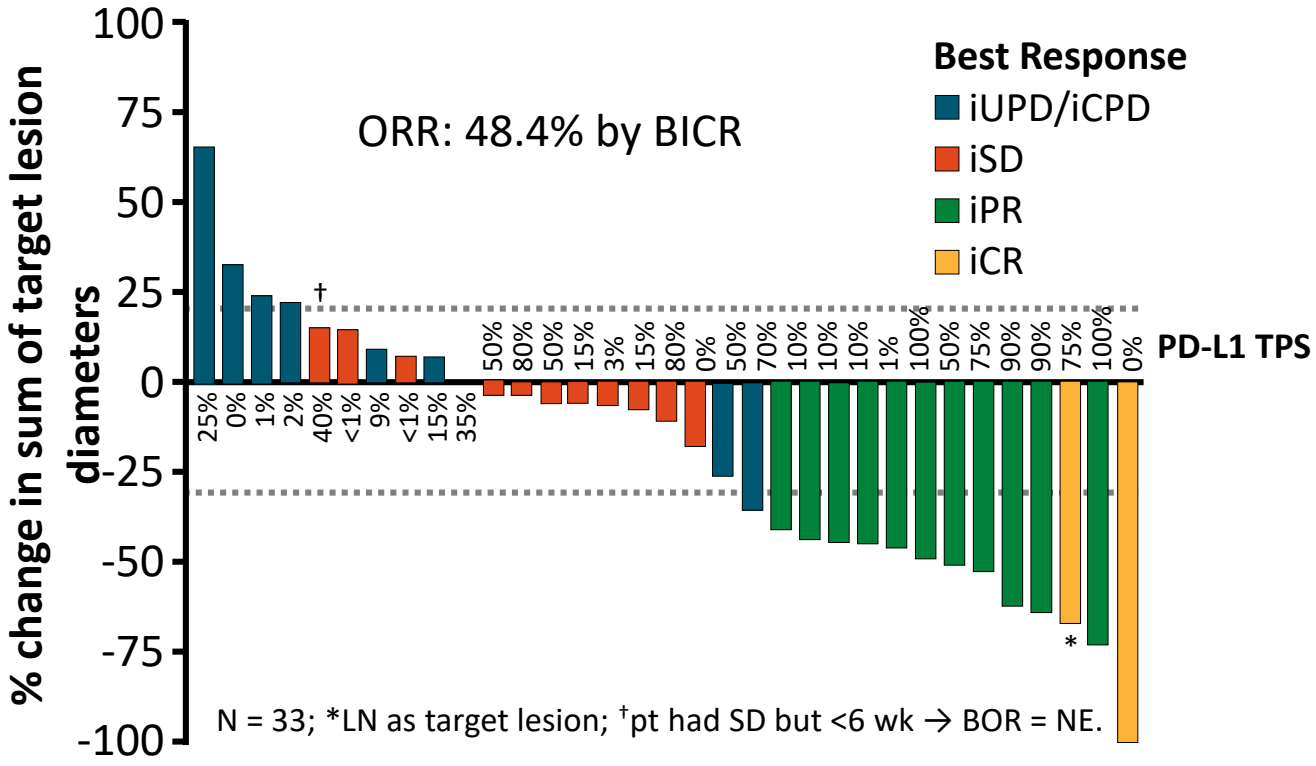
TACTI-002 Part A: Efficacy in treatment-naïve NSCLC

- Stage IIIB not amenable to curative therapy or stage IV with any PD-L1 expression status and *EGFR/ALK* wild type



Clay. ASCO 2021. Abstr 9046. NCT03625323.

Targeting LAG-3: Clinical development

- A phase 3 study has confirmed that targeting the LAG-3 immune checkpoint is a beneficial therapeutic strategy for patients with cancer.
- The LAG-3 pathway is the third immune checkpoint pathway in history, after CTLA-4 and PD-1, for which blockade has clinical benefit.
- Testing is ongoing in patients with multiple tumor types