Cancer Education Day
Systemic Therapy and Toxicities

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Disclosures

- Have participated in Advisor Board/ Small group lectures and received funding from Novartis, Bayer and Pfizer. Not directly related to current presentation.

Incidence/ Deaths:

- Melanoma is only 1% of skin cancers but accounts for majority of deaths.
- US stats : (2024) 104, 960 new cases/year. 10% more in men
- Incidence increasing.
- 5 year survival
    - Localized : > 99%
    - Regional : 75 %
    - Metastatic : 35%
- Canadian Incidence (2024) : 11,300 Mortality : 1, 300
- Ontario - Incidence : 2800 cases.

AJCC Melanoma of the Skin Staging 8th Edition

Definitions

Primary Tumor (T)

- **TX** Primary tumor cannot be assessed (for example, curettaged or severely regressed melanoma)
- **T0** No evidence of primary tumor
- **Tis** Melanoma in situ
- **T1** Melanomas 1.0 mm or less in thickness
- **T2** Melanomas 1.1 - 2.0 mm
- **T3** Melanomas 2.1 - 4.0 mm
- **T4** Melanomas more than 4.0 mm

NOTE: a and b subcategories of T are assigned based on ulceration and thickness as shown belowt:

T CLASSIFICATION	THICKNESS (mm)	ULCERATION STATUS
T1	≤1.0	a: Breslow < 0.8 mm w/o ulceration b: Breslow 0.8-1.0 mm w/o ulceration or ≤ 1.0 mm w/ ulceration.
T2	1.1-2.0	a: w/o ulceration b: w/ ulceration
T3	2.1-4.0	a: w/o ulceration b: w/ ulceration
T4	>4.0	a: w/o ulceration b: w/ ulceration

Regional Lymph Nodes (N)

- **NX** Patients in whom the regional nodes cannot be assessed (for example previously removed for another reason)
- **N0** No regional metastases detected
- **N1-3** Regional metastases based on the number of metastatic nodes, number of palpable metastatic nodes on clinical exam, and presence or absence of MSI[2]

NOTE: N1-3 and a-c subcategories assigned as shown below:

N CLASSIFICATION	# NODES	CLINICAL DETECTABILITY/MSI STATUS
N1	0-1 node	a: clinically occult[1], no MSI[2] b: clinically detected[1], no MSI[2] c: 0 nodes, MSI present[2]
N2	1-3 nodes	a: 2-3 nodes clinically occult[1], no MSI[2] b: 2-3 nodes clinically detected[1], no MSI[2] c: 1 node clinical or occult[1], MSI present[2]
N3	>1 nodes	a: >3 nodes, all clinically occult[1], no MSI[2] b: >3 nodes, ≥1 clinically detected[1] or matted, no MSI[2] c: >1 nodes clinical or occult[1], MSI present[2]

Distant Metastasis (M)

- **M0** No detectable evidence of distant metastases
- **M1a** Metastases to skin, sub cutaneous, or distant lymph nodes
- **M1b** Metastases to lung
- **M1c** Metastases to all other visceral sites
- **M1d** Metastases to brain

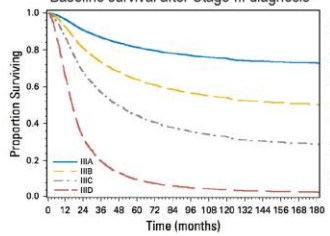
NOTE: Serum LDH is incorporated into the M category as shown below:

M CLASSIFICATION	SITE	Serum LDH
M1a-d	Skin/subcutaneous/nodule (a), lung (b) other visceral (c), brain (d)	Not assessed
M1a-d(0)	Skin/subcutaneous/nodule (a), lung (b) other visceral (c), brain (d)	Normal
M1a-d(1)	Skin/subcutaneous/nodule (a), lung (b) other visceral (c), brain (d)	Elevated

ANATOMIC STAGE/PROGNOSTIC GROUPS

	Clinical Staging[3]				Pathologic Staging[4]			
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	..	..		T1b	..	..
	T2a	..	..	IB	T2a	..	..
Stage IIA	T2b	N0	M0	IIA	T2b	M0	M0
	T3a	..	..		T2a	..	..
Stage IIB	T3b	..	..	IIB	T3b	..	..
	T4a	..	..		T4a	..	..
Stage IIC	T4b	..	..	IIC	T4b	..	..
Stage III	Any T	≥N1	M0	IIIA	T1-2a	N1a	M0
	..	..	..		T1-2a	N2a	..
	..	..	..	IIIB	T0	N1b-c	M0
	..	..	..		T1-2a	N1b-c	..
	..	..	..		T1-2a	N2b	..
	..	..	..		T2b-3a	N1a-2b	..
	..	..	..	IIIC	T0	N2b-c	M0
	..	..	..		T0	N3b-c	..
	..	..	..		T1a-3a	N2c-3c	..
	..	..	..		T3b-4a	Any N	..
	..	..	..		T4b	N1a-2c	..
	..	..	..	IIID	T4b	N3a-c	M0
Stage IV	Any N	Any N	M1	IV	Any T	Any N	M1

Baseline survival after Stage III diagnosis[5]



Conditional, 5-year survival (%)[5]

Stage	Baseline	3y survivors
IIIA	81.4	83.1
IIIB	64.0	76.0
IIIC	44.5	66.7
IIID	9.8	40.6

Notes

[1] Nodes are designated as 'clinically detectable' if they can be palpated on physical exam and are confirmed melanoma by pathology following excision/biopsy.

[2] MSI comprise any satellite, locally recurrent, or in transit lesions.

[3] Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

[4] Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 and I patients are the exceptions; they do not necessarily require pathologic evaluation of their lymph nodes. Physicians should "discuss and consider" SLNB for patients with T1b Stage IA disease; physicians should "discuss and offer" SLNB for patients with Stage IB disease.

[5] From Haydu et al., Journal of Clinical Oncology, 2017.

Produced following the 8th Ed. AJCC guidlines released January 1, 2017. Contact Dr. M. Gormally (mvgg07@gmail.com) for reprint.

Adjuvant Therapies:

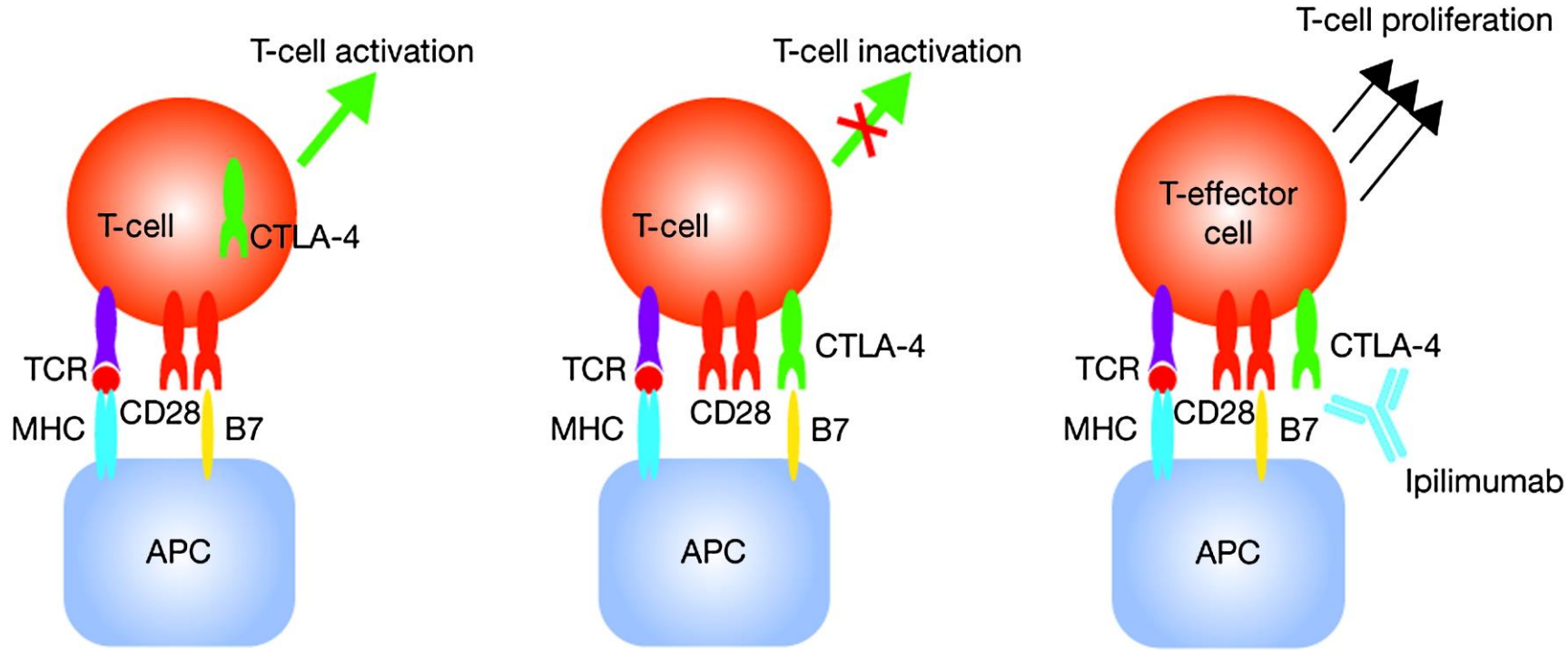
- Interferon (historic) : Too toxic, benefits small, Not used recently.
- Ipilimumab : Improvement in survival – too toxic and not indicated.

- Nivolumab : 3 mg/ kg [Checkmate 238 – superior to placebo]
- Pembrolizumab : 200 mg q 3 weeks or 2 mg/kg – sup to placebo
- Beneficial in Stage IIB, IIC, IIIB,C,D & Resected Stage IV
- Single agent b-raf inhibitor – Did not improve survival
- Debrafenib + Trematenib = Improves RFS

Activation is initiated by binding of B7 molecules on the APC to CD28 receptors on the T-cell

Inhibition results from CTLA-4 expression on the T-cell surface where it competes with CD28 for binding to B7 on APCs

Potentiation of T-cell proliferation achieved by CTLA-4 inhibition using ipilimumab, an anti-CTLA-4 monoclonal antibody



MHC = major histocompatibility complex; APC = antigen presenting cell; TCR = T-cell receptor; CTLA-4 = cytotoxic T lymphocyte-4

Metastatic Melanoma Treatment:

- Chemotherapy not of much benefit (15%) RR. Agents like DTIC or Carbo- Taxol.
- Intralesional therapies like IL-2

- Immunotherapy:
  - CTLA-4 targeted monoclonal antibody – Ipilimumab (Yervoy)
  - [Cytotoxic T- lymphocyte Antigen 4]

- PD-1 inhibitors - Nivolumab (Opdivo) and Pembrolizumab
- (Programmed cell death)
- Blocks proteins that stimulate immune system from working.

- Relatlimab (Opdulay)
- IgG4 monoclonal Ab that blocks LAG-3 protein
- Inhibits T cell function

Response to Treatment:

Response to treatment at 6.5 years (Minimum follow-up of 77 months)

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
ORR (95% CI), %	58 (53–64)	45 (39–51)	19 (15–24)
Best overall response, %			
Complete response	23	19	6
Partial response	36	26	13
Stable disease	12	9	22
Progressive disease	24	38	50
Unknown	6	8	9

Response to treatment at 7.5 years (Minimum follow-up of 90 months)

- Investigator-assessed, unconfirmed ORR was unchanged from the 6.5-year follow up
- Median DOR was NR in patients treated with NIVO + IPI (95% CI, 69.1–NR), has now been reached in patients treated with NIVO at 90.8 months (95% CI, 45.7–NR), and was 19.2 months with IPI (95% CI, 8.8–47.4)

DOR, duration of response; IPI, ipilimumab; NIVO, nivolumab; NR, not reached; ORR, objective response rate.

1. Reproduced from Wolchok JD, et al. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; June 4–8, 2021; Virtual. Abstract 9506.
2. Hodi FS, et al. Poster at the American Society of Clinical Oncology (ASCO) Annual Meeting; June 3–7, 2022; Chicago, IL & Online. Abstract 9522.

Targeted Therapies:

- In Melanomas – Test for BRAF – V600E/ K mutation (50% of cases)

- B-Raf and MEC inhibitors are more effective

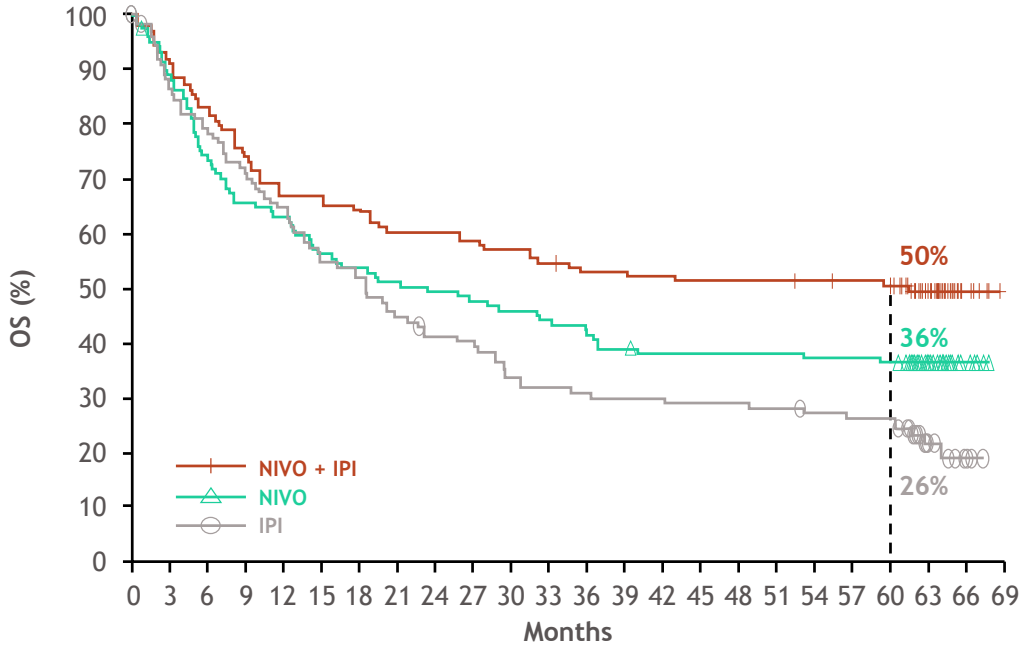
- Vemurafenib + Cobimetinib (COBRIM study)
- Debrafenib + Trametinib (COMBI-V)
- Encorafenib + Binimetinib (COLUMBUS)

60-month minimum follow-up

OS and ORR by tumor PD-L1 expression: 1% cutoff

Biomarkers, NIVO: 4 of 7
Biomarkers, NIVO + IPI: 4 of 7

Overall Survival PD-L1 Expression Level < 1%

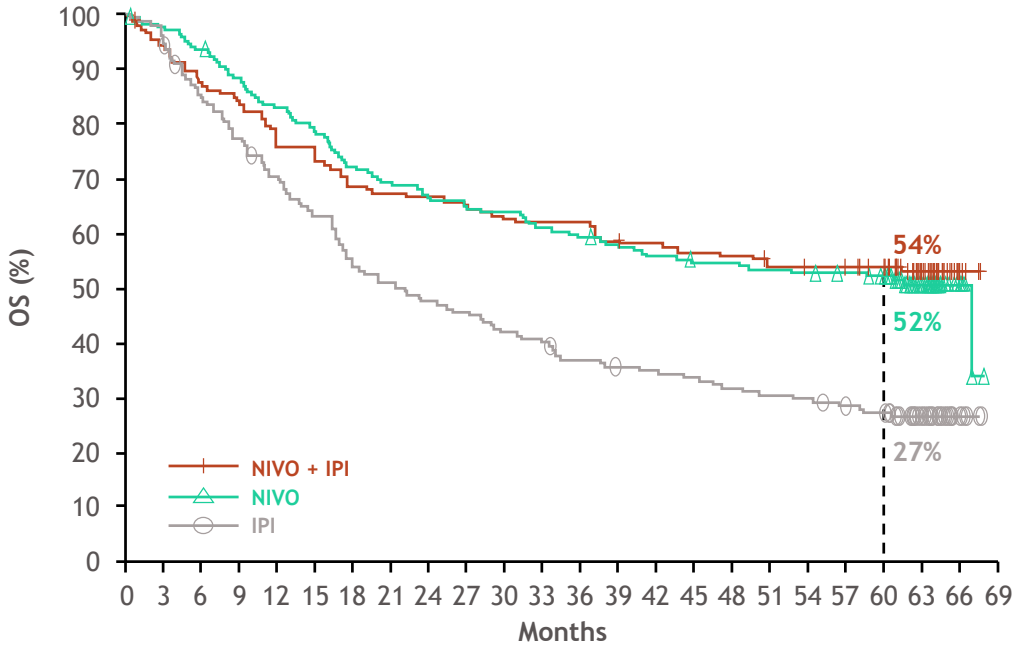


No. at risk

NIVO + IPI	123	113	102	91	82	82	79	74	74	72	70	67	65	64	63	62	62	62	61	60	59	35	6	0
NIVO	117	103	86	76	73	65	62	59	57	55	53	51	49	45	43	43	43	43	42	42	41	24	5	0
IPI	113	96	87	79	71	61	57	50	44	43	36	34	33	32	32	31	31	30	28	27	27	9	3	0

- The ORR, % (95% CI), for patients with PD-L1 expression level <1% was 54 (44-63) for Nivolumab + Ipilimumab, 36 (27-45) for Nivolumab, and 18 (11-26) for Ipilimumab

Overall Survival PD-L1 Expression Level ≥ 1%



No. at risk

NIVO + IPI	155	144	132	127	116	112	105	102	101	99	96	94	94	89	87	85	84	80	79	78	75	46	5	0
NIVO	171	165	159	149	140	132	122	117	112	109	108	103	100	96	93	90	90	88	87	85	82	50	9	0
IPI	164	155	137	125	113	101	88	82	76	73	67	64	58	55	54	52	49	47	46	43	40	22	7	0

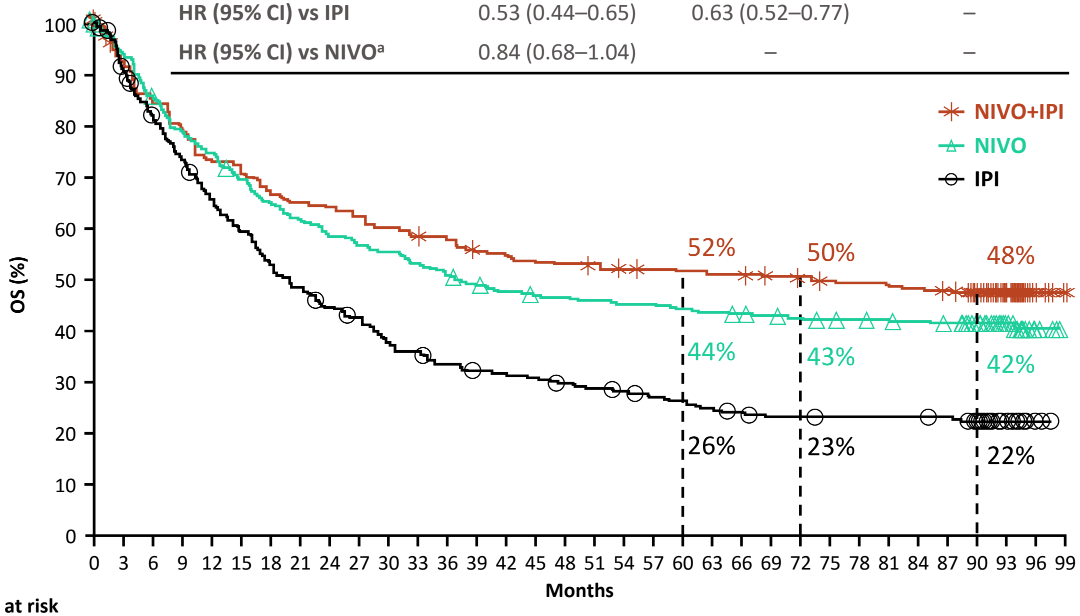
- The ORR, % (95% CI), for patients with PD-L1 expression level ≥1% was 65 (56-72) for Nivolumab + Ipilimumab, 54 (47-62) for Nivolumab, and 20 (14-26) for Ipilimumab

Database lock: July 2, 2019; minimum follow-up of 60 months for all patients.
CI, confidence interval; IPI, ipilimumab; NIVO, nivolumab; NR, not reached; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1.
Larkin J et al. *N Engl J Med*. 2019;381:1535–1546 [supplementary appendix].

Co-primary endpoints: 90-month minimum follow-up
Overall survival and progression-free survival

Overall survival

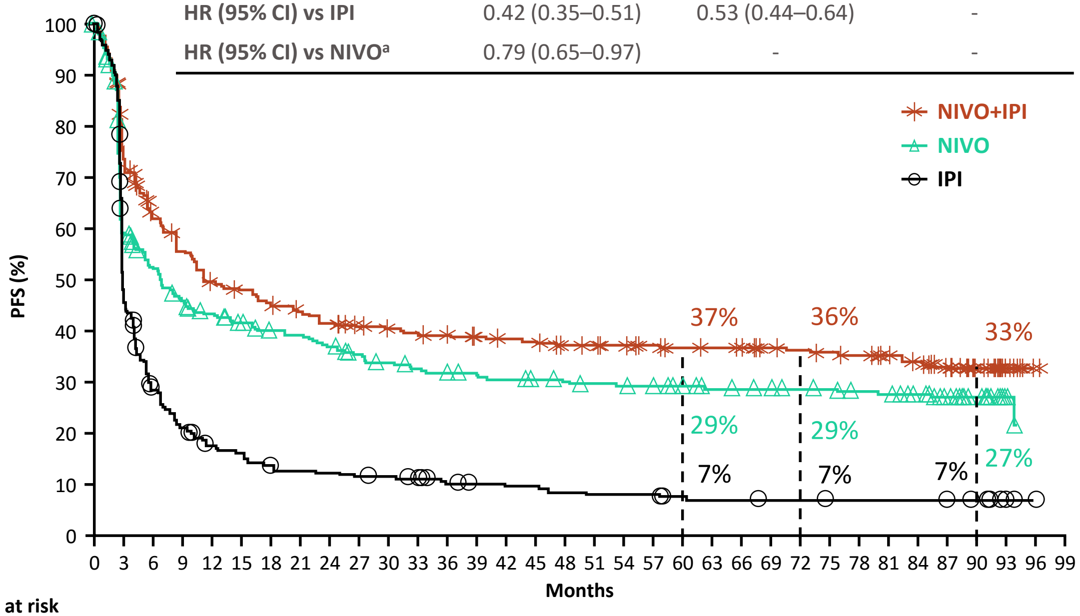
	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median, mo (95% CI)	72.1 (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.53 (0.44–0.65)	0.63 (0.52–0.77)	–
HR (95% CI) vs NIVO[a]	0.84 (0.68–1.04)	–	–



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81	84	87	90	93	96	99
NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	144	143	141	138	129	58	7	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	123	121	120	118	107	54	4	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	63	63	63	62	57	24	5	0

Progression-free survival

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median, mo (95% CI)	11.5 (8.9–20.0)	6.9 (5.1–10.2)	2.9 (2.8–3.1)
HR (95% CI) vs IPI	0.42 (0.35–0.51)	0.53 (0.44–0.64)	-
HR (95% CI) vs NIVO[a]	0.79 (0.65–0.97)	-	-



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81	84	87	90	93	96	99
NIVO+IPI	314	219	175	156	138	133	126	119	112	106	103	100	99	95	93	92	87	86	84	81	78	77	76	72	70	68	66	63	57	50	33	10	1	0
NIVO	316	177	151	132	120	112	106	103	97	89	84	80	78	76	73	71	69	67	66	65	62	58	57	56	54	53	50	49	44	37	21	5	0	0
IPI	315	135	78	58	46	42	34	32	31	29	28	26	21	19	18	18	16	15	15	15	12	11	11	10	10	9	9	9	9	9	7	3	1	0

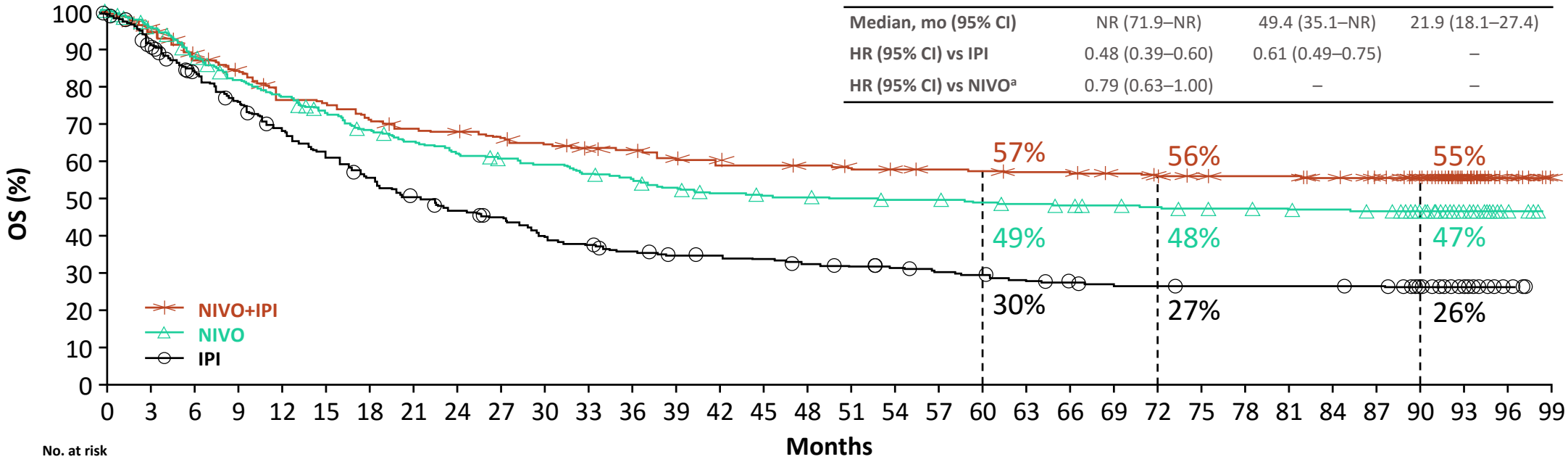
- Median duration of response was not reached, 90.8 months and 19.2 months in patients treated with NIVO + IPI, NIVO, and IPI, respectively

[a]Descriptive analysis.
Database lock: November 12, 2021; minimum follow-up of 90 months for all patients.
IPI, ipilimumab; NIVO, nivolumab; NR, not reached; OS, overall survival; PFS, progression-free survival.
Reproduced with permission from Hodi FS, et al. Poster at the American Society of Clinical Oncology (ASCO) Annual Meeting; June 3–7, 2022; Chicago, IL & Online. Abstract 9522.

Secondary endpoint: 90-month minimum follow-up
Melanoma-specific survival

Melanoma-specific survival excludes deaths unrelated to melanoma

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median, mo (95% CI)	NR (71.9–NR)	49.4 (35.1–NR)	21.9 (18.1–27.4)
HR (95% CI) vs IPI	0.48 (0.39–0.60)	0.61 (0.49–0.75)	–
HR (95% CI) vs NIVO[a]	0.79 (0.63–1.00)	–	–



No. at risk

NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	144	143	141	138	129	58	7	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	123	121	120	118	107	54	4	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	63	63	63	62	57	24	5	0

[a]Descriptive analysis.
Database lock: November 12, 2021; minimum follow-up of 90 months for all patients.
IPI, ipilimumab; NIVO, nivolumab; NR, not reached; OS, overall survival.
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60-month minimum follow-up
Treatment-related select AEs in ≥ 2% of patients in any arm

Patients Reporting Event, n (%)	NIVO + IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Skin and subcutaneous AEs	194 (62)	20 (6)	146 (47)	7 (2)	174 (56)	9 (3)
Pruritus	112 (36)	6 (2)	72 (23)	1 (< 1)	113 (36)	1 (< 1)
Rash	93 (30)	10 (3)	74 (24)	1 (< 1)	69 (22)	5 (2)
Maculopapular rash	38 (12)	6 (2)	16 (5)	2 (1)	38 (12)	1 (< 1)
Vitiligo	28 (9)	0	33 (11)	1 (< 1)	16 (5)	0
Eczema	9 (3)	0	6 (2)	0	2 (1)	0
Erythema	8 (3)	1 (< 1)	9 (3)	0	5 (2)	1 (< 1)
Generalized rash	8 (3)	1 (< 1)	3 (1)	1 (< 1)	2 (1)	1 (< 1)
Papular rash	7 (2)	0	4 (1)	1 (< 1)	4 (1)	0
Macular rash	7 (2)	0	2 (1)	0	1 (< 1)	1 (< 1)
Dermatitis	6 (2)	0	8 (3)	0	2 (1)	0
Skin hypopigmentation	6 (2)	0	7 (2)	0	2 (1)	0
Pruritic rash	5 (2)	0	1 (< 1)	0	7 (2)	0
Gastrointestinal AEs	150 (48)	48 (15)	73 (23)	11 (4)	118 (38)	36 (12)
Diarrhea	142 (45)	30 (10)	70 (22)	9 (3)	106 (34)	18 (6)
Colitis	41 (13)	26 (8)	8 (3)	3 (1)	35 (11)	24 (8)
Endocrine AEs	107 (34)	20 (6)	53 (17)	6 (2)	37 (12)	8 (3)
Hypothyroidism	54 (17)	1 (< 1)	32 (10)	0	14 (5)	0
Hyperthyroidism	35 (11)	3 (1)	14 (4)	0	3 (1)	0
Hypophysitis	25 (8)	5 (2)	2 (1)	1 (< 1)	12 (4)	5 (2)
Thyroiditis	13 (4)	1 (< 1)	3 (1)	0	1 (< 1)	0
Adrenal insufficiency	11 (4)	6 (2)	4 (1)	2 (1)	4 (1)	1 (< 1)

Minimum follow-up of 60 months.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IPI, ipilimumab; NIVO, nivolumab.
Larkin J et al. *N Engl J Med*. 2019;381:1535–1546 [supplementary appendix].

60-month minimum follow-up
Treatment-related select AEs in ≥ 2% of patients in any arm (cont'd)

Patients Reporting Event, n (%)	NIVO + IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Hepatic AEs	103 (33)	62 (20)	25 (8)	9 (3)	23 (7)	5 (2)
Increased AST	52 (17)	19 (6)	14 (4)	3 (1)	12 (4)	2 (1)
Increased ALT	61 (19)	27 (9)	13 (4)	4 (1)	12 (4)	5 (2)
Increased blood alkaline phosphatase	12 (4)	2 (1)	4 (1)	0	2 (1)	1 (< 1)
Increased transaminases	12 (4)	10 (3)	2 (1)	1 (< 1)	3 (1)	0
Increased gamma glutamyltransferase	11 (4)	4 (1)	1 (< 1)	0	6 (2)	1 (< 1)
Hepatotoxicity	10 (3)	8 (3)	1 (< 1)	1 (< 1)	1 (< 1)	0
Hyperbilirubinemia	7 (2)	0	1 (< 1)	0	3 (1)	0
Hepatitis	7 (2)	5 (2)	0	0	0	0
Hypersensitivity/infusion reactions	14 (4)	0	14 (4)	1 (< 1)	8 (3)	1 (<1)
Infusion-related reaction	10 (3)	0	8 (3)	1 (< 1)	8 (3)	1 (< 1)
Pulmonary AEs	25 (8)	3 (1)	6 (2)	1 (<1)	6 (2)	1 (< 1)
Pneumonitis	23 (7)	3 (1)	5 (2)	1 (< 1)	5 (2)	1 (< 1)
Renal AEs	22 (7)	6 (2)	6 (2)	2 (1)	8 (3)	1 (< 1)
Increased blood creatinine	14 (4)	1 (< 1)	3 (1)	1 (< 1)	5 (2)	0

Minimum follow-up of 60 months.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; **IPI, ipilimumab; NIVO, nivolumab**.
Larkin J et al. *N Engl J Med*. 2019;381:1535–1546 [supplementary appendix].

Toxicity of Targeted Therapies:

- Fatigue
- N/V/D Abd. Discomf.
- Pyrexia – worse with DAB + TRAM (57%)
- ENCO + BINI – (Pyrexia 18%)
- Rash/ skin issues/ hyperkeratosis/squamous cell cancer.
- Specific to ENCO/BINI - Visual Impairment to serious retinopathy (5%)
- ENCO – strong CYP 3A4 Inhib. Incr E level & inducer decreases E levels.
- ENCO – dose dependent QTc prolongation.

Toxicity of Immunotherapy:

- This presentation excludes all Endocrine side effects as it would be discussed in the next presentation.

Dermatological Toxicities:

- Onset 3-6 weeks up to 17 weeks
- Grades 1 to 4
- Gr 1 : < 10% of BSA – Topical Steroids/ supportive care/ Cont IO
- Gr 2 : 10-30% of BSA – Initial topical steroids. If > 1-2 wks, Dermatology ref. and p.o steroids. Hold IO when needing steroids.
- Gr. 3: > 30% BSA. Limiting ADLs/ local superinfection. Steroids p.o. +/- oral Abx. Hold IT. D/C if > 12 weeks.
- Gr 4: SJS/ full thickness rash/ ulcer. Adm. IV steroids. Methyl prednisolone 1-2 mg/kg/ day – Perm. Discontinue.

Diarrhea:

- Grade 1 : < 4 BMs/day – Loperamide/ hydration/ monitor
- Grade 2: 4-6 BMs /day – Hold IO –till Gr. 1. Steroids 05-1 mg/kg/day Pred. Supportive measures/ R/O infectious cause/ hydration/ correct electrolytes. Taper steroids after resolution.
- Grade 3: > 7 BMs/ day – Hosp. i.v. Methyl Pred – 1-2 mg/kg/day GI Consult. If no response in 3 days → Infliximab 5m/kg/iv q 2 weeks. D/C IO
- Grade 4: Gr. 3 + Fever/ peritoneal signs/ perf./ ileus →Surg. Consult. D/C IO

Hepatitis:

Inc: 1-9%; Onset 8-12 weeks

- Grade 1: AST/ALT upto 3X ULN. Bili < 1.5 ULN. Close monitoring.
- Grade 2: AST?ALT > 3-5 ULN. Bili 1.5-3 ULN. Hep. Serology. HOLD. If no improvement in 3 days – Pred 0.5 mg/kg.
- Grade 3: AST/ALT > 5-20 ULN. Bili 3-10 ULN – i.v. steroids – if no improvement in 3 days Mycofenolate or another immunosuppr. Consult expert – D/C – IO
- Grade 4: AST/ALT > 20 ULN; Bili > 10XULN. Bili > 10 – Treat as above. Discontinue IO. Consult Expert.

Neurotoxicity:

< 5% . 1-6 weeks

- Grade 1: Asymptomatic/ mildly symptomatic.
- Grade 2: Mod symptoms. Limiting ADLs. Neuro consult to rule out another cause. Steroids X 4 weeks them taper. HOLD IO
- Grade 3: Severe symptoms/ vision changes/ weakness. Prednisone . Steroids if no response – Infliximab 5mg/ kg.or Mycopheno permanantly D/C as
- Grade 4: More severe : IVIG, plasmapheresis.

Pneumonitis:

< 5%; Gr 3-4 Gr 3-4: < 1%

- Grade 1: Asymptomatic. Diag on Imaging – Monitor
- Grade 2: Symptoms limiting ADLs. R/O infection. P.o. Steroids. HOLD IO. If no improvement in3 days – treat as Gr 3 or 4. Admit for empiric antibiotics.
- Grade 3: Severe. Oxygen needed. Admit to Hosp. Pulm/ ID ref – R/O infection – iv steroids Methyl pred 2-4 mg/kg .
- Grade 4: 48 hrs no impr -- > Infliximab/ Asses need for ventilatory support.

- Grade 3 & 4 : Permanently discontinue IO

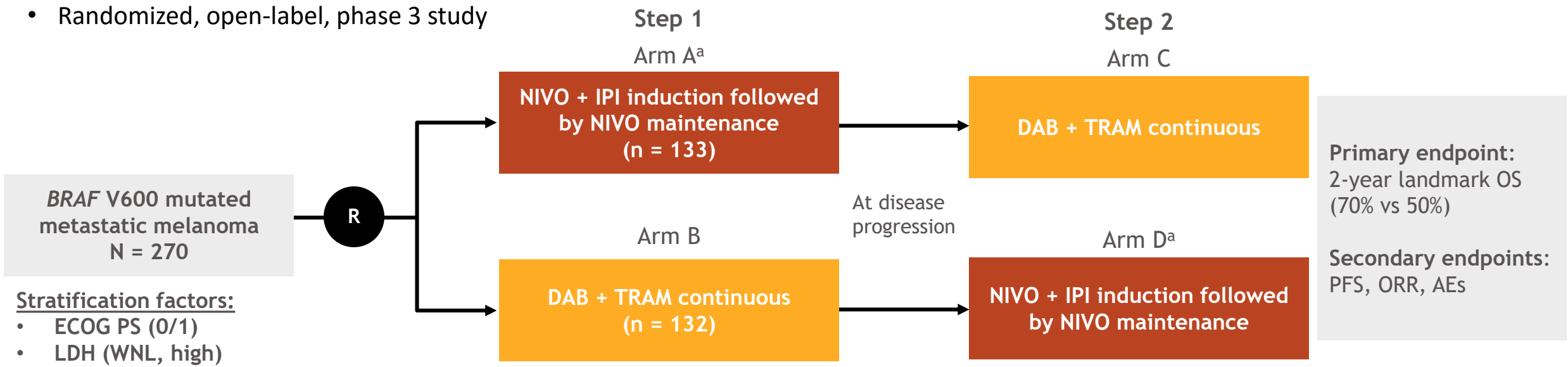
Renal Toxicity:

incidence < 5%; Med. Onset - 6-10 wks.

- Grade 1: > 1.5-2 X ULN -- > hydration/ stop nephrotox. Drugs. Monitor & cont.
- Grade 2: > 2-3 X ULN; Proteinuria 2+ → HOLD IO till < Gr 1. U/S to R/O hydro. Prednisone X 4 weeks.
- Grade 3: > 3X Baseline. Proteinuria > 3.5 g/24 hrs. D/C IO. Prednisone→ Mycofenolate – Permanently D/C.
- Grade 4: > 6 X Baseline – Assess for Dialysis.

DREAMseq trial treatment schema[1,2]

- Randomized, open-label, phase 3 study

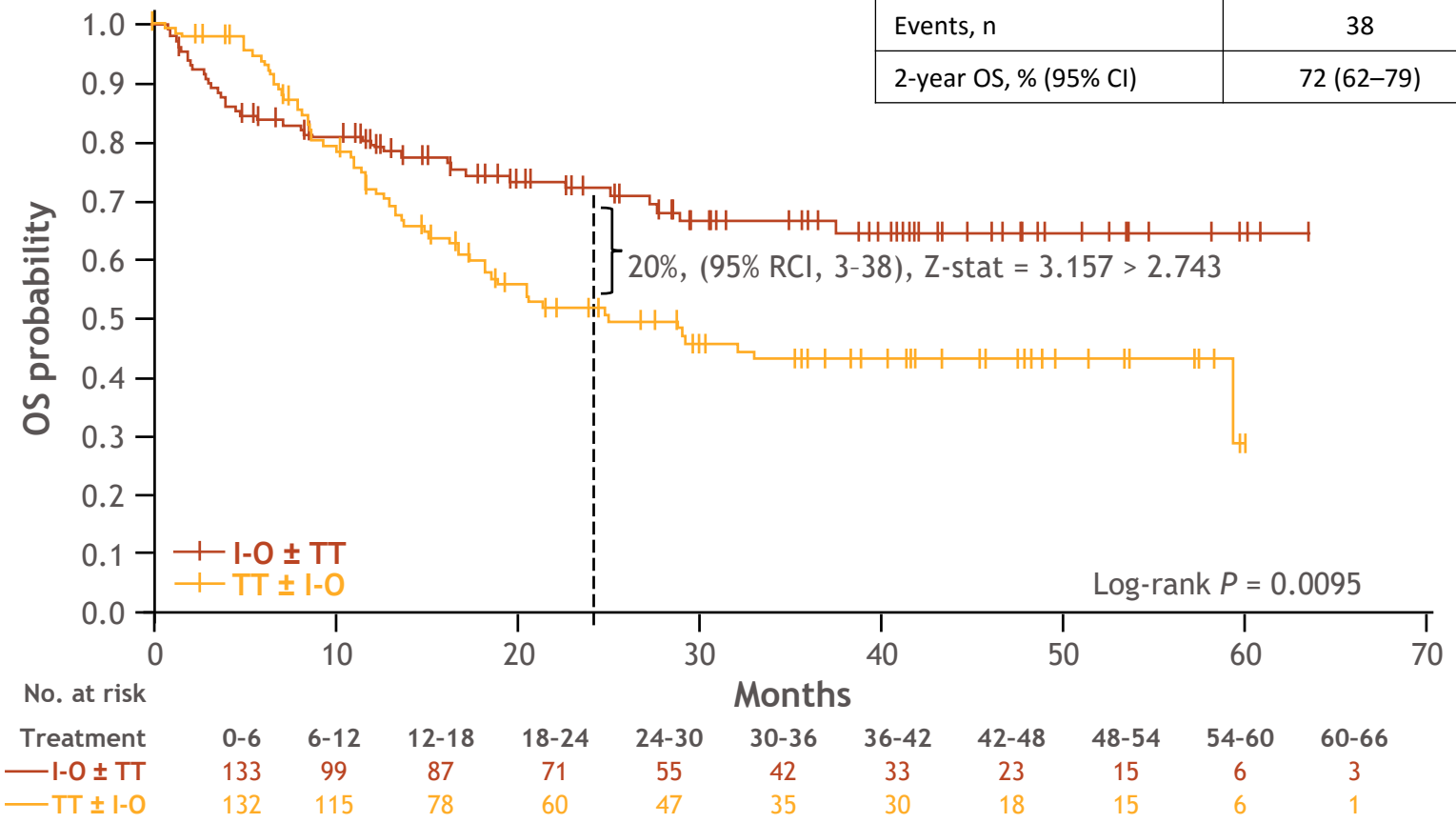


- At the 4th planned interim analysis, with only 59% of the data, the protocol specified endpoint had not been met
- While clinically meaningful, the study did not meet the primary endpoint of demonstrating a statistical significance in OS with 2 years of minimum follow-up
- The ECOG-ACRIN DSMC stopped the study early based on an observed clinically meaningful benefit with NIVO + IPI versus DAB + TRAM
- The OS data presented at the ASCO Plenary Series are descriptive and from a non-prespecified analysis of the ITT population

[a]NIVO + IPI induction = 12 weeks; NIVO maintenance = 72 weeks.
ACRIN, American College of Radiological Imaging Network; ASCO, American Society of Clinical Oncology; DAB, dabrafenib; DSMC, Data and Safety Monitoring Committee; ECOG, Eastern Cooperative Oncology Group; IPI, ipilimumab; LDH, lactate dehydrogenase; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status;
R, randomization; TRAM, trametinib; WNL, within normal limit. 1. Adapted with permission from Atkins M, et al. Presented at the American Society of Clinical Oncology (ASCO) Monthly Plenary Series; November 16, 2021; virtual. Abstract 356154. 2. ClinicalTrials.gov. NCT02224781. https://www.clinicaltrials.gov/ct2/show/NCT02224781. Accessed December 3, 2021.

Overall survival: step 1 ± step 2

	I-O ± TT (n = 133)	TT ± I-O (n = 132)
Events, n	38	62
2-year OS, % (95% CI)	72 (62–79)	52 (42–60)



Data cutoff: July 16, 2021; Median follow-up 27.7 months.
CI, confidence interval; I-O, immuno-oncology; OS, overall survival; RCI, reliable change index; TT, targeted therapy.
Adapted with permission from Atkins M, et al. **Presented at the American Society of Clinical Oncology (ASCO) Monthly Plenary Series; November 16, 2021; virtual. Abstract** 356154.

Thank you for your attention!