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Immunologic Therapy for Melanoma

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Disclosures

- Consultant: Novartis, BMS, Regeneron
- Research Support: Exelixis
- Clinical Trial Steering Committee: Genentech

Outline

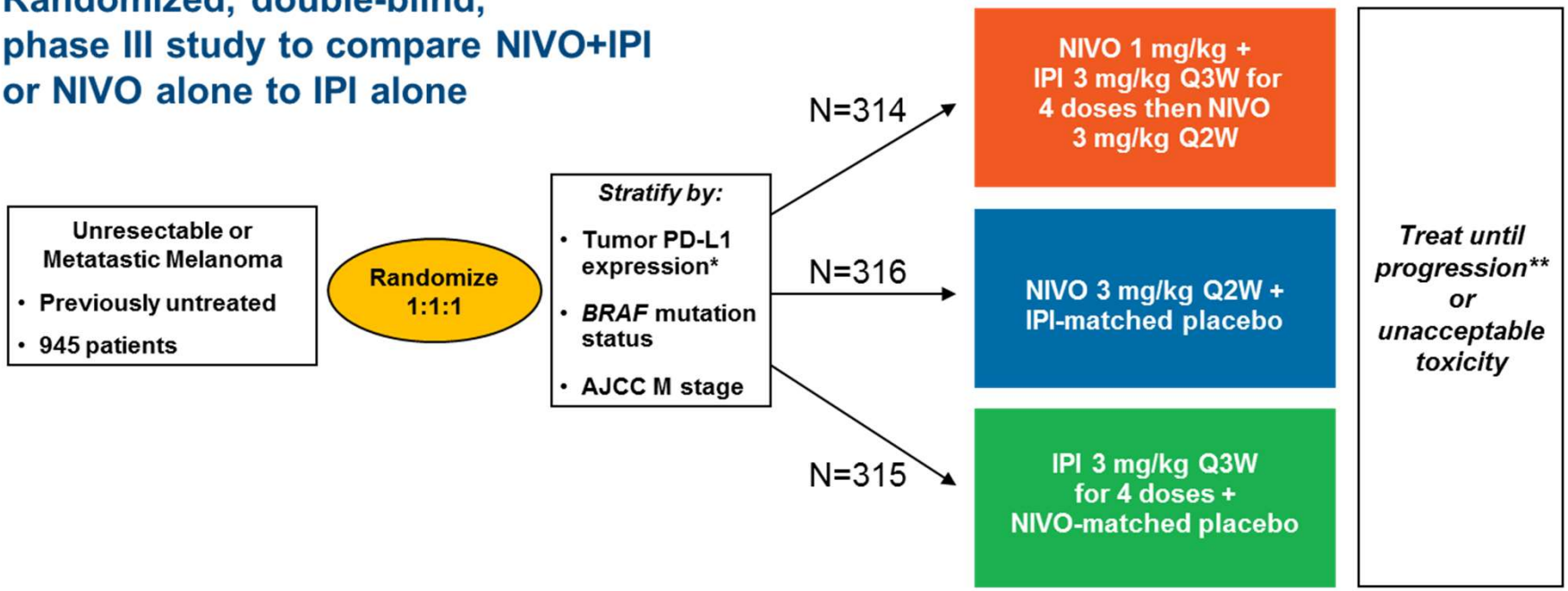
- Frontline immunotherapy in advanced melanoma – current options and emerging strategies.
- Adjuvant immunotherapies for resected high risk melanoma.
- Novel second line immunotherapy regimens in advanced melanoma.

Summary of Current Frontline Options

	ORR	4yr PFS	5yr PFS	4yr OS	5yr OS	Subsequent treatment	Reference
Nivo/Ipi	58%	37%	36%	53%	52%	46%	Larkin J, N Engl J Med, 2019
Nivo	45%	31%	29%	46%	44%	59%	Larkin J, N Engl J Med, 2019
Pembro	*46%*	*27%*	--	*46%*	*43%*	--	Robert C, Lancet Oncol, 2019
TVEC*	*16%*	--	--	*33%*	--	--	Andtbacka, RHI, J Clin Oncol, 2015
Dab/Tram	68%	21%	19%	37%	34%	53%	Nathan P, ASCO, 2019
Vem/Cobi	70%	--	--	34%	31%		MacArthur GA, SMR, 2019
Enco/Bini	62%	--	--	--	--	53%	Ascierto PA, Eur J Cancer, 2020

*Study included 30% stage III patients, objective response rate = DRR

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone



*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.

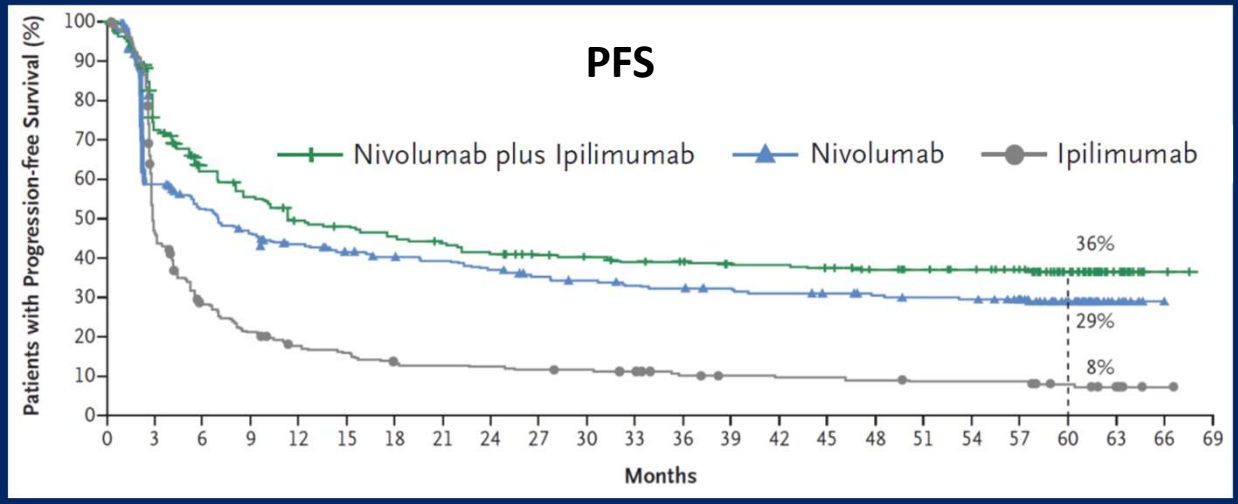
Wolchok J, ASCO, 2016

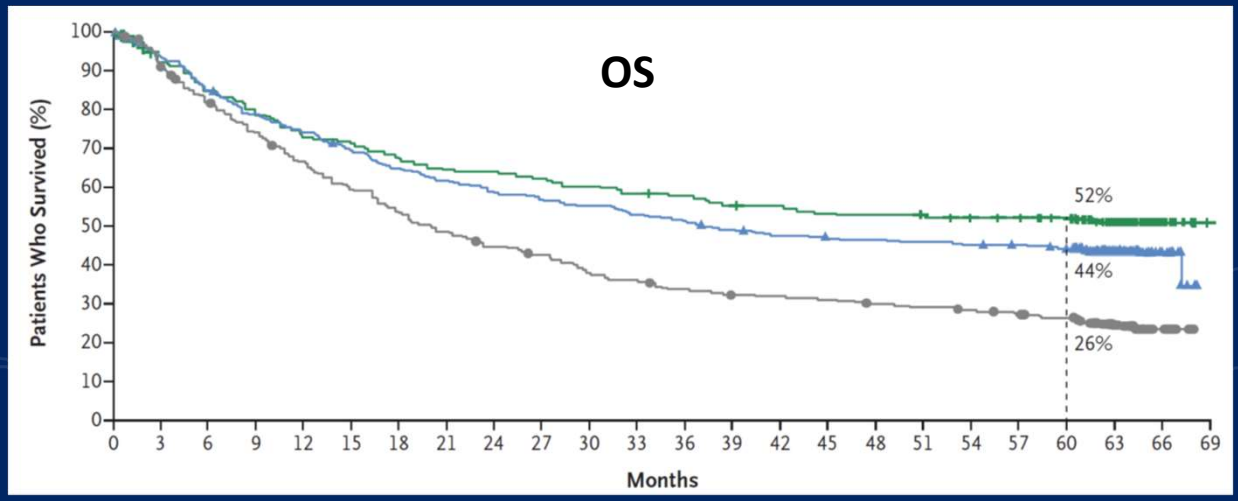
Checkmate 069: Phase III study of Nivo/Ipi, Nivo, and Ipi advanced melanoma

5 Year Follow Up

Nivo/Ipi vs Nivo

- PFS HR = 0.79
  (95% CI 0.64 to 0.96)
- OS HR = 0.83
  (95% CI, 0.67 to 1.03)
- Treatment-related Grade 3-4 AEs
  - 59% for Nivo/Ipi
  - 23% for Nivo





Larkin J, N Engl J Med, 2019

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Checkmate 069: Phase III study of Nivo/Ipi, Nivo, and Ipi advanced melanoma

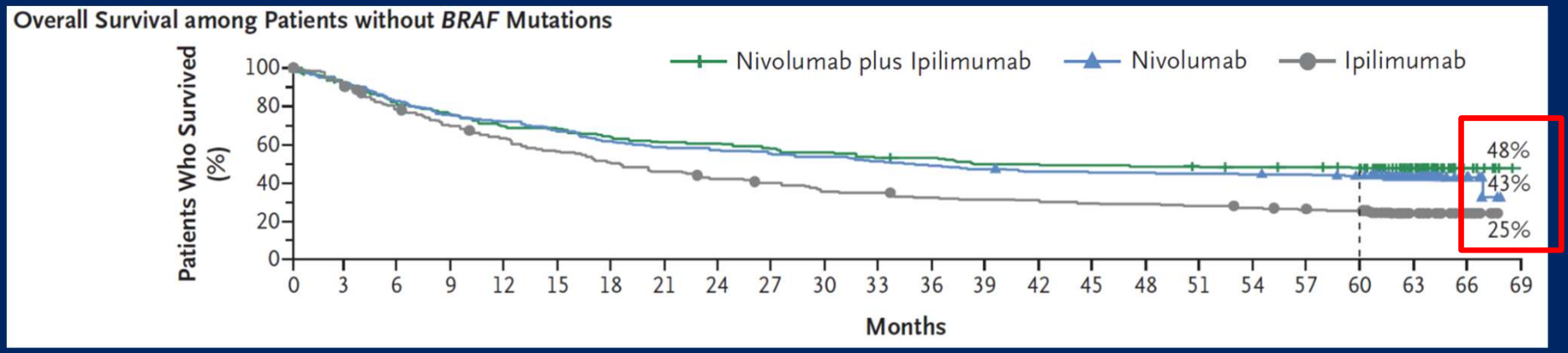
(F) Nivolumab Plus Ipilimumab Versus Nivolumab (Overall Survival).

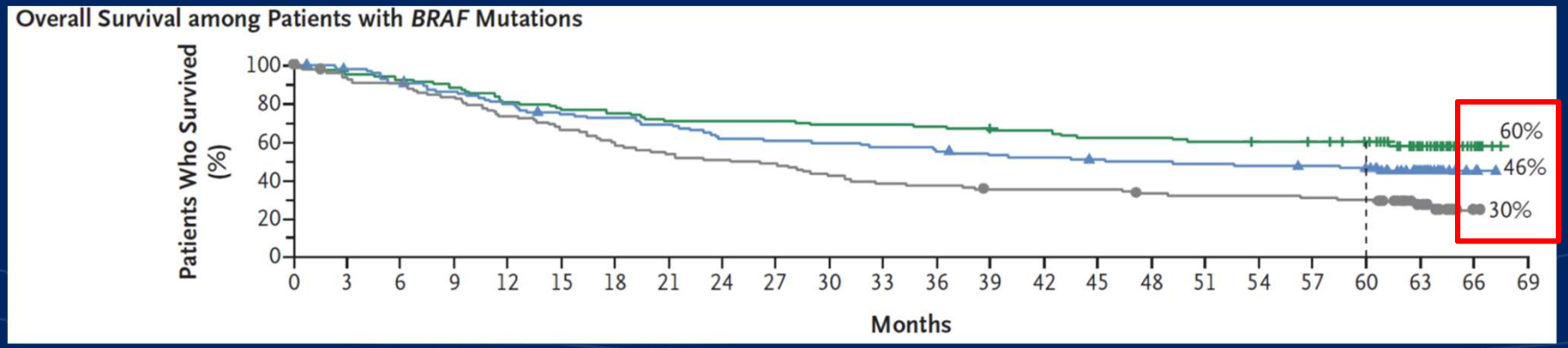
	No. of patients		5-Year OS Rate, % (95% CI)		Unstratified Hazard Ratio (95% CI)
	NIVO + IPI	NIVO	NIVO + IPI	NIVO	OS
Overall	314	316	52 (46, 57)	44 (39, 50)	0.83 (0.66, 1.03)
Age <65 years	185	198	54 (47, 61)	45 (38, 52)	0.80 (0.60, 1.06)
Age ≥65 years	129	118	48 (39, 57)	43 (34, 52)	0.86 (0.62, 1.20)
United States	64	68	62 (49, 73)	46 (34, 58)	0.60 (0.36, 1.01)
Europe	177	170	48 (40, 55)	41 (34, 49)	0.87 (0.65, 1.15)
BRAF mutant	103	98	60 (50, 69)	46 (36, 56)	0.70 (0.46, 1.05)
BRAF wild-type	211	218	48 (41, 54)	43 (37, 50)	0.89 (0.69, 1.15)
ECOG PS 0	230	237	57 (51, 63)	49 (42, 55)	0.82 (0.63, 1.06)
ECOG PS ≥1	83	79	36 (26, 47)	30 (20, 40)	0.81 (0.55, 1.18)
M0/M1a/M1b	129	132	64 (55, 72)	58 (49, 66)	0.82 (0.56, 1.21)
M1c	185	184	43 (35, 50)	35 (28, 41)	0.82 (0.63, 1.07)
LDH ≤ULN	199	197	60 (52, 66)	53 (46, 60)	0.83 (0.62, 1.12)
LDH >ULN	114	112	38 (29, 47)	28 (20, 36)	0.82 (0.59, 1.13)
LDH >2× ULN	37	37	28 (15, 43)	14 (5, 28)	0.73 (0.43, 1.24)
PD-L1 <1%	123	117	50 (41, 59)	36 (28, 45)	0.69 (0.50, 0.97)
PD-L1 ≥1%	155	171	54 (46, 61)	52 (44, 59)	0.97 (0.70, 1.32)
PD-L1 <5%	210	208	51 (44, 57)	43 (36, 50)	0.81 (0.62, 1.06)
PD-L1 ≥5%	68	80	57 (44, 68)	51 (40, 62)	0.91 (0.57, 1.46)
PD-L1 <10%	232	229	51 (44, 57)	45 (38, 51)	0.86 (0.66, 1.11)
PD-L1 ≥10%	46	59	59 (43, 71)	47 (34, 59)	0.76 (0.43, 1.32)
Tumor burden ≤31 mm	78	85	65 (54, 75)	63 (52, 72)	0.99 (0.60, 1.64)
Tumor burden >31 and ≤97 mm	154	150	53 (45, 60)	39 (31, 47)	0.69 (0.50, 0.94)
Tumor burden >97 mm	82	80	36 (25, 46)	33 (23, 44)	0.94 (0.64, 1.38)
Lesion sites: 1	89	80	64 (53, 73)	61 (49, 70)	0.92 (0.57, 1.50)
Lesion sites: 2 or 3	165	176	49 (41, 57)	40 (33, 48)	0.78 (0.58, 1.03)
Lesion sites: >3	60	59	40 (27, 52)	33 (21, 45)	0.97 (0.61, 1.53)

Larkin J, N Engl J Med, 2019

Checkmate 069: Phase III study of Nivo/Ipi, Nivo, and Ipi advanced melanoma

5 Year Follow Up – Survival by BRAF status





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Larkin J, N Engl J Med, 2019

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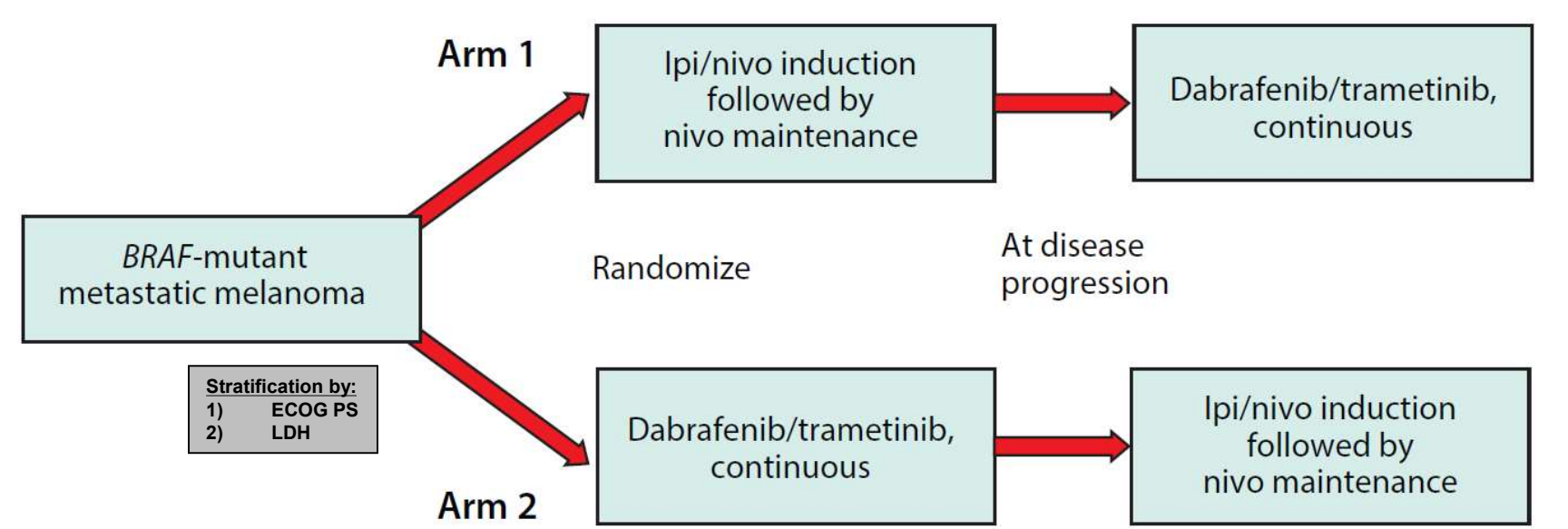
DREAM-Seq (EA6134) Trial



- Total Accrual Goal = 300 subjects
- Primary Endpoint = 2 year overall survival rate (70% vs 50%)
- Baseline tumors (pretreatment) and blood available for biomarker studies

Study Chair:
Michael B. Atkins, MD

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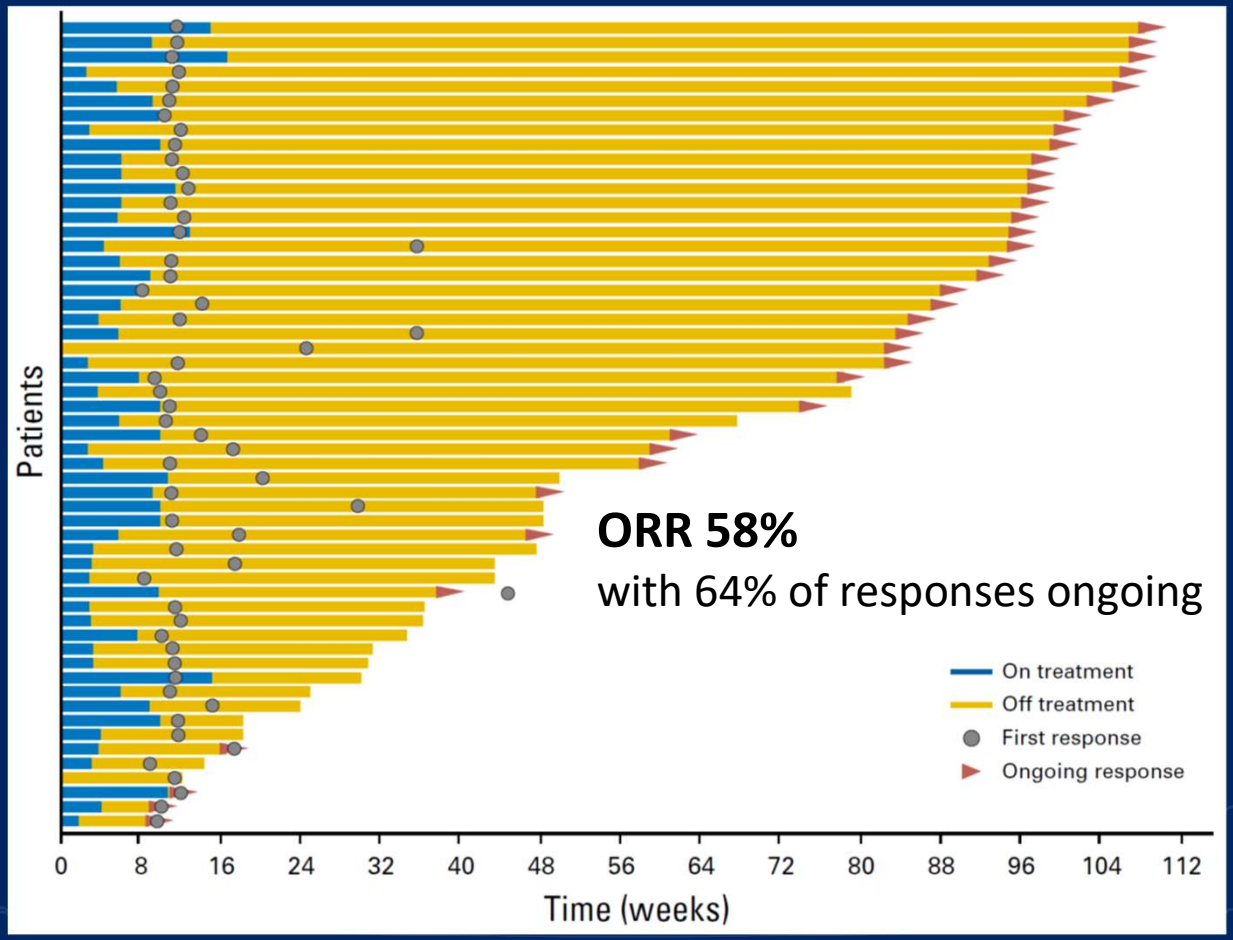
Off Treatment Survival
Nivo/Ipi Data from CM 067/06

38% of patients discontinued treatment due to AE

Efficacy of Nivo/Ipi is not diminished who come off early for toxicity.

OS rate 67% at 18 months (vs 62% for no AE discontinuation)



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Schadendorf D, J Clin Oncol 2017

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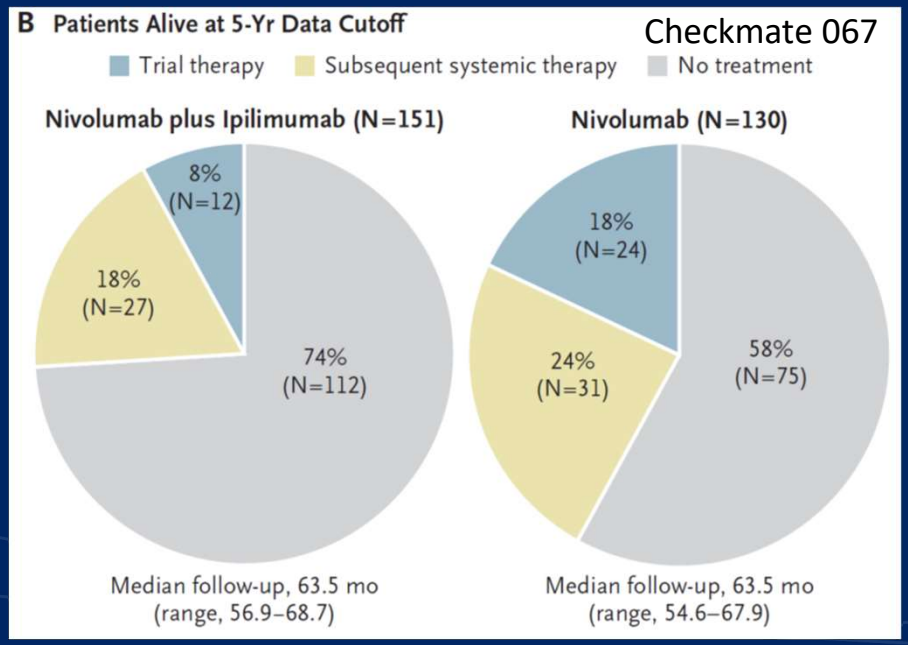
Off Treatment Survival (OTS)

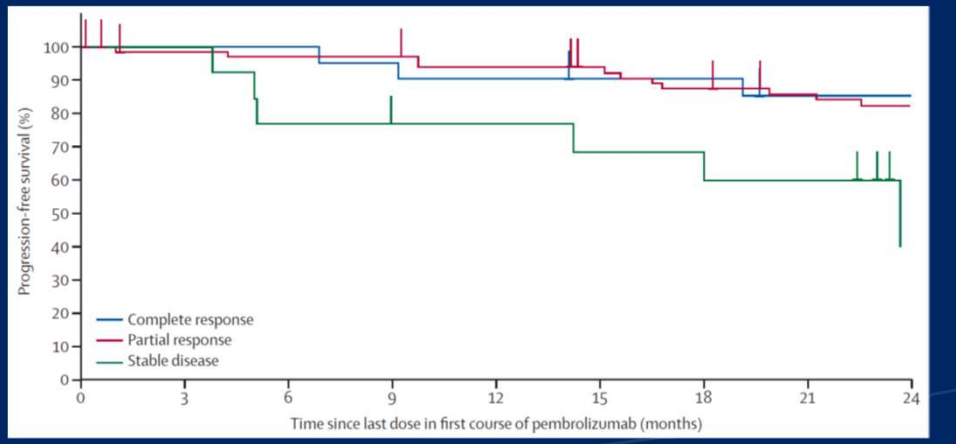
CM 067 - 5 year follow up

More patients in OTS with Nivo/Ipi



Keynote 006: D/C Pembro after 2 yrs

Stopping pembro after 2 years appears to be safe in patients with PR or CR.



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Larkin J, N Engl J Med, 2019
Robert C, Lancet Oncol, 2019

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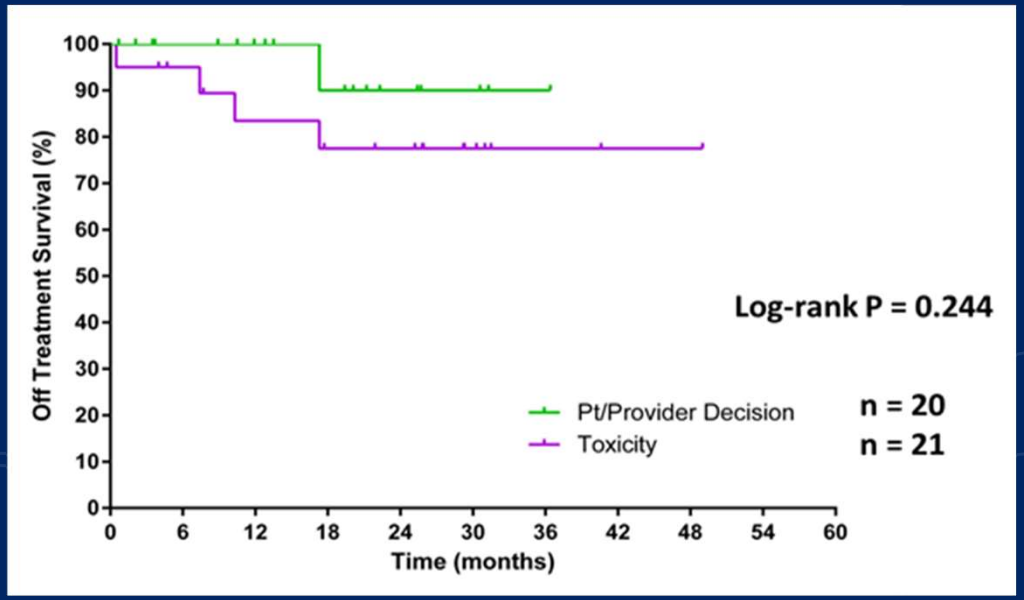
Off Treatment Survival with anti-PD-1 monotherapy vs combinations therapy

- Retrospective study at Georgetown
- Patients came of treatment by decision after CR on CT scan, PET/CT neg, or PET/CT + and biopsy negative.

Reason for DC	Mono (n=42)	mDOT	Combo (n=48)	mDOT
PD/Death	26 (62%)	2.3mos	19 (40%)	2.4mos
Toxicity	4 (12%)	2.3mos	20 (42%)	2.1mos
Pt/provider decision	11 (26%)	11.9mos	9 (19%)	11.7mos



Christiansen SA, ASCO, 2018

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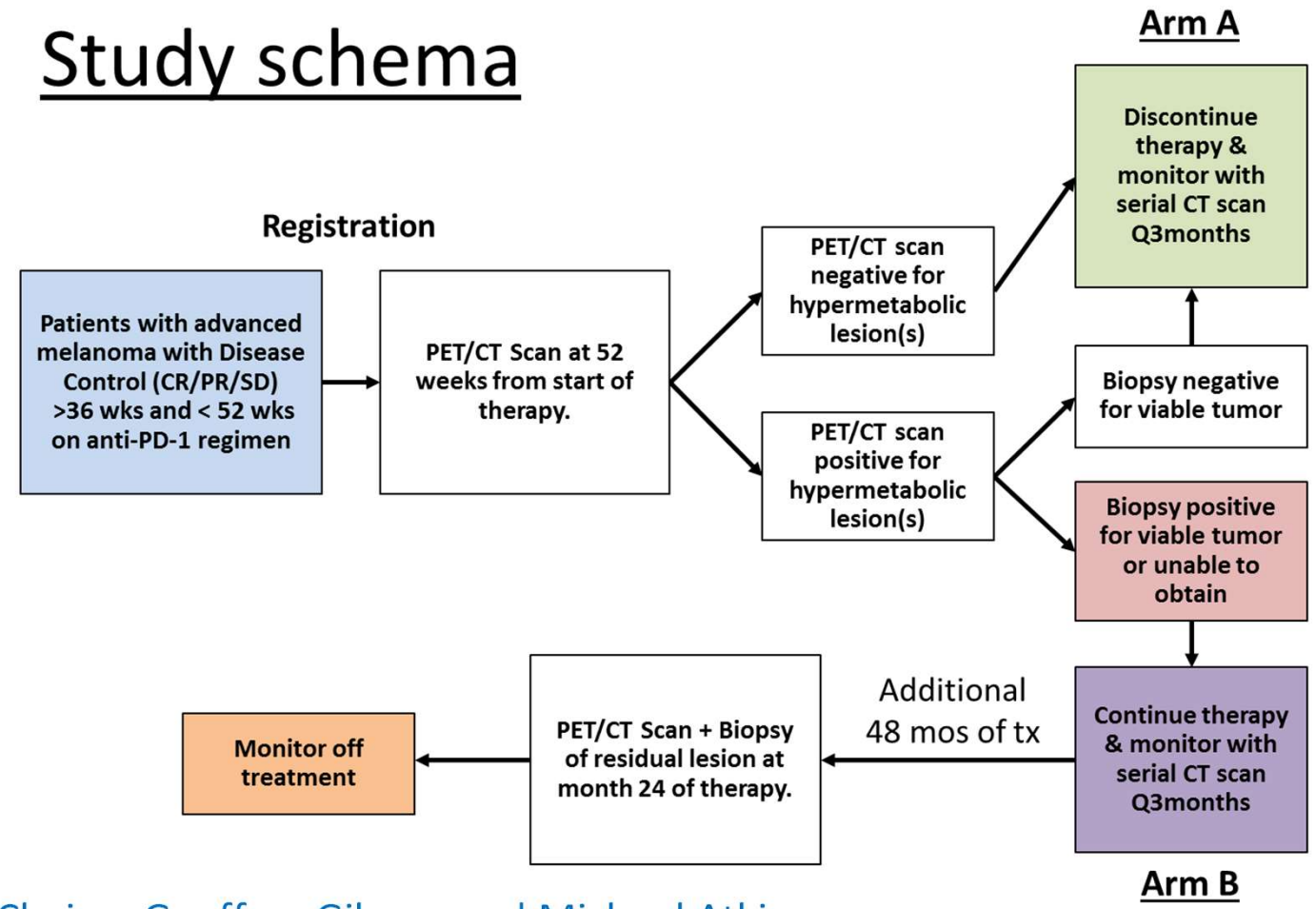
EA6192 protocol under development



Study Chairs: Geoffrey Gibney and Michael Atkins

Primary Endpoint = Event Free Survival at 12 months off treatment in Arm A

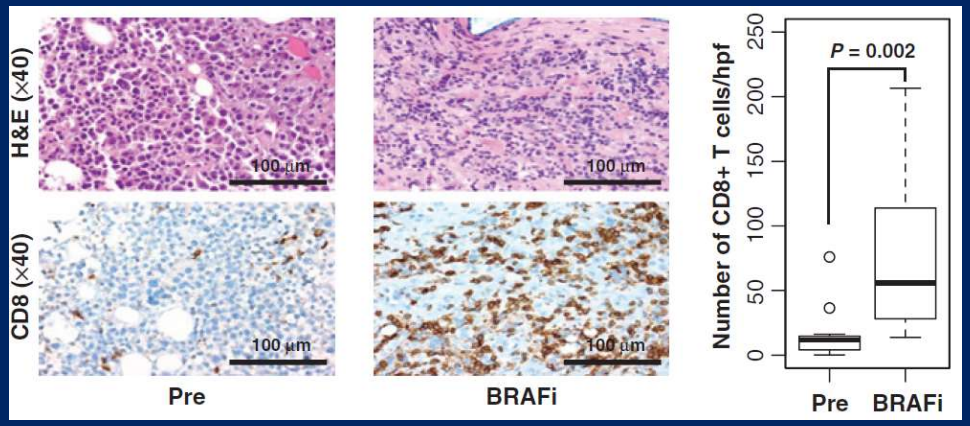
Secondary Endpoints = EFS Arm B, Pathologic negative rate, OS, AE rates

Frontline Melanoma Immunotherapy Strategies in Development

- IMspire150 (Trilogy): Vemurafenib/Cobimetinib + Atezolizumab*
- COMBI-i: Dabrafenib/Trametinib + Spartalizumab*
- CA045-001: Nivolumab + NKTR 214 (IL-2 agonist)
- CA224-041: Nivolumab + Relatlimab (anti-LAG3)
- Pembrolizumab + Personalized Cancer Vaccine
- Masterkey 265: Pembrolizumab + TVEC
- EA6141: Nivolumab/Ipilimumab + GM-CSF

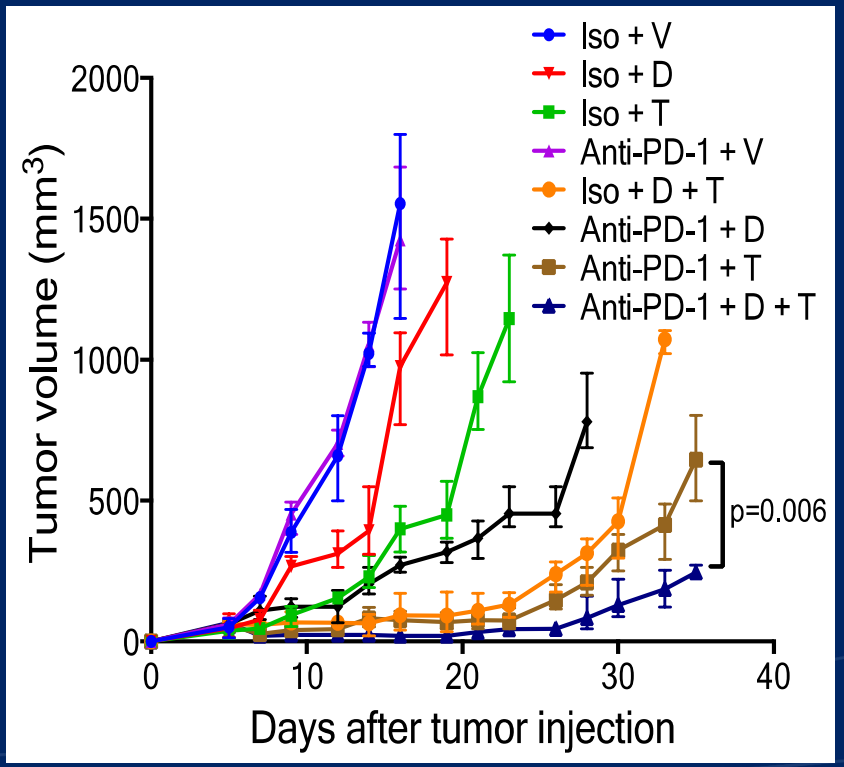
*Patients with advanced BRAF V600 mutant melanoma only

Preclinical data for Anti-PD-1/L1 plus BRAFi/MEKi



- Increase in intratumoral CD8+ T-cell density (and melanoma Ag expression) after BRAFi

Tumor control superior with triple combo



Frederick DT, et al. Clin Cancer *Res.* 2013; Hu-Lieskvoan S, et al. *Sci Transl Med.* 2015.

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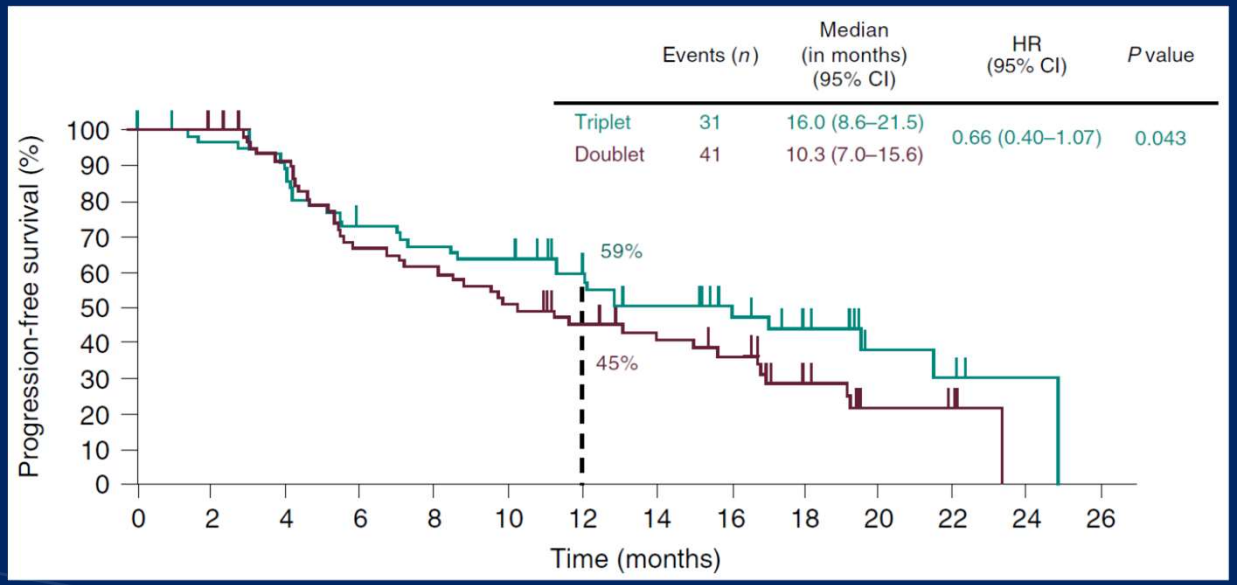
Keynote 022 Randomized Phase 2

Ascierto PA, Nat Med, 2019

- Dabrafenib/trametinib +/- pembrolizumab randomized 1:1
- Total of 120 patients with BRAF V600 mut melanoma enrolled
- ORR 63% for D/T and 72% for D/T/P*



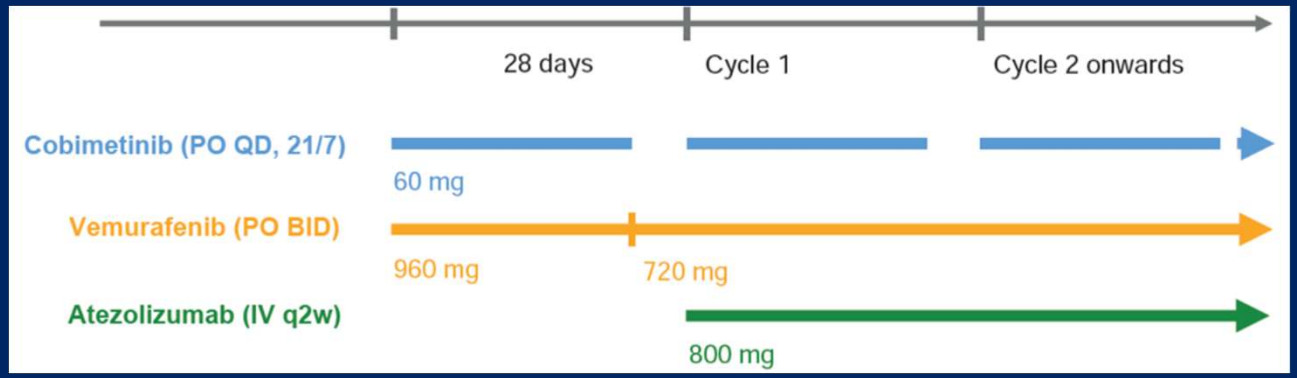
	PFS at 24 mos	DOR at 24 mos
D/T/P	41%	55%
D/T	16%	16%

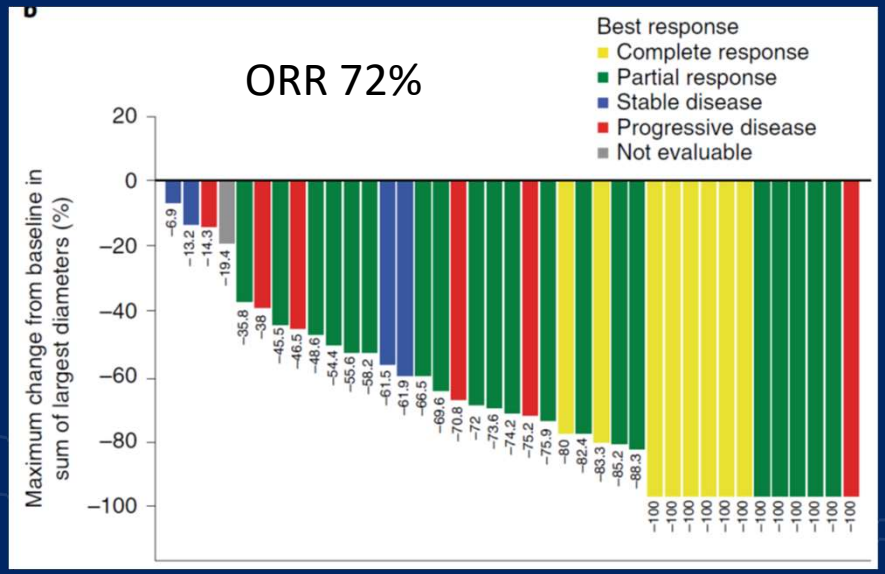
SMR 2019 *(Ferrucci PF, et al.)*

- TRAE gr3-5 AE rate 58% (D/T/P) vs 27% (D/T)
  - ➢ most often fever, increased AST/ALT and rash.

Phase Ib Vemurafenib/Cobimetinib plus Atezolizumab

Dosing schema



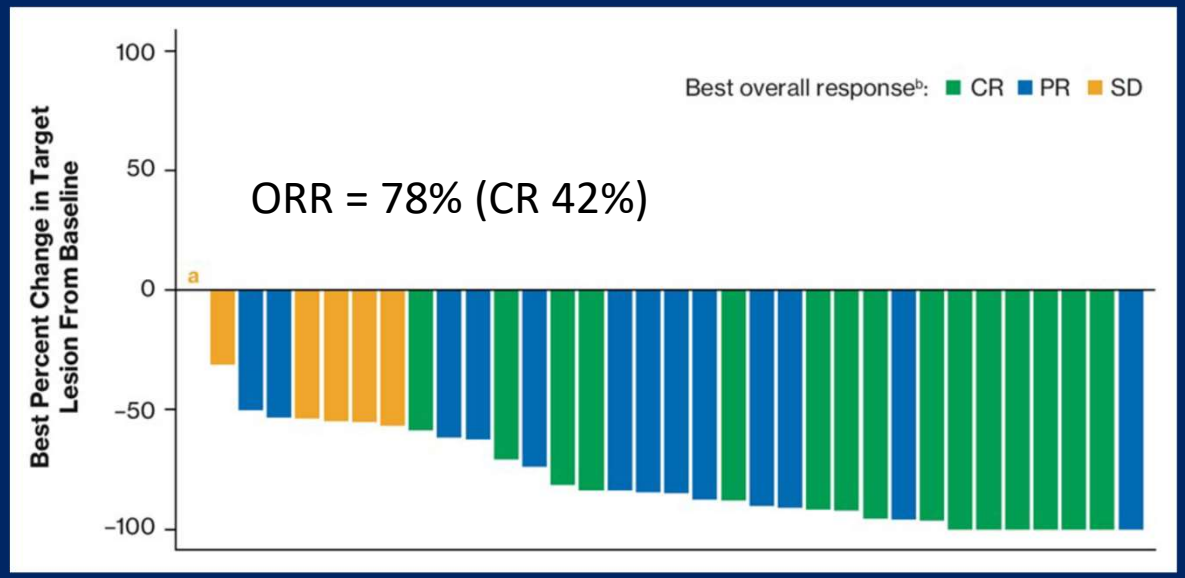


- mPFS = 12.9 months
- mOS = not reached
- Grade 3-4 AEs 26/39 (67%)
  - ➢ Hypophosphatemia and elevated LFTs most frequent gr3-4 AEs

Sullivan RJ, et al, Nat Med, 2019

COMBI-i (parts 1&2 data)

- N= 36
- Dabrafenib/trametinib plus spartalizumab

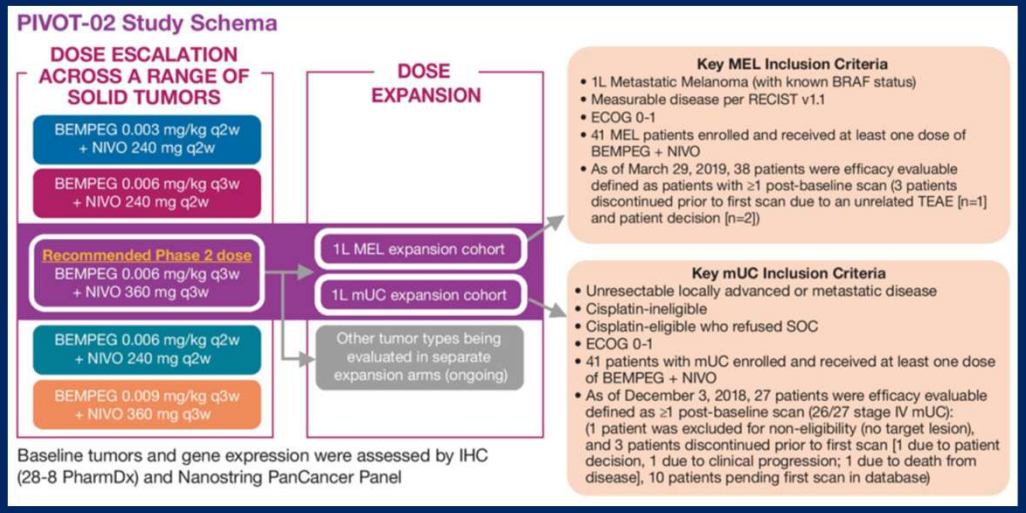


AE related	
Drug interruption	100%
Any drug discontinuation	47%
All drug discontinuation	17%

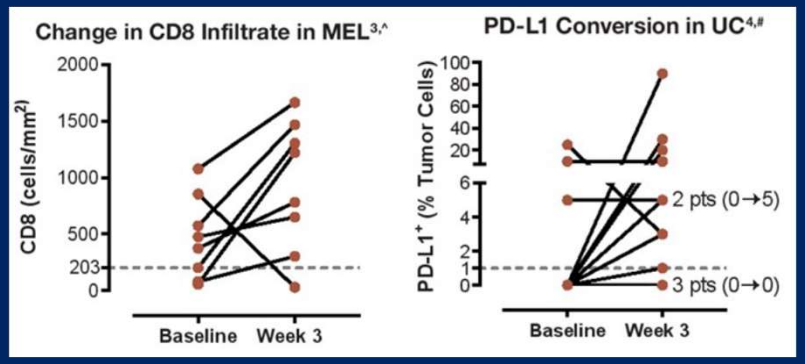
- 12 month PFS and DOR rates = 67% and 80%
- Treatment related gr3-4 AE rate = 72%, most often pyrexia; also arthralgias and elevated CPK, AST, ALT, Lipase and amylase.

Long GV, ASCO, 2019

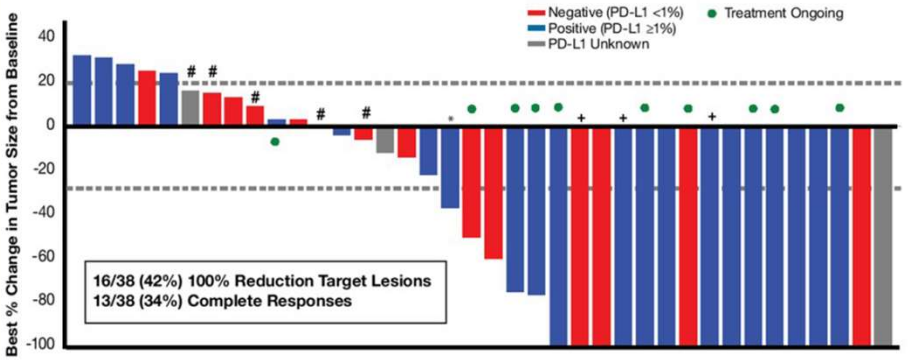
NKTR 214 + Nivolumab



Early increased CD8 T-cell and PD-L1 expression seen on study.



Stage IV 1L Melanoma Cohort at RP2D: Best Overall Response by Independent Radiology



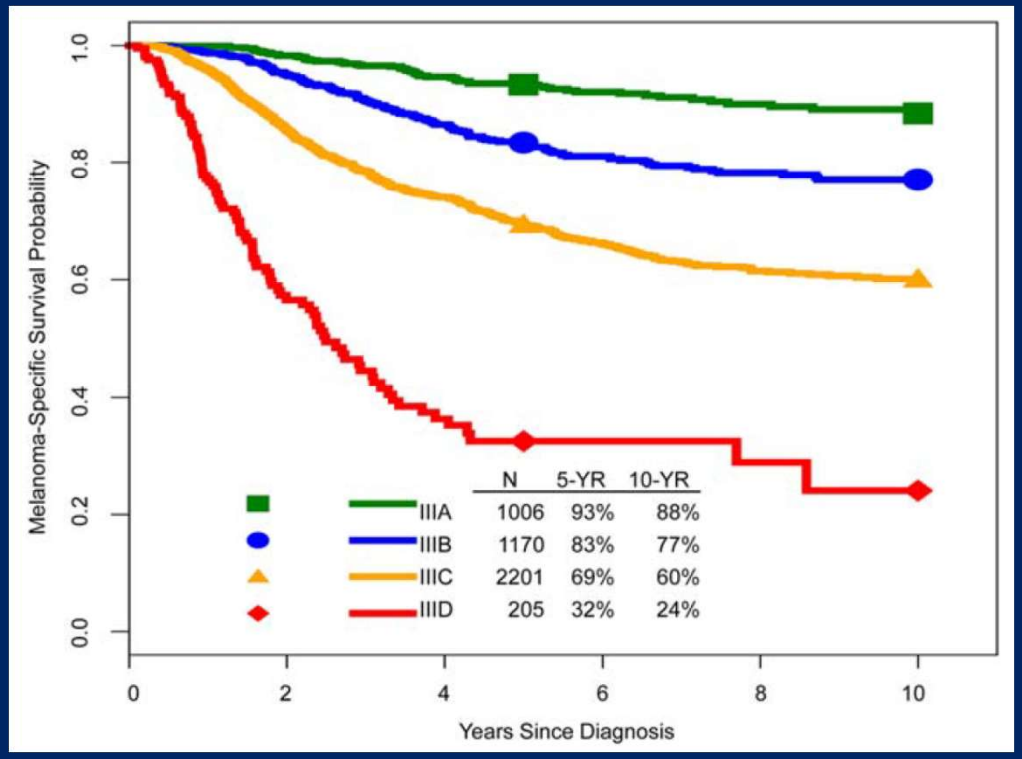
1L Melanoma (n=38 Efficacy Evaluable**)	Overall Response Rate
Confirmed ORR (CR+PR)	20 (53%)
CR	13 (34%)
DCR (CR+PR+SD)	28 (74%)
PD-L1 negative (n=14)	6 (43%)
PD-L1 positive (n=21)	13 (62%)
PD-L1 unknown (n=3)	1 (33%)
LDH > ULN (n=11)	5 (45%)
Liver metastases (n=10)	5 (50%)

#Best overall response is PD due to non-target lesion progression or presence of new lesion. *Best overall response is SD. +Best overall response is PR. CR for target lesion(s). Non-target lesion(s) still present.
**Efficacy evaluable population includes patients who have measurable disease (per RECIST 1.1) at baseline and also have at least one post-baseline tumor assessment.
ITT = 41: 3 patients are excluded because they are not response evaluable:1 patient discontinued treatment after 1 dose due to unrelated adverse event (MI); 1 patient discontinued treatment after 1 dose due to patient decision; 1 patient discontinued treatment after 3 doses due to patient decision.

- 80% with ongoing responses at median 13mos follow up
- Grade 3-4 TRAE = 15%
- Gr1-2 flu-like sxs 81%
- Gr1-2 rash 71%

Hurwitz M, ASCO, 2019

Adjuvant Systemic therapy for resected high risk stage III melanoma



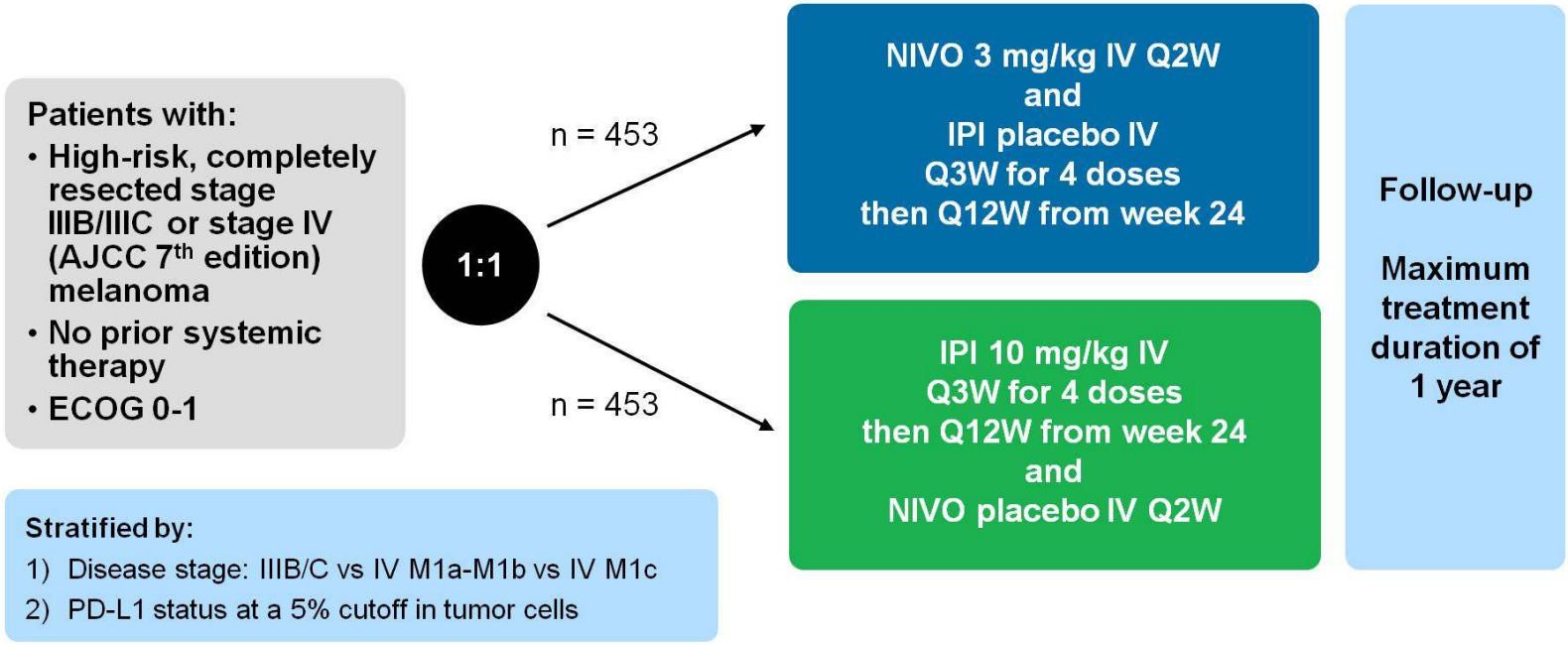
- Approved options of IFN and Ipilimumab not routinely used.
- Current standards are anti-PD-1 monotherapy (Nivolumab or Pembrolizumab) and dabrafenib/trametinib*

*BRAF V600 mutant melanoma only

Gershanwald J, CA J Clin, 2017

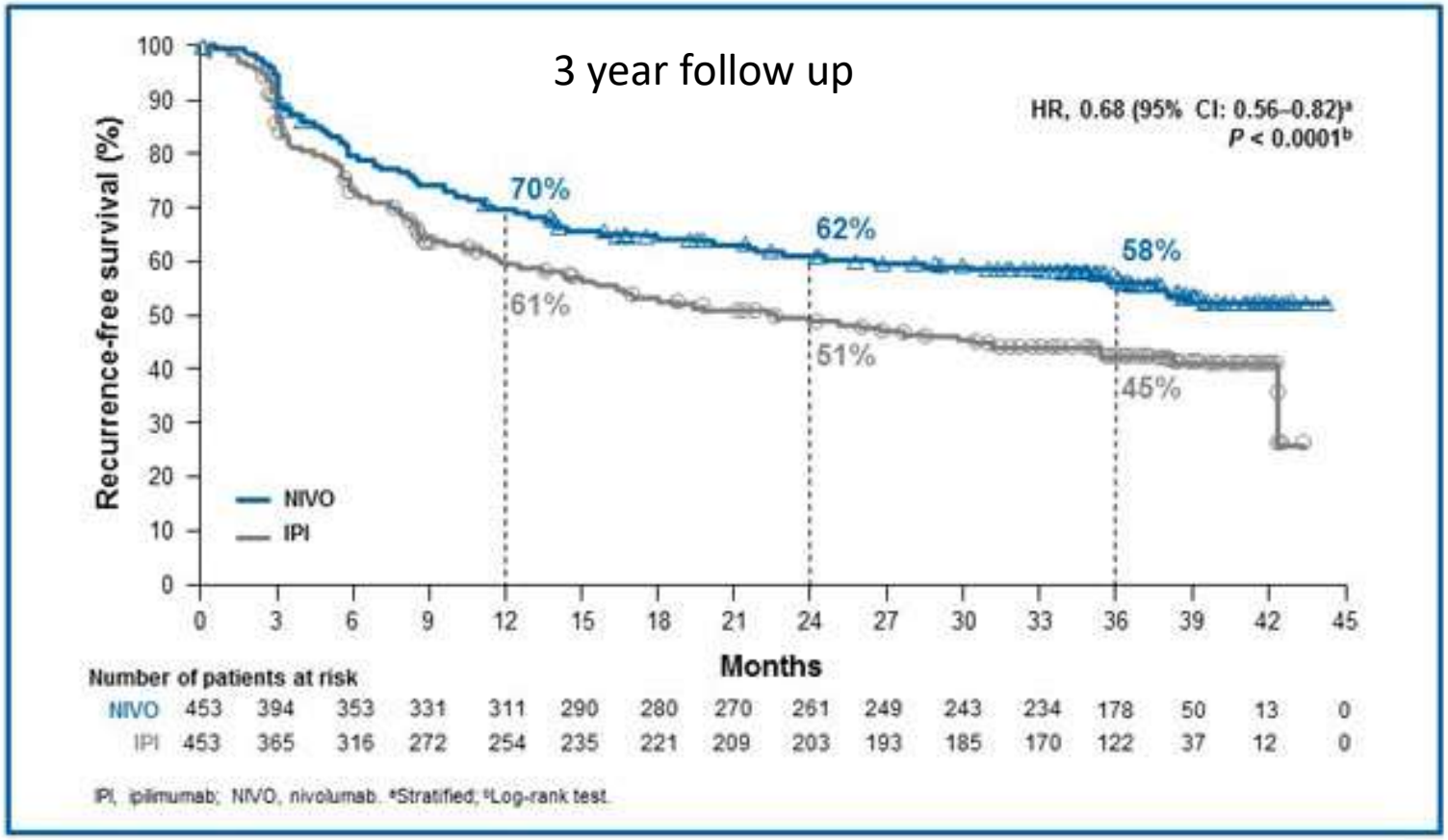
Phase III study of adjuvant Nivo vs Ipi in resected stage IIIB-IV melanoma

CheckMate 238: Study Design



Enrollment period: March 30, 2015 to November 30, 2015

Checkmate 238: Phase III adjuvant Nivo vs Ipi in resected stage IIIB-IV melanoma

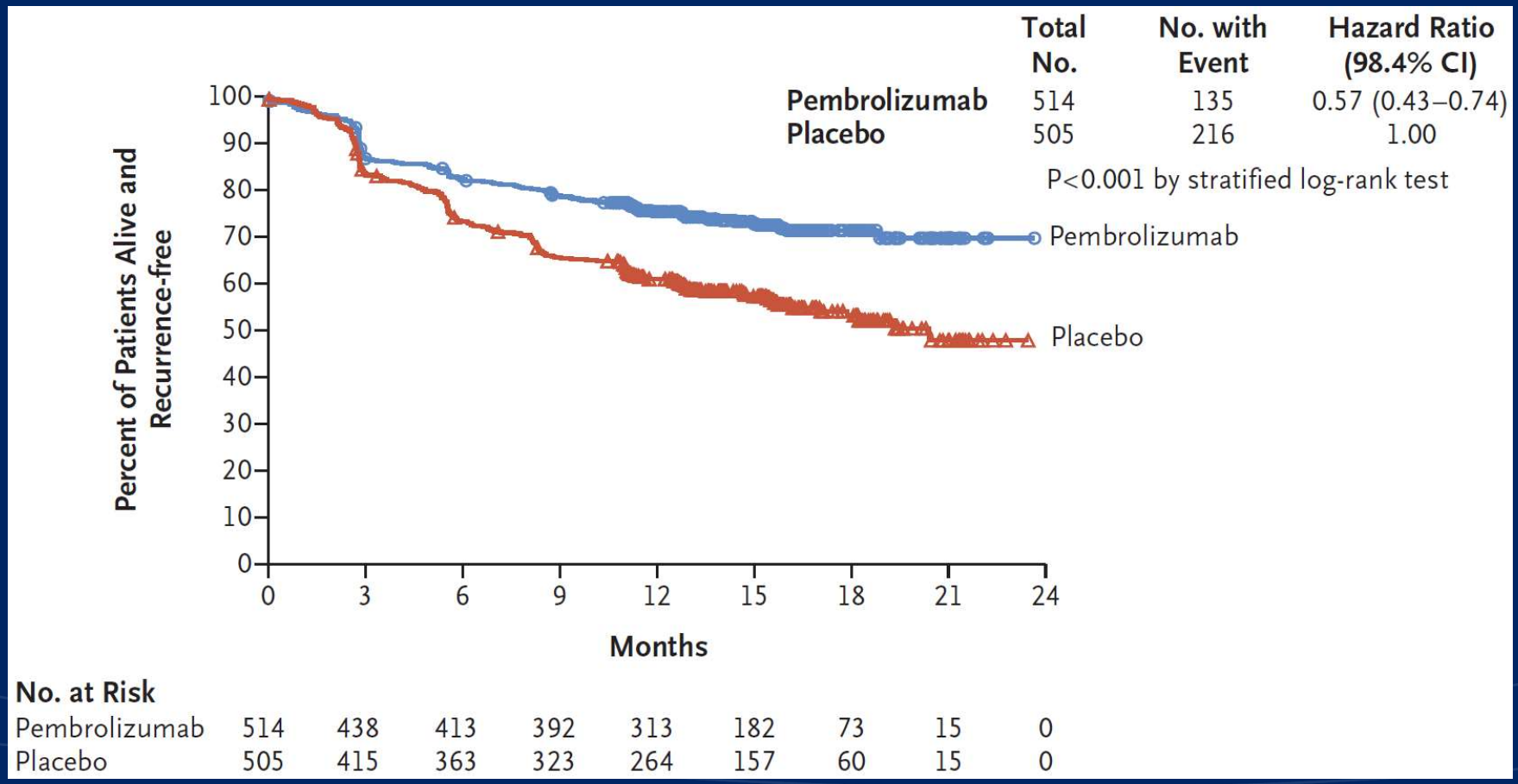


Weber J, ESMO, 2019

Checkmate 238: Safety

Event	Nivolumab (N=452)		Ipilimumab (N=453)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)			
Any adverse event	438 (96.9)	115 (25.4)	446 (98.5)	250 (55.2)
Treatment-related adverse event†	385 (85.2)	65 (14.4)	434 (95.8)	208 (45.9)
Fatigue	156 (34.5)	2 (0.4)	149 (32.9)	4 (0.9)
Diarrhea	110 (24.3)	7 (1.5)	208 (45.9)	43 (9.5)
Pruritus	105 (23.2)	0	152 (33.6)	5 (1.1)
Rash	90 (19.9)	5 (1.1)	133 (29.4)	14 (3.1)
Nausea	68 (15.0)	1 (0.2)	91 (20.1)	0
Arthralgia	57 (12.6)	1 (0.2)	49 (10.8)	2 (0.4)
Asthenia	57 (12.6)	1 (0.2)	53 (11.7)	4 (0.9)
Hypothyroidism	49 (10.8)	1 (0.2)	31 (6.8)	2 (0.4)
Headache	44 (9.7)	1 (0.2)	79 (17.4)	7 (1.5)
Abdominal pain	29 (6.4)	0	46 (10.2)	1 (0.2)
Increase in ALT level	28 (6.2)	5 (1.1)	66 (14.6)	26 (5.7)
Increase in AST level	25 (5.5)	2 (0.4)	60 (13.2)	19 (4.2)
Maculopapular rash	24 (5.3)	0	50 (11.0)	9 (2.0)
Hypophysitis	7 (1.5)	2 (0.4)	48 (10.6)	11 (2.4)
Pyrexia	7 (1.5)	0	54 (11.9)	2 (0.4)
Any adverse event leading to discontinuation	44 (9.7)	21 (4.6)	193 (42.6)	140 (30.9)
Treatment-related adverse event leading to discontinuation	35 (7.7)	16 (3.5)	189 (41.7)	136 (30.0)

Keynote 054 / EORTC 1325: *Pembrolizumab vs Placebo*

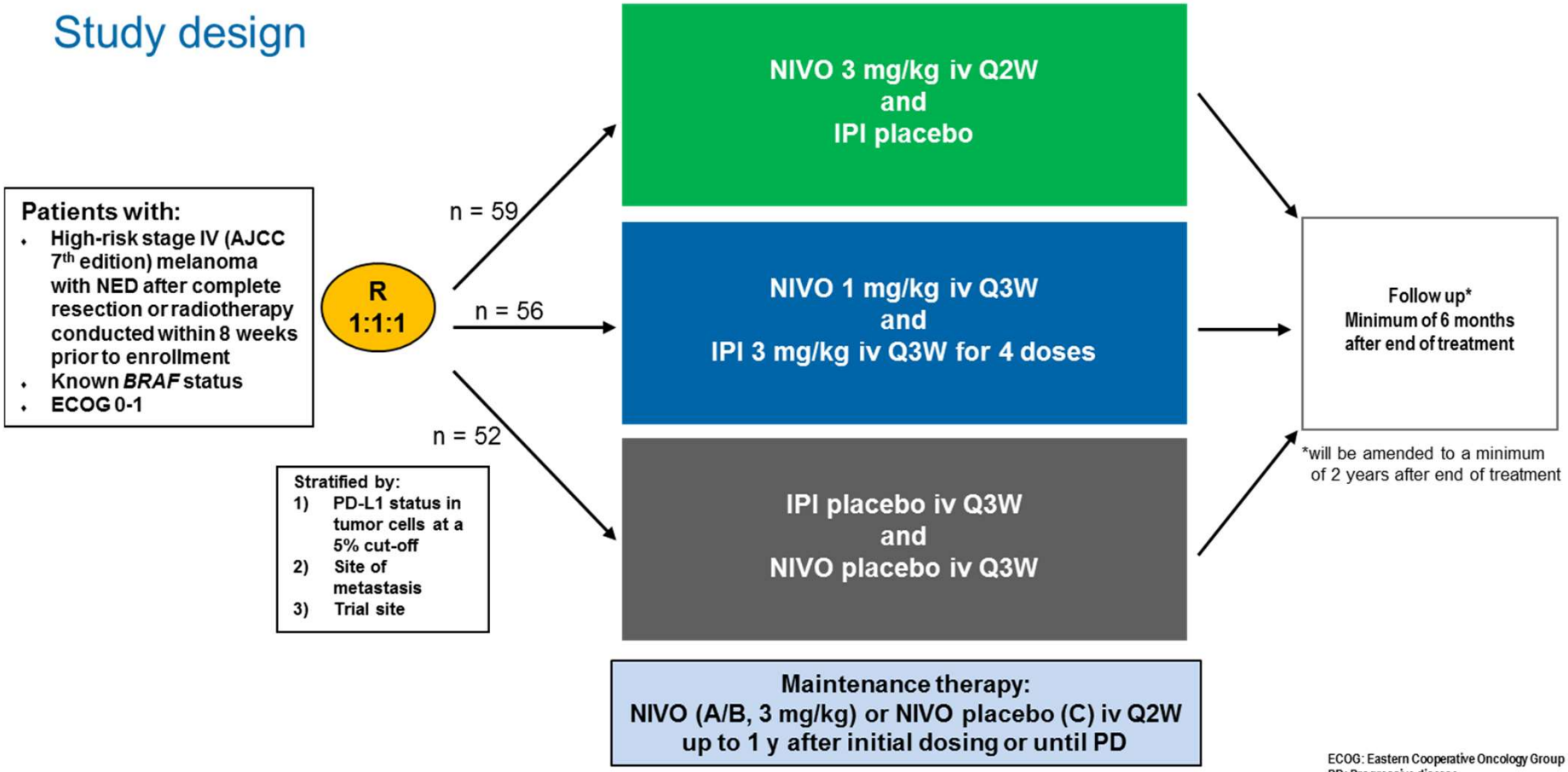


Eggermont AMM, N Engl J Med, 2018

THE IMMUNED STUDY

Enrollment period: Sept. 2015 to Nov. 2018

Study design



ECOG: Eastern Cooperative Oncology Group
PD: Progressive disease

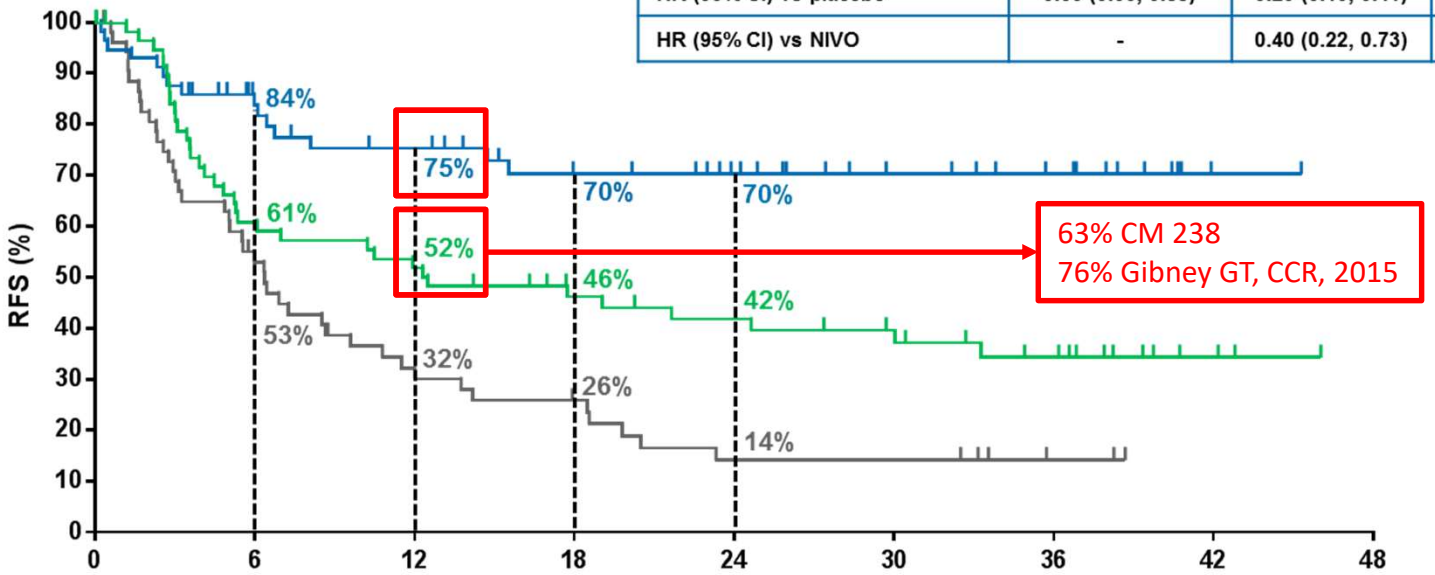
THE IMMUNED STUDY

RFS in all patients

Data cut-off date July 2nd, 2019
Median follow-up time: 28.4 months (n=167)

	NIVO (n=59)	NIVO+IPI (n=56)	Placebo (n=52)
Median RFS, mo (95% CI)	12.4 (5.30, 33.26)	NR[1]	6.4 (3.26, 9.61)
HR (95% CI) vs placebo	0.56 (0.36, 0.88)	0.23 (0.13, 0.41)	-
HR (95% CI) vs NIVO	-	0.40 (0.22, 0.73)	-

[1]NR: not reached



63% CM 238
76% Gibney GT, CCR, 2015

Patients at risk:

NIVO	59	34	29	22	19	16	11	3	-
NIVO + IPI	56	40	34	26	21	14	10	1	-
Placebo	52	26	15	11	6	6	2	-	-

THE IMMUNED STUDY

Safety overview

	NIVO (n=56)				NIVO + IPI (n=55)				Placebo (n=51)			
	All Grades		Grade 3/4		All Grades		Grade 3/4		All Grades		Grade 3/4	
	n	%	n	%	n	%	n	%	n	%	n	%
Any treatment-related AE	47	83.9	15	26.8	53	96.4	39	70.9	28	54.9	3	5.9
Skin	19	33.9	1	1.8	33	60.0	3	5.5	7	13.7	0	0
Gastrointestinal	19	33.9	1	1.8	25	45.5	8	14.5	8	15.7	0	0
Hepatic	9	16.1	5	8.9	33	60.0	26	47.3	1	2.0	0	0
Endocrine	14	25.0	2	3.6	33	60.0	7	12.7	1	2.0	0	0
Neurological	10	17.9	2	3.6	11	20.0	1	1.8	9	17.6	0	0
Musculoskeletal	14	25.0	3	5.4	14	25.5	1	1.8	5	9.8	0	0
Any immune-related AE	40	71.4	14	25.0	51	92.7	38	69.1	17	33.3	3	5.9
Treatment-related AE leading to discontinuation	7	12.5	5	8.9	34	61.8	29	52.7	1	2.0	-	-
Any AE leading to discontinuation	7	12.5	5	8.9	34	61.8	29	52.7	2	3.9	1	2.0

- No treatment-related deaths have occured!

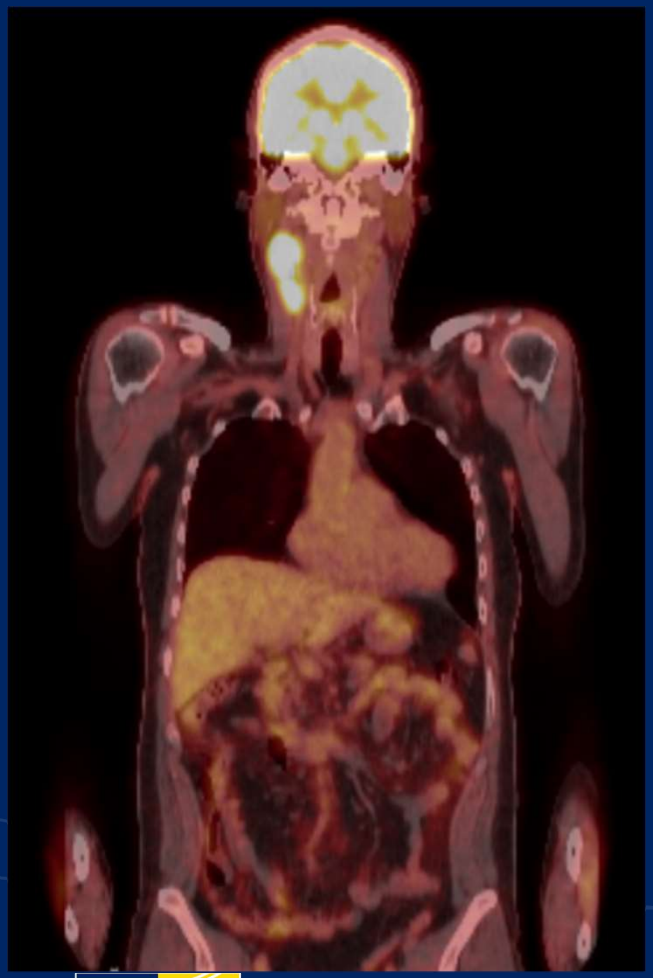
Data cut-off date July 2nd, 2019
Median follow-up time: 28.4 months (n=167)

Accrued Phase III Adjuvant Immunotherapy Melanoma Studies

- SWOG 1404: Phase III study of Pembrolizumab vs Patient/Provider Choice (IFN or Ipilimumab) in resected stage IIIA-IV melanoma patients
  - Closed to Accrual 11/2/2017; no updates yet

- Checkmate 915: Phase III study for Nivolumumab/Ipilimumab vs Nivolumab in resected stage IIIB-IV melanoma patients
  - Press release on 11/20/19: “A statistically significant benefit was not reached for the co-primary endpoint of recurrence-free survival (RFS) in patients whose tumors expressed PD-L1 <1%...”

Neoadjuvant approach to clinical stage III melanoma



- Responses can occur quickly with systemic therapy
- Pathologic response appears to predict long-term survival
- Neoadjuvant immunotherapy efficacy may be greater compared to administration after surgery.

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Modern melanoma NST trials

Trial	Regimen	N	pCR (%)	med RFS (mo)	med FU (mo)
Amaria Lancet Oncol 2018	Dab/Tram	21	58	19.7	18.6
Long Lancet Oncol 2019*	Dab/Tram	35	49	23.0	27.0
Blank Nat Med 2018	Ipi+nivo	10	33	NR	32
Amaria Nat Med 2018	Nivo Ipi+nivo	12 11	25 45	NR NR	20
Huang Nat Med 2019	Pembro	30	19	NR	18
Rozeman Lancet Oncol 2019*	Ipi+nivo	86	57^	NR	8.3

*In press

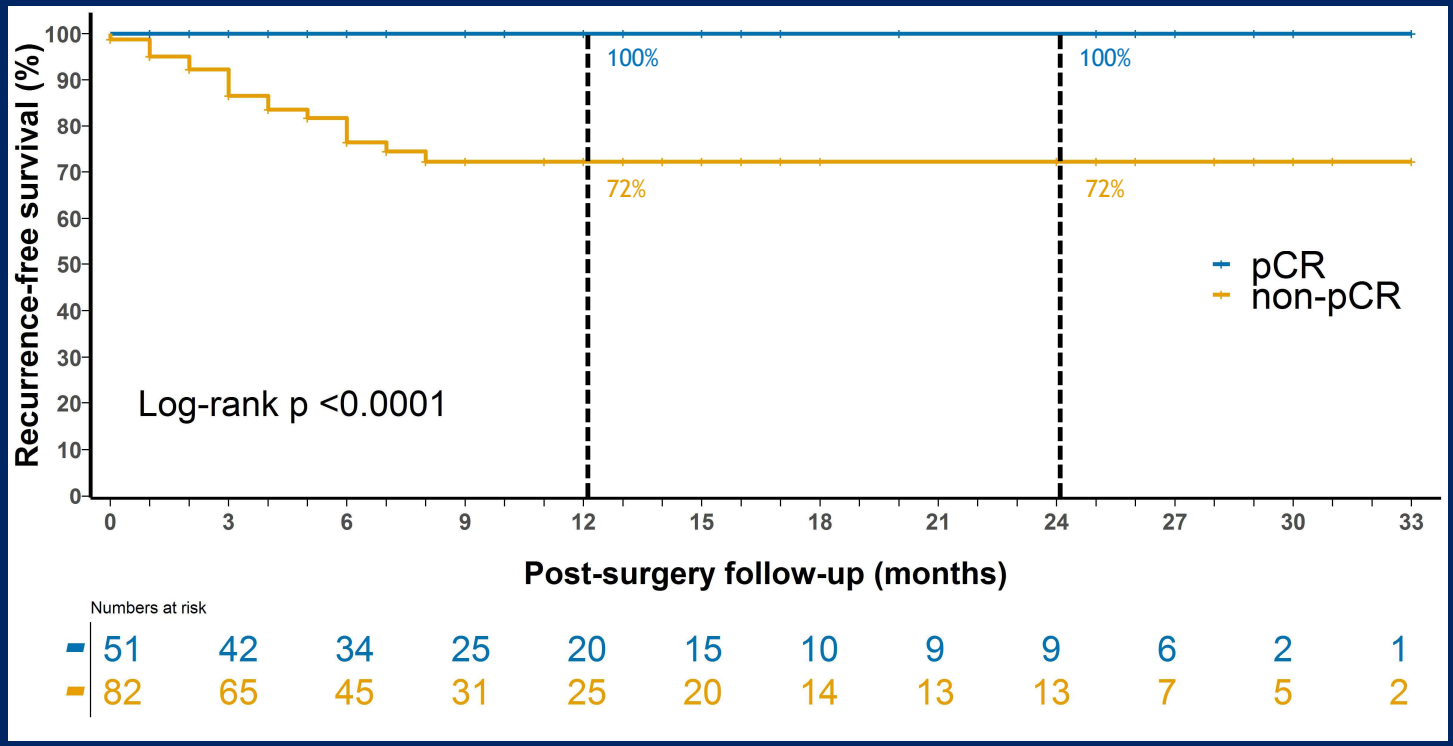
^arm B = I1N3

pCR for IO = 38%

5% of IO patients progressed prior to surgery

Menzies AM, ASCO, 2019

RFS by pathological response with IO



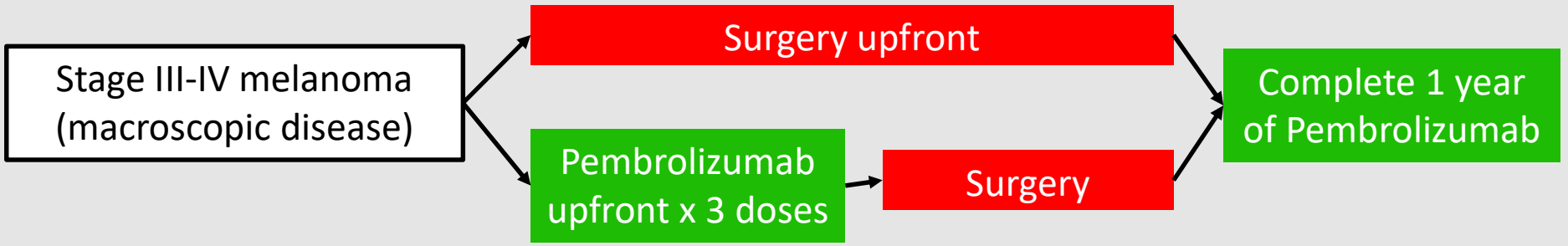
Med f/u 10 mo

* 1 pt died from toxicity without recurrence, censored at time of death

Menzies AM, ASCO, 2019

Approach to management of stage III melanoma patient with macroscopic disease (or limited stage IV disease)

SWOG 1801 Study

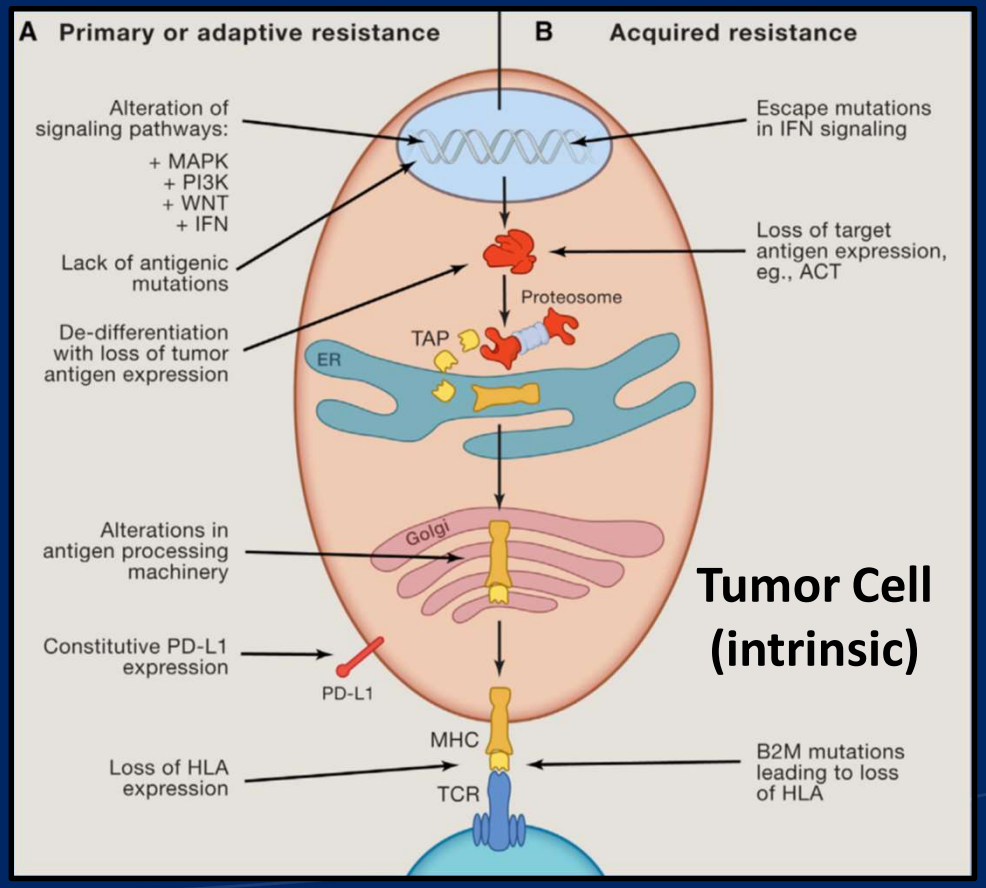


Primary endpoint: Event Free Survival

IO Resistance mechanisms

Table 2. Mechanisms of Primary and Adaptive Resistance to Immunotherapy

	Mechanism	Examples
tumor cell intrinsic	absence of antigenic proteins	low mutational burden lack of viral antigens lack of cancer-testis antigens overlapping surface proteins
	absence of antigen presentation	deletion in TAP deletion in B2M silenced HLA
	genetic T cell exclusion	MAPK oncogenic signaling stabilized b-catenin mesenchymal transcriptome oncogenic PD-L1 expression
	insensibility to T cells	mutations in interferon gamma pathway signaling
tumor cell extrinsic	absence of T cells	lack of T cells with tumor antigen-specific TCRs
	inhibitory immune checkpoints	VISTA, LAG-3, TIM-3
	immunosuppressive cells	TAMs, Tregs



Sharma P, Cell 2017

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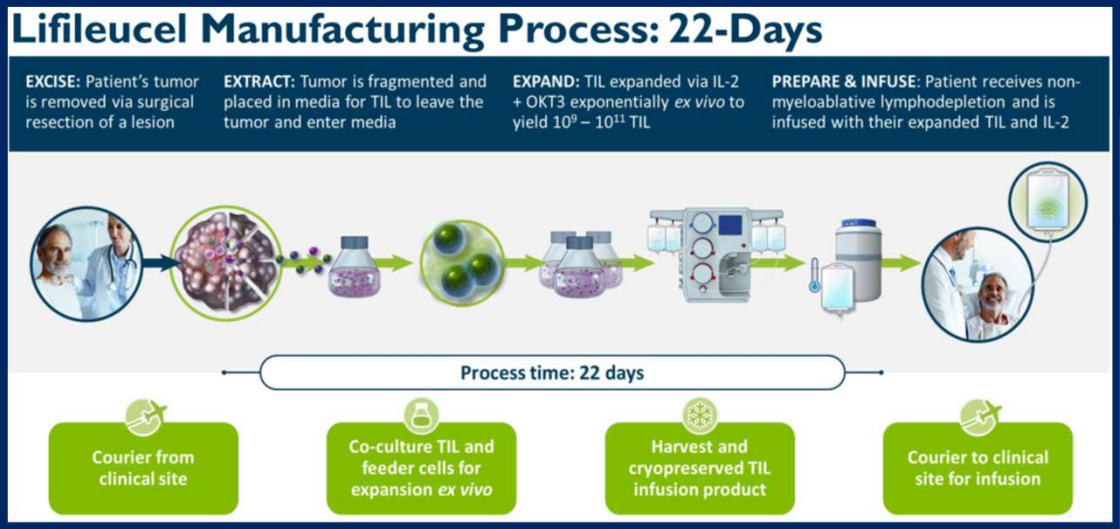
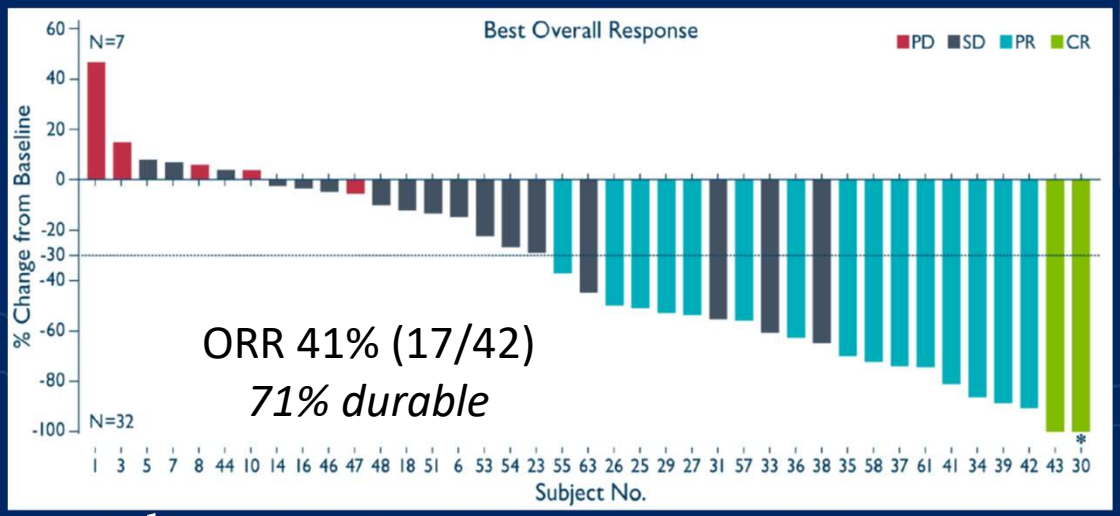
Emerging Immunotherapy Salvage Regimens After Anti-PD-1/Anti-CTLA-4

- 46% of patients treated with Nivo/Ipi on CM 067 received subsequent systemic therapy
- Outside of IL-2, no FDA approved immunotherapy options.
- Phase I-II studies with novel immunotherapy agents have demonstrated responses in anti-PD-1 refractory melanoma patients.
  - **Autologous TIL (lifileucel, aka LN-144)**
  - **TLR9 agonists (CMP-001, SD-101, tilsotolimod)**
  - **Anti-LAG-3 antibody (relatlimab)**
  - **HDAC inhibitor (epacadostat)**

Iovance C-144-01 Phase 2 Trial in Metastatic Melanoma

Anti-PD-1/PD-L1 Refractory Cohort





ORR 41% (17/42)

71% durable

Treatment Emergent Adverse Events

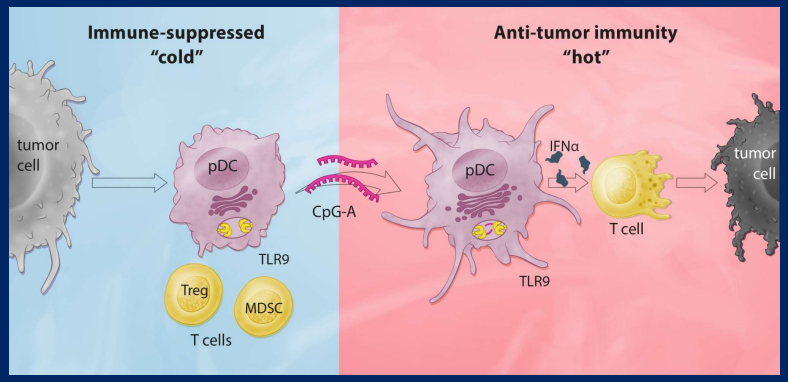
PREFERRED TERM	GRADE ≥3 n (%)	GRADE 5 n (%)
Number of subjects reporting at least one TEAE	41 (97.6)	2 (4.8)
Thrombocytopenia	33 (78.6)	0
Chills	3 (7.1)	0
Anemia	25 (59.5)	0
Pyrexia	7 (16.7)	0
Febrile neutropenia	23 (54.8)	0
Neutropenia	15 (35.7)	0
Hypophosphatemia	12 (28.6)	0
Leukopenia	15 (35.7)	0
Fatigue	1 (2.4)	0
Lymphopenia	13 (31.0)	0
Hypotension	5 (11.9)	0
Hypocalcemia	3 (7.1)	0
Aspartate aminotransferase increased	0	0
Diarrhea	1 (2.4)	0
Tachycardia	1 (2.4)	0

Most AEs occurred in first 30 days from TIL dose.

Sarnaik A, SMR, 2019

Phase 1B Study of Intratumoral CMP-001 +/- Pembrolizumab in Anti-PD-1 Refractory Melanoma

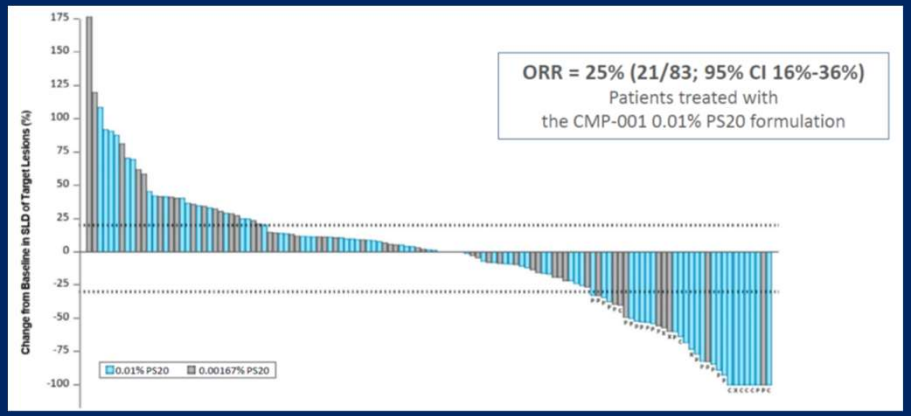
- CMP-001 is a CpG-A DNA packaged in a virus-like particle for enhanced systemic anti-tumor T cell response : TLR 9 agonist

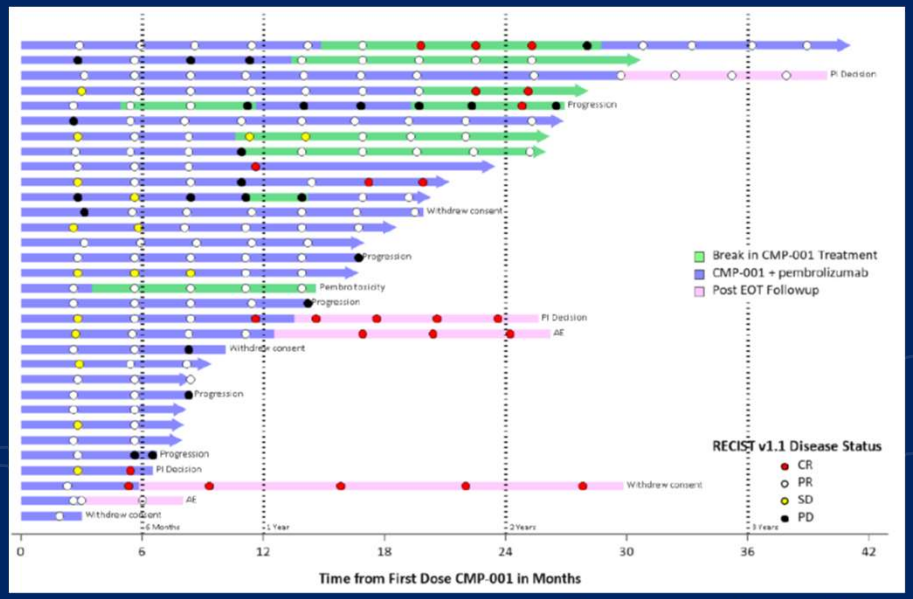


- 3+3 Dose Escalation (1, 3, 5, 7.5, 10mg; n=44) / Expansion (5, 10mg; n=100, ongoing)
- CMP-001 intratumoral/pembrolizumab IV

Two schedules of escalation with CMP-001 evaluated:

Weekly x 7	→	then Q3 weeks until discontinuation
Weekly x 2	→	





Kirkwood J, SITC 2019

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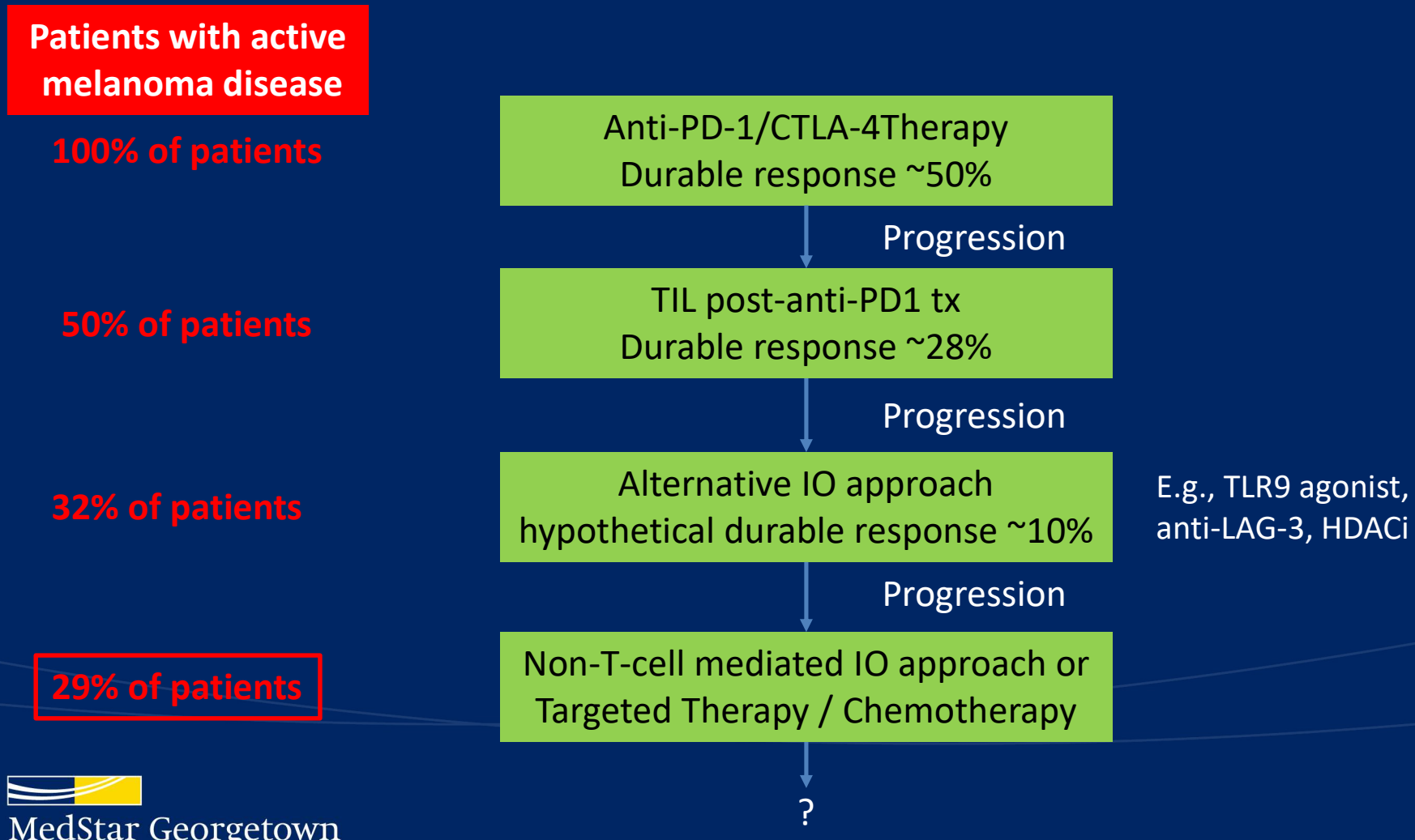
How close are we to achieving during durable response with IO for all patients?



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Conclusions/Take-Away Points

- Long-term survival (5 years) seen in 43-52% of advanced melanoma patients treated with anti-PD-1 therapy.
- Adjuvant anti-PD-1 therapy reduces recurrence risk by >40%; yet to know impact on overall survival
- Neoadjuvant therapy is promising for resected high risk melanoma patients
- Novel immunotherapy approaches can achieve durable responses in patients who progressed on anti-PD-1/anti-CTLA-4 therapies.