Immunotherapy for cancer: the journey so far, and where are we headed?

Cancer Crosslinks 2018

Jeffrey S Weber MD PhD

Laura and Isaac Perlmutter Cancer Center

NYU-Langone Health

Disclosures

- **Stock or Other Ownership:** Altor BioScience, Biond, CytomX Therapeutics
- **Honoraria:** Bristol-Myers Squibb, Merck, Genentech, AbbVie, AstraZeneca, Daiichi Sankyo, GlaxoSmithKline, Eisai, Altor BioScience, Lion Biotechnologies, Amgen, Roche, Ichor Medical Systems, Celldex, CytomX Therapeutics, Nektar, Novartis, Medivation
- **Consulting or Advisory Role:** Celldex, Ichor Medical Systems, Biond, Altor BioScience, Bristol-Myers Squibb, Merck, Genentech, Roche, Amgen, AstraZeneca, GlaxoSmithKline, Daiichi Sankyo, AbbVie, Eisai, CytomX Therapeutics, Nektar, Novartis, Medivation
- **Research Funding (Inst):** Bristol-Myers Squibb, Merck, GlaxoSmithKline, Genentech, Astellas Pharma, Incyte, Roche, Novartis
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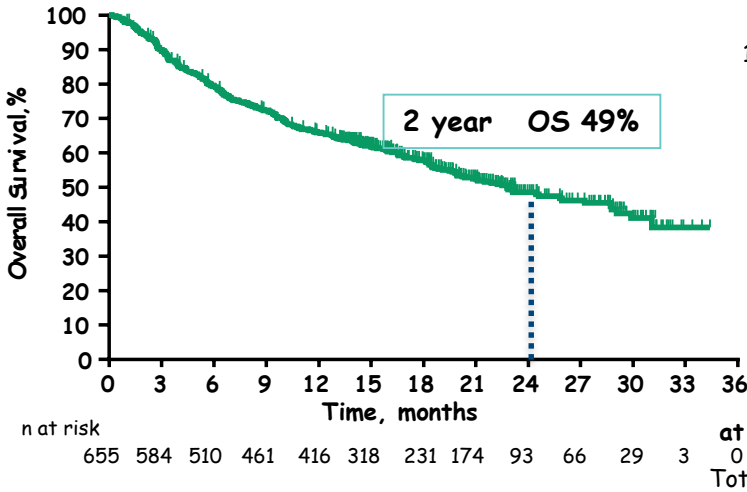
- **I did not vote for Donald Trump**

Where are we? Anti-PD-1: 2 Phase I-II trials

Response rates 30 to 40%

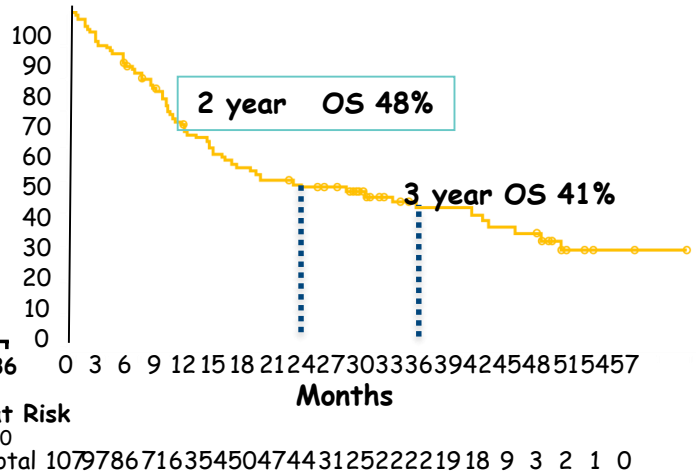
Grade 3-4 adverse events : 15%

Pembrolizumab



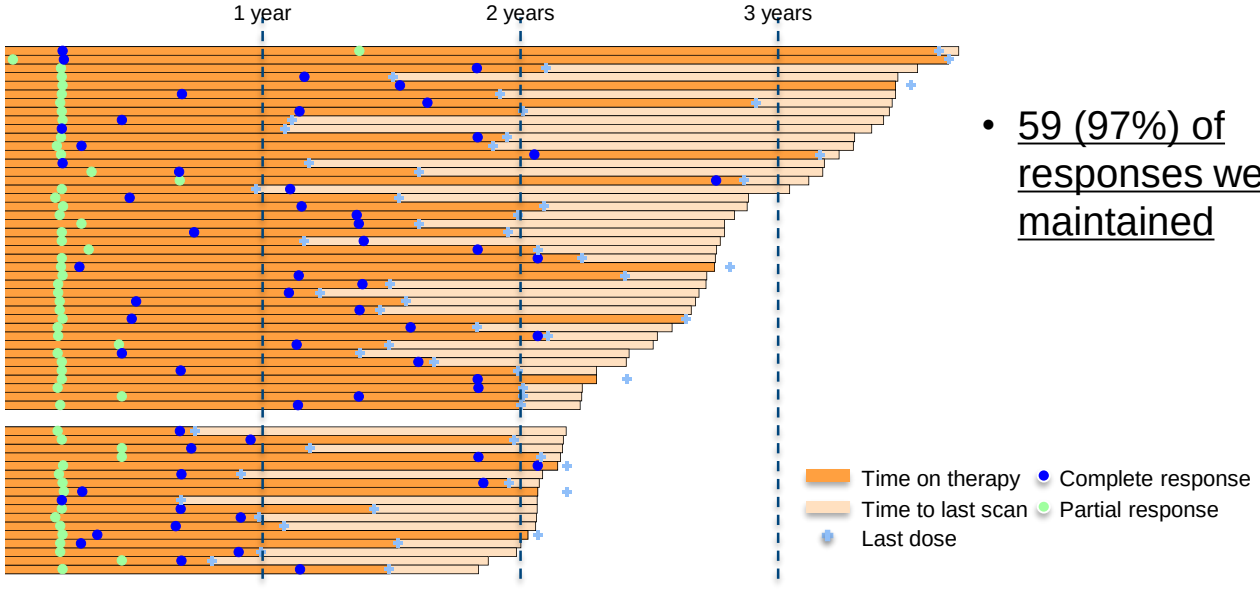
Hamid, O et al NEJM 2013

Nivolumab



Sznol, M et al JCO 2015

Complete Responders Who Stopped Pembrolizumab for Observation (N = 61) in Keynote -001 Did Not Progress!



- 59 (97%) of responses were maintained

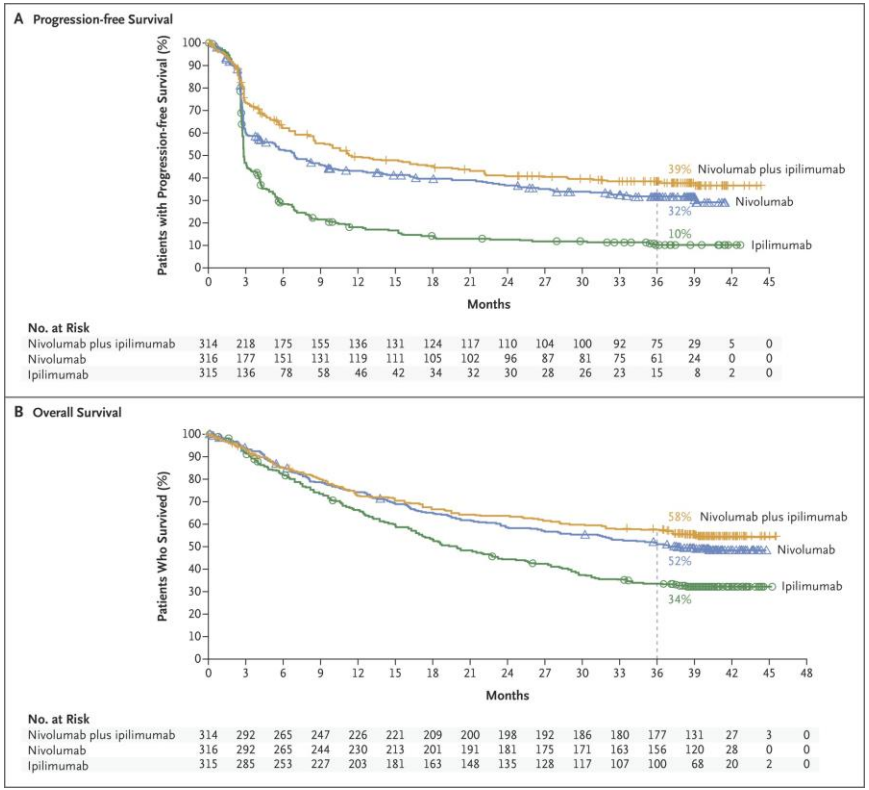
Total bar length represents the time to the last scan.
Analysis cutoff date: Sep 18, 2015.

Robert, C et al ASCO 2016

Single agent PD-1 therapy in melanoma

- Best overall response rates of 42-44%
- Few complete responses (< 5%)
- Progression-free survival of 7 months
- Median survival of 32 – 36 months
- Median duration of response not reached
- 70-90% of patients stay in remission at 1-2 years
- 48% 2 year, 41% 3 three-year survival
- 10-15% rate of stopping therapy due to toxicity

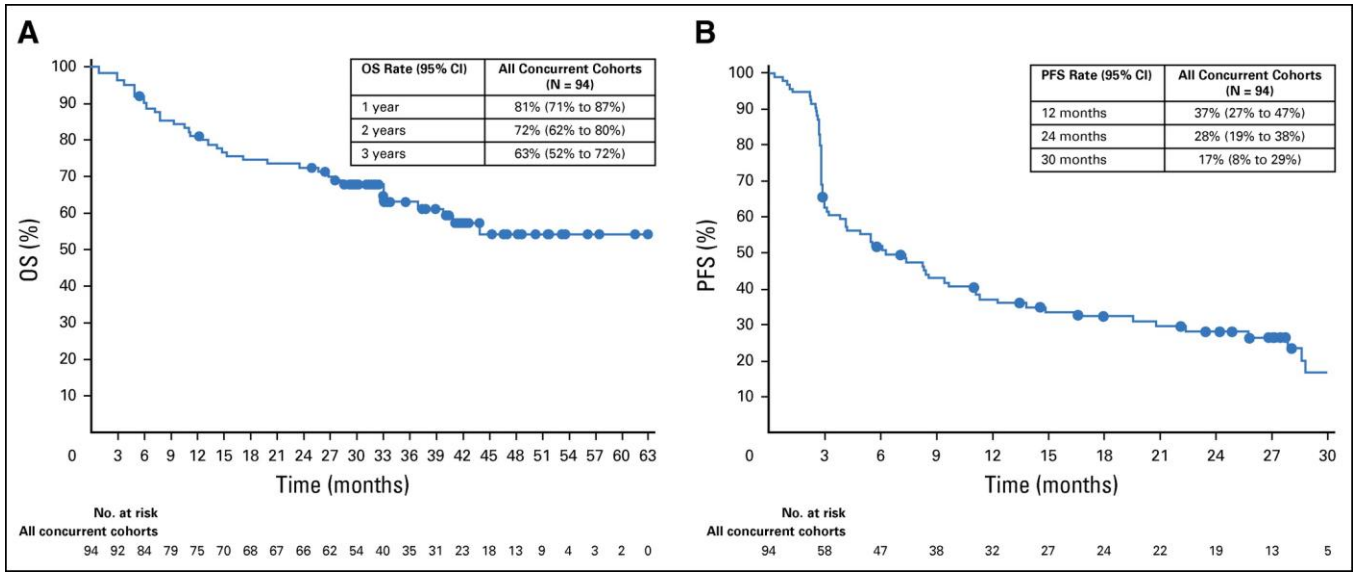
Checkmate-067 Ipilimumab + Nivolumab trial: Progression-free and Overall Survival.



Wolchok JD et al. N Engl J Med 2017;377:1345-1356

The NEW ENGLAND JOURNAL of MEDICINE

Overall and progression-free survival for all concurrent cohorts in the combination ipilimumab + nivolumab phase Ib protocol



Published in: Margaret K. Callahan; Harriet Kluger; Michael A. Postow; Neil H. Segal; Alexander Lesokhin; Michael B. Atkins; John M. Kirkwood; Suba Krishnan; Rafia Bhore; Christine Horak; Jedd D. Wolchok; Mario Sznol; *JCO* Ahead of Print
DOI: 10.1200/JCO.2017.72.2850

Checkmate -067: Treatment-Related Adverse Events.

Table 2. Treatment-Related Adverse Events.*

Event	Nivolumab plus Ipilimumab (N=313)		Nivolumab (N=313)		Ipilimumab (N=311)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)					
Any treatment-related adverse event	300 (96)	184 (59)	270 (86)	67 (21)	268 (86)	86 (28)
Rash	93 (30)	10 (3)	72 (23)	1 (<1)	68 (22)	5 (2)
Pruritus	112 (35)	6 (2)	67 (21)	1 (<1)	113 (36)	1 (<1)
Vitiligo	28 (9)	0	29 (9)	1 (<1)	16 (5)	0
Maculopapular rash	38 (12)	6 (2)	15 (5)	2 (1)	38 (12)	1 (<1)
Fatigue	119 (38)	13 (4)	114 (36)	3 (1)	89 (29)	3 (1)
Asthenia	30 (10)	1 (<1)	25 (8)	1 (<1)	17 (5)	2 (1)
Pyrexia	60 (19)	2 (1)	21 (7)	0	21 (7)	1 (<1)
Diarrhea	142 (45)	29 (9)	67 (21)	9 (3)	105 (34)	18 (6)
Nausea	88 (28)	7 (2)	41 (13)	0	51 (16)	2 (1)
Vomiting	48 (15)	7 (2)	22 (7)	1 (<1)	24 (8)	1 (<1)
Abdominal pain	26 (8)	1 (<1)	18 (6)	0	28 (9)	2 (1)
Colitis	40 (13)	26 (8)	7 (2)	3 (1)	35 (11)	24 (8)
Headache	35 (11)	2 (1)	24 (8)	0	25 (8)	1 (<1)
Arthralgia	43 (14)	2 (1)	31 (10)	1 (<1)	22 (7)	0
Increased lipase level	44 (14)	34 (11)	27 (9)	14 (4)	18 (6)	12 (4)
Increased amylase level	26 (8)	9 (3)	20 (6)	6 (2)	15 (5)	4 (1)
Increased aspartate aminotransferase level	51 (16)	19 (6)	14 (4)	3 (1)	12 (4)	2 (1)
Increased alanine aminotransferase level	60 (19)	27 (9)	13 (4)	4 (1)	12 (4)	5 (2)
Decreased weight	19 (6)	0	10 (3)	0	4 (1)	1 (<1)
Hypothyroidism	53 (17)	1 (<1)	33 (11)	0	14 (5)	0
Hyperthyroidism	35 (11)	3 (1)	14 (4)	0	3 (1)	0
Hypophysitis	23 (7)	5 (2)	2 (1)	1 (<1)	12 (4)	5 (2)
Decreased appetite	60 (19)	4 (1)	36 (12)	0	41 (13)	1 (<1)
Cough	25 (8)	0	19 (6)	2 (1)	15 (5)	0
Dyspnea	36 (12)	3 (1)	19 (6)	1 (<1)	12 (4)	0
Pneumonitis	22 (7)	3 (1)	5 (2)	1 (<1)	5 (2)	1 (<1)
Treatment-related adverse event leading to discontinuation	123 (39)	95 (30)	37 (12)	24 (8)	49 (16)	43 (14)

* Shown are treatment-related adverse events of any grade that occurred in more than 5% of the patients in any treatment group who had one or more treatment-related adverse events of grade 3 or 4. The relatedness of the adverse event to treatment was determined by the investigators. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Two deaths that were considered by the investigators to be related to a study drug occurred in the nivolumab group (neutropenia) and in the ipilimumab group (colonic perforation) within 100 days after the last dose of study drug; two additional deaths in the nivolumab-plus-ipilimumab group (one due to cardiac insufficiency and autoimmune myocarditis, and one due to liver necrosis) that were considered by the investigator to be related to a study drug were reported more than 100 days after the last dose of study drug.

Wolchok JD et al. N Engl J Med 2017;377:1345-1356

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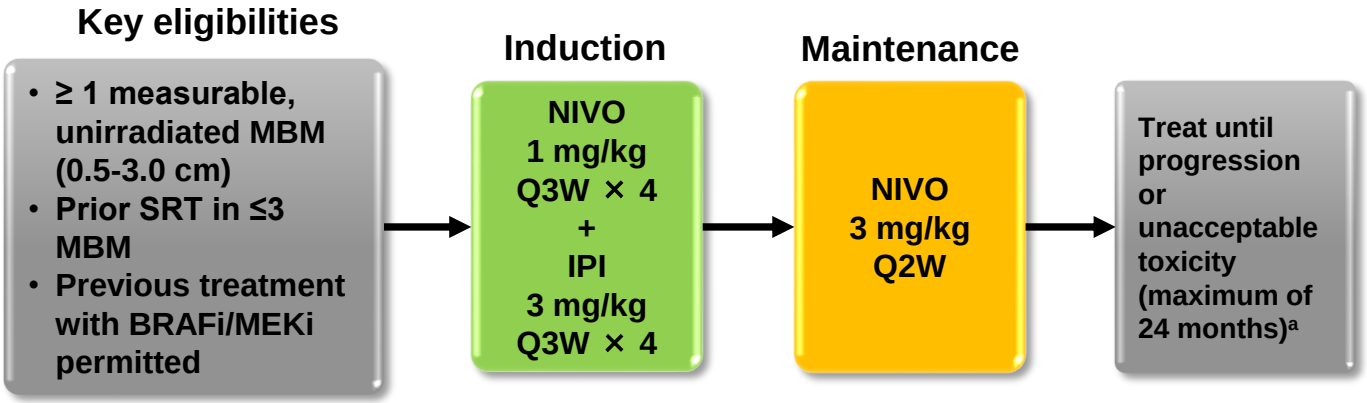
Combination immune therapy in melanoma

- Best overall response rates of 56-58%
- High number of complete responses (15-20%)
- Progression-free survival of 11.7 months
- Median survival > 42 months
- Median duration of response not reached
- 80-90% of patients stay in remission at 1-2 years
- 63% 2 year, 58% 3 three-year survival
- 45-55% rate of stopping therapy due to toxicity

Is there evidence that immunotherapy has activity in patients with melanoma brain metastases?

CheckMate 204: Trial Design



- Exclusion criteria included neurological symptoms; steroids > 10 days; WBRT; prior treatment with checkpoint inhibitors; leptomeningeal disease
- Original planned enrollment of 110 asymptomatic patients

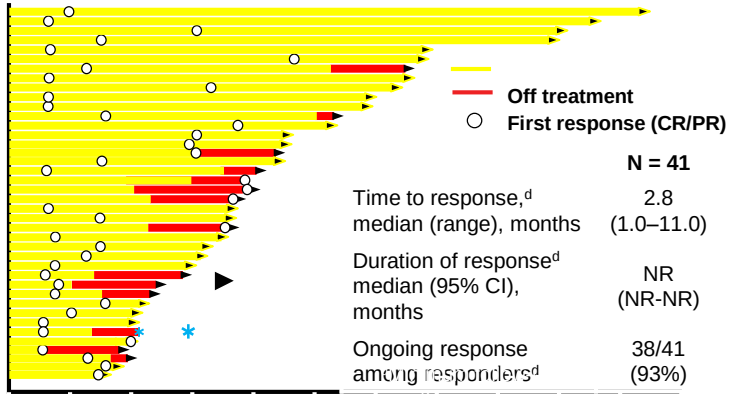
[a]Patients with grade 3-4 adverse events (AEs) during NIVO+IPI induction could resume NIVO when toxicity resolved; all patients who discontinued proceeded to follow-up

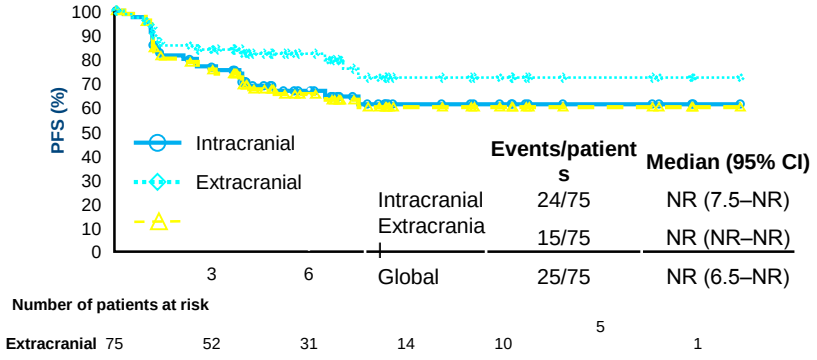
Tawbi, H. et al. Presented at: ASCO. 2017 (abstr 9507).

Summary of Results: CheckMate 204

Response to Treatment – All Patients (N = 75)

	Global	Intra-cranial	Extra-cranial
Best overall response, n (%)			
Complete response	4 (5)	16 (21)	5 (7)
Partial response	36 (48)	25 (33)	32 (43)
Stable disease	4 (5)	4 (5)	2 (3)
Progressive disease[a]	18 (24)	18 (24)	16 (21)
Not evaluable[b]	13 (17)	12 (16)	20 (27)
Objective response rate, % (95% CI)	53 (41–65)	55 (43–66)	49 (38–61)
Clinical benefit rate[c], % (95% CI)	59 (47–70)	60 (48–71)	52 (40–64)





[a]Confirmed and unconfirmed progressive disease, [b]Includes unconfirmed responses,
[c]Clinical benefit rate = complete response + partial response + stable disease ≥ 6 months

Tawbi, H. et al. Presented at: ASCO. 2017 (abstr 9507).

Comparable IC/EC ORR that appear durable
- Intracranial ORR = 55%, CR = 21%
- Landmark PFS 67% @ 1 yr
- 93% of responses ongoing

Overall safety profile similar to previous
- CNS/neuro safety profile acceptable

Comparable results for the aPD1 Brain Collaboration Ph2 study
- For asymptomatic brain metastases, no prior local therapy
  - Nivo + Ipi (n=26) IR rate = 42%; 6 month PFS = 46%
  - Nivo alone (n=25) IR rate = 20%; 6-month PFS = 28%
- For treated-naïve patients (upfront treatment)
  - Nivo + Ipi IR rate = 50%

What has been the Landscape for Adjuvant Melanoma Therapy?

- **High-dose interferon α-2B was approved by the US FDA in 1996 for resected stages 2c and 3 melanoma, based on a controlled phase III study**
- **One-year regimen, 4 weeks of intravenous therapy at 20 μ/m^2 followed by 11 months of SC therapy at 10 μ/m^2 TIW**
- **27% increase in RFS, 2%-3% absolute change in survival**
- **Significant rate of grade 2 and some grade 3 toxicities, chiefly fevers, flu-like symptoms, malaise, some AST/ALT elevations**
- **Until 2016, only 30% rate of use in the US, not used at all in the EU[1]**

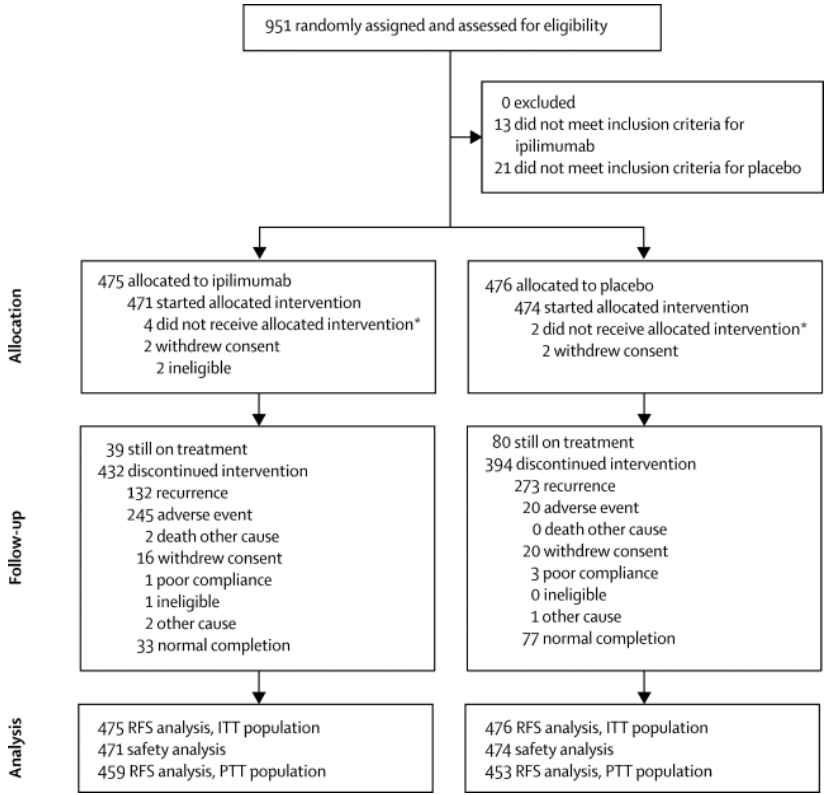
FDA, Food and Drug Administration; irAE, immune-related adverse event; RFS, recurrence-free survival; TIW, three times per week; 1. Mohr et al, ASCO 2017

Ipilimumab As Adjuvant Therapy for Melanoma?

- **75 patients with resected stage IIIc/IV melanoma received ipilimumab every 6 to 8 weeks for 1 year**
- **Eligible patients received further maintenance treatments, every 12 weeks, up to 5 years**
- **The first 25 patients received 3 mg/kg of ipilimumab, and an additional 50 patients received 10 mg/kg**
- **All were HLA-A*0201+ patients and received multi-peptide immunizations in combination with ipilimumab**
- **Median overall and relapse-free survivals were not reached after a median follow-up of 29.5 months; estimated median RFS 4 years**
- **Significant grades 2-3-4 irAEs causing discontinuation seen in 28 of 75 patients (37%) and were positively associated with longer RFS**

Sarnaik AA, et al. *Clin Cancer Res.* 2011;17(4):896-906.

Schema: EORTC 18071: Ipilimumab vs Placebo

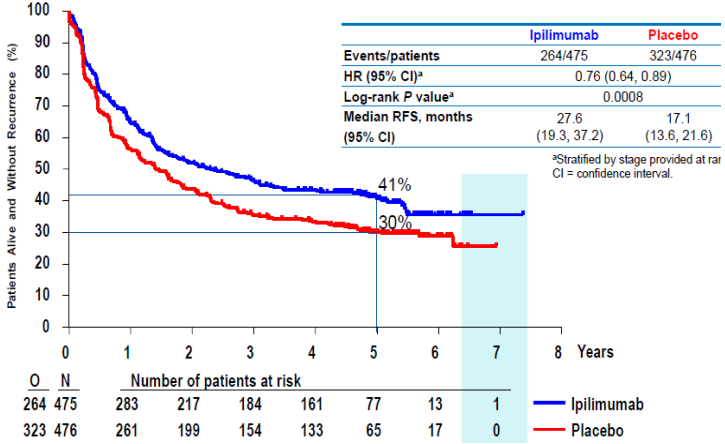


ITT, intention-to-treat. PPT, per-protocol treatment (eligible patients who started the treatment allocated at randomization).
*One patient had follow-up for a long period of time and the other five were lost to follow-up. Because of a lack of disease assessment after randomization, recurrence-free survival duration was censored at 1 day.

Eggermont AM, et al. *Lancet Oncol.* 2015;16(5):522-530.

EORTC 18071

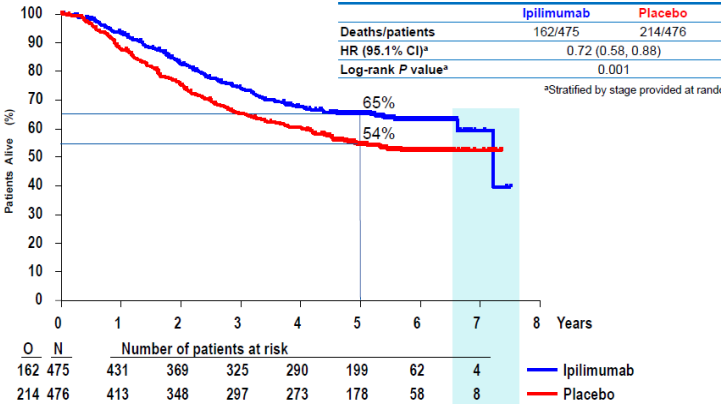
RFS (per IRC)



	Ipilimumab	Placebo
Events/patients	264/475	323/476
HR (95% CI)[a]	0.76 (0.64, 0.89)	
Log-rank *P* value[a]	0.0008	
Median RFS, months (95% CI)	27.6 (19.3, 37.2)	17.1 (13.6, 21.6)

[a]Stratified by stage provided at rar
CI = confidence interval.

OS



	Ipilimumab	Placebo
Deaths/patients	162/475	214/476
HR (95.1% CI)[a]	0.72 (0.58, 0.88)	
Log-rank *P* value[a]	0.001	

[a]Stratified by stage provided at rand

Safety Summary

	Ipilimumab (n = 471)	
	Any Grade	Grade 3/4
Any AE, %	98.7	54.1
Treatment-related AE, %	94.1	45.4
Treatment-related AE leading to discontinuation, %	48.0	32.9
Any immune-related AE, %	90.4	41.6

Deaths due to drug-related AEs

- 5 patients (1.1%) in the ipilimumab group
  - 3 patients with colitis (2 with gastrointestinal perforations)
  - 1 patient with myocarditis
  - 1 patient had multiorgan failure with Guillain-Barré

Eggermont et al. NEJM 2016

Which led to an intergroup trial testing 3 versus 10 mg/kg ipilimumab versus IFN-alpha….

Intergroup E1609: Study Design and Accrual

Resected
IIIB, IIIC
M1a, M1b

Stratification Factors: IIIB, IIIC, M1a, M1b

N = 1673

RANDOMIZE

Ipi3 INDUCTION
Ipilimumab 3 mg/kg
Q 3 week × 4

→ **Ipi3** MAINTENANCE
Ipilimumab 3 mg/kg
Q 3 month × 4

HD-IFN INDUCTION
IFN-α2b 20 MU/m^2/d
IV x1 month

→ **HD-IFN** MAINTENANCE
10 MU/m^2 SC TIW
x11 months

Ipi10 INDUCTION
Ipilimumab 10 mg/kg
Q 3 week × 4

→ **Ipi10** MAINTENANCE
Ipilimumab 10 mg/kg
Q 3 month × 4

Arm	Activation	Termination	Final
Ipi10	5/25/11	4/4/14	511
HD-IFN	5/25/11	8/15/14	636
Ipi3	2/7/12	8/15/14	523

Presented by: Ahmad Tarhini, MD, PhD, ASCO 2017

ECOG-ACRIN cancer research group
Reshaping the future of patient care

Safety Summary E 1609

(Based on all toxicity data as of 3/2/17)

	Ipilimumab 3 mg/kg (n = 516)		Ipilimumab 10 mg/kg (n = 503)	
	Any Grade	Grade 3/4	Any grade	Grade 3/4
Any AE, %	98.4	53.3	100	65.4
Treatment-related AE, %	96.0	36.6	98.8	56.5
Treatment-related AE leading to discontinuation, %	34.9	25.0	53.7	42.9
Any immune-related AE, %	73.6	18.8	86.9	34.0

Presented by: Ahmad Tarhini, MD, PhD, ASCO 2017

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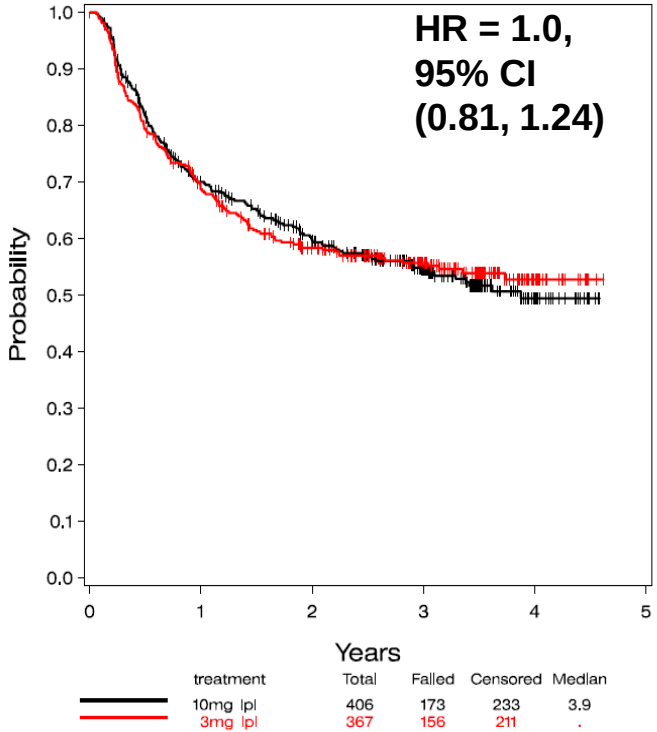
RFS: Ipilimumab 10 mg/kg versus 3 mg/kg

(Concurrently randomized patients)



Presented by: Ahmad Tarhini, MD, PhD ASCO 2017

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Reshaping the future of patient care

Pilot Trial of Adjuvant Nivolumab Therapy for Resected Stage IIIC and IV Melanoma

Induction

Cohort 1

- **NIVO (1 mg/kg) IV + peptide vaccine q2 weeks X 12**

Cohort 2

- **NIVO (3 mg/Kg) IV + peptide vaccine q2 weeks X 12**

Cohort 3

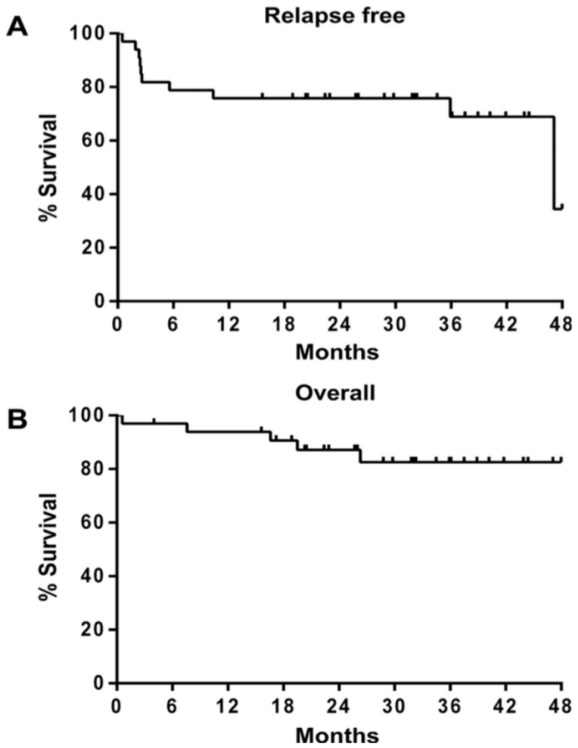
- **NIVO (10 mg/kg) IV + peptide vaccine q2 weeks X 12**

Maintenance

- **NIVO (3 mg/mg) IV q12 weeks X 2 years**

Gibney G, et al. *Clin Cancer Res.* 2015;21(4):712-720.

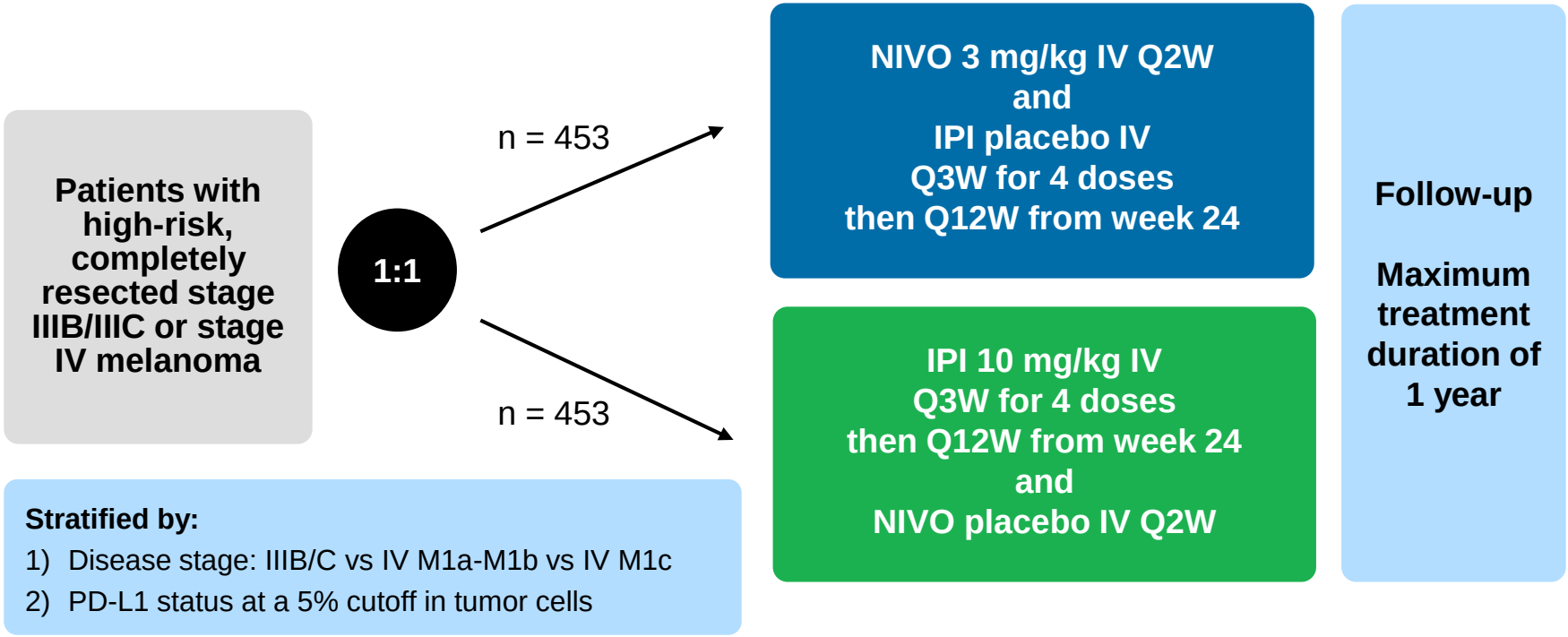
Pilot Trial of Adjuvant Nivolumab Therapy for Resected Stage IIIC and IV Melanoma



Gibney G, et al. *Clin Cancer Res.* 2015;21(4):712-720.

These pilot data justified a trial of adjuvant nivolumab versus standard ipilimumab

CA209-238: Study Design



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

Presented by Jeffrey Weber ESMO 2017 LBA8

Study Overview

Primary endpoint

- RFS: time from randomization until first recurrence (local, regional, or distant metastasis), new primary melanoma, or death

Secondary endpoints

- OS
- Safety and tolerability
- RFS by PD-L1 tumor expression
- HRQoL

Current interim analysis

- Primary endpoint (RFS), safety, and HRQoL
  - DMFS (exploratory)
- Duration of follow-up: minimum 18 months; 360 events

DMFS = distant metastasis-free survival; HRQoL = health-related quality of life

Presented by Jeffrey Weber ESMO 2017 LBA8

Baseline Patient Characteristics

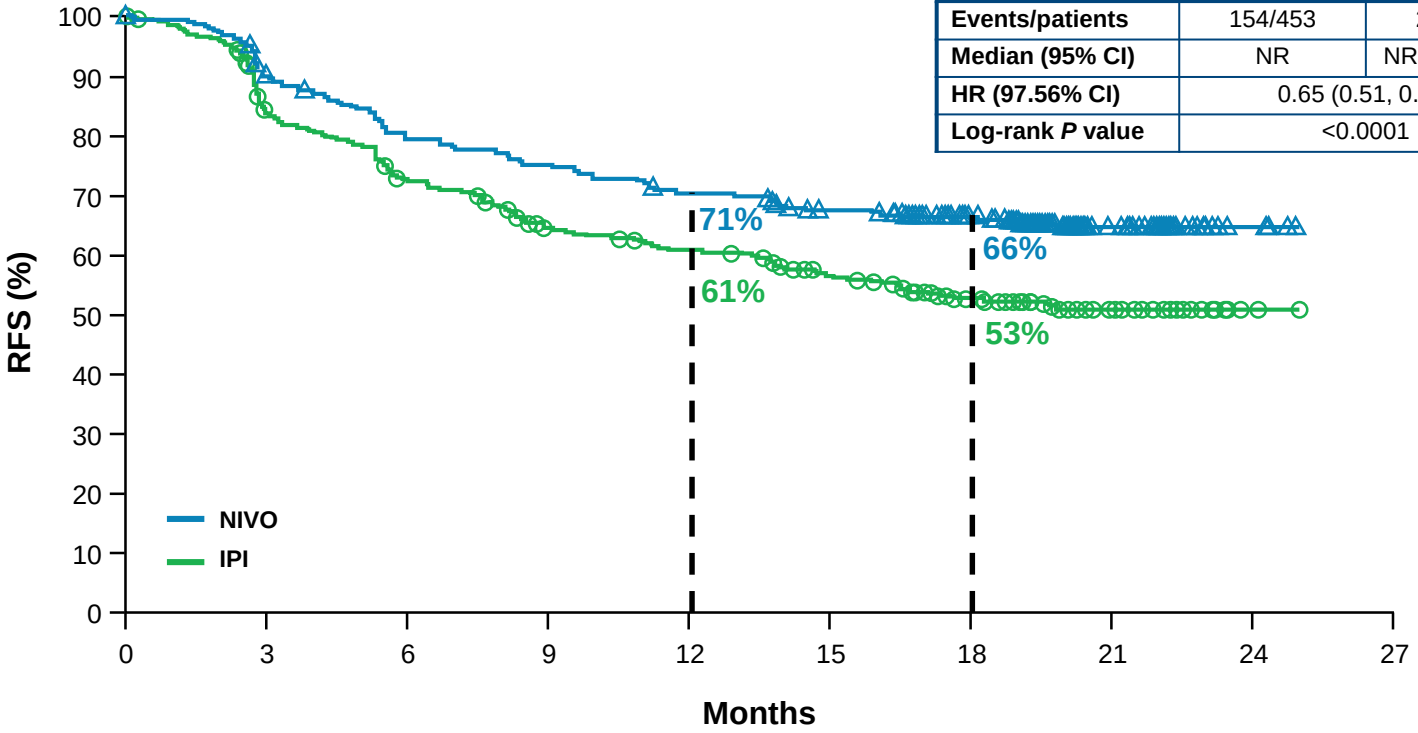
	NIVO (n = 453)	IPI (n = 453)
Median age, years	56	54
Male, %	57	59
Stage, IIIB+IIIC, %	81	81
Macroscopic lymph node involvement (% of stage IIIB+IIIC)	60	58
Ulceration (% of stage IIIB+IIIC)	42	37
Stage IV, %	18	19
M1c without brain metastases (% stage IV)	17	17
PD-L1 expression ≥5%, %	34	34
***BRAF* mutation, %**	41	43
LDH ≤ ULN, %	91	91

- Most of the patients had cutaneous melanoma (85%), and 4% had acral and 3% had mucosal melanoma
- All 905 patients are off treatment; median doses were 24 (1-26) in the NIVO group and 4 (1-7) in the IPI group
- 397 patients completed 1 year of treatment (61% of the NIVO group and 27% of the IPI group)

Presented by Jeffrey Weber ESMO 2017 LBA8, Weber J et al NEJM 2107

Primary Endpoint: RFS

	NIVO	IPI
Events/patients	154/453	206/453
Median (95% CI)	NR	NR (16.6, NR)
HR (97.56% CI)	0.65 (0.51, 0.83)	
Log-rank *P* value	<0.0001	



Number of patients at risk

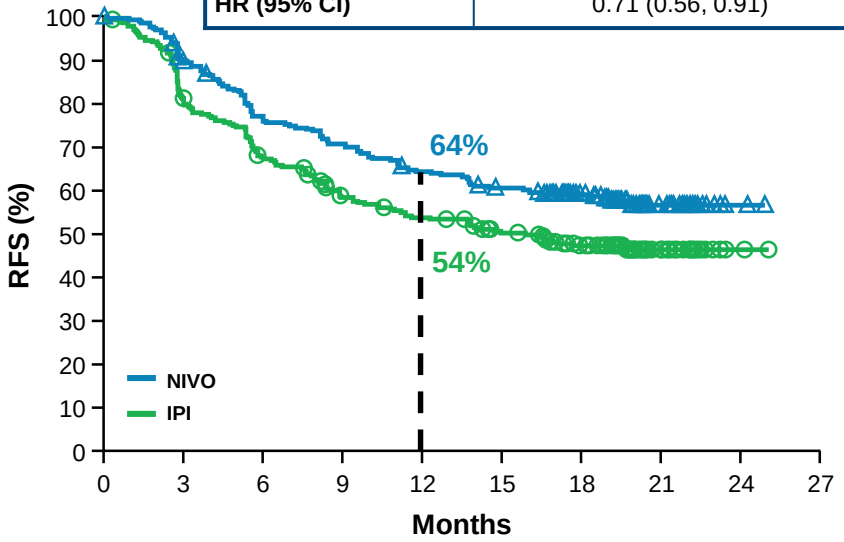
NIVO	453	399	353	332	311	291	249	71	5	0
IPI	453	364	314	269	252	225	184	56	2	0

Presented by Jeffrey Weber ESMO 2017 LBA8; Weber J et al NEJM 2107

Subgroup Analysis of RFS: PD-L1 Expression Level

PD-L1 Expression Level <5%

	NIVO	IPI
Events/patients	114/275	143/286
Median (95% CI)	NR	15.9 (10.4, NR)
HR (95% CI)	0.71 (0.56, 0.91)	

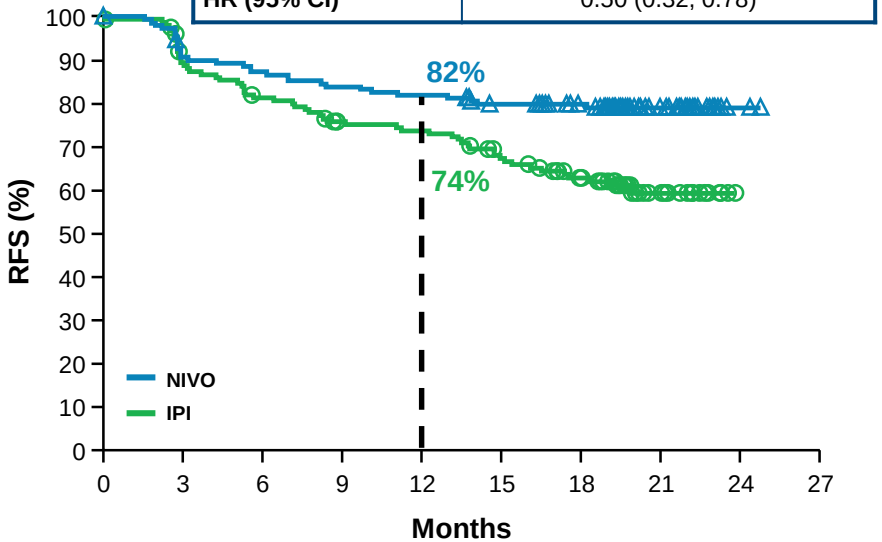


Number of patients at risk

NIVO	275	242	204	189	171	159	129	41	3	0
IPI	286	219	184	153	139	124	100	31	2	0

PD-L1 Expression Level ≥5%

	NIVO	IPI
Events/patients	31/152	57/154
Median (95% CI)	NR	NR
HR (95% CI)	0.50 (0.32, 0.78)	



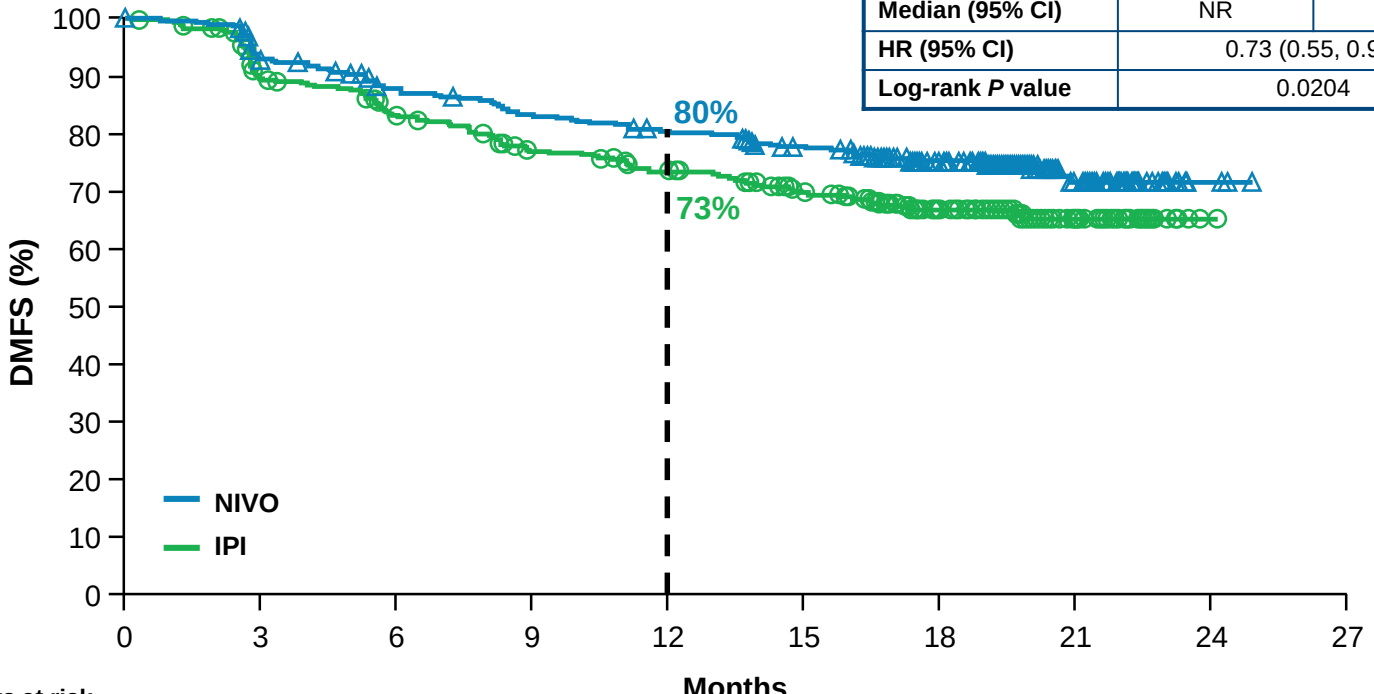
Number of patients at risk

NIVO	152	135	130	125	122	114	105	26	2	0
IPI	154	133	120	108	105	93	78	21	0	0

Presented by Jeffrey Weber ESMO 2017 LBA8; Weber J et al NEJM 2107

Exploratory Endpoint: DMFS for Stage III Patients

	NIVO	IPI
Events/patients	93/369	115/366
Median (95% CI)	NR	NR
HR (95% CI)	0.73 (0.55, 0.95)	
Log-rank *P* value	0.0204	



Number of patients at risk

NIVO	369	335	309	292	280	264	214	62	3	0
IPI	366	312	284	254	239	217	176	51	1	0

Presented by Jeffrey Weber ESMO 2017 LBA8; Weber J et al NEJM 2107

Safety Summary

AE, n (%)	NIVO (n = 452)		IPI (n = 453)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AE	438 (97)	115 (25)	446 (98)	250 (55)
Treatment-related AE	385 (85)	65 (14)	434 (96)	208 (46)
Any AE leading to discontinuation	44 (10)	21 (5)	193 (43)	140 (31)
Treatment-related AE leading to discontinuation	35 (8)	16 (4)	189 (42)	136 (30)

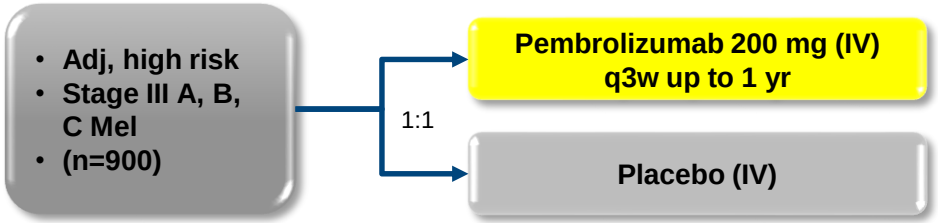
- There were no treatment-related deaths in the NIVO group
- There were 2 (0.4%) treatment-related deaths in the IPI group (marrow aplasia and colitis), both >100 days after the last dose

Presented by Jeffrey Weber ESMO 2017 LBA8; Weber J et al NEJM 2107

Additional Adjuvant Melanoma Studies

KEYNOTE-054: Phase III Pembrolizumab vs. Placebo (EORTC)

Status: fully recruited

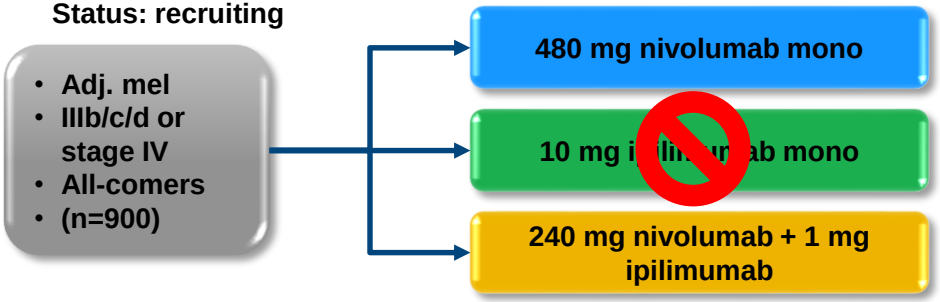


Primary endpoints
RFS (All & PD-L1+)
Secondary endpoints
DMFS (All & PD-L1+),
OS (All & PD-L1+)

First data January 8th, 2018: HR=0.57 for RFS, p=0.0001*

CheckMate 915: Phase 3 Study of Nivo, Ipi, Nivo + Ipi

Status: recruiting



Primary endpoints
RFS
Secondary endpoints
OS, PDL1 expression

KEYNOTE-054: https://clinicaltrials.gov/ct2/show/NCT02362594
CheckMate 915: https://clinicaltrials.gov/ct2/show/record/NCT03068455 Press release, Merck, January 8, 2018*

Next steps? Pilot NIVO + IPI data have justified a new adjuvant trial of NIVO + IPI vs NIVO with new biomarkers

Pilot Trial of Adjuvant Nivolumab/Ipilimumab Therapy for Resected Stage IIIC and IV Melanoma

Induction

Cohort 4

- **NIVO (1 mg/kg) + IPI (3 mg/kg) IV q3 weeks X 4**

Cohort 5

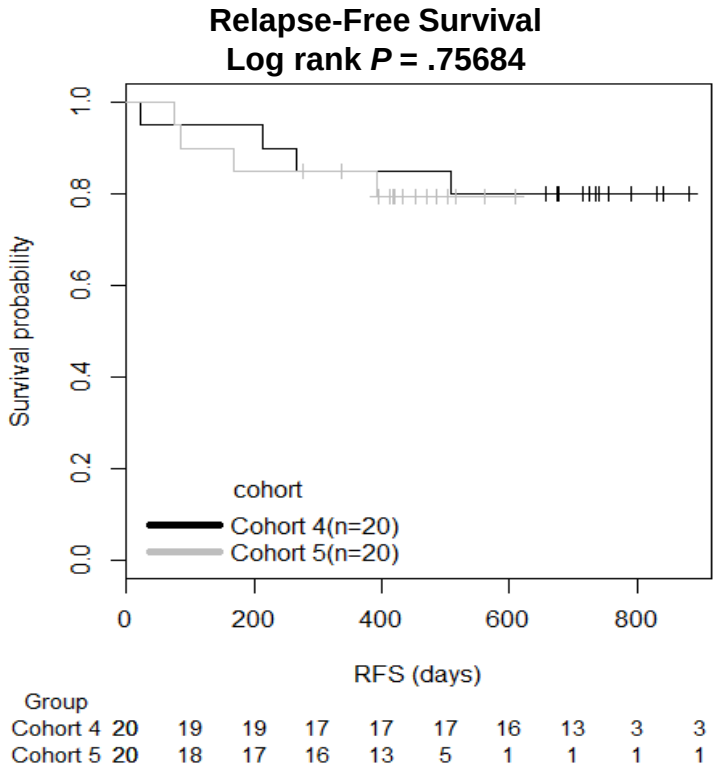
- **NIVO (3 mg/kg) + IPI (1 mg/kg) IV q3 weeks X 4**

Maintenance

- **NIVO (3 mg/mg) IV q2 weeks X 2 years**

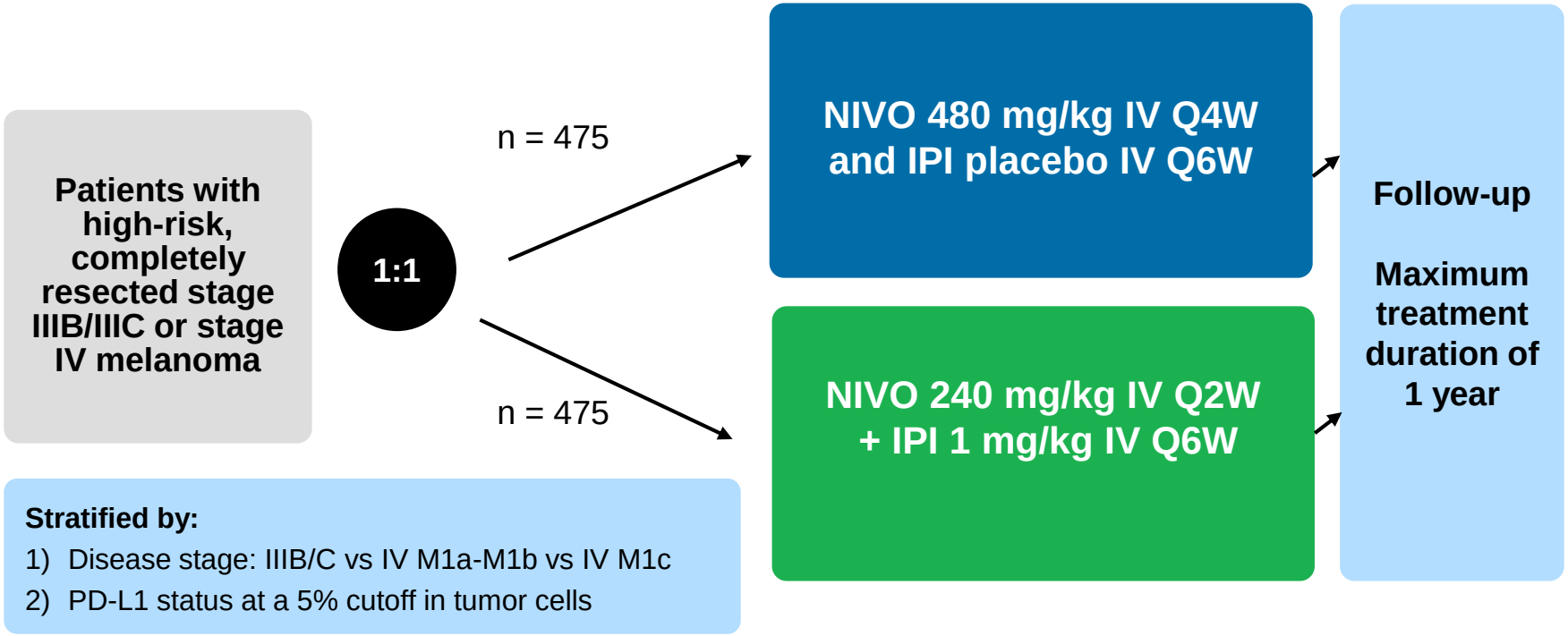
Khushalani NI, et al. *J Clin Oncol.* 2016;34(suppl): Abstract 9586.

Pilot Trial of Adjuvant Nivolumab/Ipilimumab Therapy for Resected Stage IIIC and IV Melanoma



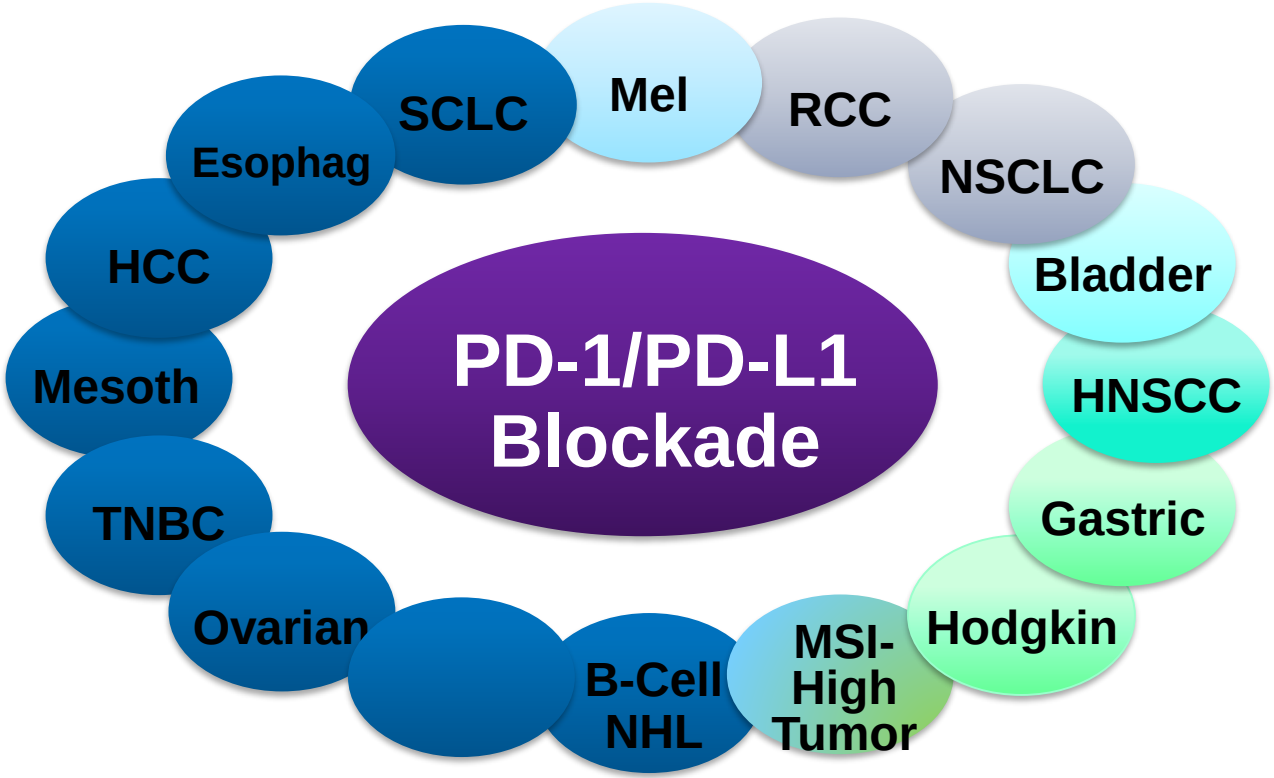
Khushalani NI, et al. *J Clin Oncol.* 2016;34(suppl): Abstract 9586.

CA209-915: Study Design



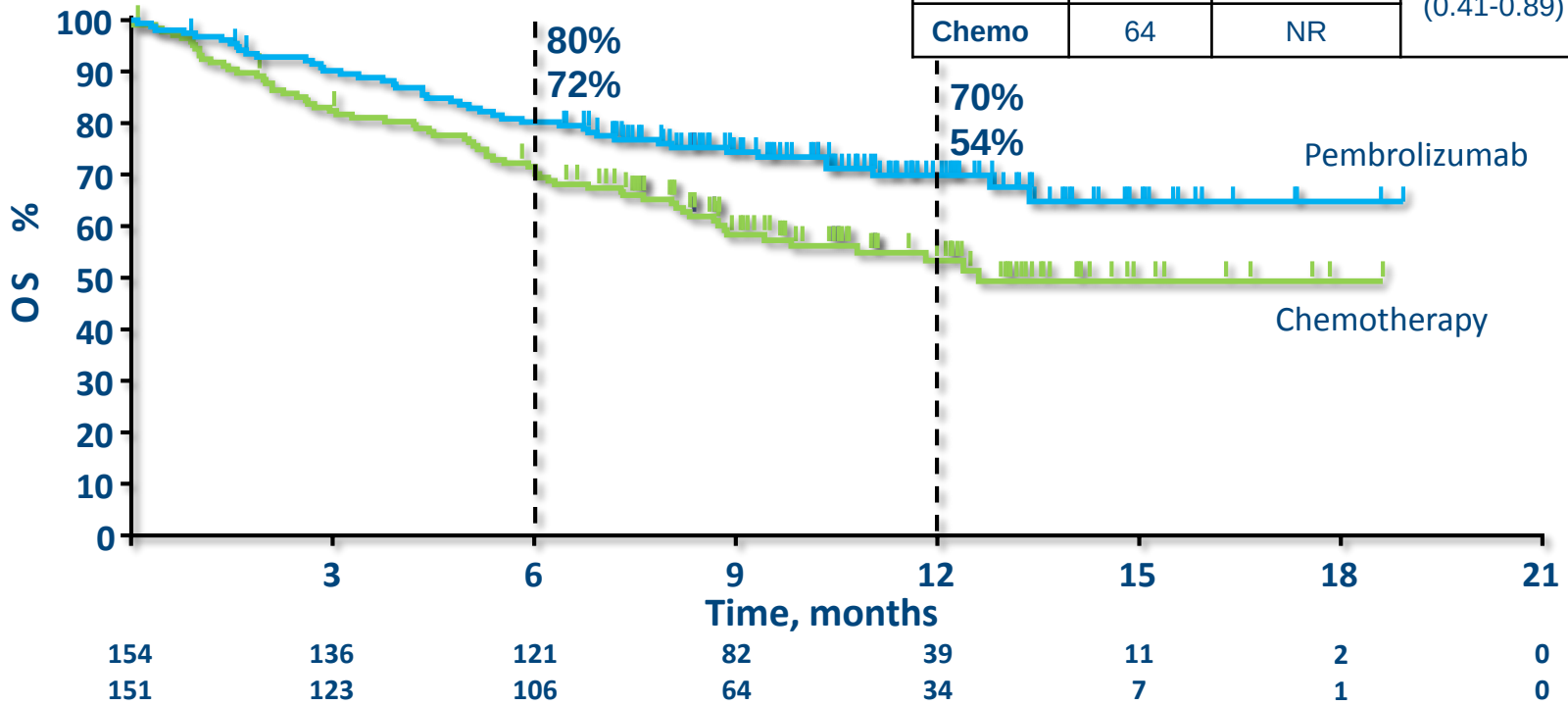
Anticipated enrollment period: September 30, 2017 to November 30, 2018

PD-1/PDL1 blockade is now an approved and accepted therapy in oncology; the end of the beginning



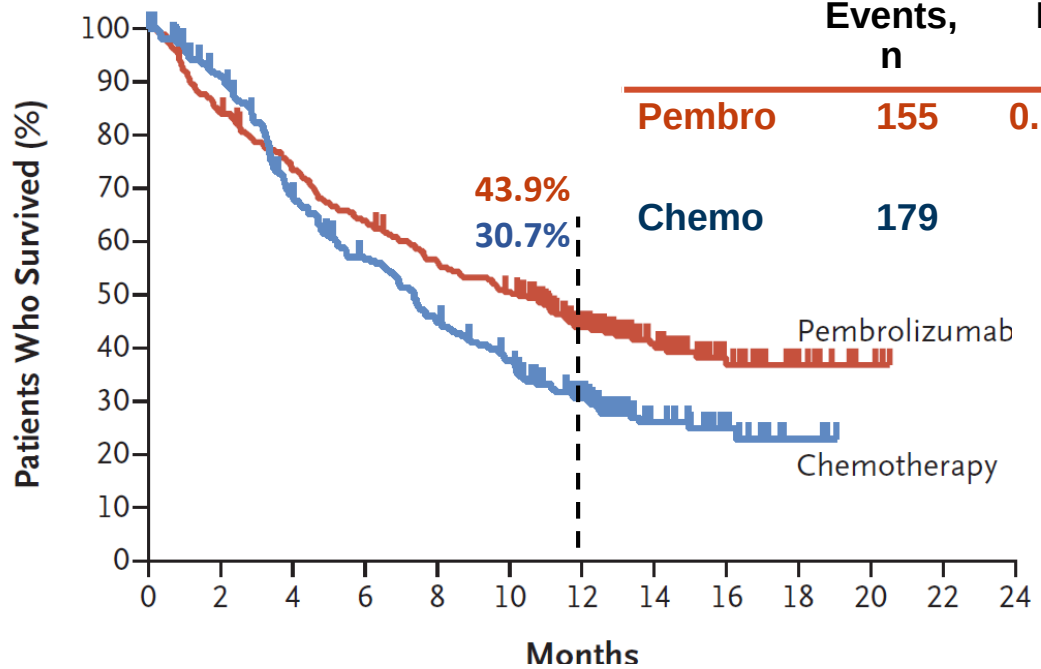
KEYNOTE-024: NSCLC Overall Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	44	NR	0.60 (0.41-0.89)	.005
Chemo	64	NR		



Reck M, et al. *N Engl J Med*. 2016.

KEYNOTE-045 Study: Overall Survival for First-line CDDP Ineligible Bladder CA



	Events, n	HR (95% CI)	*P*
Pembro	155	0.73 (0.59-0.91)	0.0022
Chemo	179		

Median (95% CI)
10.3 mo (8.0-11.8)
7.4 mo (6.1-8.3)

No. at risk

270	226	194	169	147	131	87	54	27	13	4	0	0
272	232	171	138	109	89	55	27	14	3	0	0	0

Bellmunt J, et al. *N Engl J Med.* 2017.

What About The Future of Immunotherapy for Cancer?

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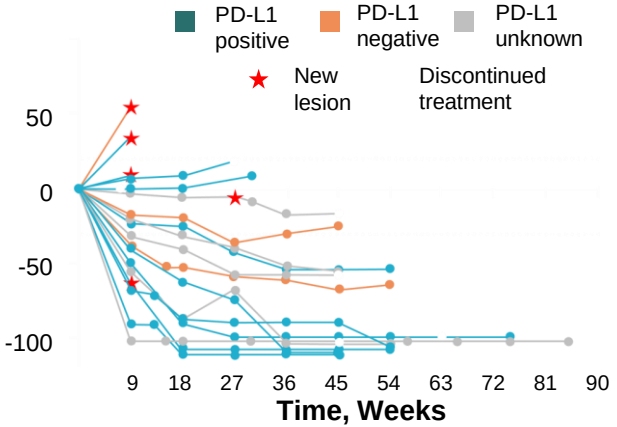
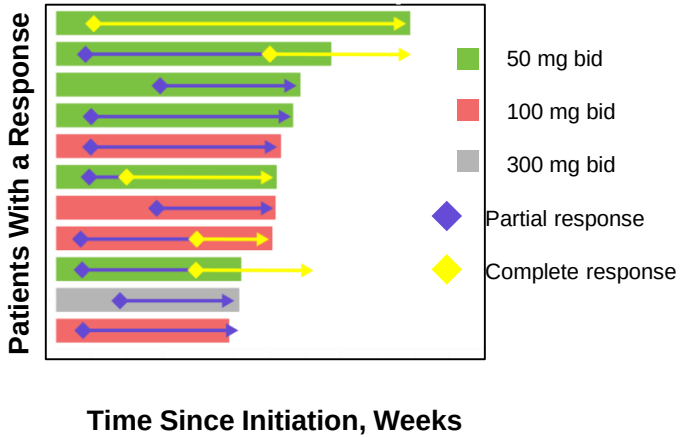
Phase 1b Pembrolizumab + Epacadostat: Efficacy

Best Overall Response by RECIST

Response	Treatment-Naïve Melanoma, n (%) (n=19)
ORR (CR + PR)	**11 (58)**
CR	5 (26)
PR	6 (32)
SD	3 (16)
DCR (CR+PR+SD)	**14 (74)**
PD	5 (26)

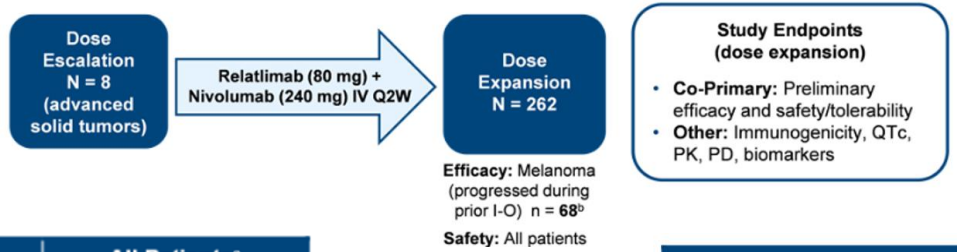


Best Percentage Change in Target Lesions



Gangadhar TC, et al. Poster. ESMO. 2016 (abstr 1110PD).

LAG-3 Antibody Relatlimab (BMS-986016) with Nivolumab to Overcome PD-1 Resistance

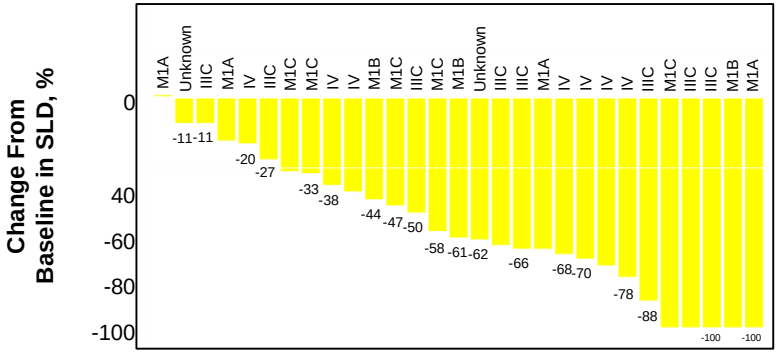


	All Patients[a] N = 270	
	Any Grade n (%)	Grade 3–4 n (%)
Any TRAE[b]	137 (51)	27 (10)
TRAEs in ≥ 5% of patients		
Fatigue	30 (11)	0
Pruritus	19 (7.0)	0
Diarrhea	18 (6.7)	3 (1.1)
Arthralgia	17 (6.3)	0
Infusion-related reaction	15 (5.6)	0
Any serious TRAE[b]	18 (6.7)	12 (4.4)
Serious TRAEs in > 1 patient		
Colitis	4 (1.5)	3 (1.1)
Pneumonitis	2 (0.7)	2 (0.7)
Myocarditis[c]	2 (0.7)	0
Pyrexia	2 (0.7)	0
Any TRAE leading to discontinuation[b]	11 (4.1)	8 (3.0)

	Mel Prior PD-(L)1[a]	
	All n = 61	LAG-3 ≥ 1%[b] n = 33
ORR, n (%)[c] 95% CI	7 (11.5)[d] 4.7, 22	6 (18)[d] 7, 35.5
BOR, n (%)[c]		
CR	1 (1.6)	1 (3.0)
PR	6 (9.8)[d]	5 (15)[d]
SD	23 (38)	15 (45)
PD	25 (41)	8 (24)
Clinical progression[e]	6 (9.8)	4 (12)
DCR (CR + PR + SD), n (%)[c] 95% CI	30 (49) 36, 62	21 (64) 45, 80

Ascierto et al, presented at ESMO 2017

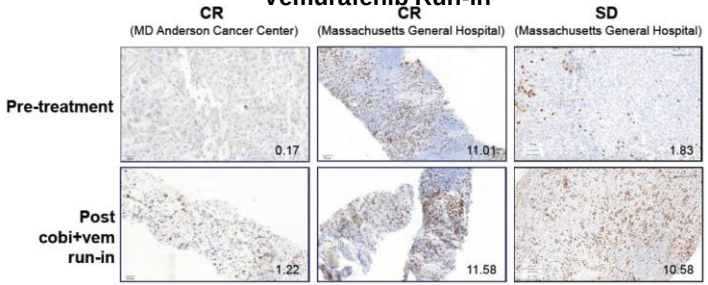
GP28384 Triplet of Vemurafenib + Cobimetinib + Atezolizumab: Melanoma Expansion Cohort Reduction in Tumor Burden



Any Reduction in Tumor Burden	28/29 (96.5%)
100% Reduction in Tumor Burden*	5//29 (17%)
Median Duration of Response†	NE
Median PFS†	NE (95% CI, 6.8 months-NE)

*3 patients who had a 100% reduction in tumor burden were considered PRs due to the lack of confirmatory scans or remaining non-target lesions.
†Due to limited follow-up time at the time of data cutoff, the median DOR was not estimable. For the same reason, the median PFS was not estimable.

Tumor CD8⁺ T Cells Before and After Cobimetinib + Vemurafenib Run-in



Numbers in each panel represent percentage of CD8⁺ cells in the tumor center. All images are shown at 40x magnification.

Sullivan R et al ASCO 2017

The Future of Immunotherapy for Cancer

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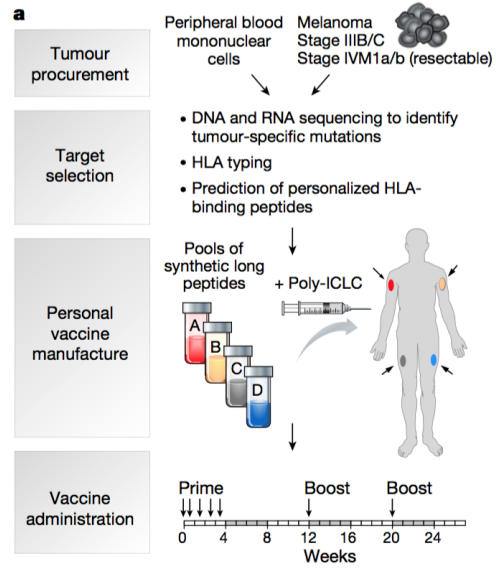
Schema of the peptide neoantigen vaccine trial

16-18 weeks to prepare vaccine peptides

Low level of CD8 responses, little evidence of potent anti-neo epitope reactivity by CD8 cells without re-stimulation, good level of CD4 responses

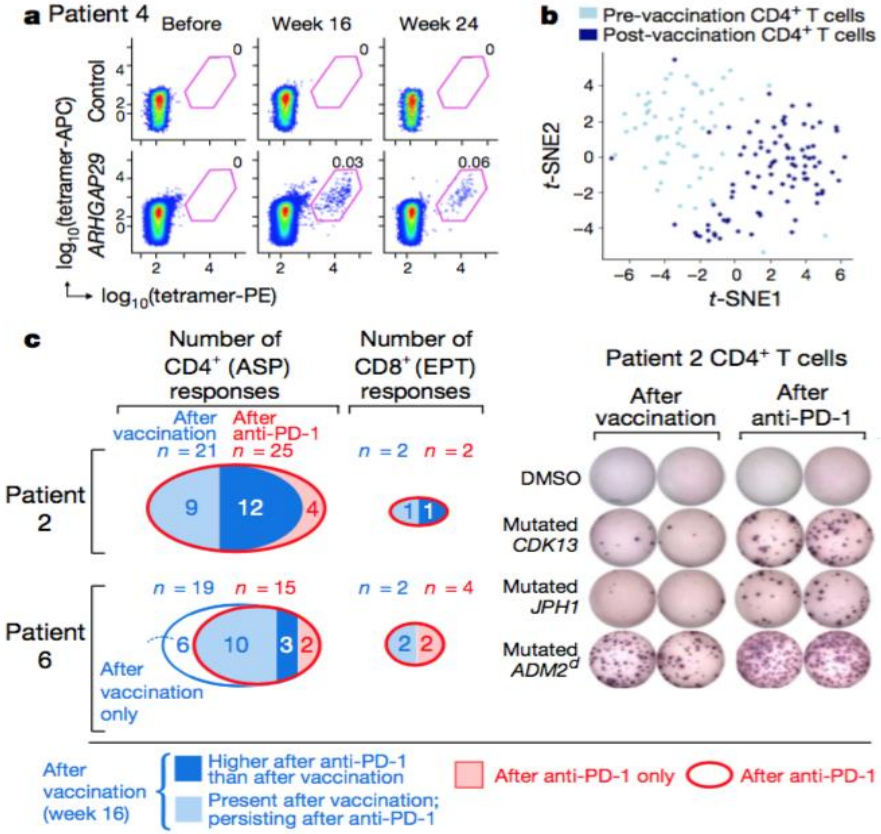


Responses seen in the supplementary data seemed mostly by PET and with small volume disease

Impossible to interpret the four resected stage III patients that did not relapse; the two responders both had no response to peptides alone but did respond to nivolumab post vaccination

Ott P et al Nature 2017

Evolution of CD4 T cell responses post vaccine



Ott P et al Nature 2017

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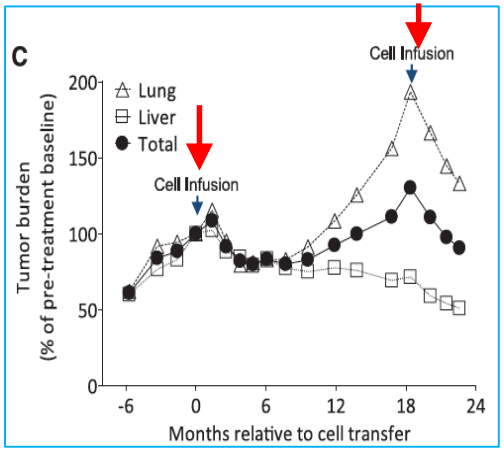
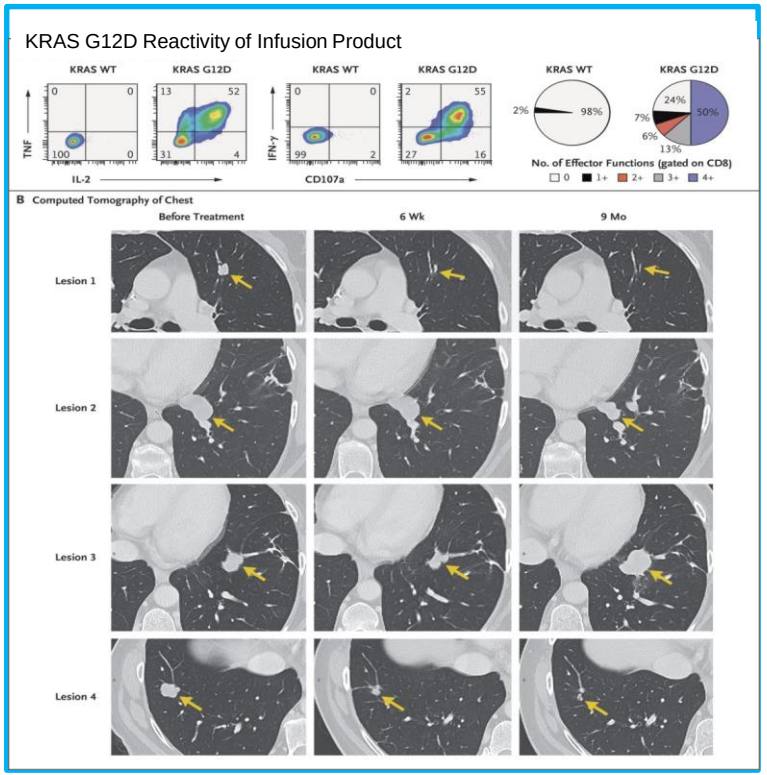
Mutated neo-epitopes can be harnessed to induce potent anti-cancer immunity in advanced solid tumors

1. Neoepitopes can be harnessed to induce effective T cell responses
2. Tumor regression after **neoepitope directed** TIL therapy in a patient with cholangiocarcinoma (Left) and KRAS-mutated CRC (Right)

Infusion ERBB2IP mutation specific CD4 TILs leads to tumor regression



Infusion of KRAS G12D mutation specific CD8 TILs leads to tumor regression



Tran E et al NEJM 2016

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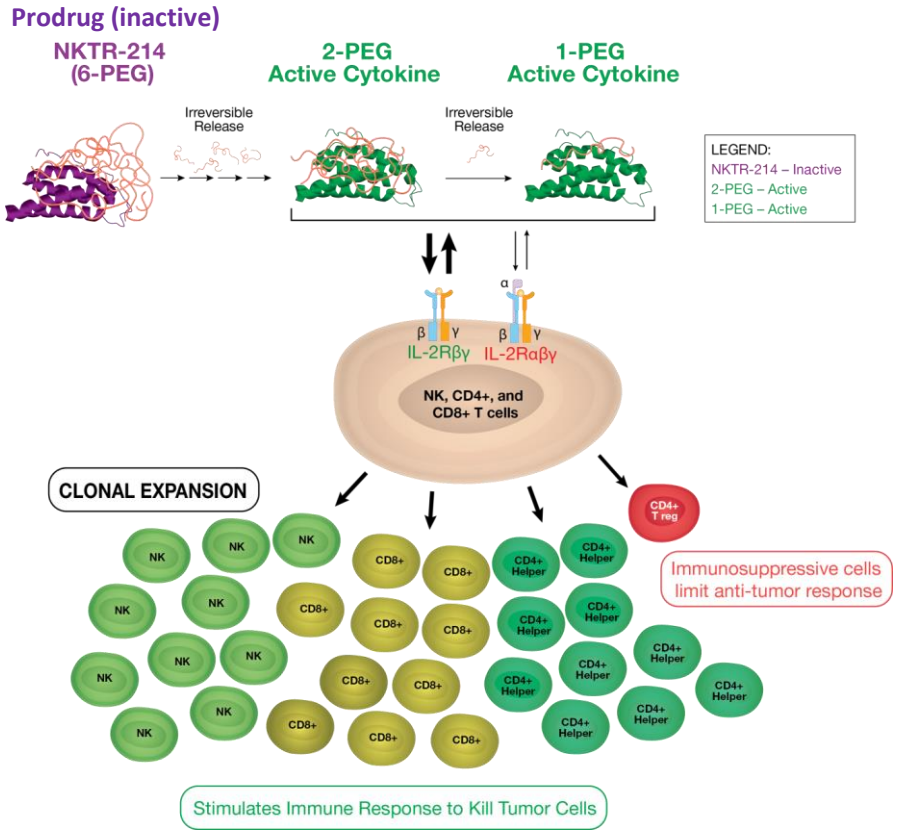
NKTR-214 Background: Harnessing the IL-2 Pathway to Increase TILs



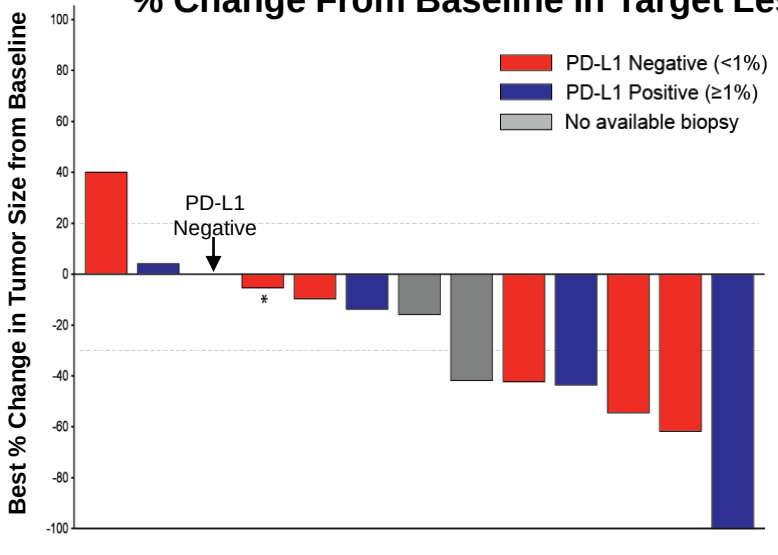
- NKTR-214 prodrug design with sustained signaling
- Q2W or Q3W Dosing
- Mitigation of rapid immune stimulation to achieve safe, outpatient regimen
- Biased signaling preferentially activates and expands effector T cells and NK cells over Tregs in the tumor microenvironment
- Increases proliferation of TILs and PD1 expression on effector T cells in the tumor microenvironment

Stage IV Treatment-Naïve 1L Renal Cell Carcinoma (N=13)

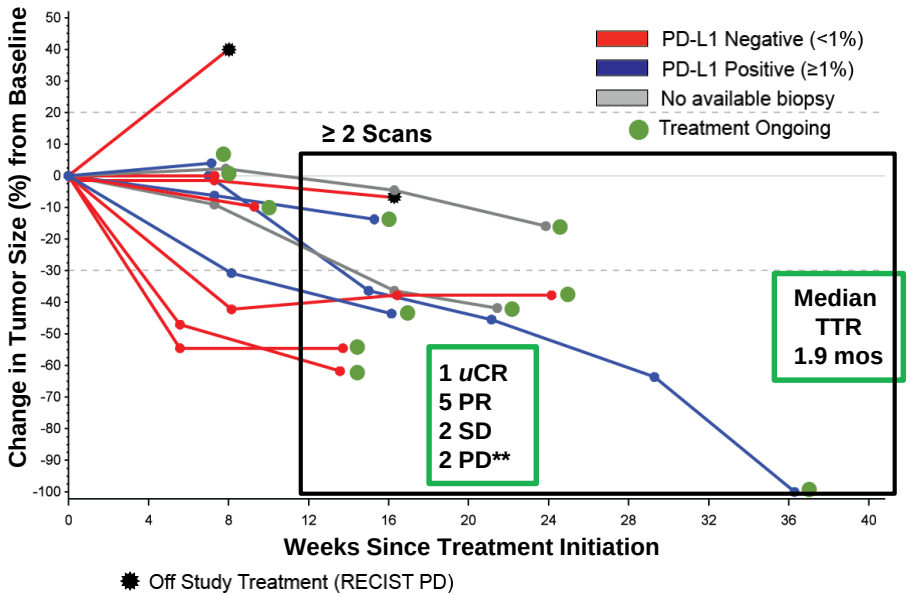
Efficacy-evaluable patients with ≥1 or ≥2 post baseline scans

Best ORR by RECIST ≥1 post baseline scan: ORR=6/13 (46%); DCR=11/13 (85%)
Best ORR by RECIST ≥2 post baseline scans: ORR=6/10 (60%); DCR=8/10 (80%)

% Change From Baseline in Target Lesions



% Change in Target Lesions Over Time



Daub, A et al SITC 2017

Horizontal dotted lines indicate the thresholds for PD and response according to RECIST (version 1.1) criteria. * Best overall response is PD (SD for target lesions, PD per non-target lesions). **Includes PD with 1 post base-line scan

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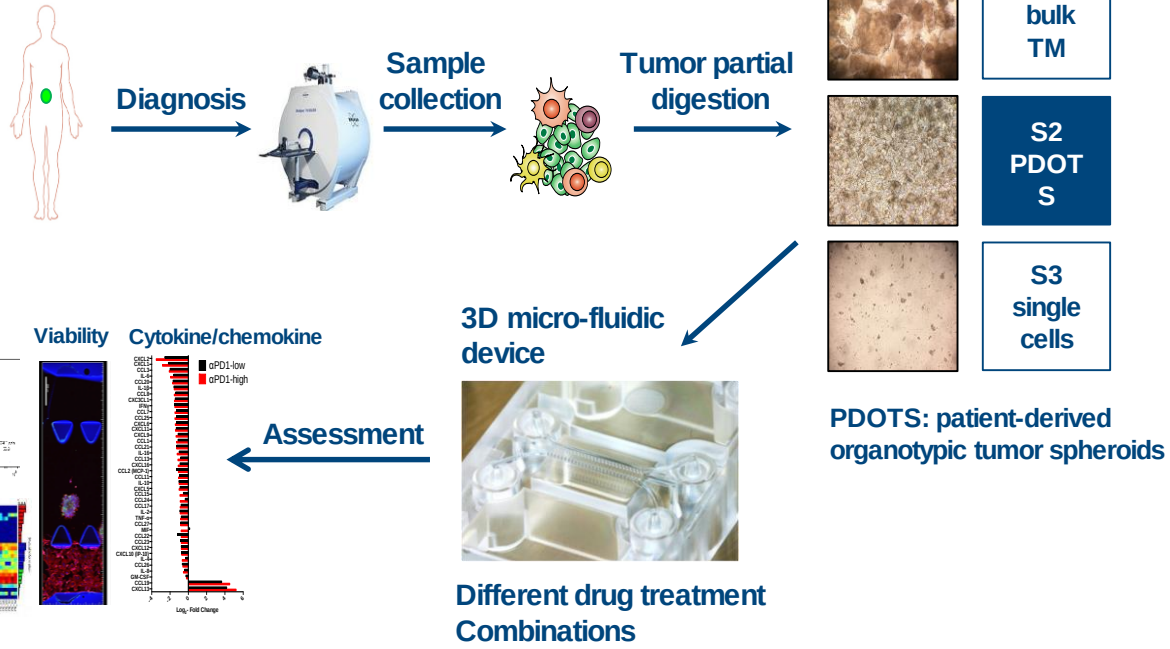
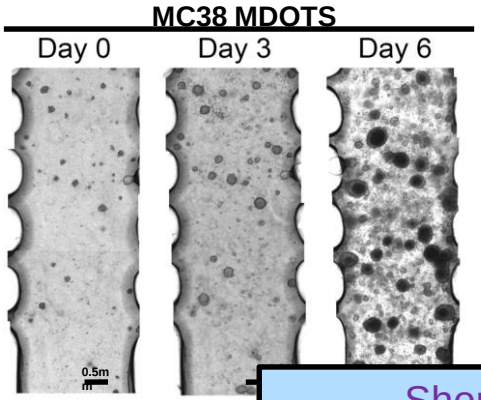
A NEW SYSTEM FOR CO/PRE CLINICAL CANCER TREATMENT STUDIES

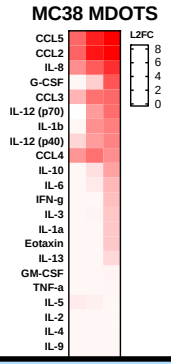
Organotypic tumor spheroid three-dimensional microfluidic culture system

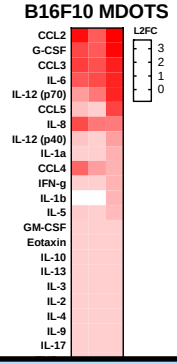


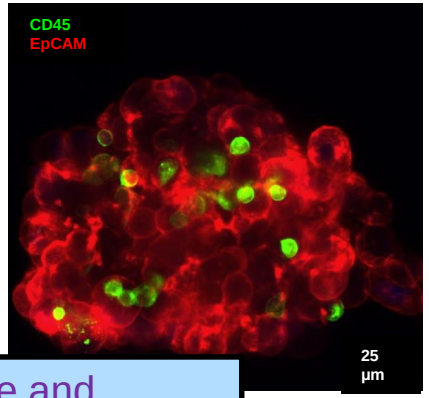
Wong, K-K et al 2017 unpublished

Ex vivo culture of MDOTS/PDOTS

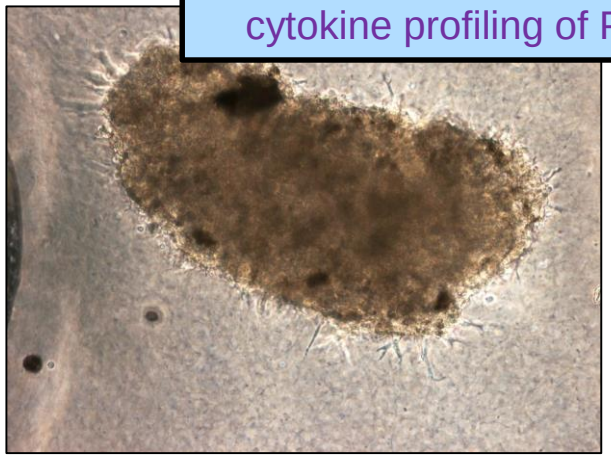


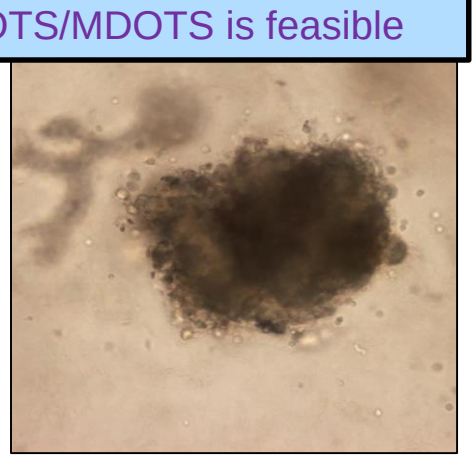






Short-term 3D microfluidic culture and cytokine profiling of PDOTS/MDOTS is feasible





Wong, K-K et al 2017 unpublished

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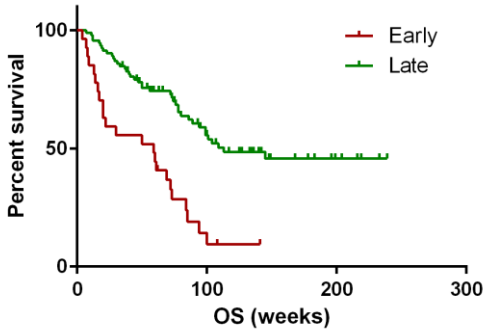
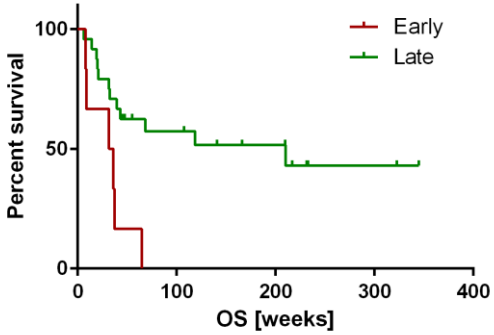
Are there peripheral blood markers predictive of benefit from PD-1 blockade: Mass spec protein serum signature

(Weber, J et al Can Immunol Res 2017)

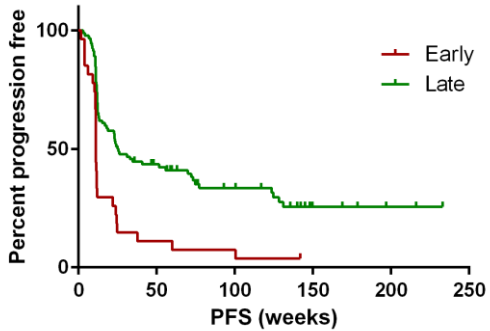
OS with nivolumab



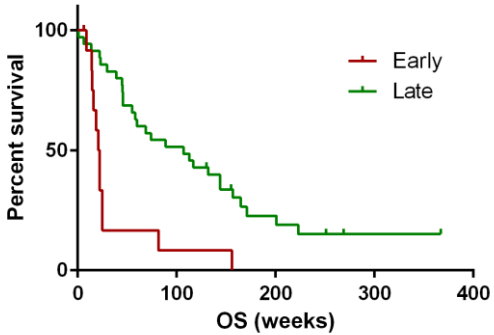
OS with pembrolizumab



PFS with nivolumab



PFS with ipilimumab



Correlation of Protein Sets with Mass Spec/MALDI-TOF Signature

ProteinSetDescription	Enrichment score	p value
Acute inflammatory response	0.347	0.132
Activation of innate immune response	0.550	0.242
Regulation of adaptive immune response	0.328	0.585
Positive regulation of glycolytic process	-0.338	0.756
Immune T-cells	-0.220	0.669
Immune B-cells	-0.111	1.00
Cell cycle regulation	0.165	0.981
Natural killer regulation	-0.383	0.457
Complement system	0.502	0.036
Acute response	0.497	0.162
Cytokine activity	-0.284	0.384
Wound healing	-0.477	0.007
Interferon	0.209	0.809
Interleukin-10	0.175	0.891
Growth factor receptor signaling	-0.176	0.876
Immune Response Type 1	-0.225	0.981
Immune Response Type 2	0.430	0.675
Acute phase	0.608	0.004
Hypoxia	0.189	0.920
Cancer	0.193	0.544

Proteins significantly associated in the reference sets.

Complement:

+: CRP, C9, C3a, C3, SAP, mannose binding C, C3b, C1r, CFB,CF1

-: P-Selectin

Wound healing:

-: Histidine/proline rich GP, gelsolin, ApoE2, ApoE, ApoE4, Prekallikrein, platelet GP Ibα, α2-antiplasmin, angiostatin

Acute phase:

+: CRP, SAA, α1-antitrypsin, Q14624, SAP, lipopolysaccaride binding, mannose binding C, haptoglobin

+/-: relates to sign of correlation.

At the $p < 0.05$ level there are correlations of the class labels with the protein sets corresponding to pathways related to wound healing, acute phase, and complement.

J Weber et al., Can Immunol Res 2017

Conclusions:

- There is a bright future for cancer immunotherapy
- The best is yet to come, but….

Remember those who resist…...