Updates in Melanoma

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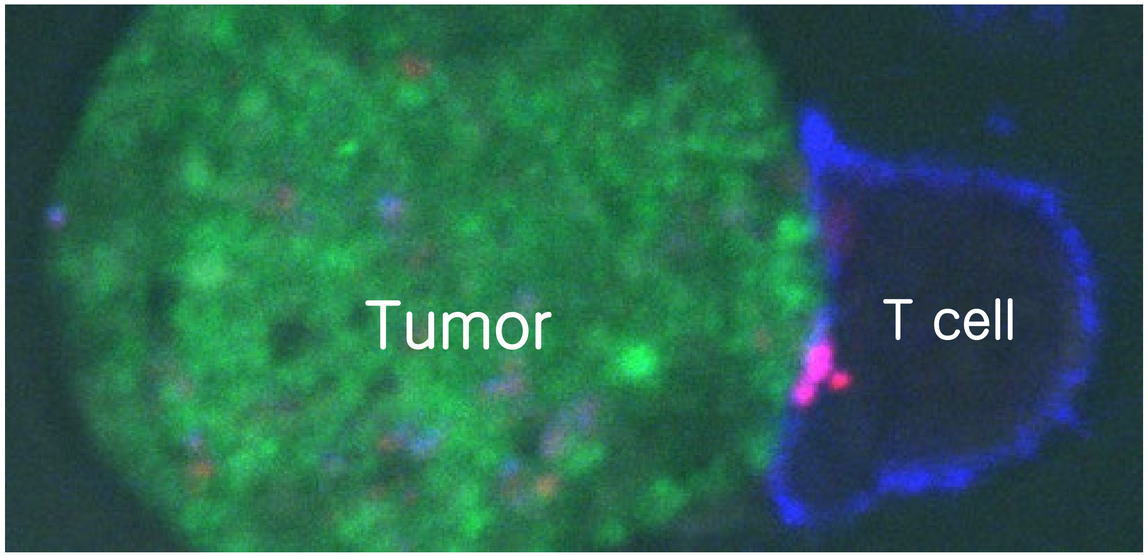

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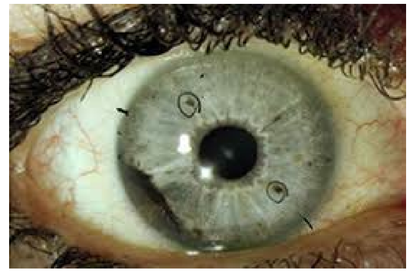
Disclosure of Conflicts of Interest

Daniel Johnson, MD, has the following financial relationships to disclose:

- Speaker – Astrazeneca, BMS, Pfizer
- Advisory Board/Consultant – Nektar Therapeutics

Melanoma Subtypes



Cutaneous

> 95%

Most common

Strong association with UV light

Acral

2-3%

Palms, Soles, Nail Beds

Not associated with UVR

Mucosal

1-2%

C-KIT mutations

Not associated with UVR

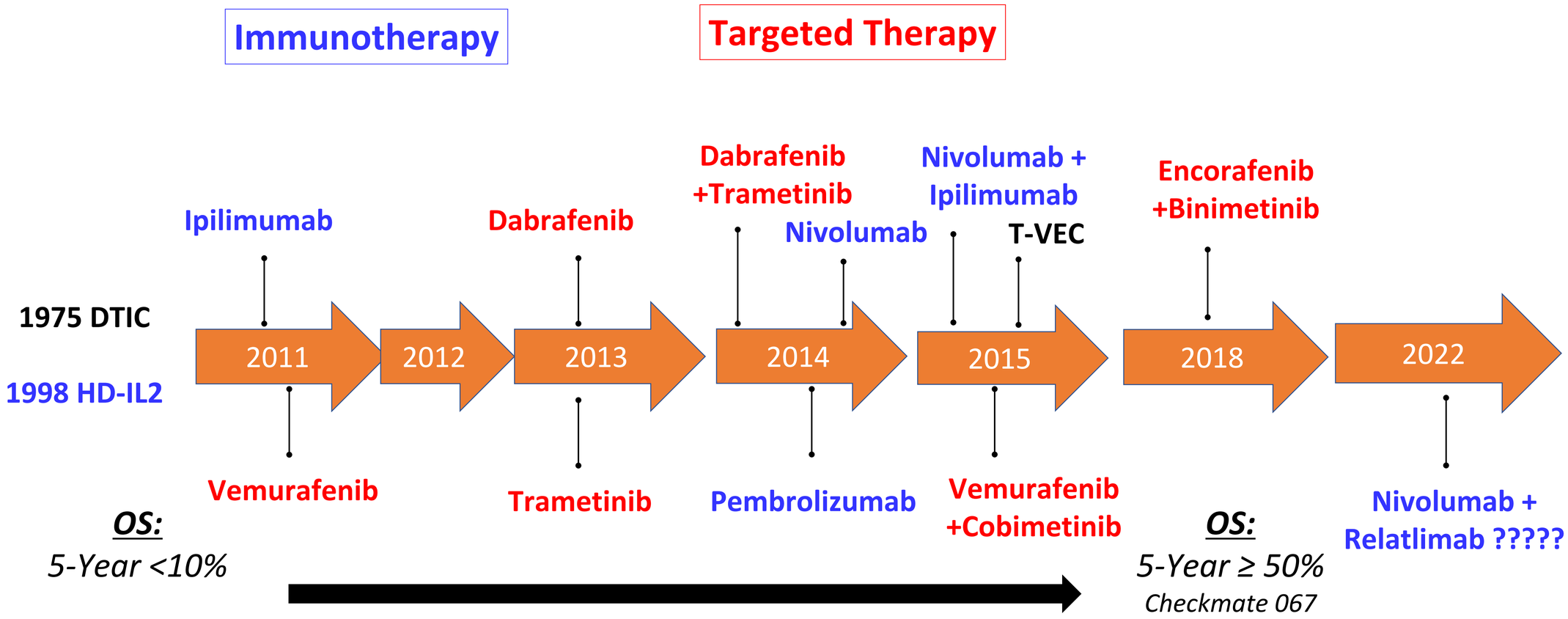
Uveal

<1%

GNA11, GNAQ mutations

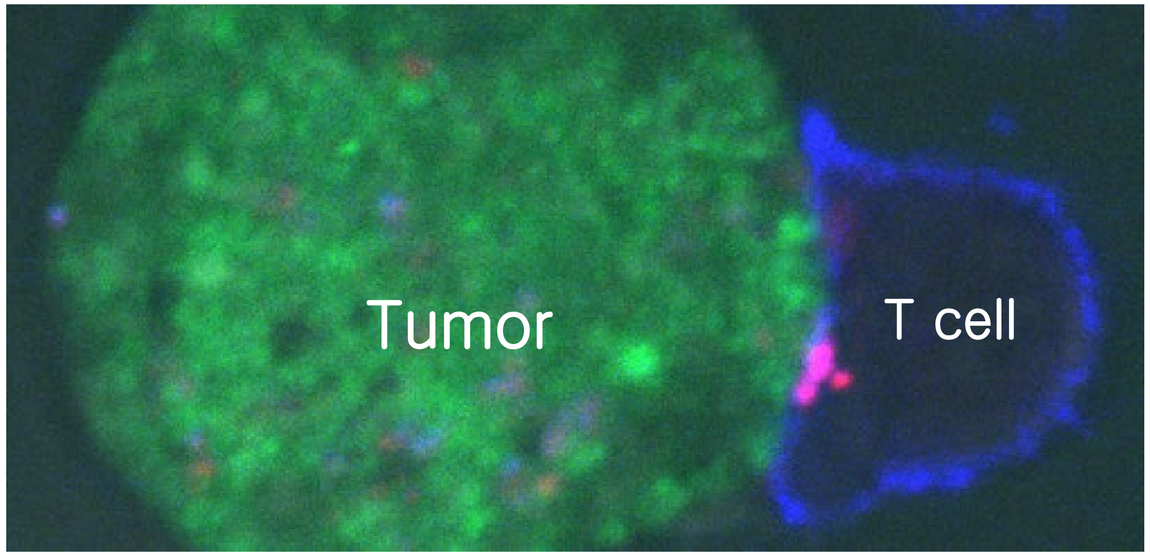
Not associated with UVR, Mets to liver

Advancements in Systemic Therapy Melanoma

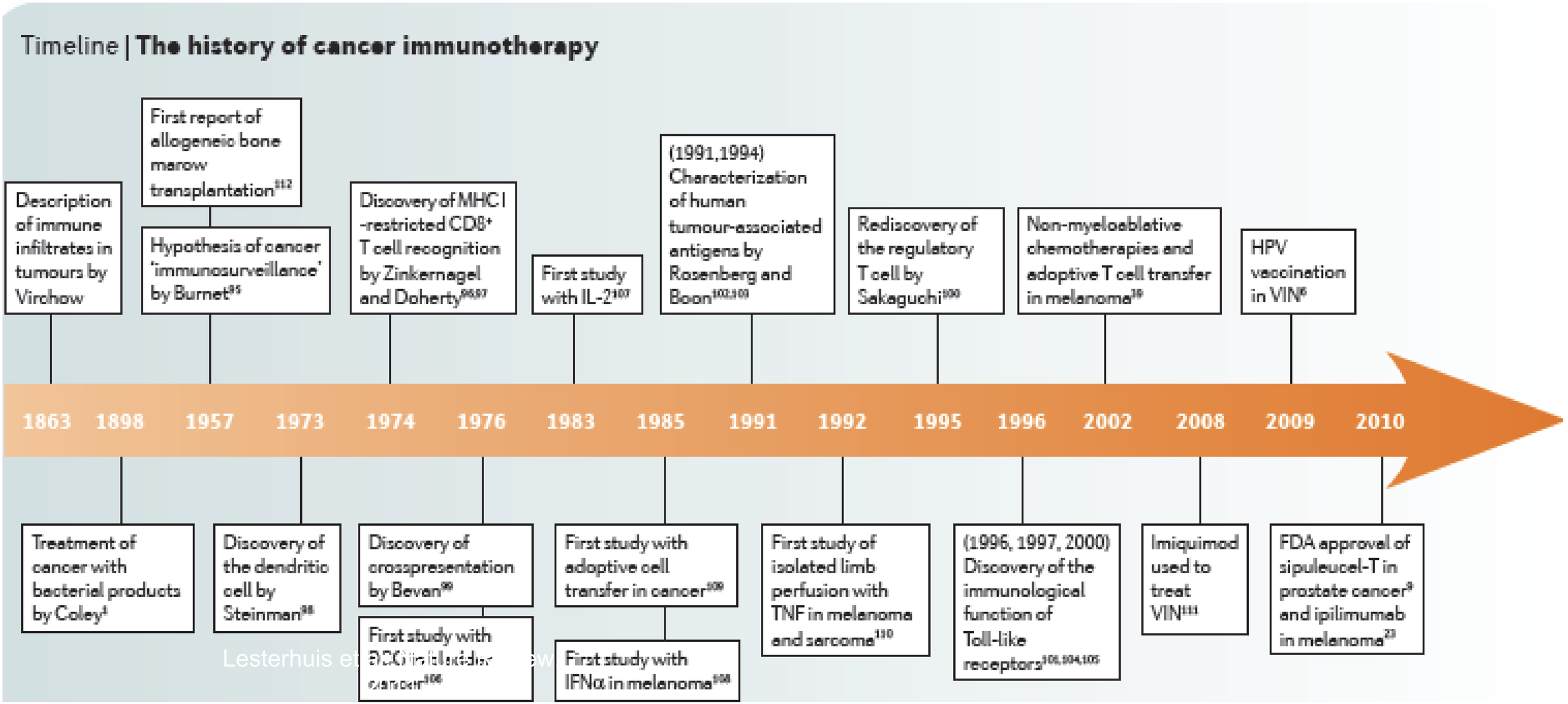


Advancements in Systemic Therapy Melanoma

Immunotherapy!!!!!



History


Timeline | The history of cancer immunotherapy
Description of immune infiltrates in tumours by Virchow
First report of allogeneic bone marow transplantation[112]
Hypothesis of cancer 'immunosurveillance' by Burnet[95]
Discovery of MHC I -restricted CD8+ T cell recognition by Zinkernagel and Doherty[96,97]
First study with IL-2[107]
(1991,1994) Characterization of human tumour-associated antigens by Rosenberg and Boon[102,103]
Rediscovery of the regulatory T cell by Sakaguchi[100]
Non-myeloablative chemotherapies and adoptive T cell transfer in melanoma[39]
HPV vaccination in VIN[8]
1863
1898
1957
1973
1974
1976
1983
1985
1991
1992
1995
1996
2002
2008
2009
2010
Treatment of cancer with bacterial products by Coley[4]
Discovery of the dendritic cell by Steinman[98]
Discovery of crosspresentation by Bevan[99]
First study with BCG in bladder cancer[106]
First study with adoptive cell transfer in cancer[109]
First study with IFNα in melanoma[108]
First study of isolated limb perfusion with TNF in melanoma and sarcoma[110]
(1996, 1997, 2000) Discovery of the immunological function of Toll-like receptors[101,104,105]
Imiquimod used to treat VIN[111]
FDA approval of sipuleucel-T in prostate cancer[9] and ipilimumab in melanoma[23]

Did You Say Cure?

High Dose IL-2

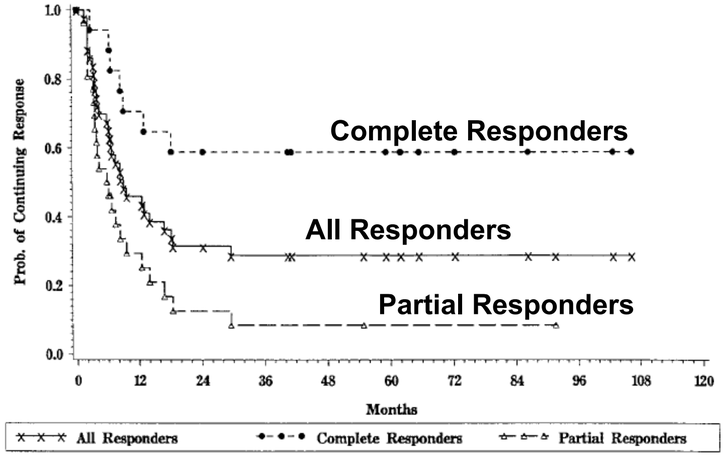
- FDA Approval for Stage IV, 1998
- Cytokine that stimulates effector T-cells
- ORR ~15%, Complete Response Rate (CR) ~6%
- Very Toxic
  - Hypotension, third spacing, renal, respiratory, psych
  - ~2% mortality in initial trials

Strengths

- Long-term OS in 5%
- Proof-of-concept that stage IV melanoma pts can be cured

Weaknesses

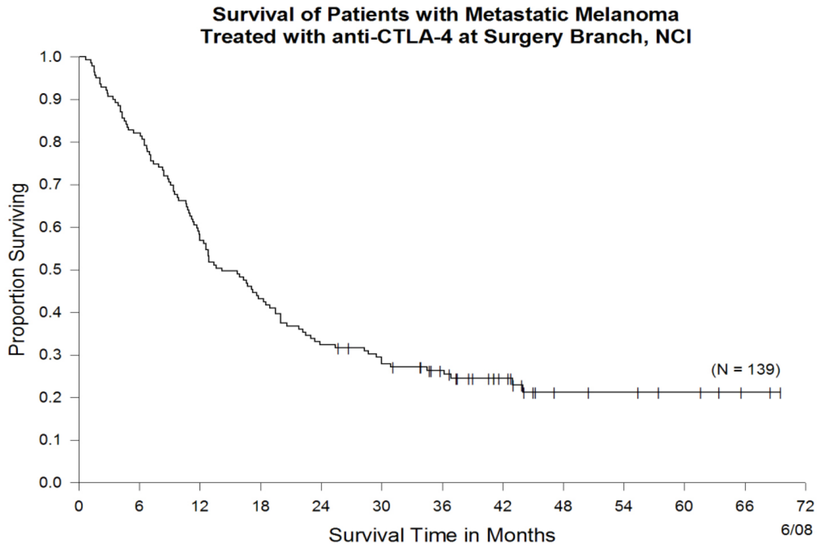
- Low response rate
- Can only be given in specialized centers
- Patients must be selected carefully



Atkins, *JCO*, 1999

CTLA-4 Blockade

Ipilimumab/Yervoy



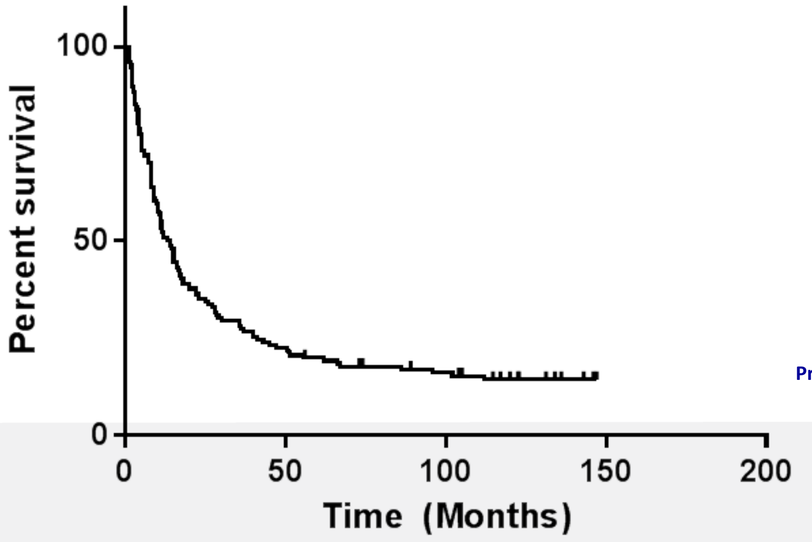
10 yr survival rate: 22%

Hodi, et al, ESMO 2013

Dr. Jim Allison

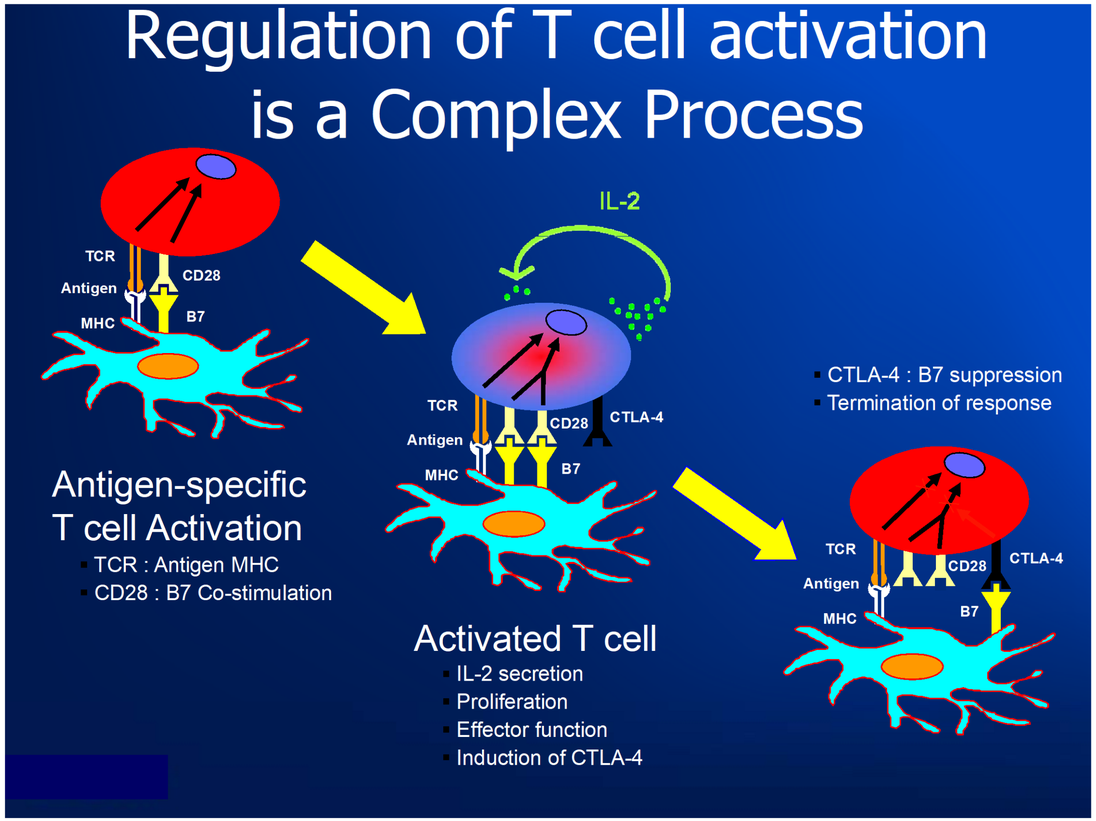
Tremelimumab

10 yr outcome UCLA and MDACC



N= 147 (M1c:54%)
Median OS= 14 months
Response rate: 15%
5 yr survival rate: 19.7%
10 yr survival rate: 18.6%

Prieto P A et al. Clin Cancer Res 2012;18:2039-2047



CTLA-4 Blockade

Ipilimumab

- FDA Approval for Stage IV, 2011
- Anti-CTLA4 antibody
- 3 mg/kg q 3 weeks X 4 doses
- 1st (+) phase III trial in stage IV melanoma

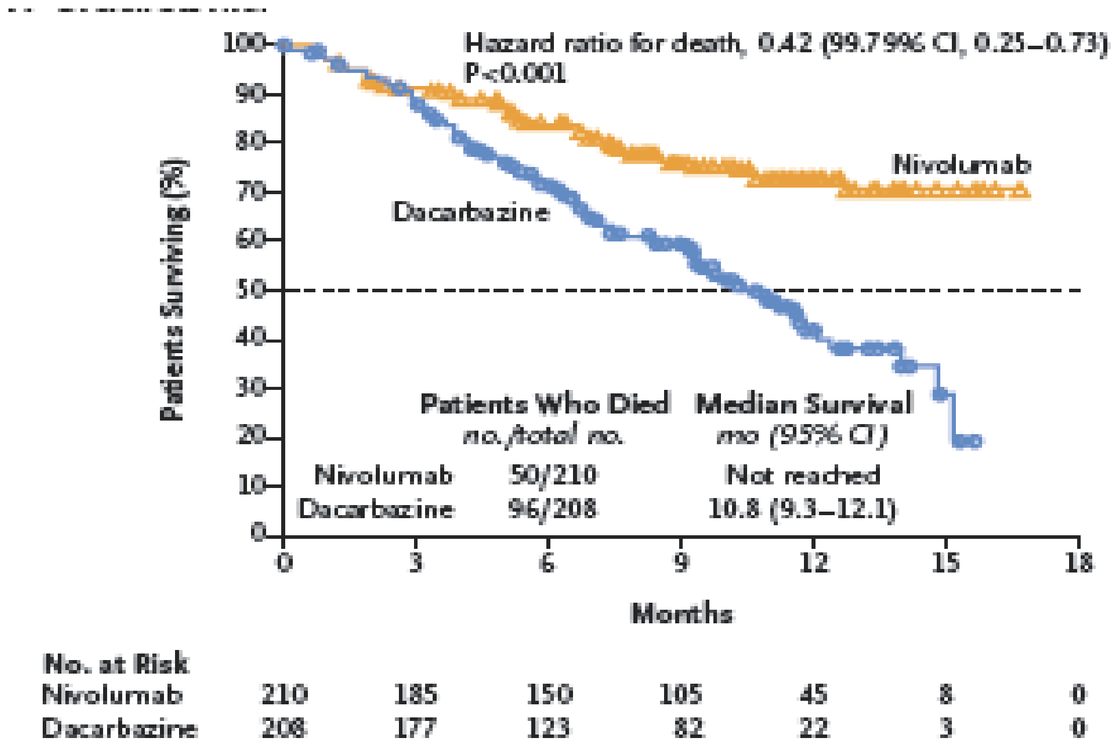
Strengths vs HD IL2

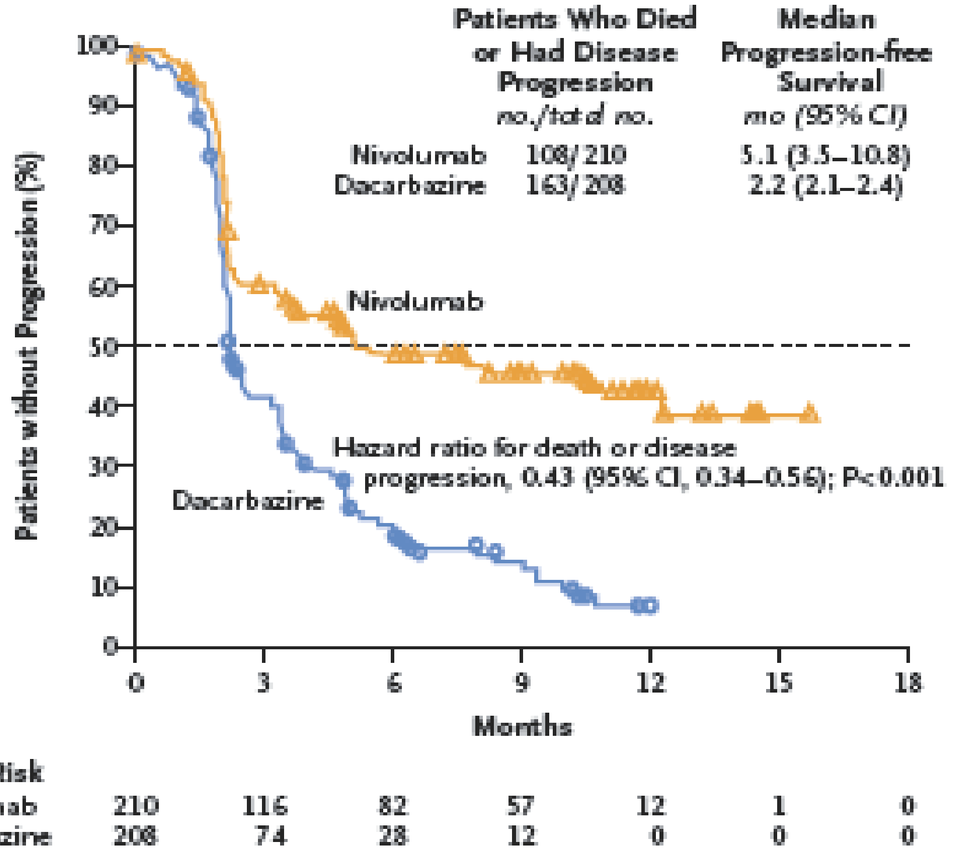
- Higher Response Rates
- Long-term OS in ~20%
- Minimal acute toxicity

Weaknesses

- Responses often slow in onset, or after pseudoprogression
- Autoimmune toxicities can be severe (~20% grade 3-4)

PD-1 Blockade





	ORR	CR	PR	SD	PD
Nivolumab	40%	7.6%	32.4%	16.7%	32.9%
Chemotherapy	13.9%	1.0%	13.0%	22.1%	48.6%

Long, et al SMR 2014; Robert, *NEJM,* 2014

PD-(L)1 Blockade

- FDA Approvals
  - Pembrolizumab, 2014: q 3 weeks for up to 2 years
    2020: q 6 weeks for up to 2 years
  - Nivolumab, 2014: q 2 weeks for up to 2 years
    2018: q 4 weeks for up to 2 years
- Clinical Activity
  - Clinical Response rates 30-45%
    - More rapid than ipilimumab
  - Superior ORR, PFS, and OS in RCT versus
    - Chemotherapy
    - Ipilimumab
- Safety
  - <5% Grade III-IV autoimmune toxicities
  - ~10% stop treatment due to toxicity
  - Safe in patients with toxicities with prior Ipi or autoimmune disease (Weber et al, Lancet 2017; Menzies et al, ASCO 2016)

Strengths vs Ipi

- Higher ORR; Faster responses
- Markedly less toxicity
- Improved PFS & OS

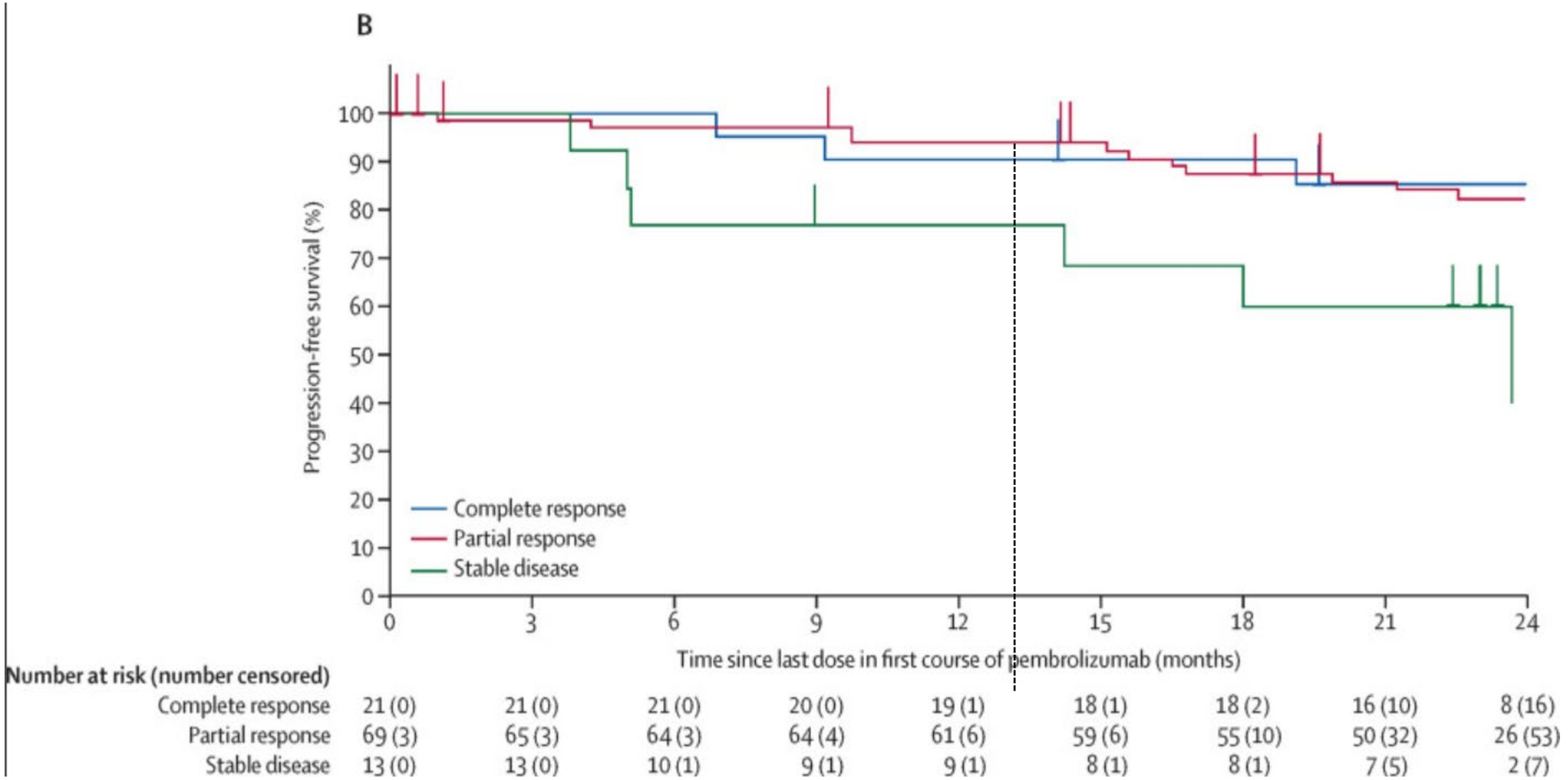
Weaknesses

- 2 years of treatment
- Still defining how many patients are cured (Late recurrences, less long-term follow up)

Can we discontinue anti-PD-1?

Keynote-006 PFS after D/C Pembro

- 103 pts who completed 2 years Pembro, stopped tx per protocol
- Min. 18 mos follow up PFS by best OR:
  - **CR 96%**
  - **PR 91%**
  - **SD 67%**
- 8 patients were re-treated with pembro and evaluable:
  - 1 CR
  - 4 PR
  - 1 SD
  - 1 PD

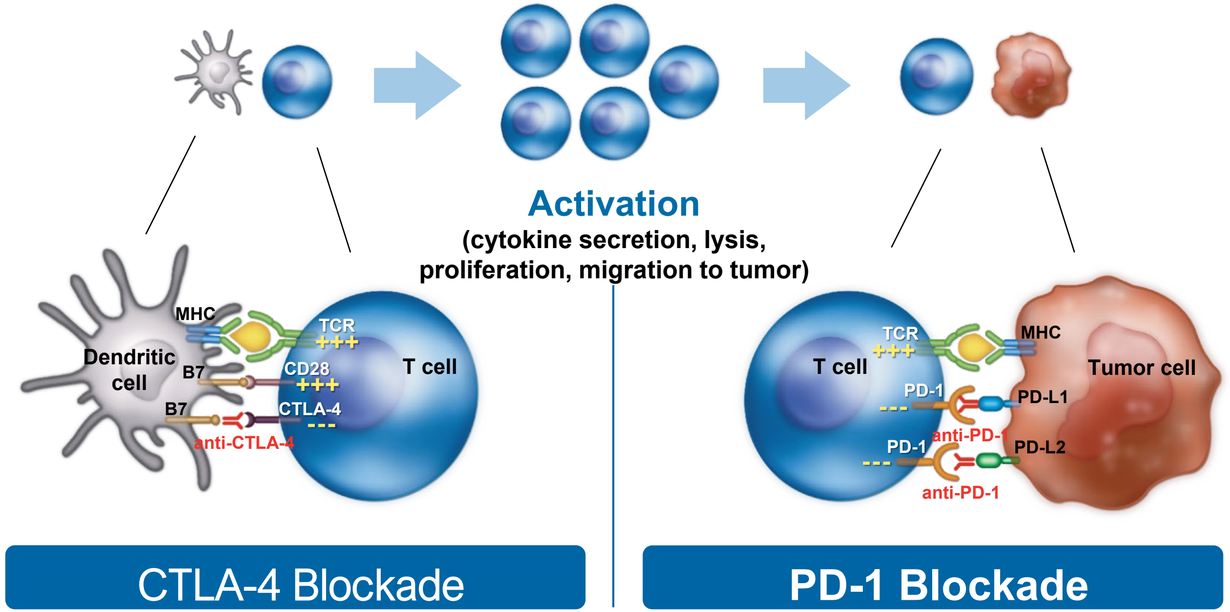


Long et al, Lancet 2018

Mechanistic Differences CTLA-4 vs PD-1

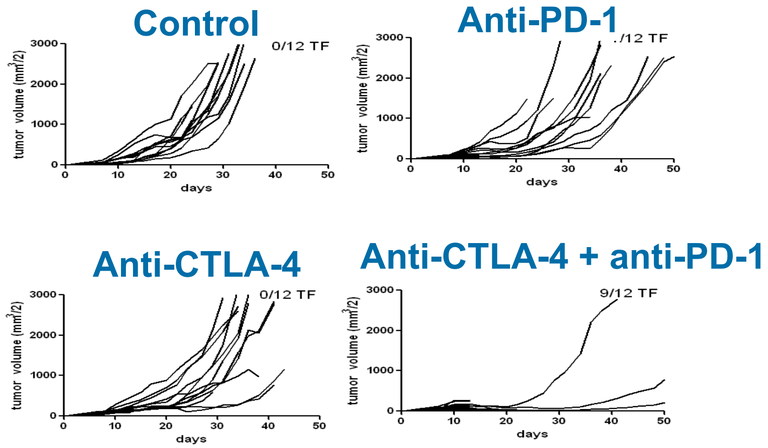
APC – T-cell Interaction

Tumor Microenvironment

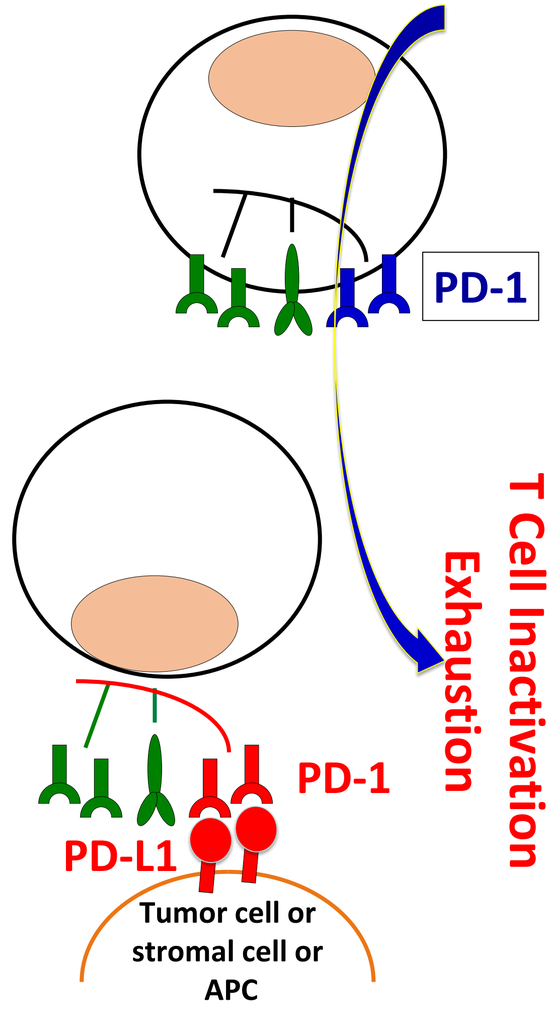


CTLA-4 Blockade

PD-1 Blockade

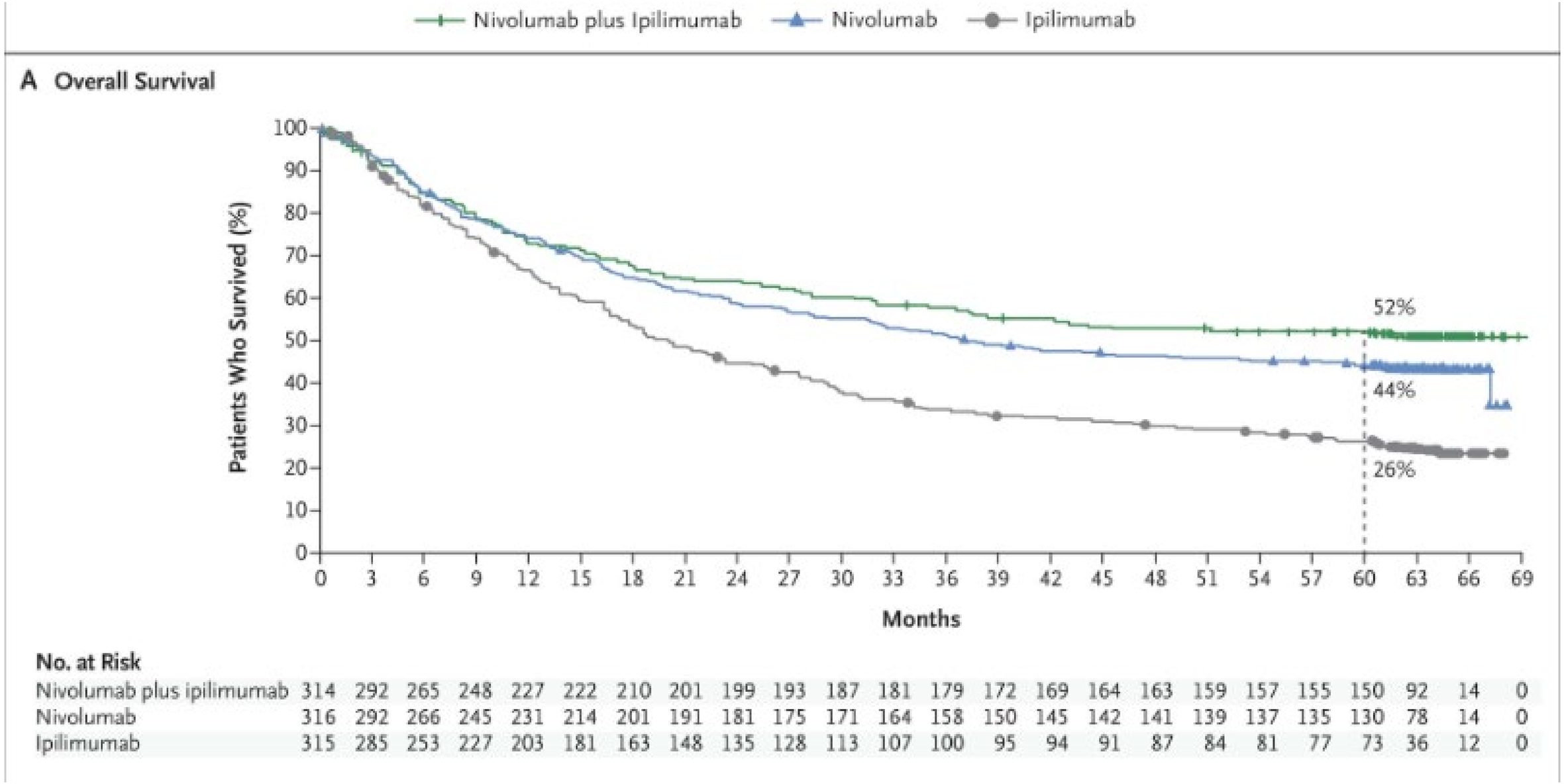


Adaptive Immune Resistance



1.Korman et al. *J Immunol* 2007;178:48.37.
2.Selby et al. ASCO 2013, abs 3061.

Ipilimumab + Nivolumab – Checkmate 067



No. at Risk

Nivolumab plus ipilimumab	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
Nivolumab	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

Larkin, LAncet, 2021

Combination Ipilimumab/Nivolumab AE Data

Table 3. Adverse Events.*

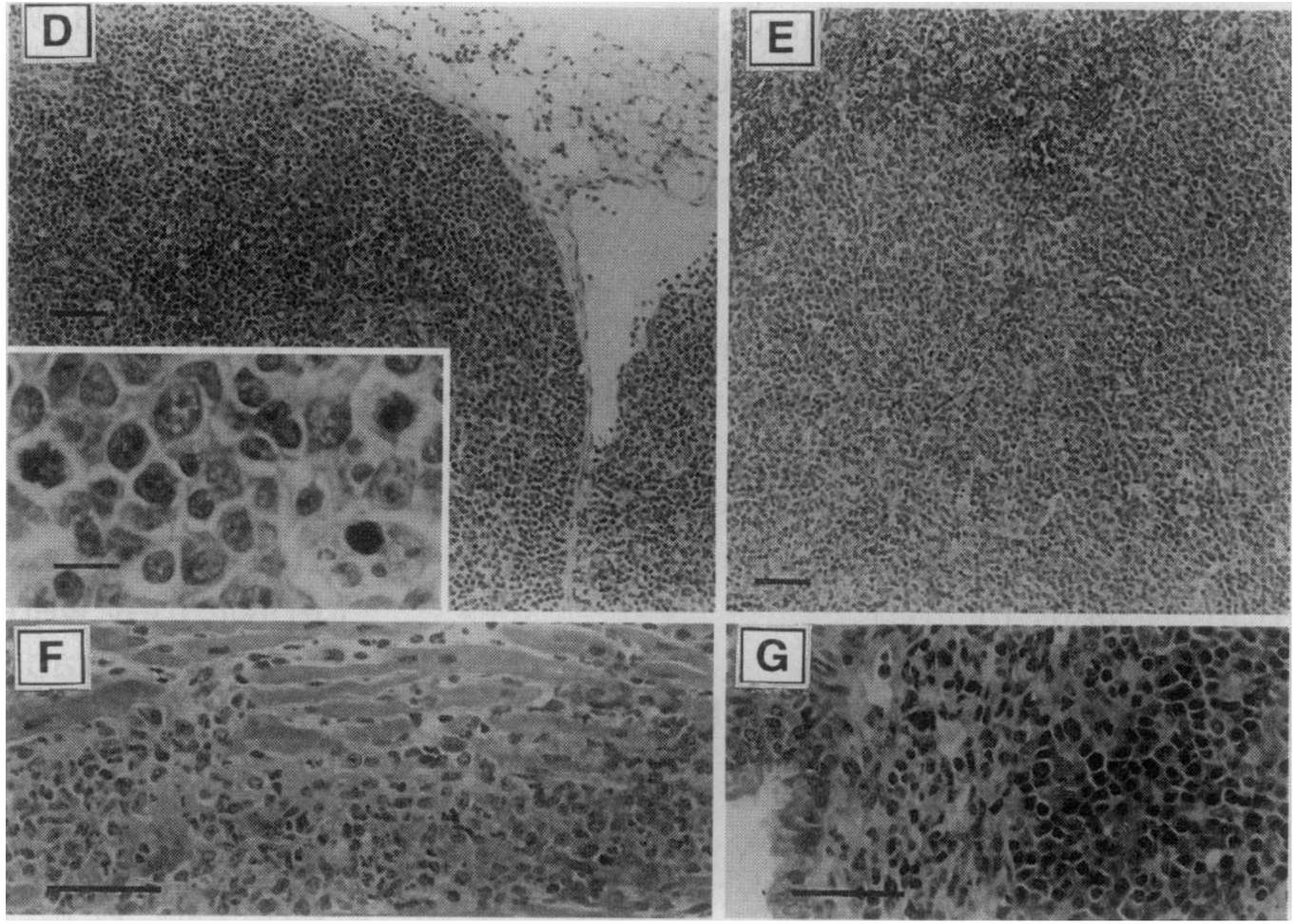
Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine amino-transferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate amino-transferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

* The safety population included all the patients who received at least one dose of study drug. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

† The treatment-related adverse events listed here were those reported in at least 10% of the patients in any of the three study groups.

Larkin J et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504030

Lymphoproliferative Disorders with Early Lethality in Mice Deficient in Ctla-4

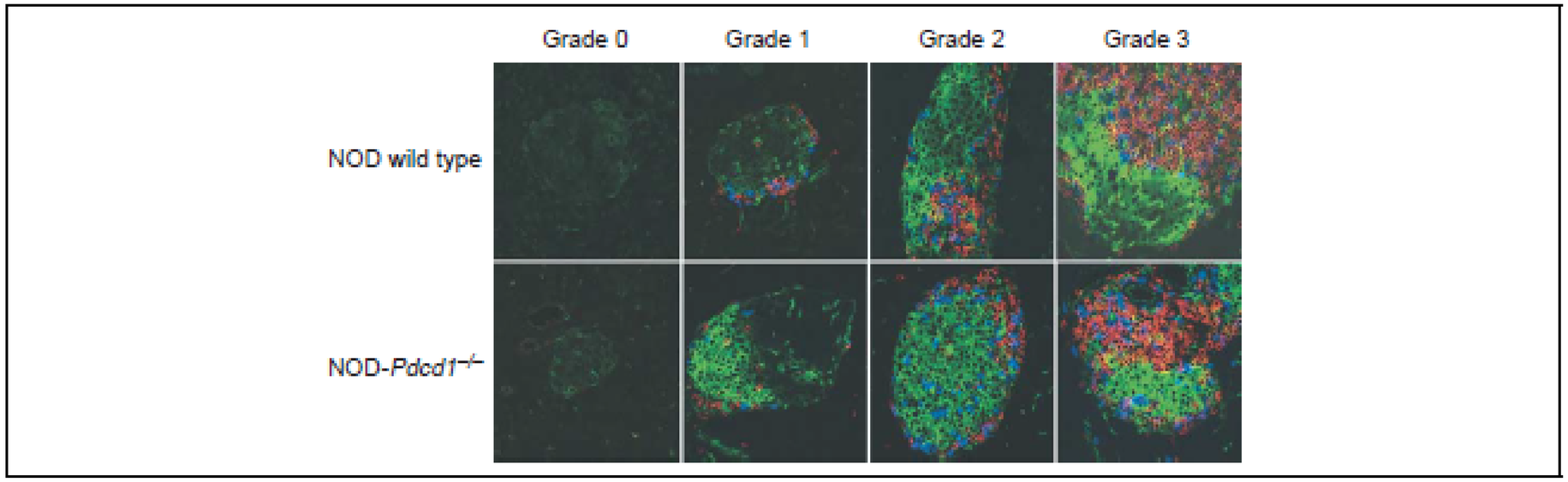


PD-1/L-1 ko mice - Higher risk for AI but compatible with life

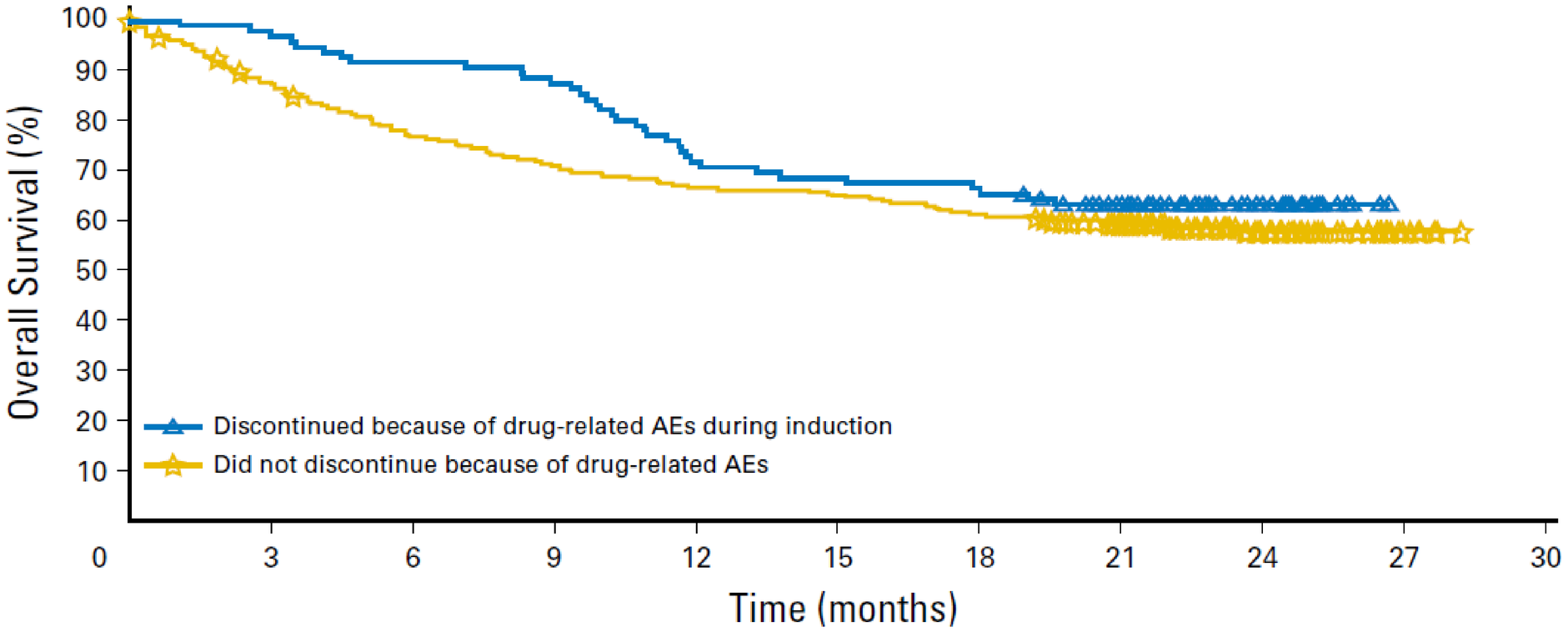
Table 1. Autoimmune phenotypes of *Pdcd1*$^{-/-}$ mice

Genotype	Phenotype	Age at onset	Penetrance	Refs
C57BL/6-*Pdcd1*$^{-/-}$	SLE-like	>6 months	~50%	[29]
BALB/c-*Pdcd1*$^{-/-}$	DCM	5–25 weeks	10–60%[a]	[30,49]
	Gastritis	10–20 weeks	~80%	[49]
NOD-*Pdcd1*$^{-/-}$	Diabetes	4–10 weeks	100%	[33]
BALB/c-*Fcgr2b*$^{-/-}$*Pdcd1*$^{-/-}$	Hydronephrosis	10–20 weeks	35%	[49]
2C-*Pdcd1*$^{-/-}$H-2$^{b/d}$	GVH-like	5–10 weeks	25–100%[b]	[29]

[a]The penetrance of dilated cardiomyopathy (DCM) is variable among the different colonies of mice examined ([49] and our unpublished observations). [b]The penetrance of GVH-like disease is variable depending on the genetic background (our unpublished observations).



Ipilimumab + Nivolumab Toxicity ≠ Poor Outcomes



No. at risk:											
Discontinued because of drug-related AEs during induction	98	93	88	84	69	66	64	52	23	0	0
Did not discontinue because of drug-related AEs	233	201	175	162	152	148	140	117	50	6	0

Schadendorf et al, *JCO,* 2017

ABSTRACT ONLY | VOLUME 32, SUPPLEMENT 5, S869, SEPTEMBER 01, 2021

1040O Phase II trial of ipilimumab, nivolumab and tocilizumab for unresectable metastatic melanoma

J.S. Weber • T. Muramatsu • O. Hamid • ... R. Sullivan • M. Faries • I. Mehmi • Show all authors

DOI: https://doi.org/10.1016/j.annonc.2021.08.1425

- Used “flipped dosing” of Ipi Nivo (Ipi 1 mg/kg + Nivo 3 mg/kg)
- **58% ORR** – historical control from checkmate-511 for flipped dosing is 34%
- **17% grade 3 or higher** irAEs – historical control from checkmate-511 was 34%

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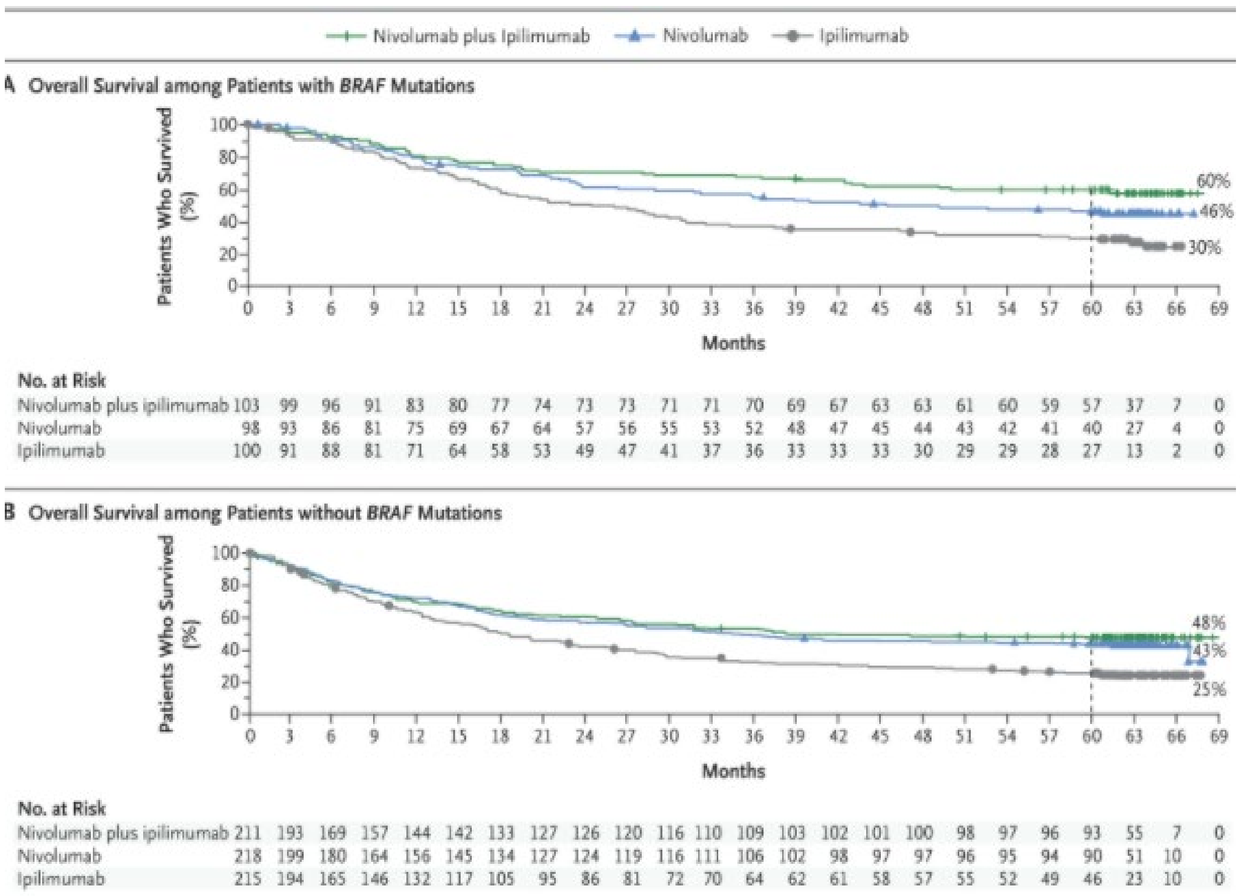
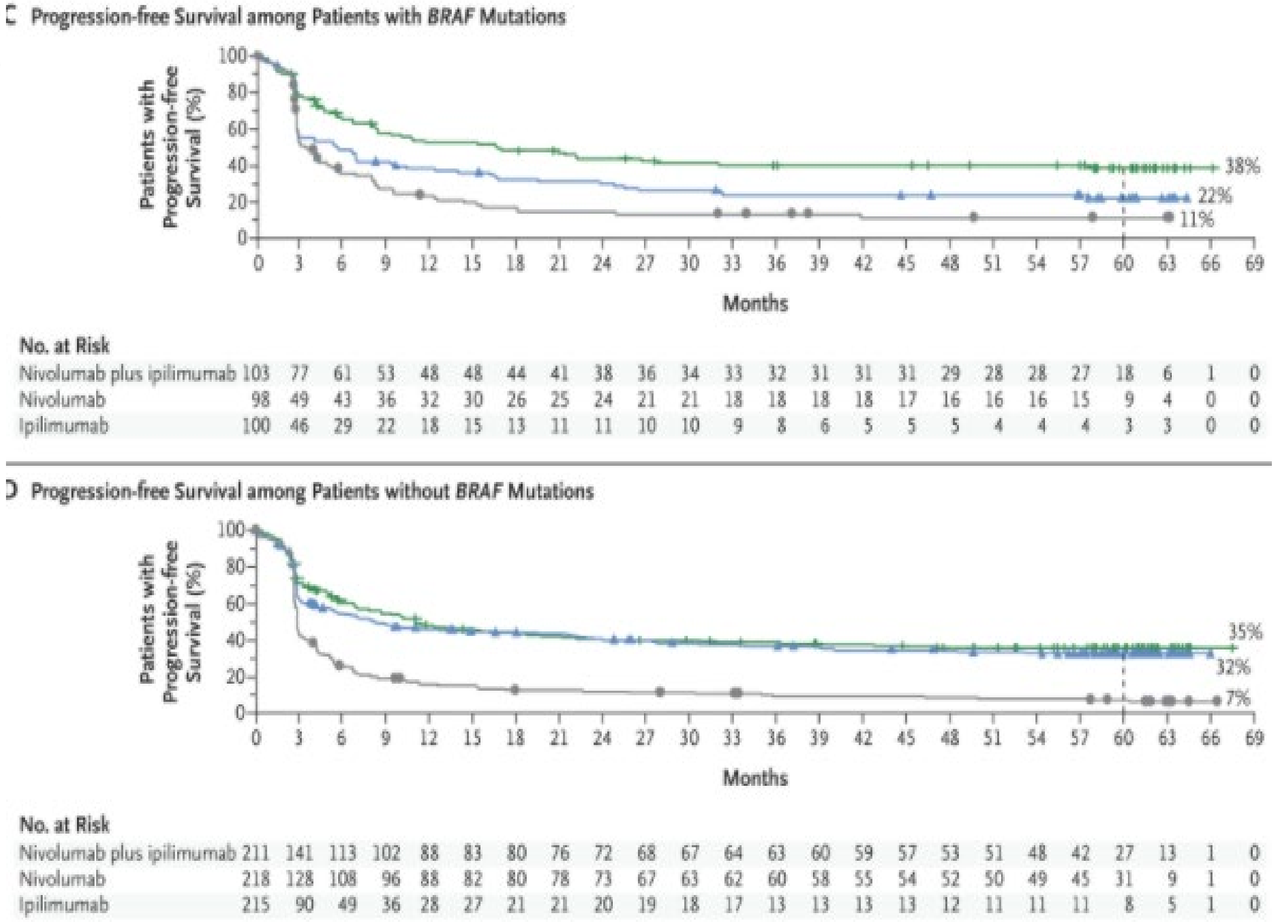
Combination Immunotherapy or PD-1 monotherapy????

Ipilimumab + Nivolumab (Checkmate 067) – BRAF subgroup

Overall Survival – BRAF WT or BRAF MT



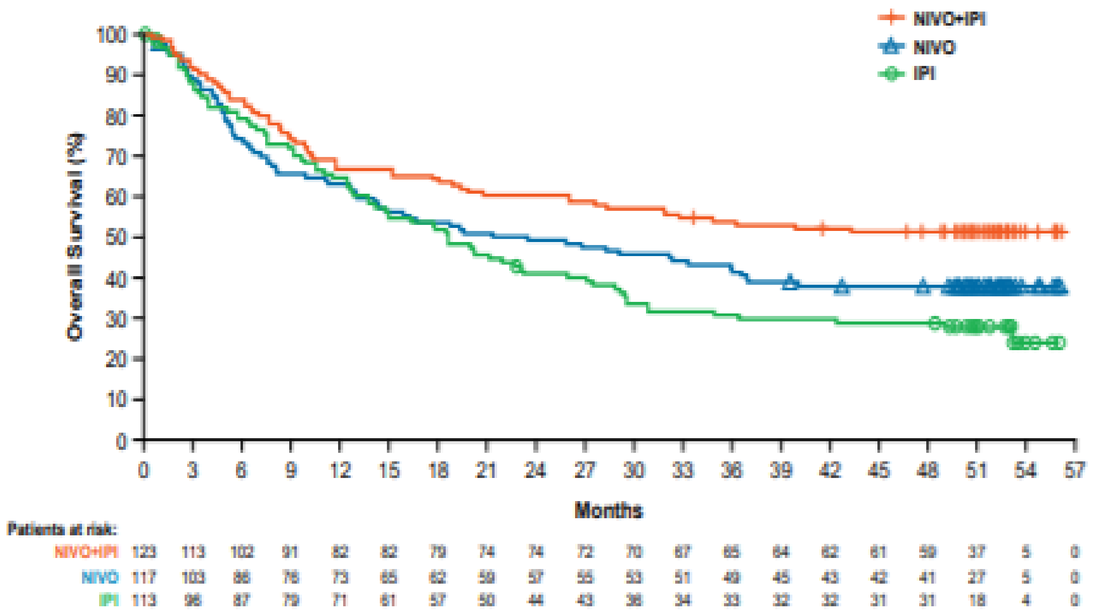
Progression Free Survival – BRAF WT or BRAF MT



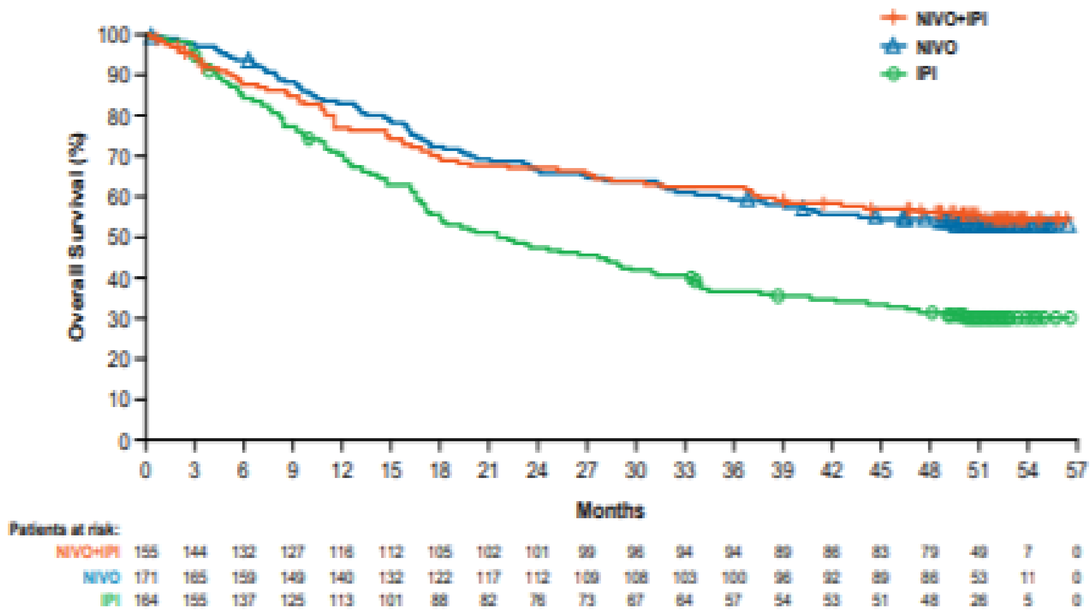
Larkin et al, NEJM*, 2019*

OS by PD-L1 Expression Level (1%)

A PD-L1 expression level <1%



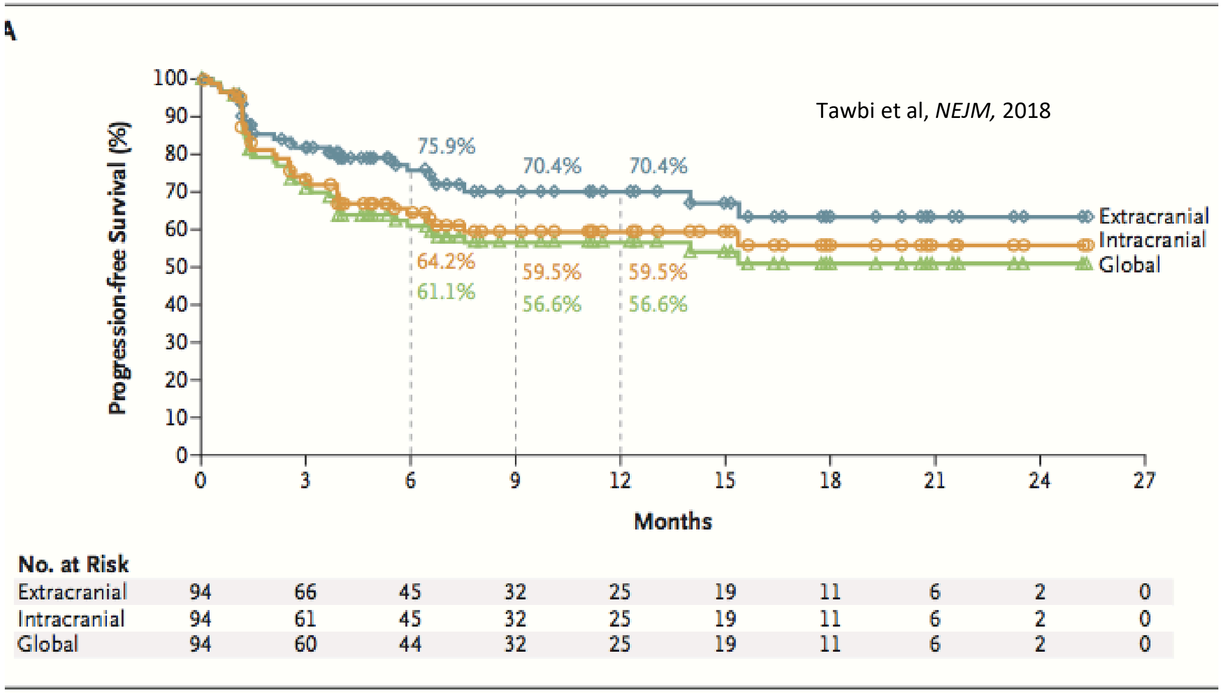
B PD-L1 expression level ≥1%



Hodi, Lancet 2017

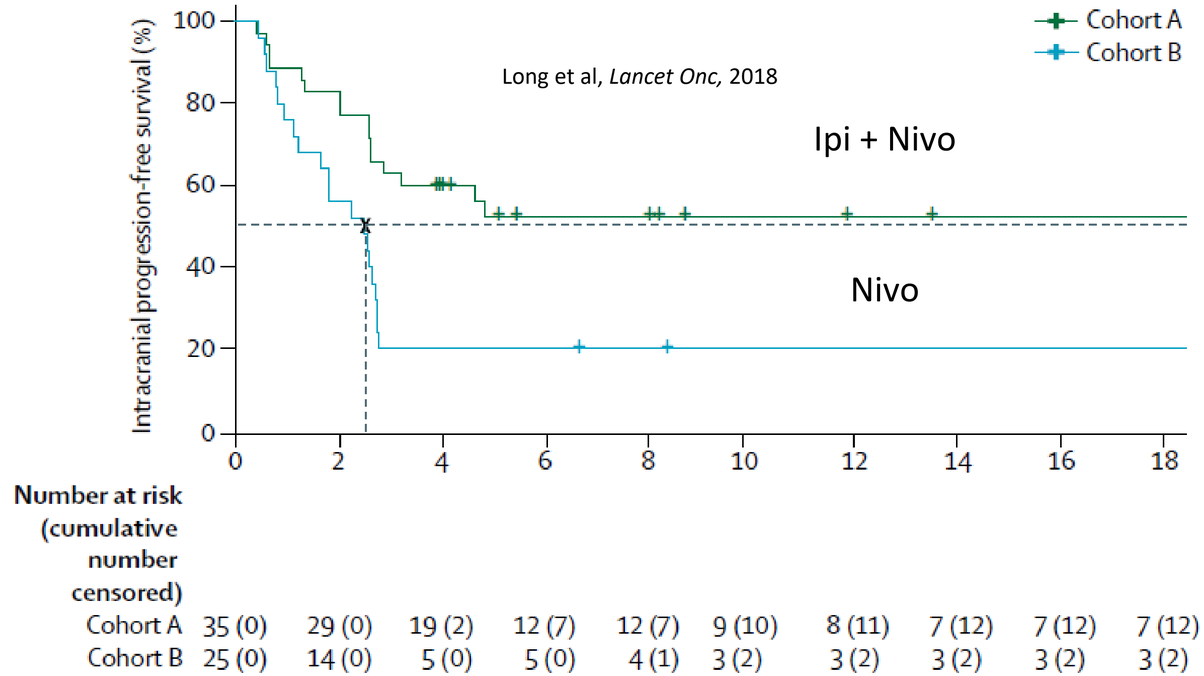
Asymptomatic Brain Metastases: Immunotherapy

- Checkmate 204 (Ipi 3 mg/kg + Nivo 1 mg/kg)
  - 94 patients
    - No steroids; at least 1 met w/o XRT
  - Intracranial ORR 55% (CR 26%, PR 30%)
  - 59.5% CNS PFS & 81.5% OS at 12 months
  - No new/unexpected toxicities



Tawbi et al, *NEJM,* 2018

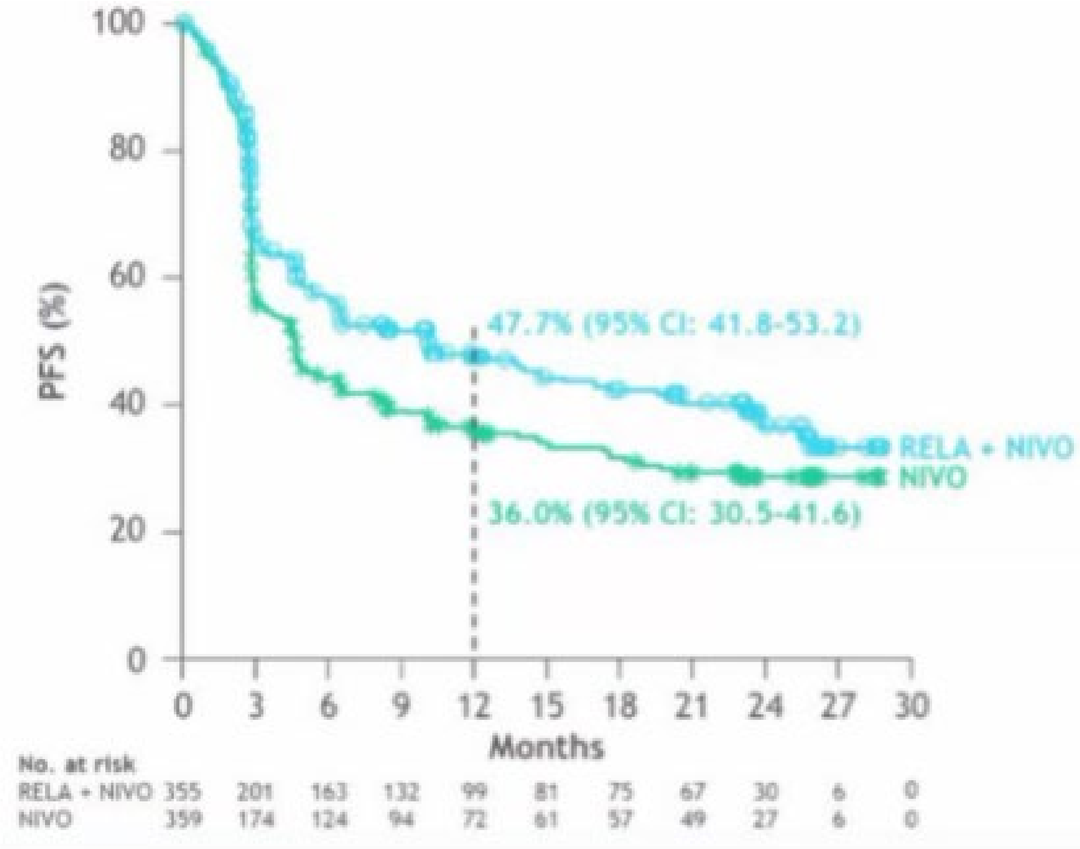
- ABC Trial: Nivo vs Ipi + Nivo (Ipi 3 + Nivo 1)
  - Ipi + Nivo (n=35), Nivo (n=25)
    - No steroids; no prior XRT
  - Intracranial ORR: 46% vs 20%
  - No new/unexpected toxicities



Long et al, *Lancet Onc,* 2018

RELATIVITY-047

Relatlimab + Nivolumab Frontline Metastatic Melanoma



	RELA + NIVO (n = 355)	NIVO (n = 359)
Median PFS, months	10.12	4.63
(95% CI)	(6.37-15.74)	(3.38-5.62)
HR (95% CI)	0.75 (0.62-0.92)	
P value	0.0055	

CI, confidence interval; HR, hazard ratio.
All randomized patients. Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3 (≥ 1% vs < 1%), BRAF (mutation positive vs mutation wild-type), AJCC M stage (M0/M1any[0] vs M1any[1]). PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

- Relatlimab + Nivolumab significantly improved PFS verus Nivo
- Grade 3/4 treatment-related adverse events 18.9% in RELA + NIVO versus NIVO (9.7%). Discontinuation due to toxicity 14.6% versus 6.7%

Summary Immunotherapy Stage IV Melanoma

- Activity highest in cutaneous melanoma > mucosal/acral >> uveal
- Potential for long-term responses and OS, even after stopping treatment
- Combination vs PD-1 monotherapy – *My approach*
  - BRAF mutated, PD-L1 negative, high volume of disease, and brain mets – combination
  - Pre-existing autoimmune – PD-1 monotherapy
    - Deaths reported with Yervoy, minimal data for combo in patients with AI disease
  - Others – discuss risks/benefits
    - Combination – more toxic, but potentially less treatment needed
    - Monotherapy – less toxic, but lower response rate and less known about ipi second line
- On the Horizon
  - Will Monotherapy PD-1 blockade be replaced with more tolerable combinations (ie. Relatlimab + nivolumab)?

Advancements in Systemic Therapy Melanoma

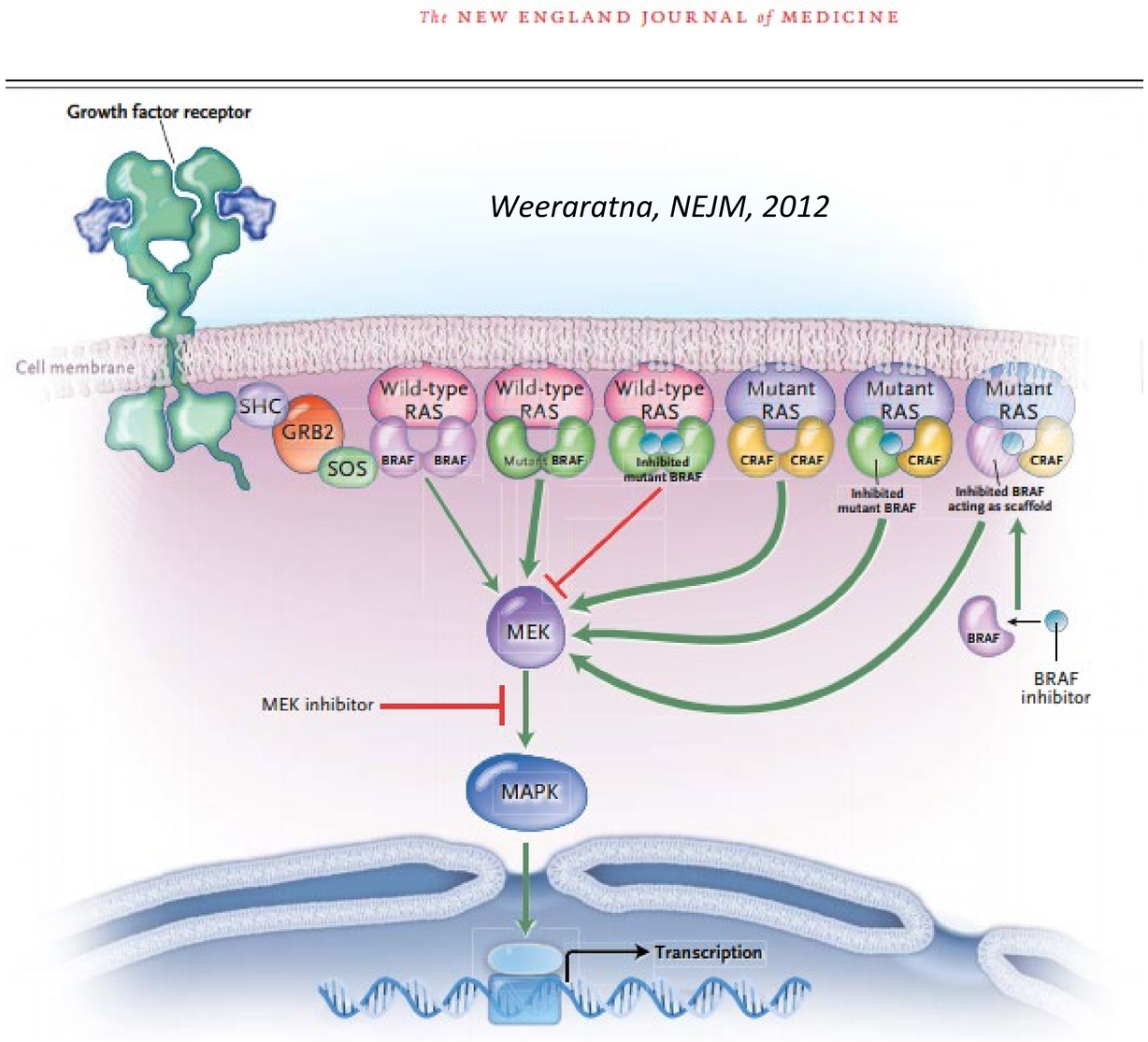
Targeted Therapy

- 50% of all melanomas have activating mutations in BRAF with 90% of those being BRAF V600E

- When BRAF is mutated, the requirement for RAS to activate the pathway is bypassed
  - BRAFi – improves PFS and OS in BRAF V600 mutated melanoma

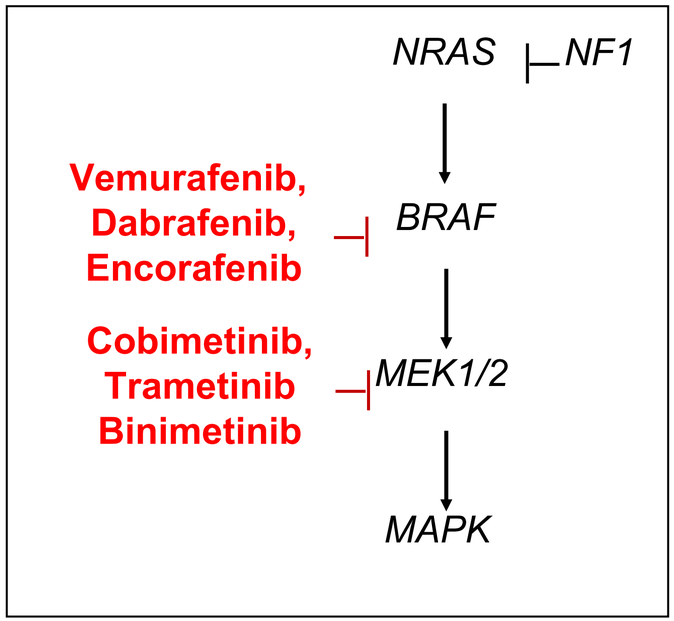
- When BRAF is WT, BRAFi transactivate CRAF -> paradoxical increase MAPK signaling.
  - When RAS is mutated and BRAF is WT, BRAFi can cause **hyperprogression**
  - Paradoxical activation from BRAFi can cause new skin cancers.

- MEKi work downstream to both RAS and RAF to inhibit paradoxical MAPK signalling.
  - The addition of MEKi to BRAFi improves PFS compared to BRAFi alone.
    - Most mechanisms of resistance to BRAFi reactivate MAPK.
  - MEKi also decreases hyperproliferative cutaneous events from BRAFi.



Weeraratna, NEJM, 2012

BRAFi + MEKi Combinations



Dabrafenib + Trametinib

- Dabrafenib 150 mg BID + Trametinib 2 mg QD
- Toxicity: More fevers
- Trametinib must be refrigerated

•Vemurafenib + Cobimetinib

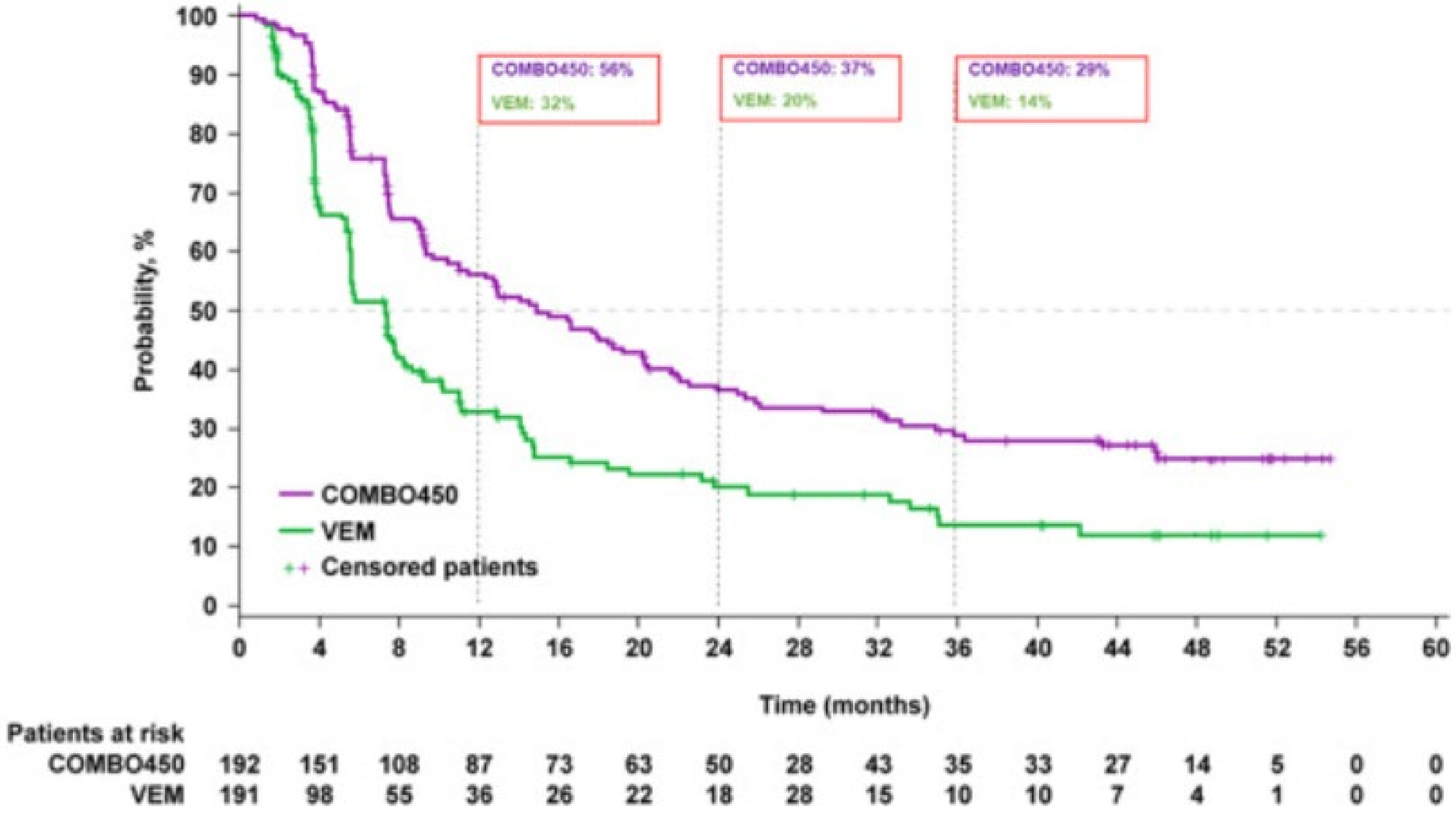
- Vemurafenib 960 mg BID (d1-28) + Cobimetinib 60 mg QD (d1-21)
- Toxicity: Photosensitivity
- No need to refrigerate

Encorafenib + Binimetinib

- Encorafenib 450 mg QD + Binimetinib 45 mg BID
- GI side effects. Very few fevers or photosensitivity
- No need to refrigerate

Columbus Trial

- Encorafenib 450 mg QD + Binimetinib 45 mg BID
  - ↑ Enco dose more tolerated with combo than with single agent
  - FDA approval for stage IV, April 2018
  - ORR 64%, median PFS 14.9 mo



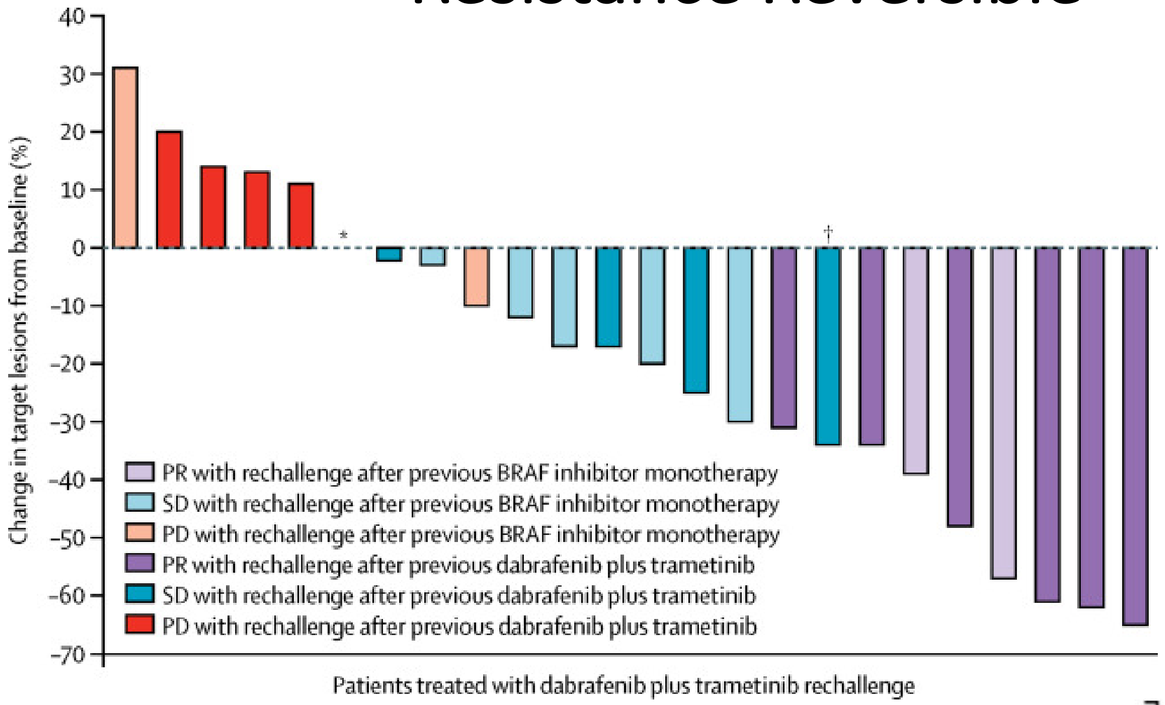
Ascierto, Eur J Cancer, 2020

Summary of Toxicities

	COMBI-D	COMBI-V	co-BRIM	COLUMBUS
Toxicity (% all/ % ≥ Gr 3)	Dabrafenib Trametinib	Dabrafenib Trametinib	Vemurafenib Cobimetinib	Encorafenib Binimetinib
Pyrexia	52 / 7	53 / 4	26 / 2	18/4
Photosensitivity		4 / 0	28 / 2	5 / 1
Nausea	20 / 0	36 / 1	40 / 1	41/2
Arthralgia	16 / <1	24 / 1	32 / 2	26/1
ALT increase	10 / 2		23 / 11	13/6
Hyperkeratosis	6 / 0	4 / 0	10 / 0	14/1
Hand-foot	6 / <1	4 / 0		7/0
cuSCC	3 / 3	1 / 1	1 / 1	4/0
EF down	4 / 1	8 / 4	8 / 1	8/2

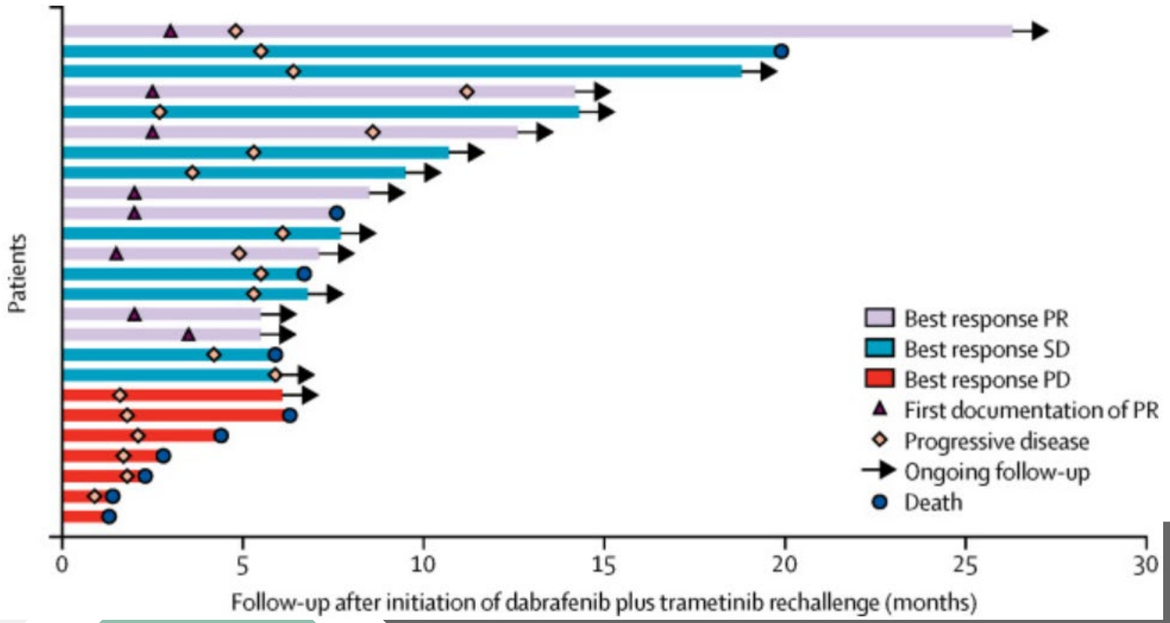
Long et al. NEJM 2015; Robert et al. NEJM 2015; Larkin et al. NEJM 2015; Dummer et al. Lancet Oncol 2018;

Resistance Reversible



- 25 patients who previously progressed on BRAFi +/- MEKi (at least 12 weeks prior)
- Rechallenged with Dabrafenib + Trametinib → ORR 32%, DCR 72%
- Responses Durable

Schreuer et al, *Lancet Onc*, 2017

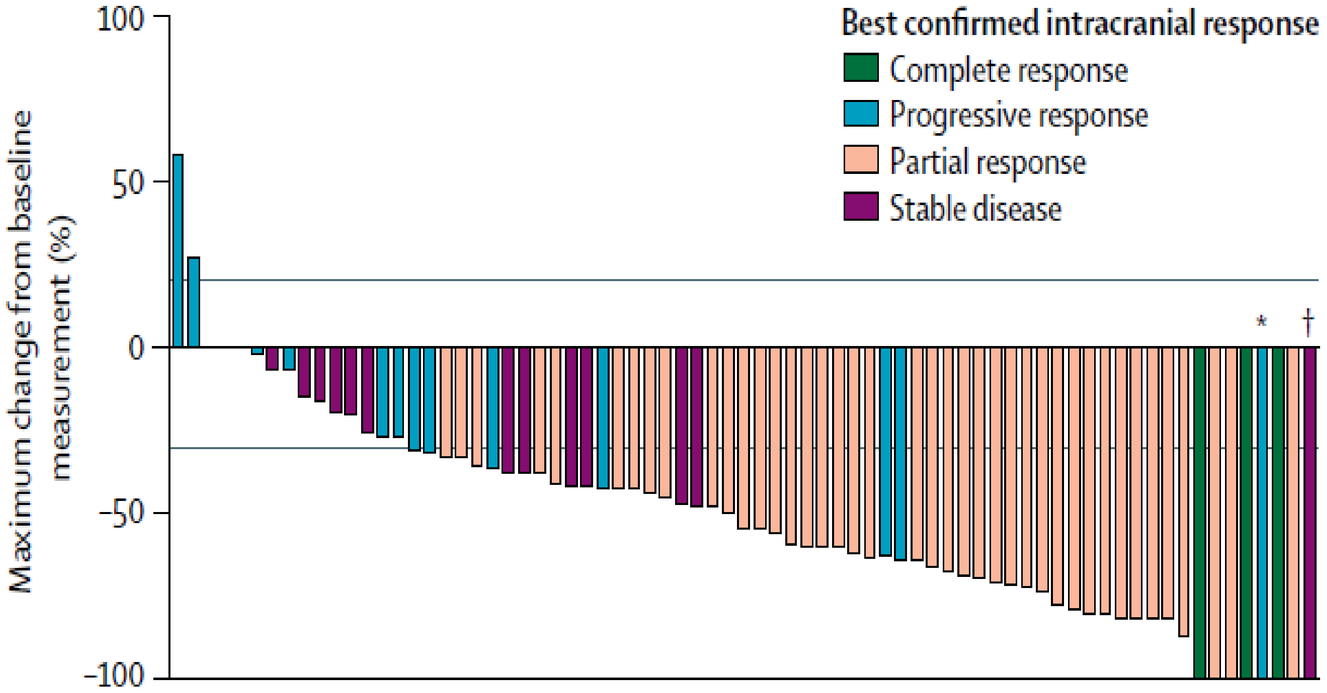


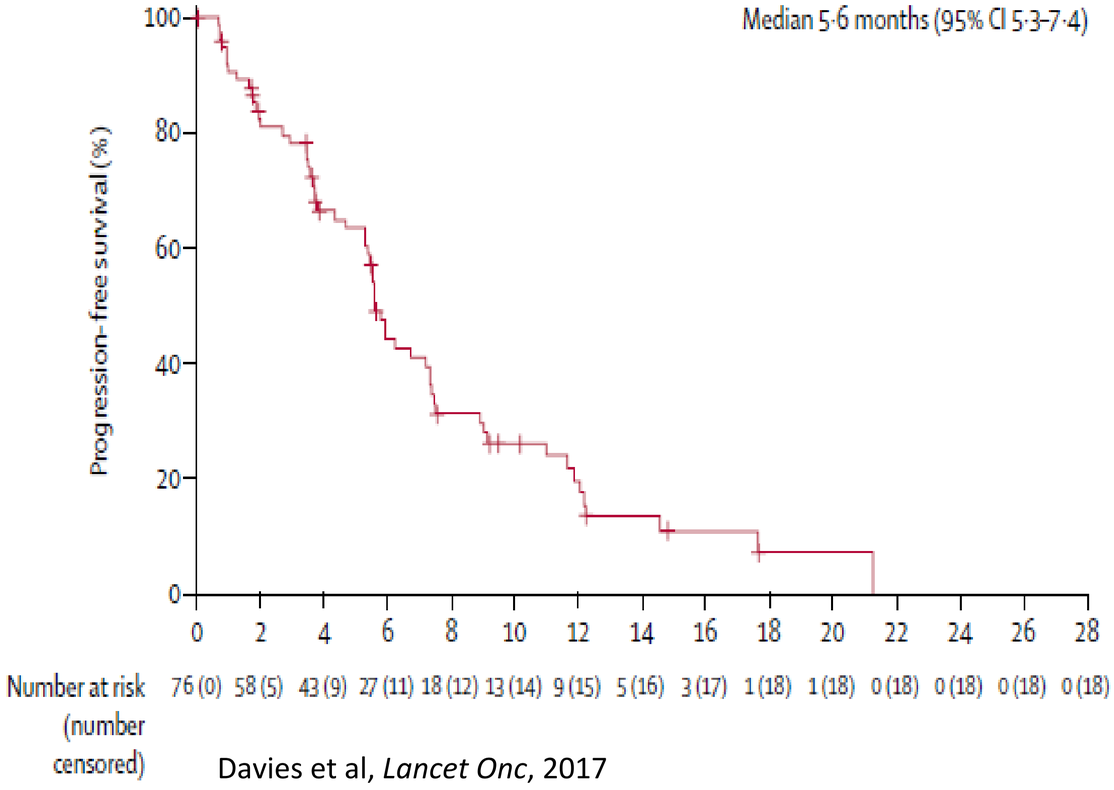
Preclinical Rationale

- BRAFi resistant melanoma cells found to be dependent on BRAF inhibition
- Treatment break causes regression in resistant clones, then can re-challenge subsequent line.

Brain Metastases

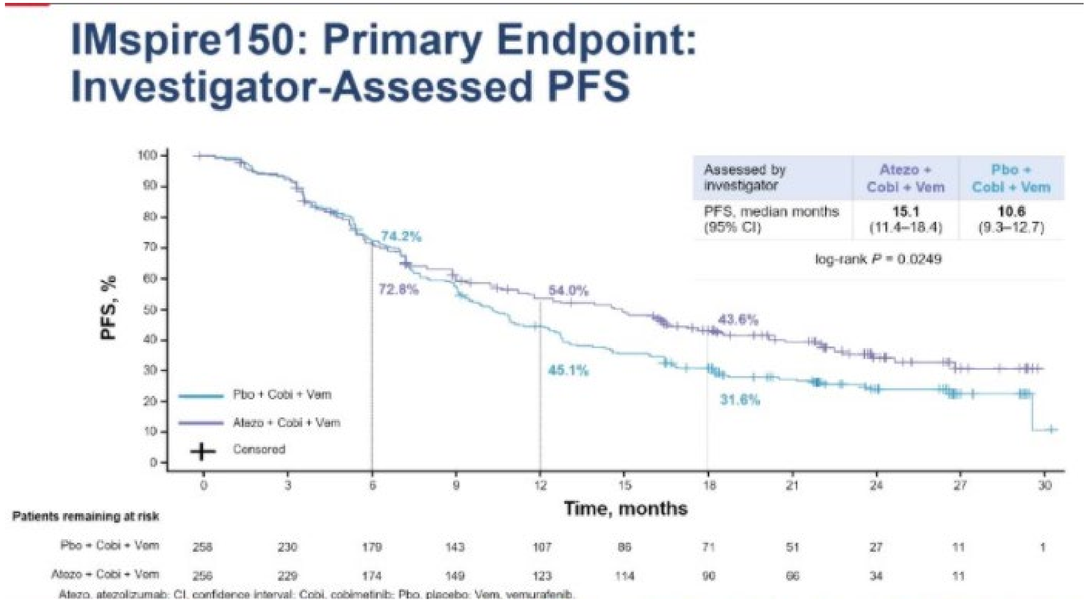
- COMBI-MB: Phase II study of DT in BRAF V600-mutant metastatic melanoma patients with new or progressive brain metastases
  - Intracranial ORR 58%, Intracranial DCR 78%
  - Median Intracranial DOR 6.5 mos, **Median PFS 5.6 mos**
  - **50% pts progressed in brain** while extracranial still controlled



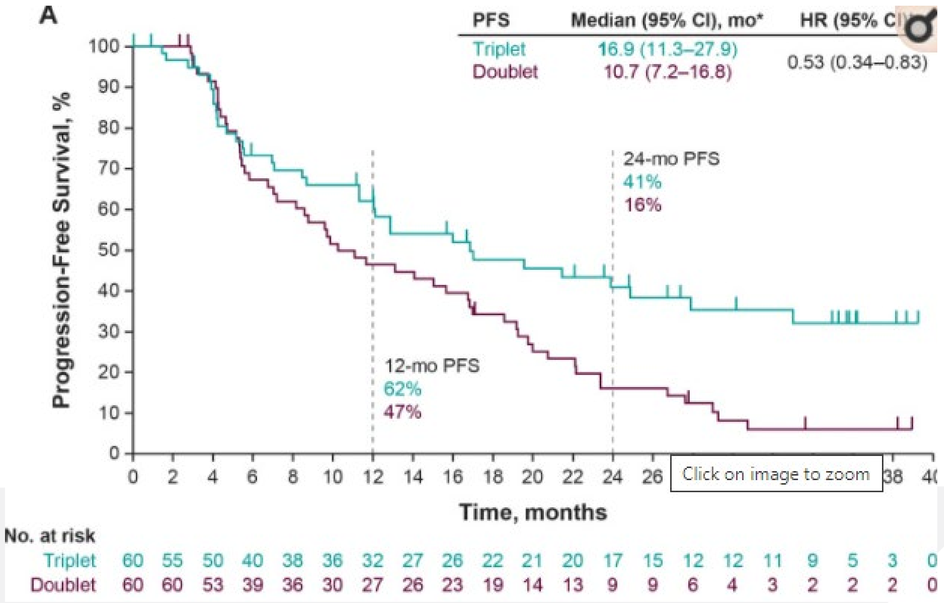


Davies et al, *Lancet Onc*, 2017

Combining BRAFi + MEKi + Anti–PD-1/L1



McArthru et al, AACR, 2020



Ferrucci et al, JITC, 2020

NCCN Guidelines

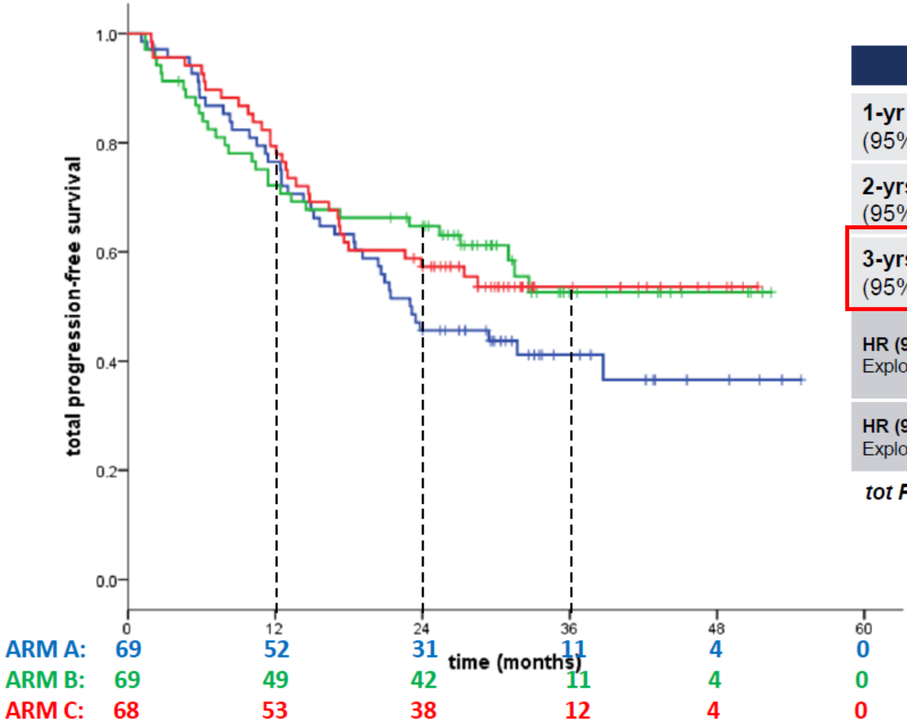
Metastatic or unresectable disease

- **Preferred regimens**
  - **Anti PD-1 monotherapy[d,e]**
    - ◊ **Pembrolizumab (category 1)**
    - ◊ **Nivolumab (category 1)**
  - **Nivolumab/ipilimumab (category 1)[d,e,f]**
  - **Combination targeted therapy if *BRAF* V600-activating mutation[g,h,i,j]**
    - ◊ **Dabrafenib/trametinib (category 1)**
    - ◊ **Vemurafenib/cobimetinib (category 1)**
    - ◊ **Encorafenib/binimetinib (category 1)**
- **Other recommended regimens**
  - **Pembrolizumab/low-dose ipilimumab[k] (category 2B)**
  - **Combination targeted therapy and immunotherapy if *BRAF* V600-activating mutation present[d,g,h]**
    - ◊ **Vemurafenib/cobimetinib + atezolizumab[l]**
    - ◊ **Dabrafenib/trametinib + pembrolizumab (category 2B)[m]**

How to Sequence?

SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT) STUDY: TOTAL PROGRESSION FREE SURVIVAL

Ascierto et al, *ESMO*, 2021



	Arm A	Arm B	Arm C
1-yr tot PFS% (95% CI)	77% (67-87)	72% (61-83)	78% (68-88)
2-yrs tot PFS% (95% CI)	46% (34-58)	65% (54-76)	57% (45-69)
3-yrs tot PFS% (95% CI)	41% (29-53)	53% (43-63)	54% (42-66)
HR (95% CI) Arm B vs A Exploratory analysis	0.71 (0.44-1.14)	-	-
HR (95% CI) Arm C vs A Exploratory analysis	0.74 (0.46-1.18)	-	-

***tot PFS**: time from randomization until the date of the second progression*

ARM A: Enco/Bini PD → Ipi/Nivo
ARM B: Ipi/Nivo PD → Enco/Bini
ARM C: Enco/Bini (8 weeks) → Ipi/Nivo PD → Enco/Bini

- Secombit - Sequencing question Frontline IO versus Frontline targeted versus Sandwich (Targeted x 8 weeks, then IO prior to progression).
  - Trend to improvement over time for First line IO whether uupfront or with Sandwich approach.
- Favor Combo if patient can tolerate as BRAF mutated subgroup from Checkmate 067 had a more pronounced numerical improvement in OS and PFS outcomes.

- DREAMseq trial – Starting with CPI combination provided superior OS versus starting with targeted, which became evident by 10 months.

- First line targeted therapy or triplet or sandwich approach from Secombit
  - More aggressive disease (symptomatic, high LDH, M1c) – NEED A FAST RESPONSE

Adjuvant Therapy

AJCC 8 StagingCutaneous Melanoma

- Stage I : T1 -T2a
- Stage II: T2b-T4b
- Stage III: LN, satellites, in-transit
- Stage IV: Distant Mets

- T1: < 1.0 mm
- T2: 1-2 mm
- T3: 2-4 mm
- T4: > 4 mm

(b – ulcerated; a – not)

- N1: 1 regional mets
- N2: 2-3 regional mets
- N3: ≥ 4

(a – occult; b – clinical; c – in-transit/satellitosis)

AJCC Eighth Edition
Melanoma Stage III Subgroups

N Category	T Category								
	T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	N/A	A	A	A	B	B	C	C	C
N1b	B	B	B	B	B	B	C	C	C
N1c	B	B	B	B	B	B	C	C	C
N2a	N/A	A	A	A	B	B	C	C	C
N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C
N3a	N/A	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	D

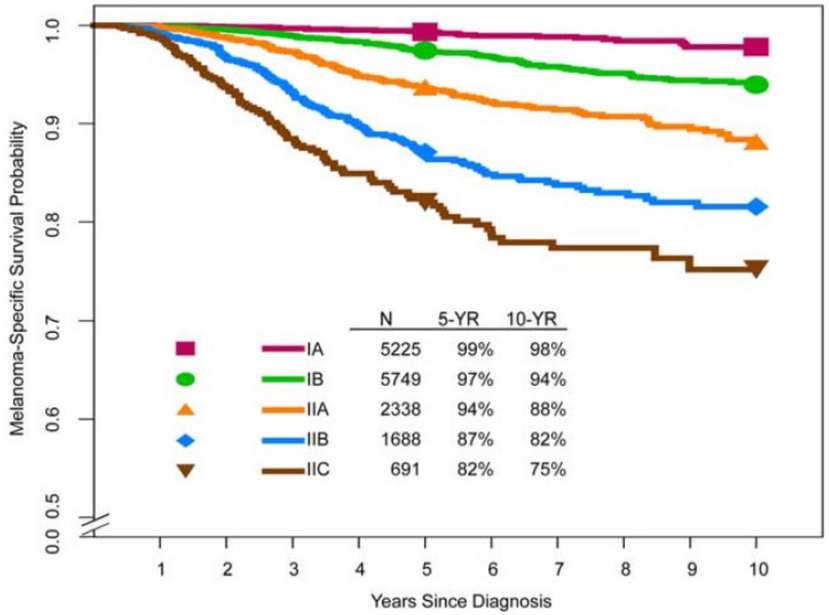
Instructions

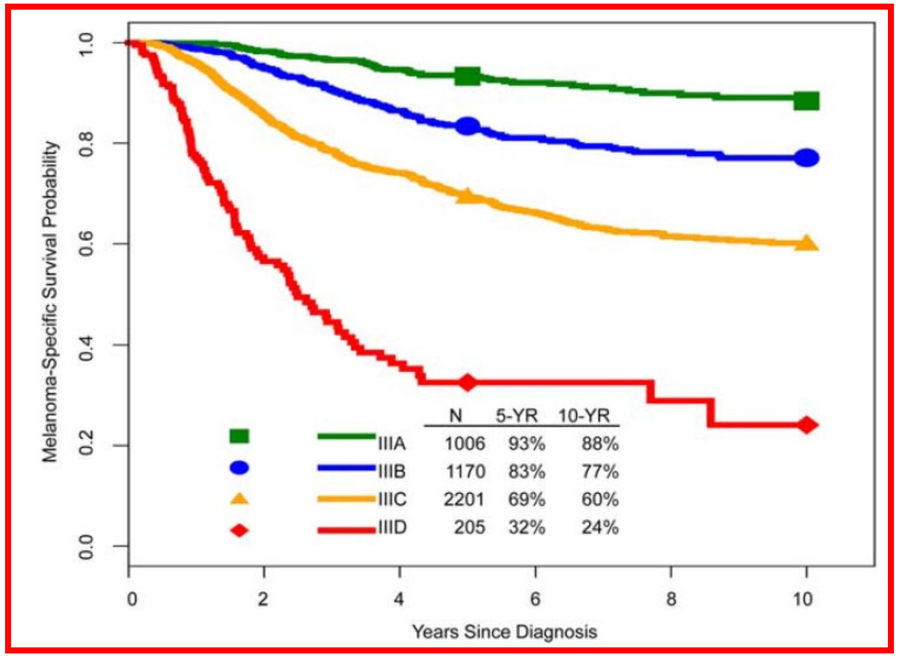
(1) Select patient's N category at left of chart.
(2) Select patient's T category at top of chart.
(3) Note letter at the intersection of T&N on grid.
(4) Determine patient's AJCC stage using legend.

N/A=Not assigned, please see manual for details. [REF]

Legend

A	Stage IIIA
B	Stage IIIB
C	Stage IIIC
D	Stage IIID



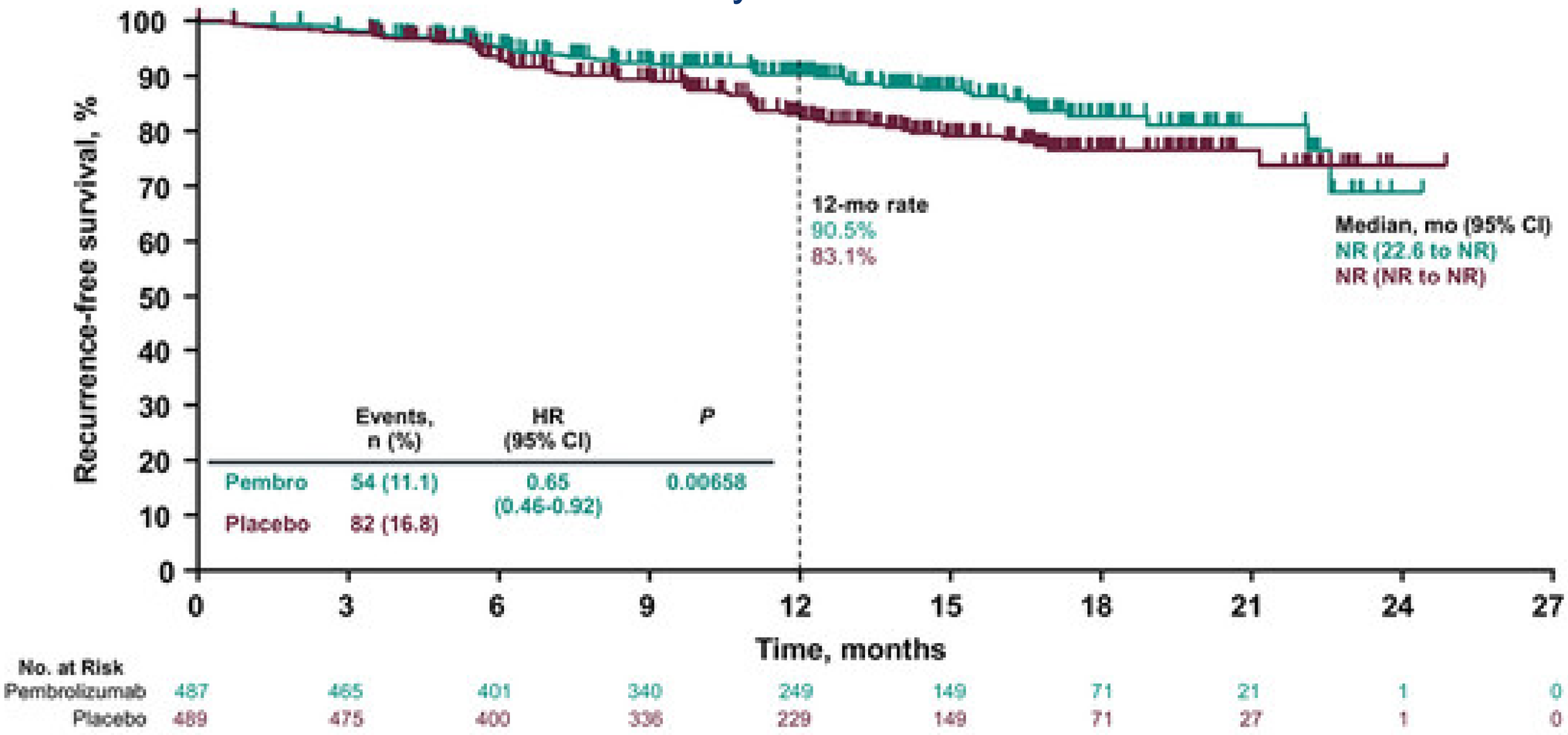


Summary Phase III Adjuvant Trials

	Checkmate 238		COMBI-AD		Keynote-054	
	Nivolumab	**Ipilimumab**	**D + T**	**Placebo**	**Pembro**	**Placebo**
Stages	IIIB (35%), IIIC (40%), IV (20%)		IIIA (20%), IIIB (40%), IIIC(40%)		IIIA (15%), IIIB (46%), IIIC (38%)	
Median FU	1.5 years		2.8 years		1.25 years	
RFS HR	0.65 (0.51 to 0.83), p<0.001		0.47 (0.39 – 0.58), p<0.001		0.57 (0.43 to 0.74), p<0.001	
RFS % 1 yr 2 yr 3 yr	70.5%	60.8%	88% 67% 58%	56% 44% 39%	75.4%	61.0%
DMFS HR	0.73 (0.55 – 0.95)		0.51 (0.40-0.65), p<0.001		0.53 (0.37 – 0.76)	
OS HR	No OS Benefit – ESMO 2020		Not Mature		Not Mature	
Toxicity						
Grade 3-4 AE	14.4%	45.9%	**36%**	10%	14.7%	9.0%
Tx D/C for AE	9.7%	42.6%	**26%**	3%	13.8%	2.2%

Stage IIB and Stage IIC

Keynote-716



NR, not reached; Data cut-off date: 4 Dec 4, 2020.

Luke JJ et al. ESMO Congress 2021

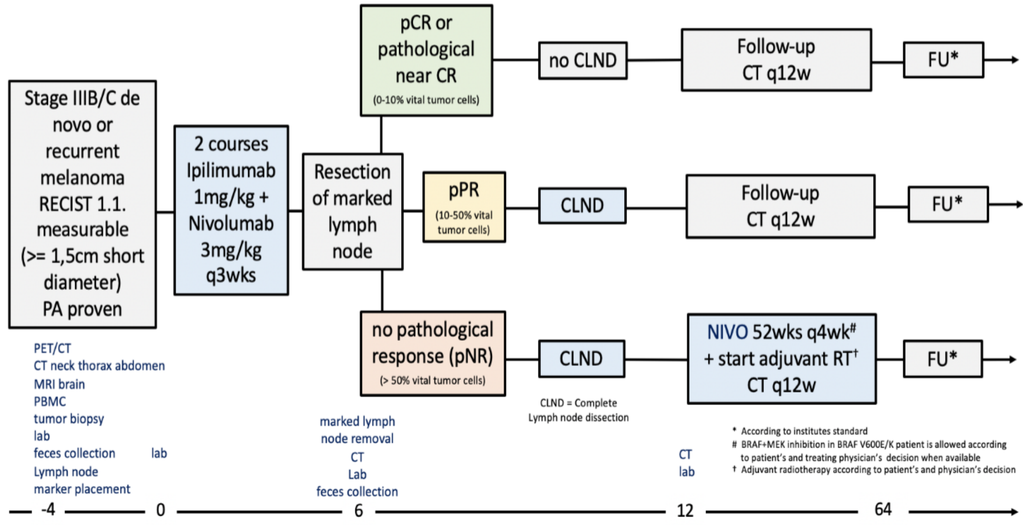
Neoadjuvant Therapy

	Treatment arm		
	A: 2xI3+N1 (n=30)	B: 2xI1+N3 (n=30)	C: 2xI3-2xN3 (n=26)
pRR	24 (80)	23 (77)	17 (65)
pCR	14 (47)	17 (57)	6 (23)
near pCR	7 (23)	2 (7)	6 (23)
pPR	3 (10)	4 (13)	5 (19)
pNR	6 (20)	7 (23)[a]	8 (31)
Not evaluable	-	-	1 (4)[b]

[a]One patient had only palliative resection of largest lymph node, b Surgery was not performed because of toxicity, this patient had a radiologic CR
Data are presented as n, (%).
Rozeman EA, *et al.* Lancet Oncol 2019;20(7):948–60

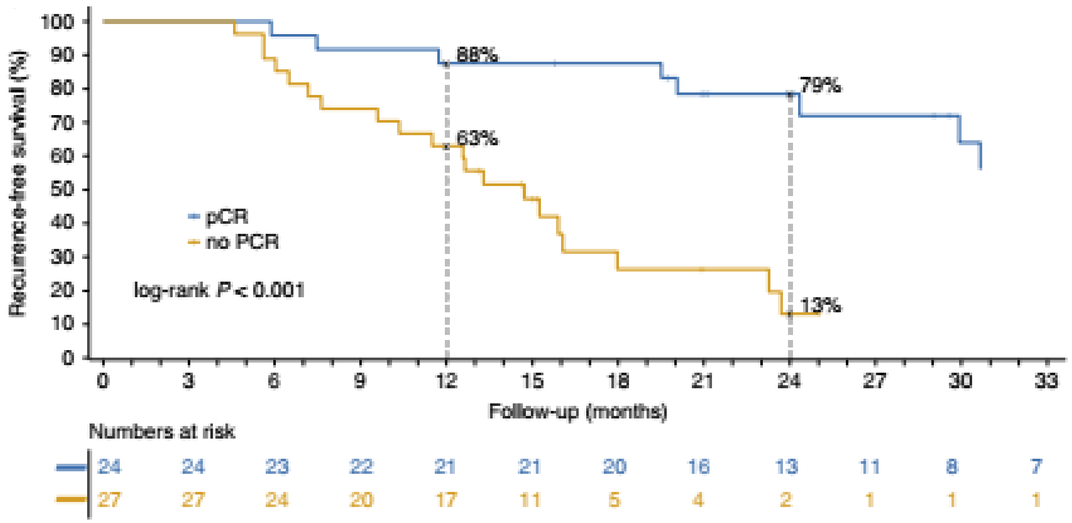
Rozeman et al, *Lancet*, 2019

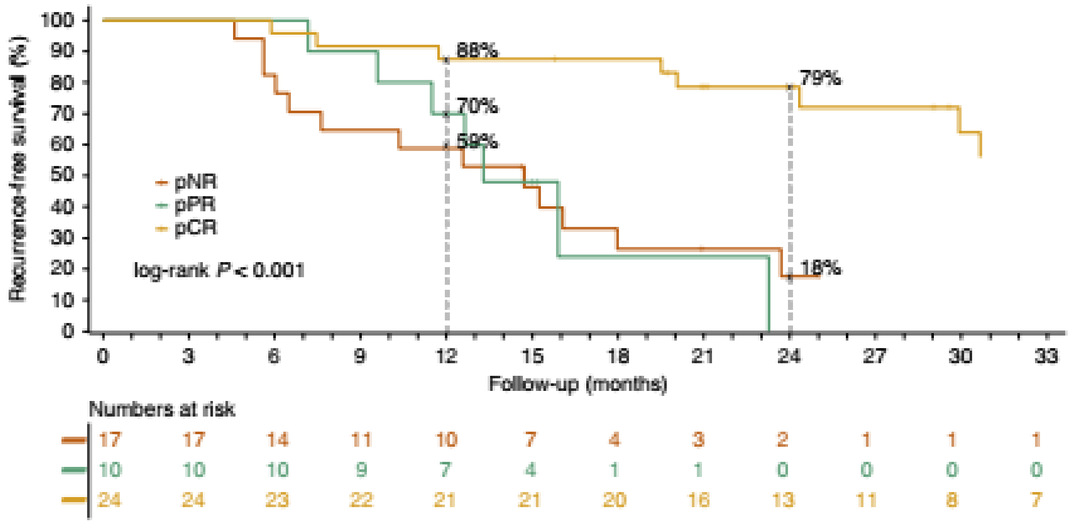
Expansion cohort OpACIN-neo: **P**ersonalised **R**esponse-driven **Ad**juvant C**o**mbination o
Ipilimumab and Nivolumab in stage IIIB/C melanoma -



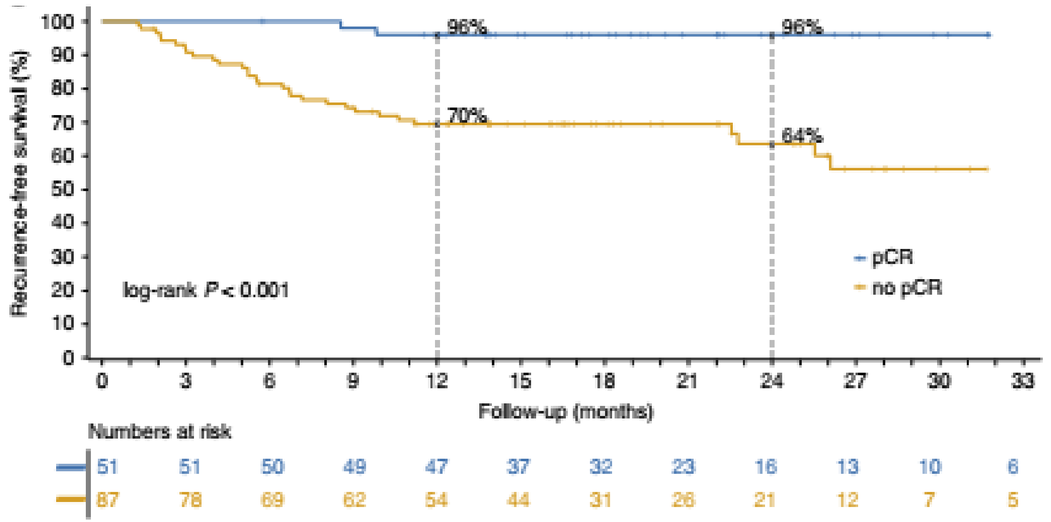
Any pathologic response from neoadjuvant immunotherapy results in better RFS

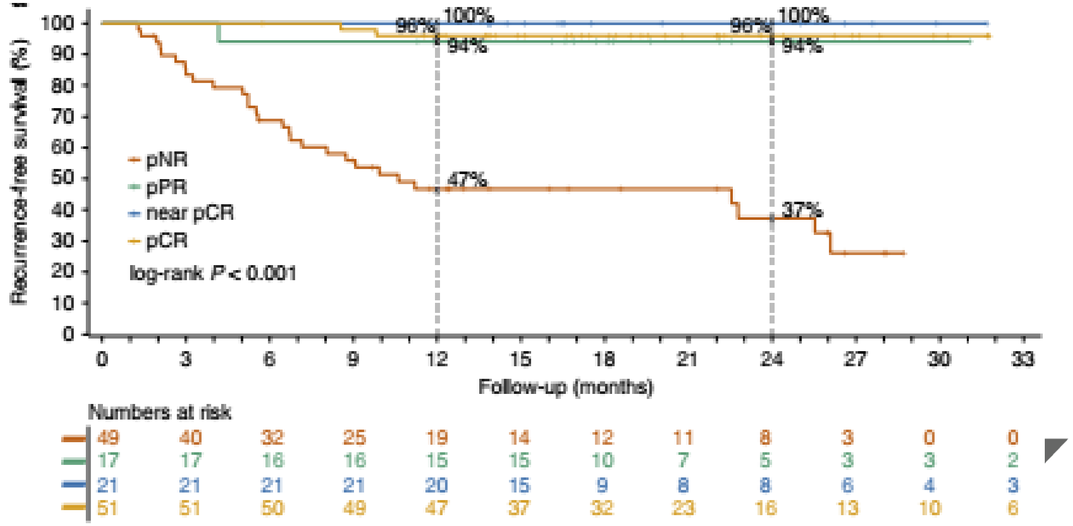
BRAF/MEK Targeted Therapy





Immunotherapy

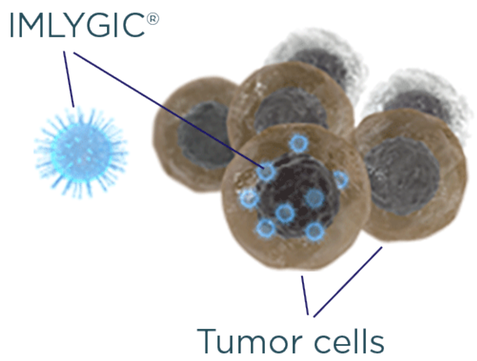




Menzies AM, et al. Nature 2021

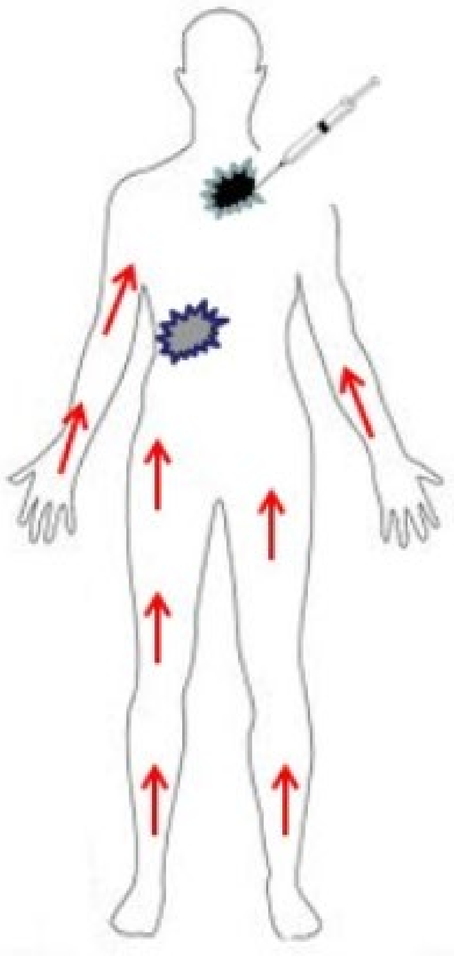
Intratumoral Immunotherapies

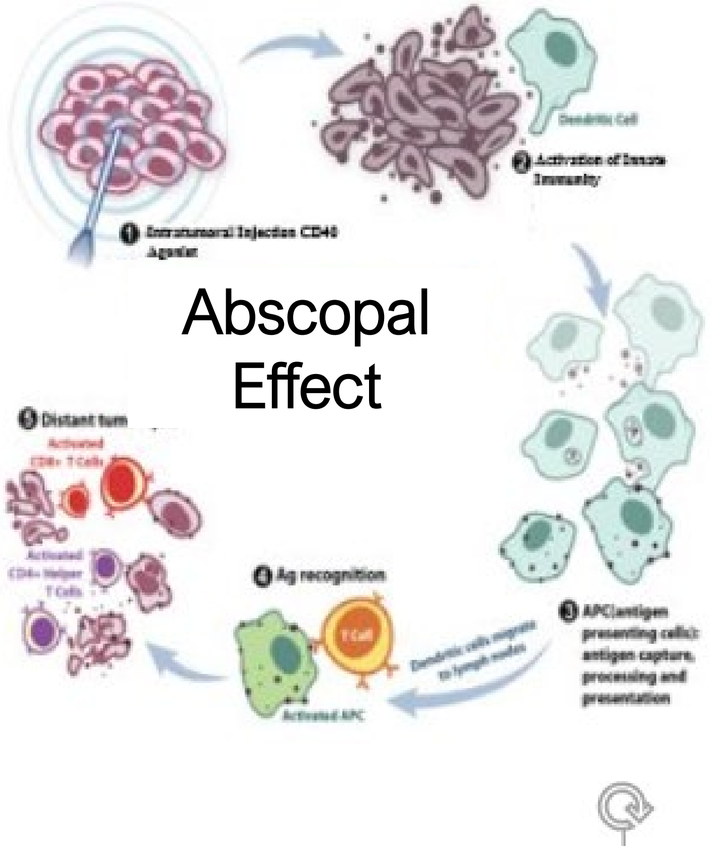
Talimogene Laherparepvec (TVEC)



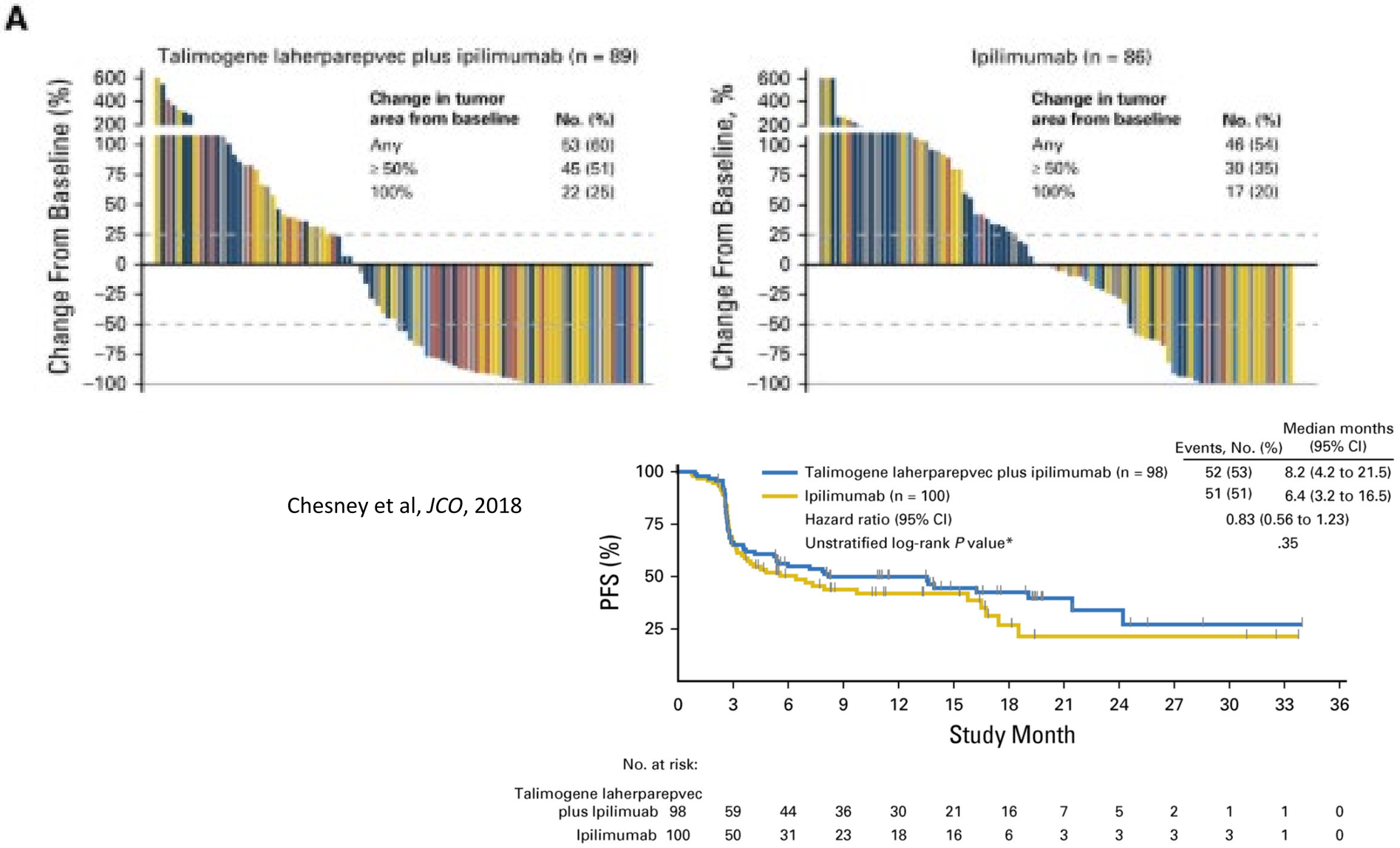
- Oncolytic viruses

- Potent cytokines and immune cell stimulatory molecules (ie. IL12, CD40, STING, TLR agonists)



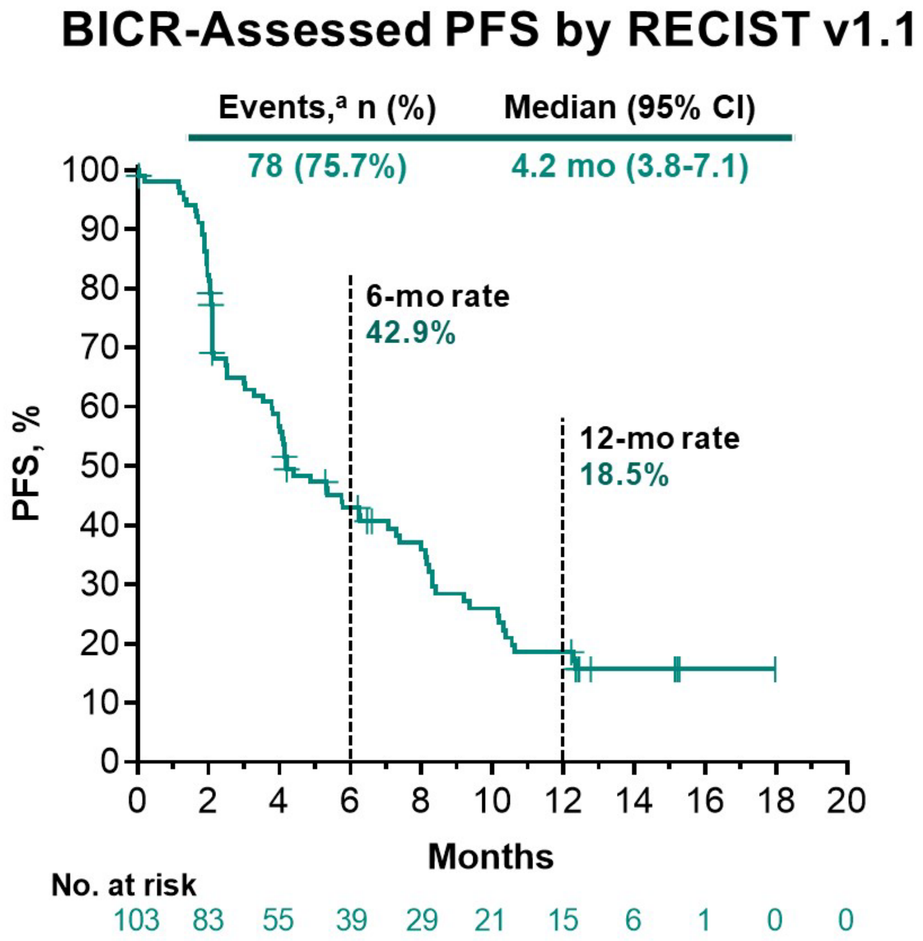


TVEC + Yervoy

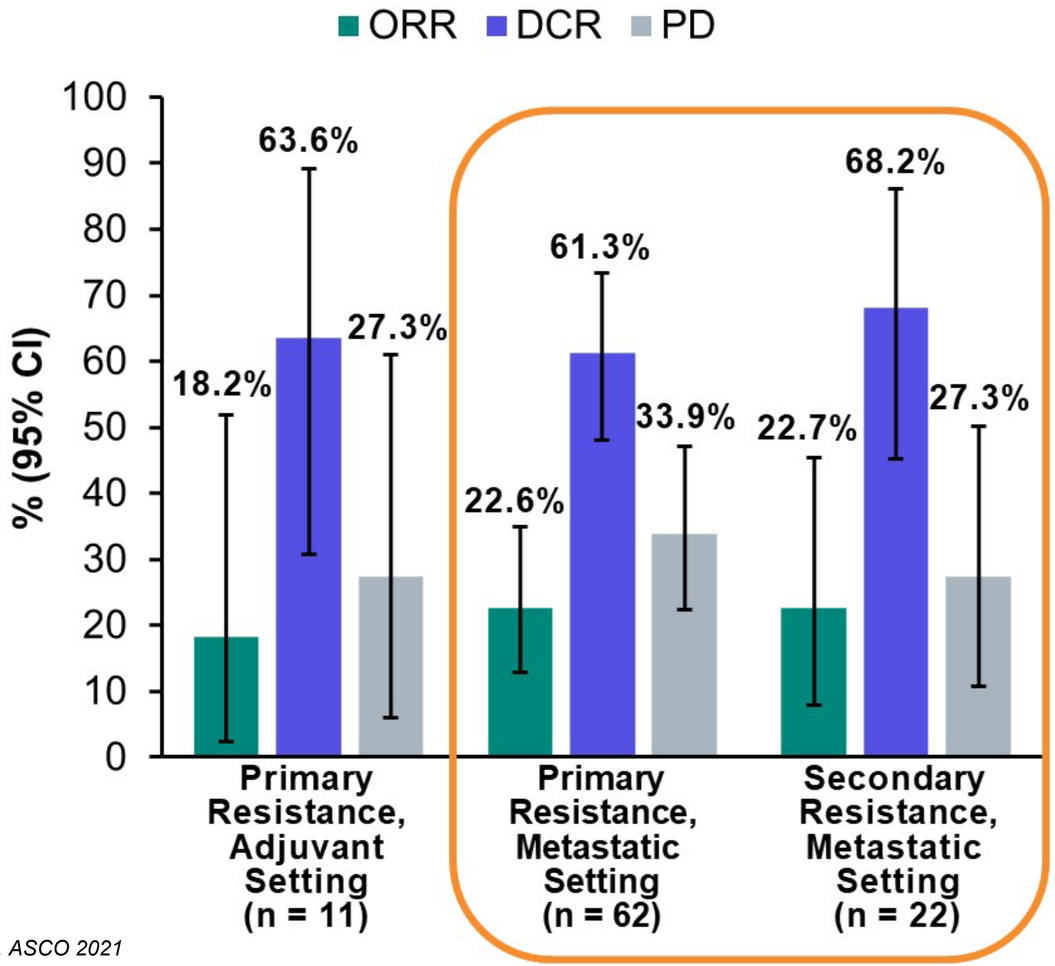


Chesney et al, *JCO*, 2018

LEAP-004



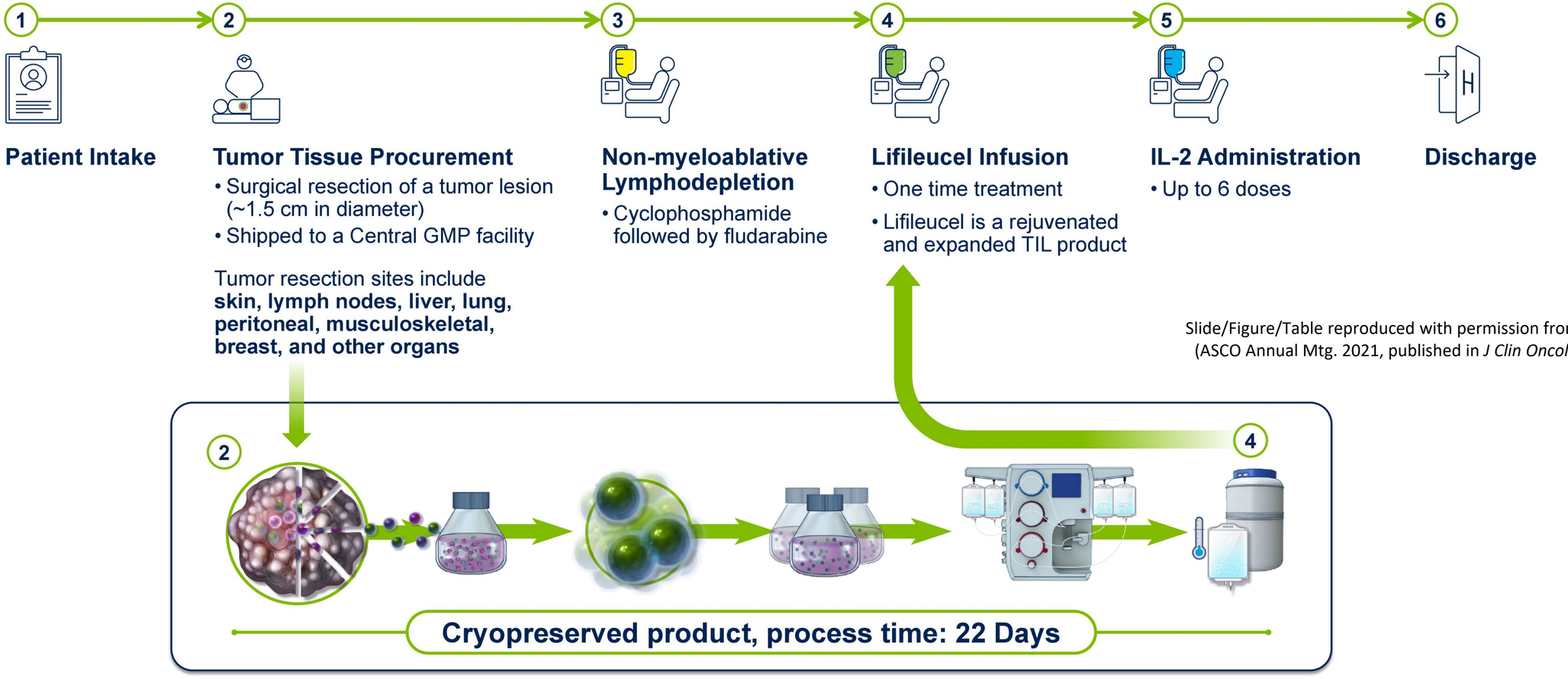
[a]Patients who died or had PD. Data cutoff date: Sep 18, 2020 (median study follow-up, 15.3



Arance, et. al. ASCO 2021

IOVANCE – Tumor Infiltrating Lymphocytes

Patient Journey and TIL Manufacturing



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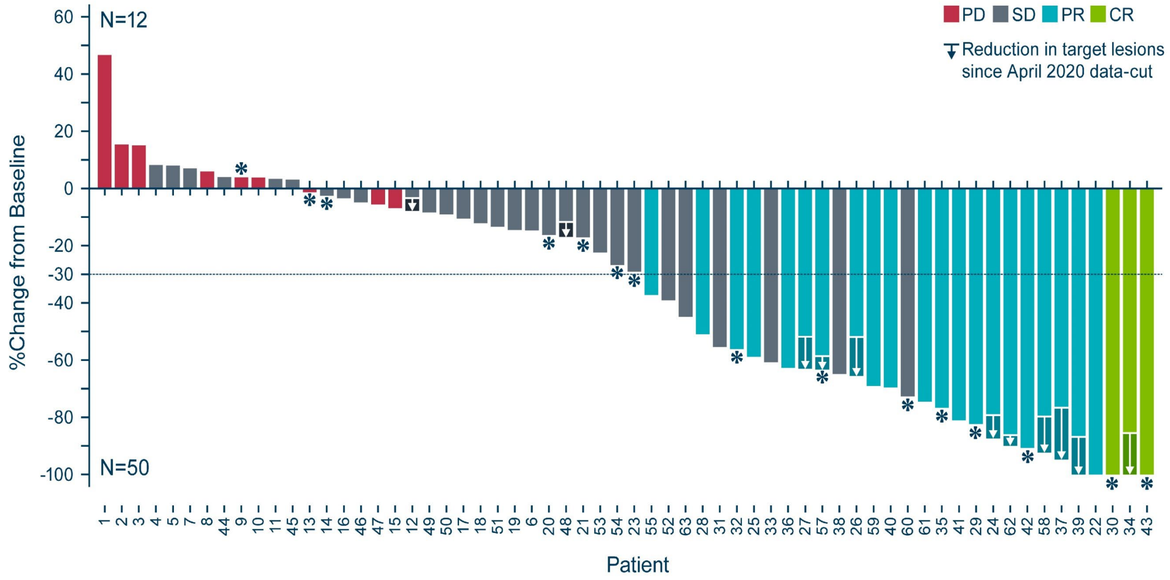
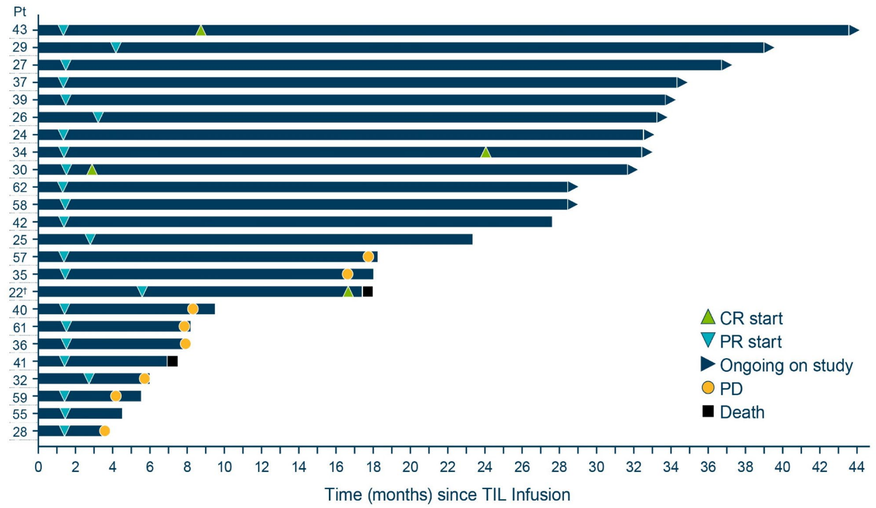
GMP, good manufacturing practices; IL-2, interleukin-2; NMA-LD, non-myeloablative lymphodepletion; TIL, tumor infiltrating lymphocytes.

IOVANCE – Tumor Infiltrating Lymphocytes

Best Overall Response

- 36% ORR
- 81% (50/62) of patients had reduction in tumor burden
- 79% of responders received prior anti-CTLA-4.
- 46% received prior combination IO.
- Median DOR not reached





*Patients with BRAF V600 mutation. 3 patients had no post-TIL disease assessment due to early death, and 1 due to start of new anticancer therapy.
DOR, duration of response; SOD, sum of diameters; TIL, tumor infiltrating lymphocytes.

disease; PD-1, programmed cell death protein-1; PR, partial response; SD, stable disease; TIL, tumor infiltrating lymphocytes; TPS, tumor proportion score; U, unknown.

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Summary Systemic Therapy in Melanoma

- Update for combination immunotherapies show a 49% 6.5 year overall survival for patients with stage IV melanoma.

- Frontline metastatic systemic therapy options include:
  - Combination anti-CTLA-4 + anti-PD-1
  - Single agent anti-PD(L)1
    - Potentially a new combination immunotherapy LAG-3i + PD-1i in the future
  - BRAFi + MEKi – *BRAF mutated only*
  - Triplet PD-1i + BRAFi + MEKi – *BRAF mutated only*

- Stage III
  - Choice of PD-1 blockade versus targeted for 1 year based on side effect profiles and individual patient factors.
  - Neoadjuvant combination immunotherapy or targeted therapies have shown promise, long-term follow up pending for this strategy.

- Stage IIB and IIC
  - RFS benefit with 1 year of Keytruda

- Intratumoral agents – may be good adjunct treatment in combination with standard checkpoint blockade, but data is limited.

- After Immune Checkpoint Progression – Tumor infiltrating lymphocytes or Keytruda + Lenvatinib on the horizon