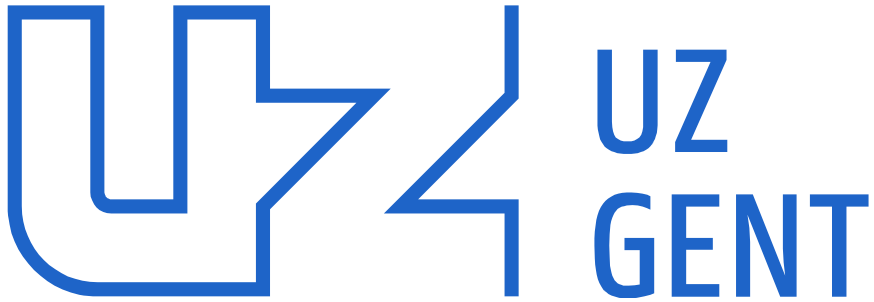

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Clinical challenges of checkpoint inhibitors in solid tumors

Prof. dr. Vibeke KRUSE

24 November 2018

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DISCLOSURES

I have provided consultation, attended advisory boards, and/or provided lectures for: Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Amgen and Sanofi. My institution received a honoraria for my contribution.

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- How do we identify responders?
- How do we increase response rates?
- What is the right time for discontinuing immunotherapy ?

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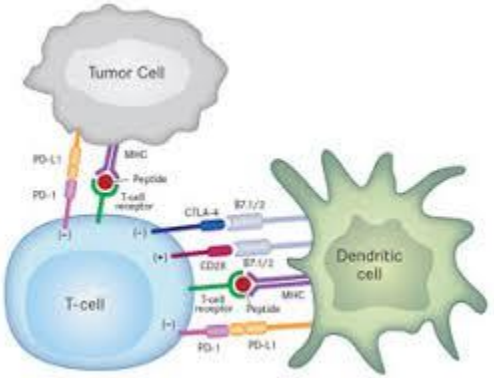
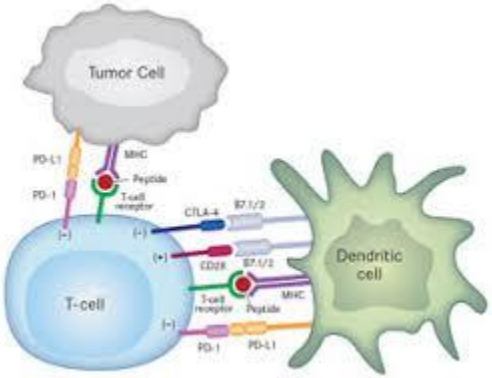


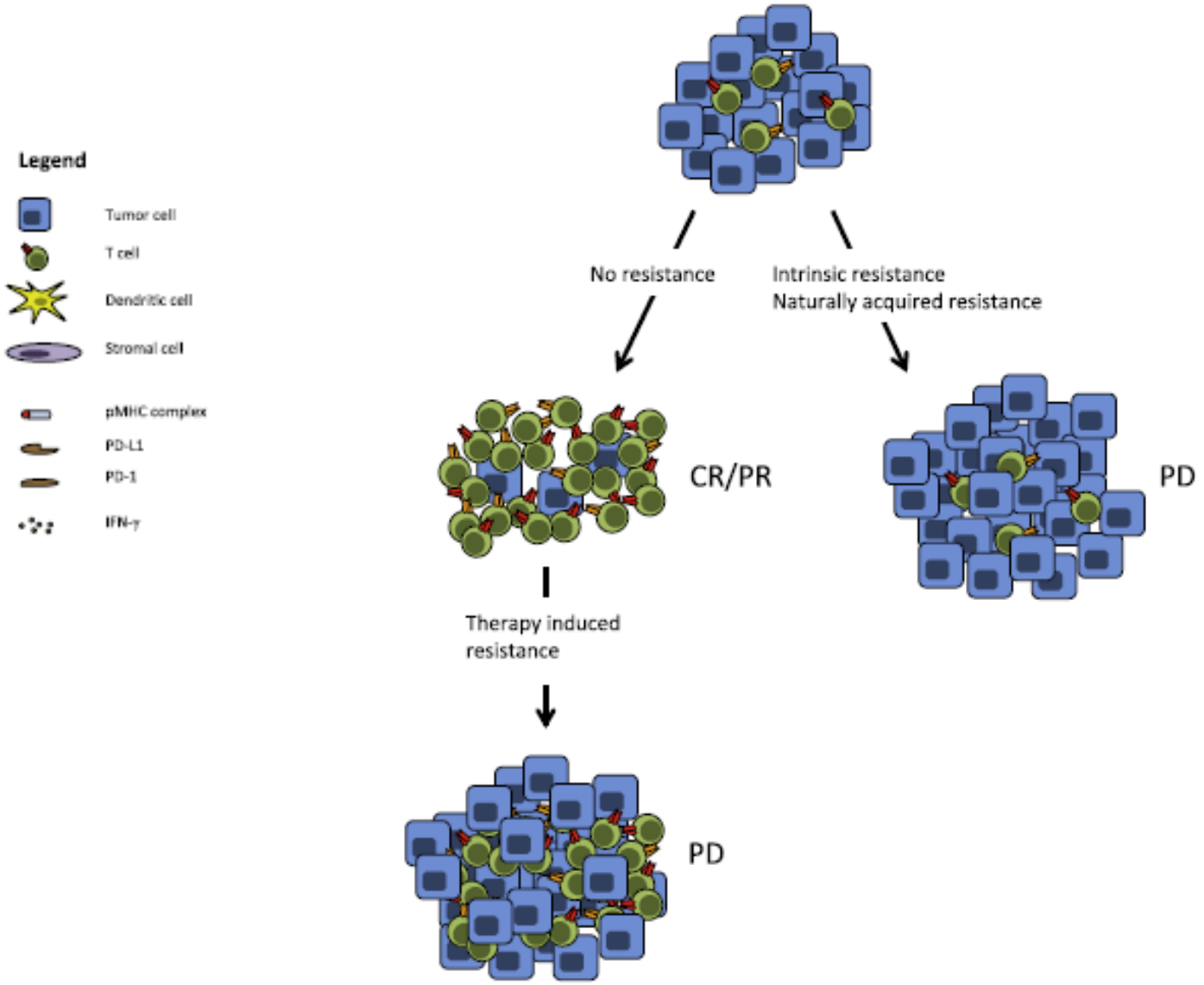
- How do we identify responders?



GROUP	INDICATION	ORR (%)	Agents approved	Main driver of response
High response rate	Hodgkin's disease	87	Nivolumab Pembrolizumab	PDJ amplicon
	Desmoplastic Melanoma	70	Nivolumab Pembrolizumab	Mutations from chronic sun exposure
	Merkel cell	56	Avelumab Pembrolizumab	Merkel cell virus
	MSI-h cancers	53	Nivolumab Pembrolizumab	Mutations from mismatch-repair deficiency
Intermediate response rate	Skin Melanoma	35-40	Nivolumab Pembrolizumab	Mutations from intermittent sun exposure
	NSCLC	20	Nivolumab Pembrolizumab Atezolizumab	Mutations from cigarette smoking
	Head and neck	15	Nivolumab Pembrolizumab	Mutations from cigarette smoking
	Gastroesophageal	15	Pembrolizumab	Mutations from cigarette smoking
	Bladder and Urinary tract	15	Nivolumab Pembrolizumab Atezolizumab Avelumab Durvalumab	Mutations from cigarette smoking
	Renal cell carcinoma	25	Nivolumab Pembrolizumab	Insertions and deletions (indels)
	Hepatocellular carcinoma	20	Nivolumab	Hepatitis virus

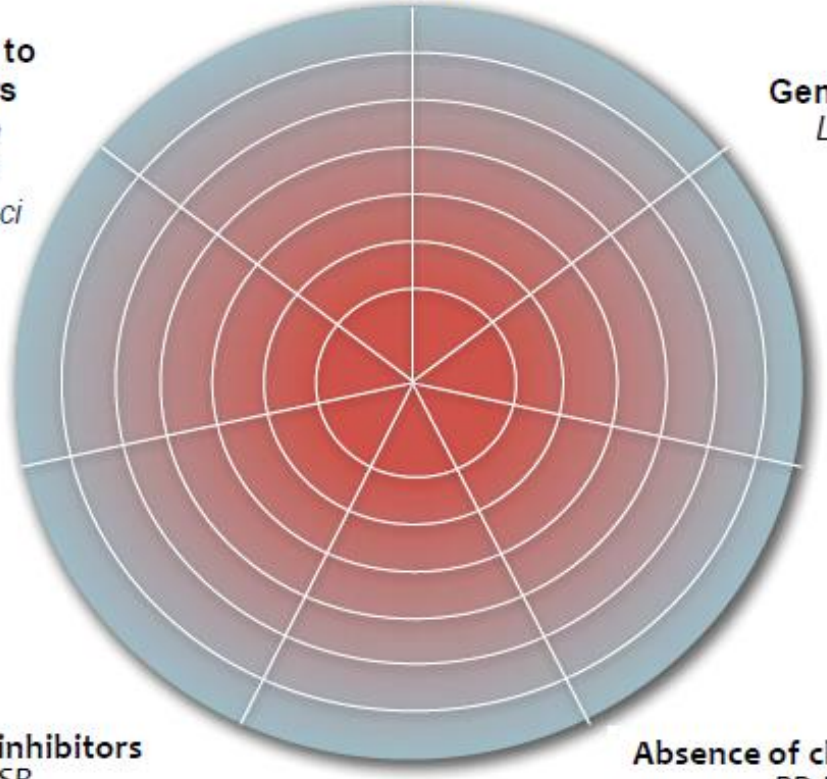
Adpated from Ribas et al. Science 2018

Acquired and intrinsic resistance to immunotherapy



Kelderman et al Mol Oncol 2014

An evolving immunogram : a complexity to acknowledge



Tumor foreignness
Mutational load
Neoantigen load

Tumor sensitivity to immune effectors
MHC expression
IFN-γ sensitivity
Heterozygocity at all MHC loci

General immune status
Lymphocyte count, LAG3, TIGIT, CD27
Ki67 PD1+ CD8

Microbiome
Low bacteroides
High faecalibacterium prausnitzii

Absence of inhibitory tumor metabolism
LDH, glucose utilization
IDO1, tumor acidity

Immune cell infiltration
Intratumoral T cells
Shared T cell clones
B7-H3/CD276 macrophages
CCL5 attracting T cells
CCR5 expressing BATF3 DC
LAG3, TIM3, TIGIT, CTLA4

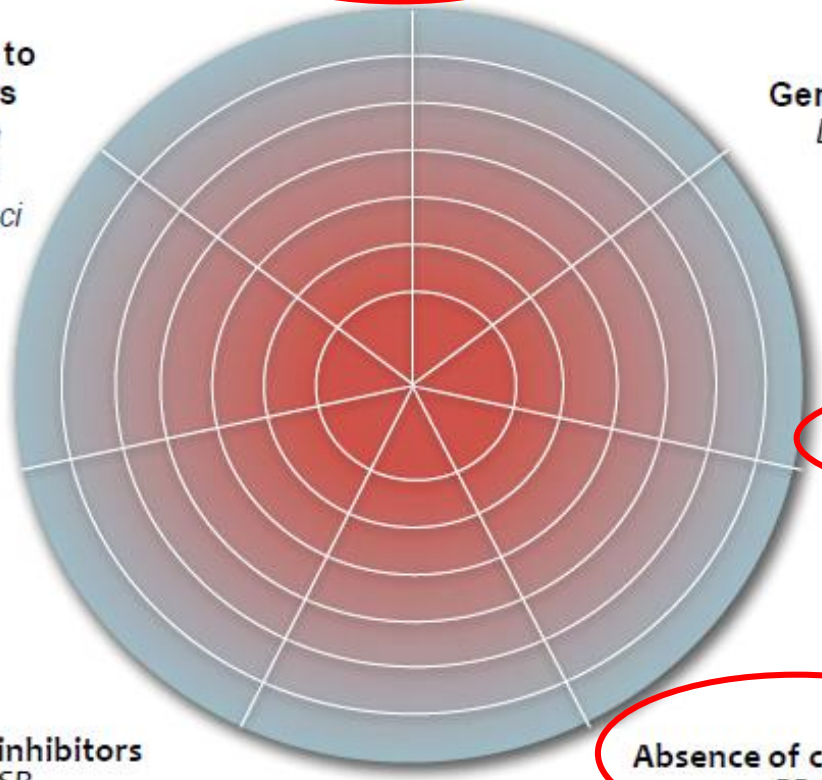
Absence of soluble inhibitors
IL-6 → CRP/ESR
CD73 → adenosine

Absence of checkpoints
PD-L1

MUNICH 2018 ESMO congress

Adapted from Blank Science 2016

An evolving immunogram : a complexity to acknowledge



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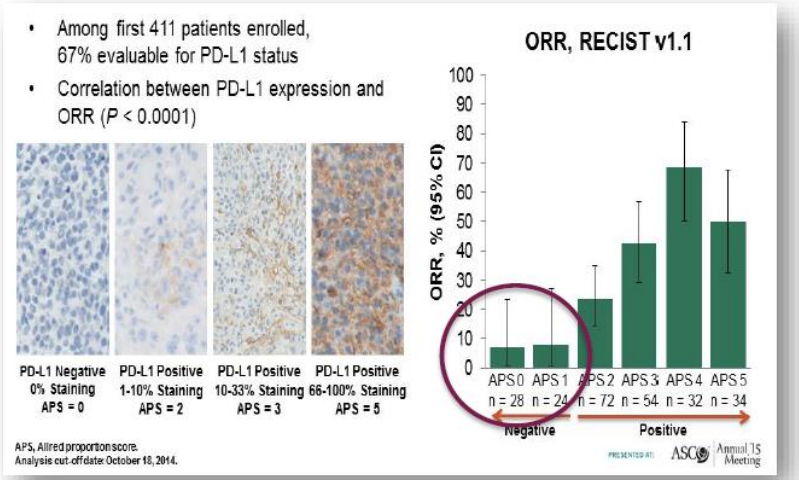
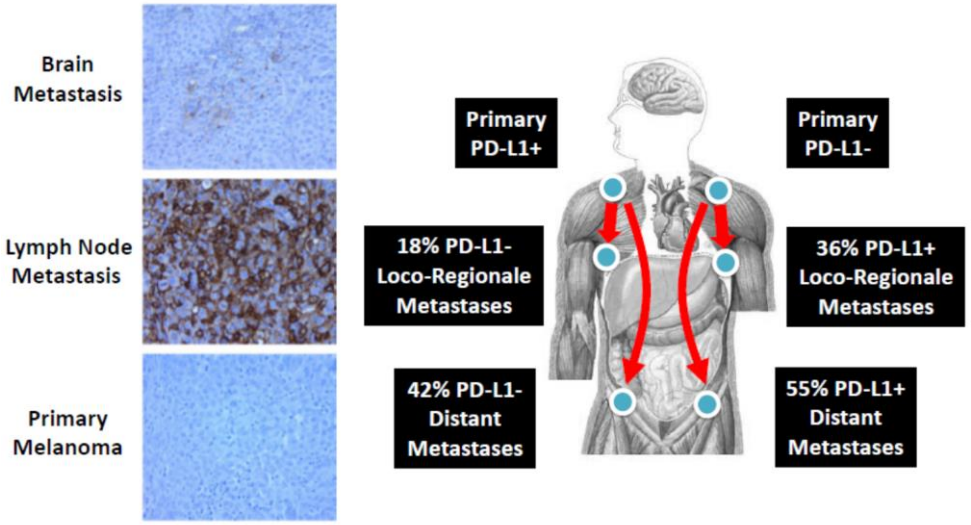
PD-L1 expression

PD-L1 expression and relationship with response to anti-PD-1 in melanoma



Daud et al., J Clin Oncol 2016

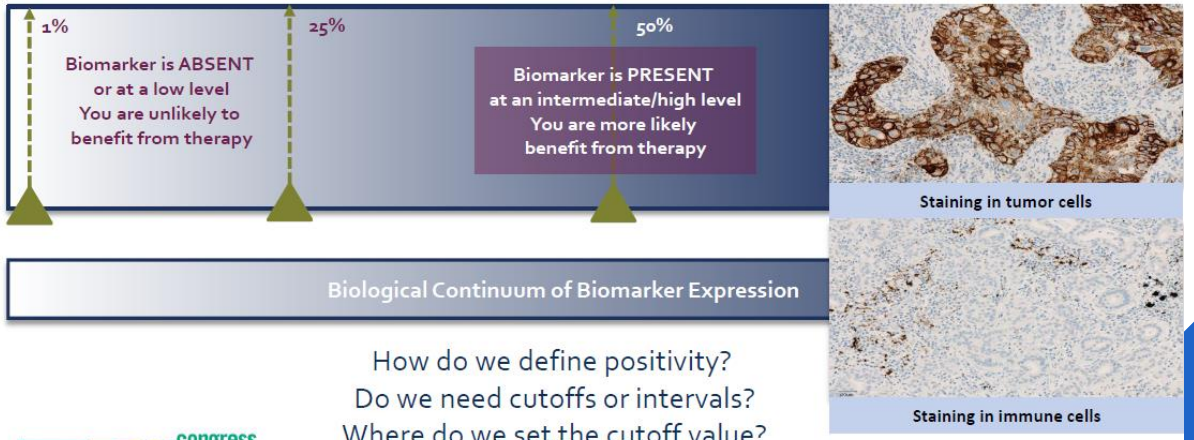
Intrapatient PD-L1 Discordance



anti-PD-L1, Merck 22C3 IHC clone, 40x

Adapted from Madore J, et al. Pigment Cell Melanoma Res 2015

Biomarker "Positivity": Present, Absent, or Graduated?

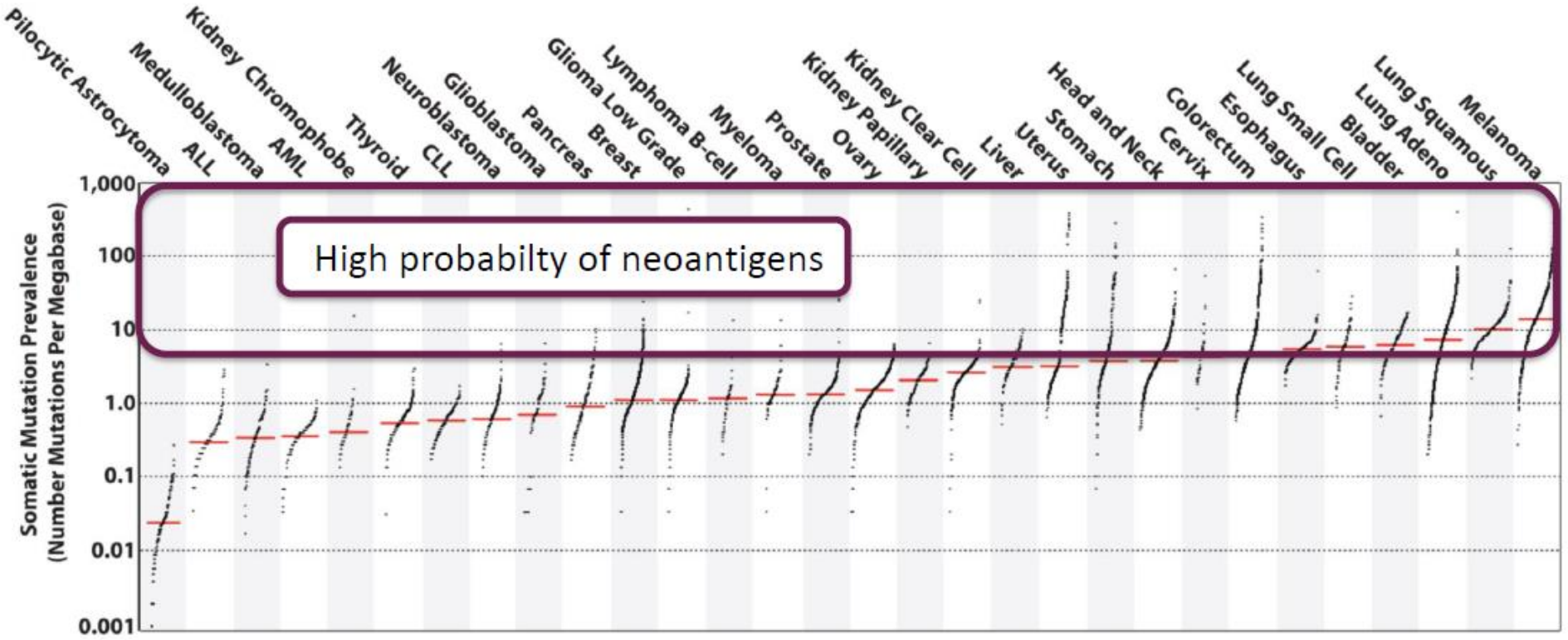


How do we define positivity?
Do we need cutoffs or intervals?
Where do we set the cutoff value?

Courtesy S Peters

Tumor mutational burden

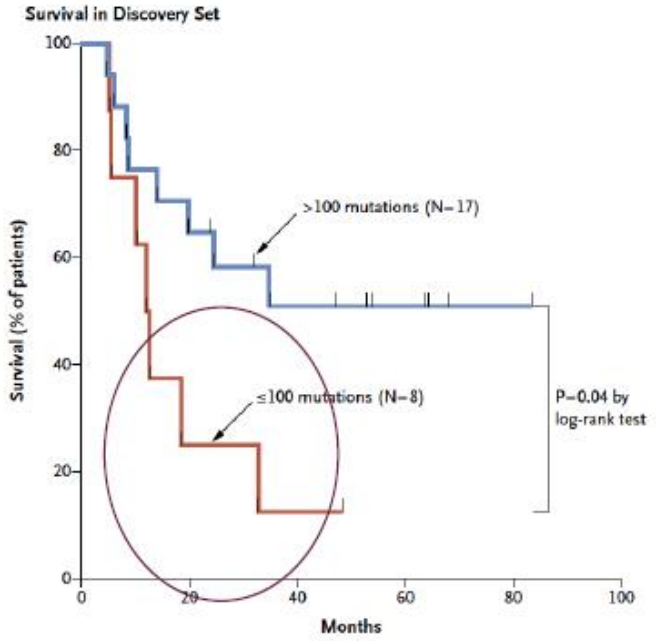
TMB is an independant biomarker, increasing the likelihood a tumour will be recognized as foreign

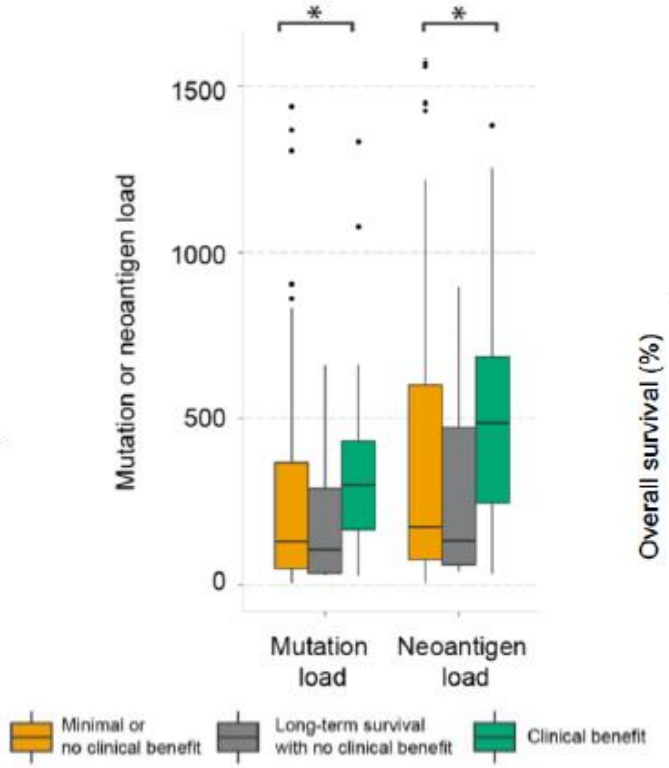


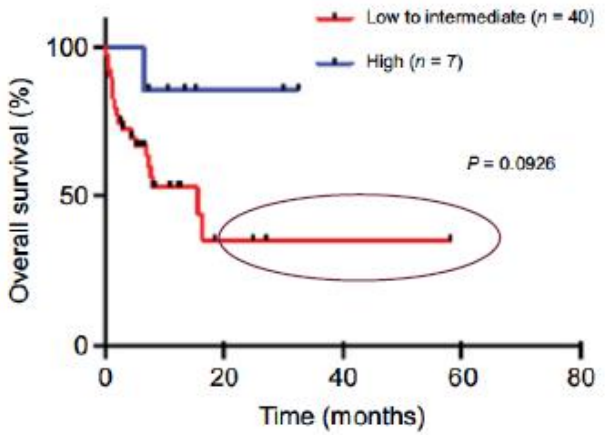
Lawrence, Nature 2015; Alexandrov, Nature 2013; Schumacher & Schreiber Science 2016

Tumor mutational burden

Low mutational load correlates with little clinical benefit from CTLA-4 or PD-1 blockade in melanoma



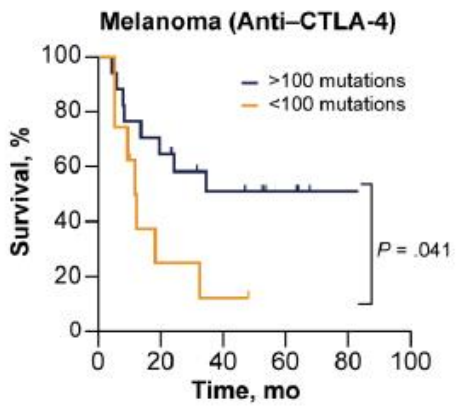


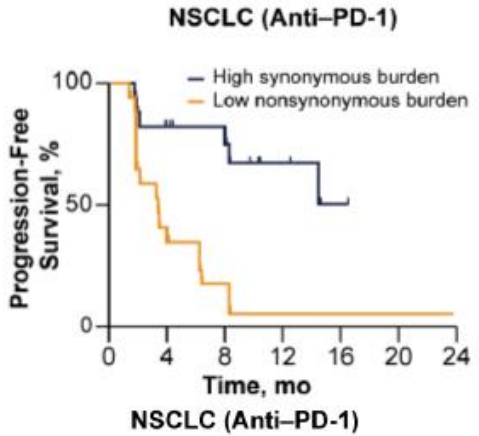


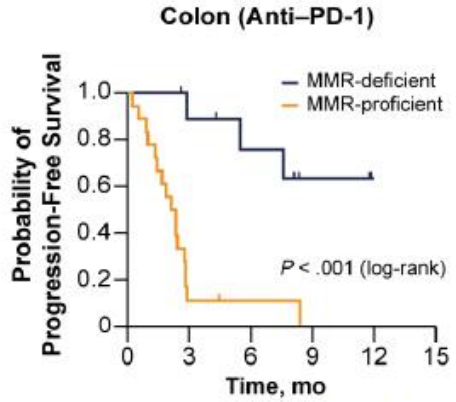
Snyder et al., N Engl J Med 2014; Van Allen et al., Science 2015; Goodman et al., Mol Canc Ther 2017

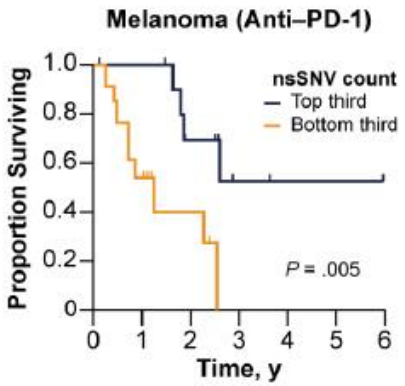
Tumor mutational burden

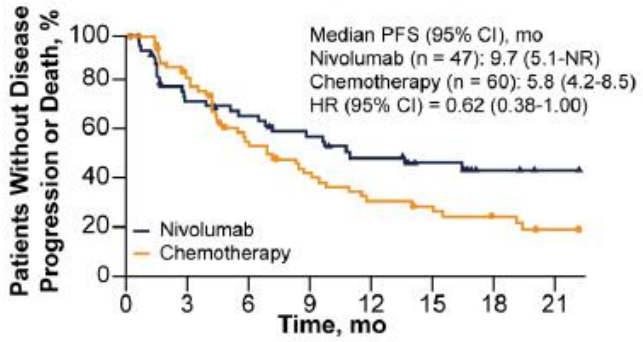
TMB by Whole Exome Sequencing (WES) is predictive of IO activity across disease

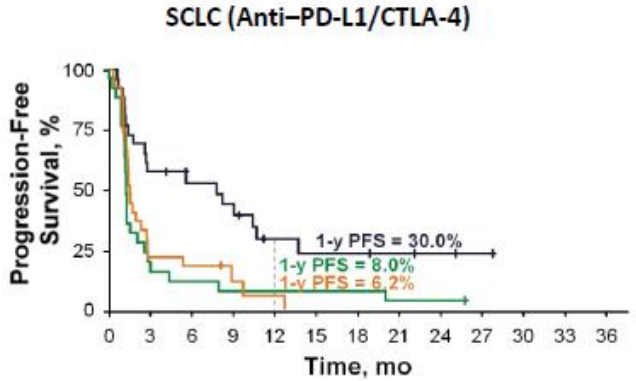












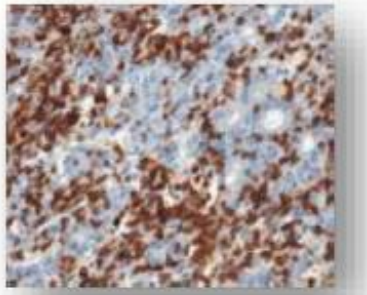
yder, N Engl J Med. 2014; 2. Rizvi, Science. 2015; 3. Le DT , N Engl J Med. 2015; 4. Van Allen EM , Science. 2015 ; 5. Hugo , Cell. 2016 ; 6. Carbone, N Engl J Med. 2017; 7. Rizvi, WCLC 2017.

Courtesy of S Peters

Immune cell infiltration

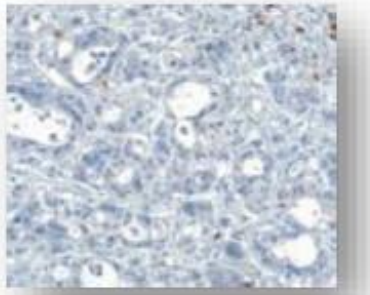
‘Inflamed’ (hot) vs ‘non-inflamed’ (cold) tumors and response to immune checkpoint inhibition

Inflamed

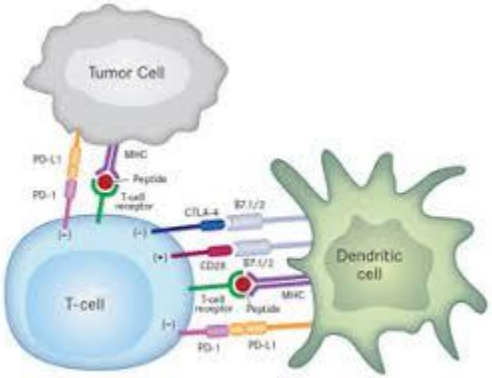


TILs
CD8+ T cells
IFN-γ gene signature
PDL1 expression
Pre-existing immunity

Non-inflamed



- How do we increase response rates?



How do we increase response rates?

- Combination therapies
- Selecting patients on the presence of biomarkers
- Bringing immunotherapy to frontline
- Defining the right time to initiate immunotherapy / sequence
- Using immunotherapy in earlier disease stages (adjuvant)

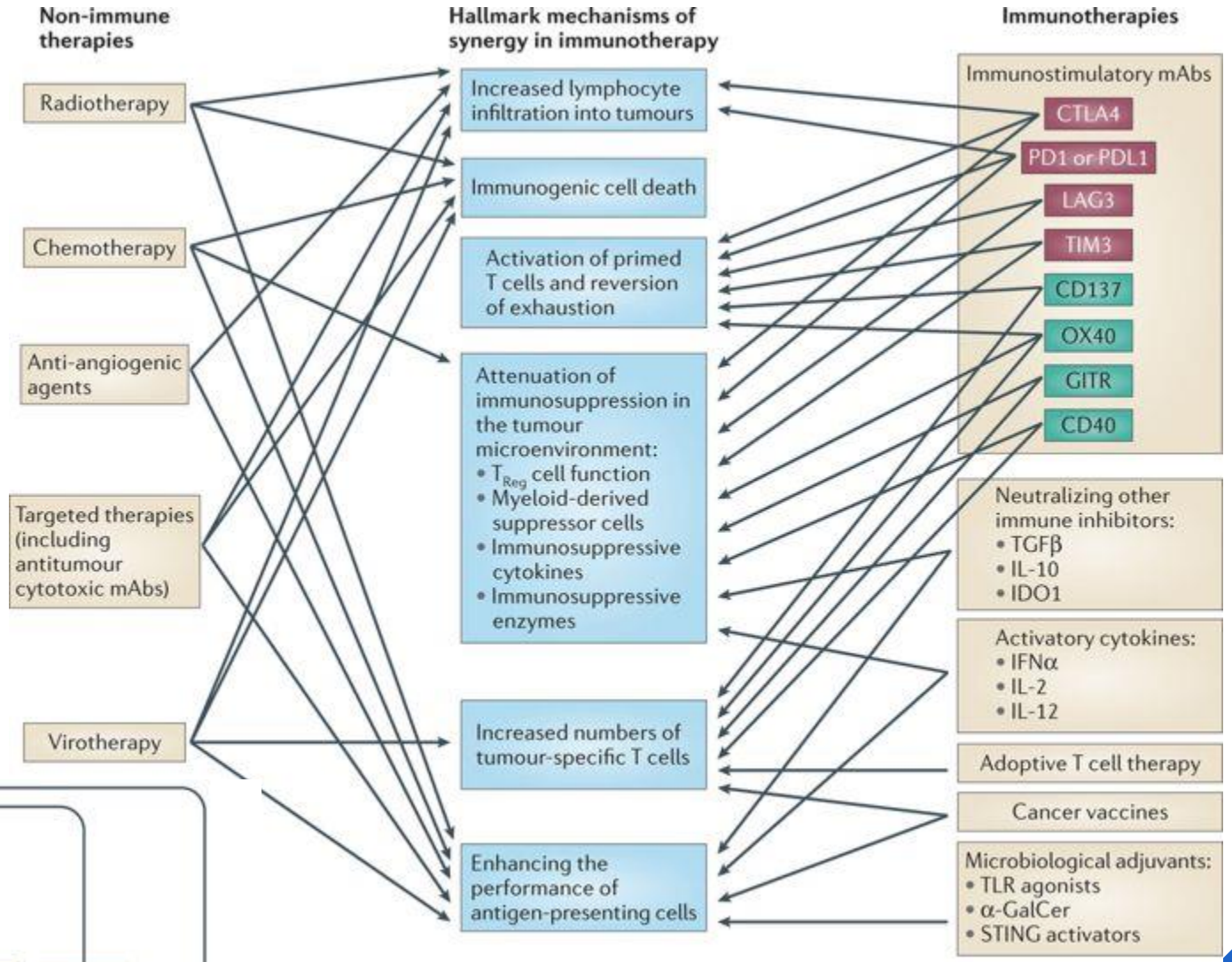
How do we increase response rates?

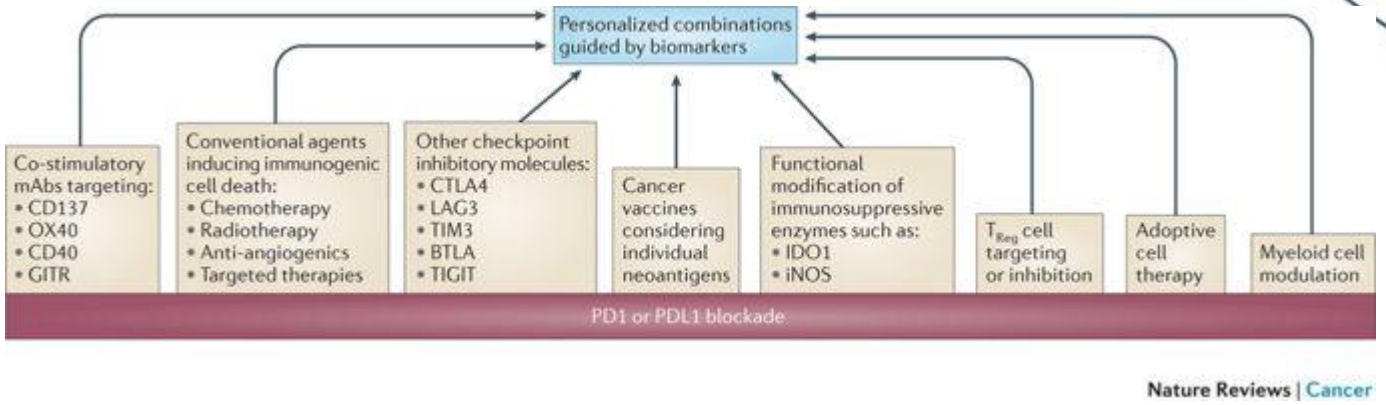
- **Combination therapies**
- Selecting patients on the presence of biomarkers
- **Bringing immunotherapy to frontline**
- Defining the right time to initiate immunotherapy / sequence
- **Using immunotherapy in earlier disease stages (adjuvant)**

Combination strategies

- Using anti-PD1/PDL1 as backbone

- Today, a solid scientific rational & strong activity signals are required for new combinations to be tested



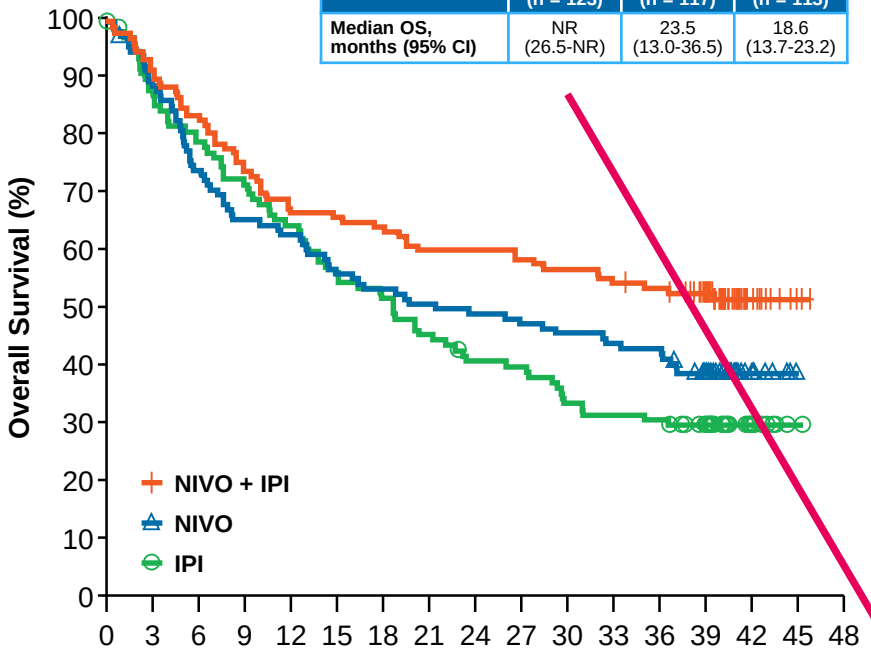


Melero, Haanen Nat Rev Canc 2015;

Overall Survival by Tumor PD-L1 Expression, 1% Cutoff

PD-L1 Expression < 1 %

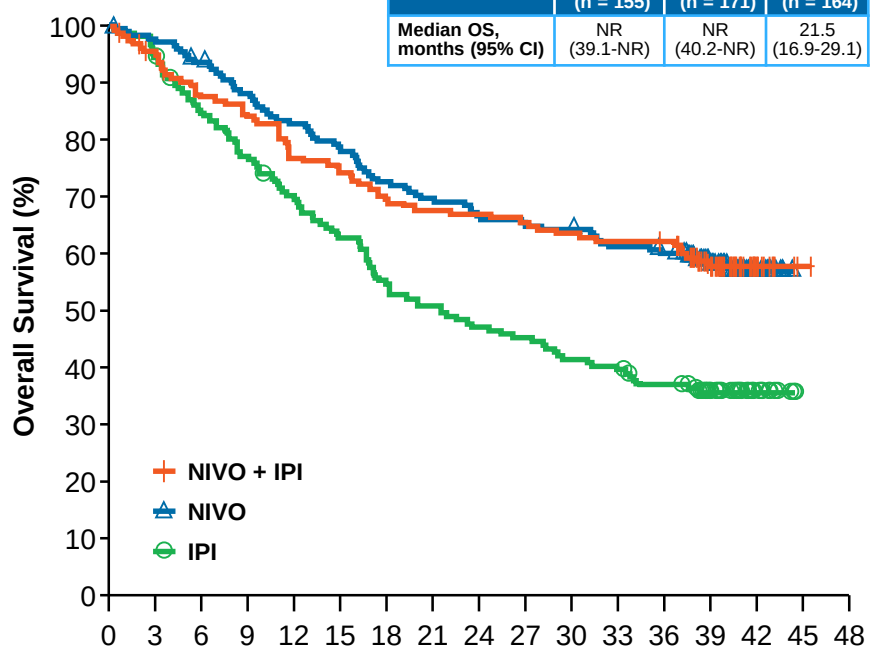
	NIVO + IPI (n = 123)	NIVO (n = 117)	IPI (n = 113)
Median OS, months (95% CI)	NR (26.5-NR)	23.5 (13.0-36.5)	18.6 (13.7-23.2)



Patients at risk:																	
NIVO + IPI	123	113	102	91	82	82	79	74	74	72	70	67	65	50	11	2	0
NIVO	117	103	86	76	73	65	62	59	57	55	53	51	49	37	7	0	0
IPI	113	96	87	79	71	61	57	50	44	43	36	34	33	24	8	1	0

PD-L1 Expression ≥ 1 %

	NIVO + IPI (n = 155)	NIVO (n = 171)	IPI (n = 164)
Median OS, months (95% CI)	NR (39.1-NR)	NR (40.2-NR)	21.5 (16.9-29.1)



Patients at risk:																	
NIVO + IPI	155	144	132	127	116	112	105	102	101	99	96	94	93	66	14	1	0
NIVO	171	165	158	148	139	131	122	117	112	109	108	102	99	76	18	0	0
IPI	164	155	137	125	113	101	88	82	76	73	67	64	58	38	10	0	0

PD-L1<5%

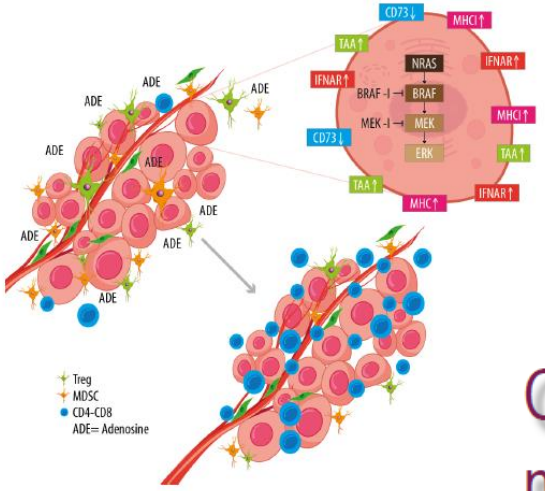
	NIVO + IPI (n = 210)	NIVO (n = 208)	IPI (n = 202)
Median OS, months (95% CI)	NR (32.7-NR)	35.9 (23.1-NR)	18.4 (13.7-22.5)

Database lock May 24, 2017; minimum follow up of 36 months.
CI, confidence interval; IPI, ipilimumab; NIVO, nivolumab; NR, not reached; OS, overall survival; PD-L1, programmed death ligand 1.

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

Anti-PD1 + BRAF/MEK inhibitors

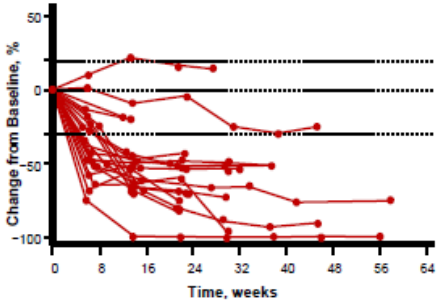
BRAF/MEK inhibitors as immunomodulating agents



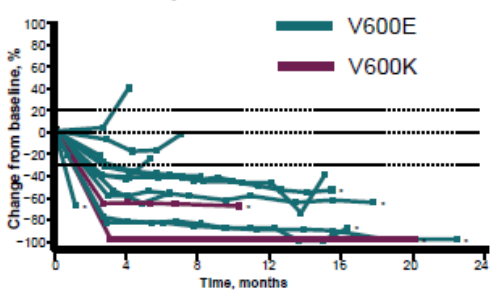
Ascierto and Dummer. *Oncoimmunology* 2018

Combining BRAF/MEK inhibitors with IO drugs in BRAF V600 mutant melanoma

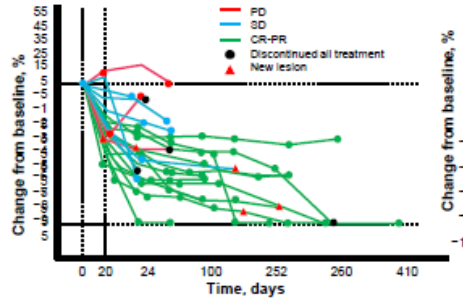
Dabrafenib + trametinib + durvalumab[1]



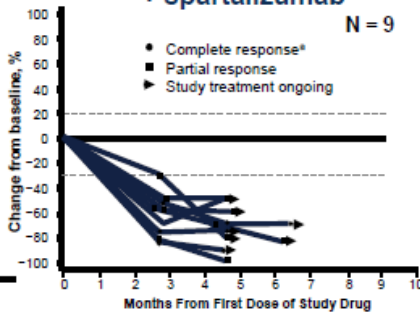
Dabrafenib + trametinib + pembrolizumab[2,3]



Vemurafenib + cobimetinib + atezolizumab[4]



Dabrafenib + trametinib + spartalizumab[5]



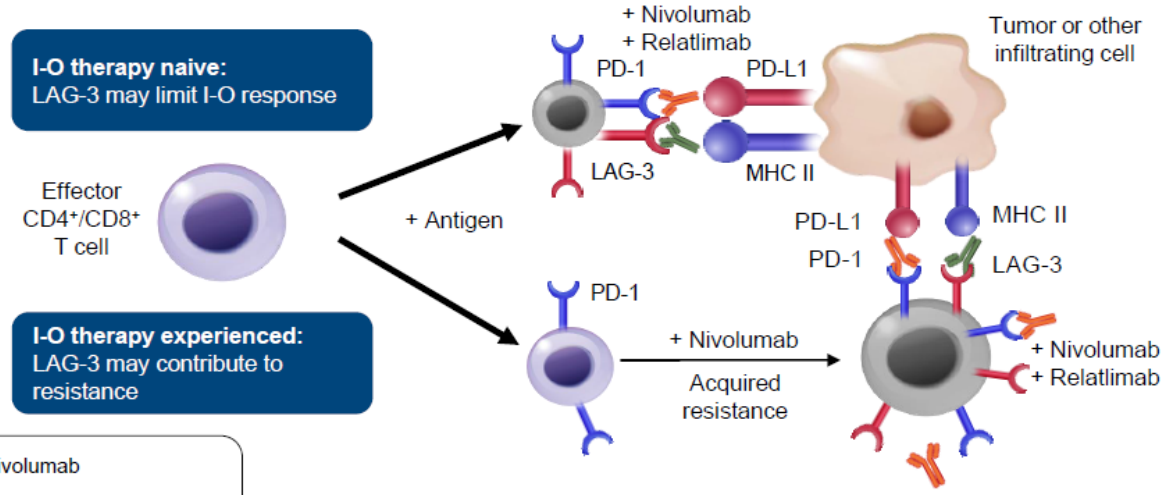
1. Ribas A, et al. *J Clin Oncol*. 2015; 33(suppl) [abstract 3003]; 2. Ribas A, et al. *J Clin Oncol*. 2016; 34(suppl) [abstract 3014]; 3. Ribas A, et al. *Ann Oncol*. 2017; 28(suppl 5) [abstract 1216O]; 4. Hwu P, et al. *Ann Oncol*. 2016; 27(suppl 6) [abstract 1109PD]; 5. Dummer, R, et al. *J Clin Oncol*. 2018;36(suppl 5S) [abstract 189].

PRESENTED BY R DUMMER AT AACR 2018
Courtesy of Dr Dummer

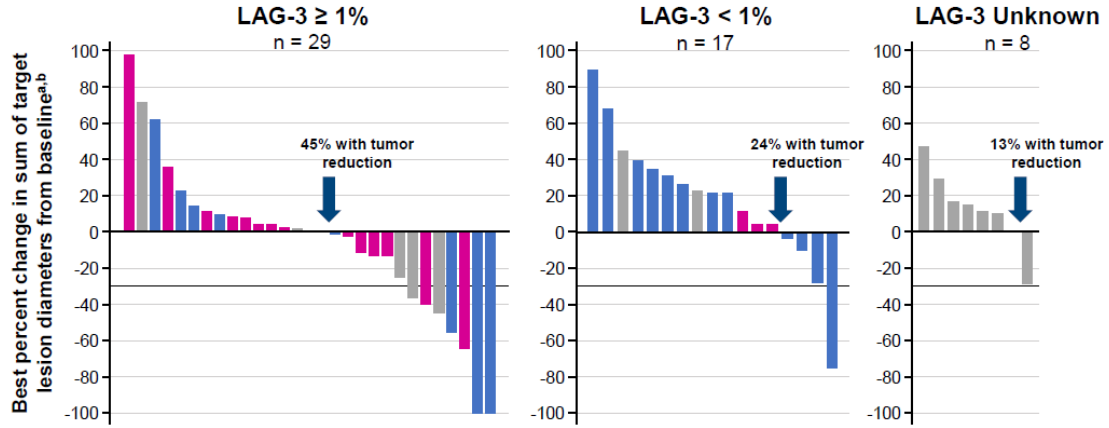
Anti-PD1 + anti-LAG3

Potential Role of LAG-3 in T-Cell Exhaustion and Anti–PD-1 Resistance

- **LAG-3 regulates a checkpoint pathway that limits the activity of T cells**[1]
- **LAG-3 and PD-1 receptors are overexpressed and/or co-expressed on tumor-infiltrating lymphocytes in melanoma**[2,3]



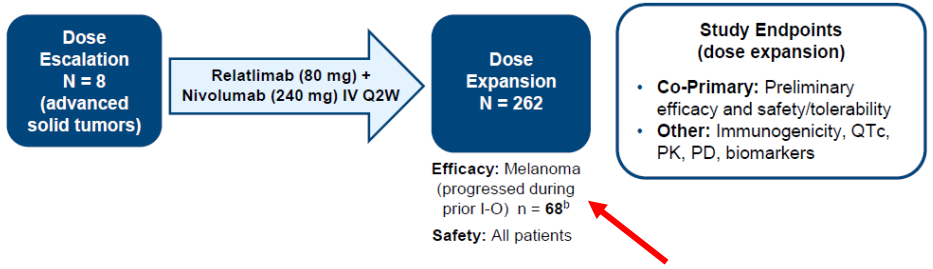
Best Change in Target Lesion Size by LAG-3 and PD-L1 Expression



I-O, immuno-oncology; MHC II, major histocompatibility complex class II; PD-1, programmed death-1; PD-L1, programmed death ligand 1.

1. Grosso JF et al. *J Clin Invest*. 2007;117:3383–3392. 2. Goding SR et al. *J Immunol*. 2013;190:4899–4909. 3. Taube JM et al. *Clin Cancer Res*. 2015;21:3969–3976.

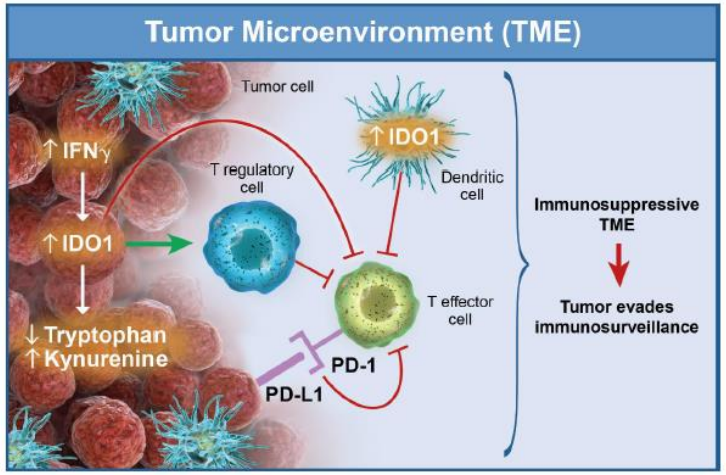
4



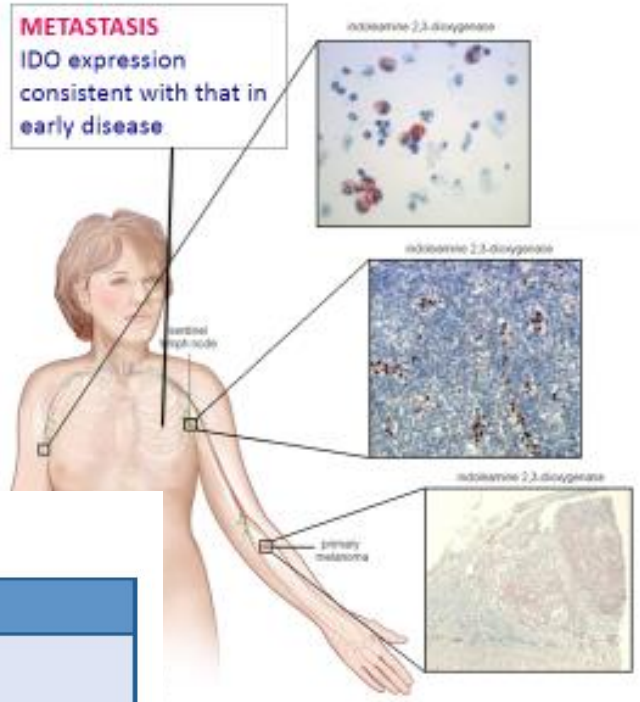
IDO-inhibition

Rationale to target IDO1

- Upregulation of IDO1 is a potential mechanism to evade immunosurveillance
  - ↓ Tryptophan ↑ Kynurenine
  - ↓ T_{eff} and NK cells
  - ↑ T_{reg} cells, MDSCs, TAMs
- Epacadostat: IDO1 enzyme inhibitor
- Pembrolizumab: anti-PD-1 humanized antibody



The rationale of indoleamine 2,3-dioxygenase inhibition for cancer therapy



BLOOD
- ✓ Higher IDO expression in PBMCs
- ✓ Correlation with PD-L1 and CTL4

SENTINEL
IDO expression independent negative prognostic factor on DFS and OS

PRIMARY MELANOMA
- ✓ Correlated with peritumoral IDO expression
- ✓ Negative effect on TIL infiltrate

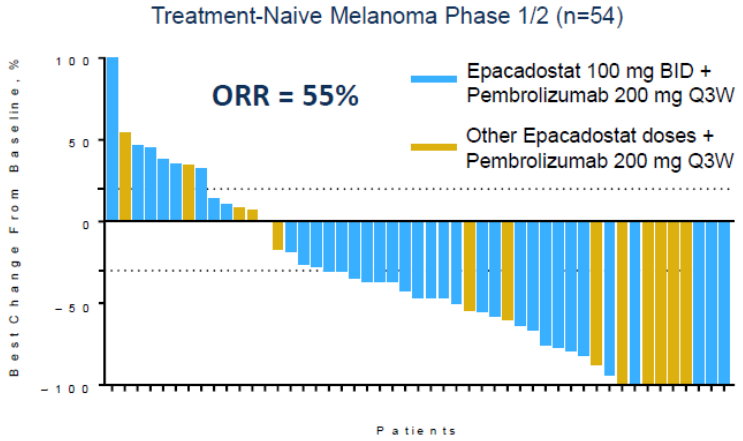
BROCHEZ 2016

IDO1, indoleamine 2,3 dioxygenase 1; IFNγ, interferon gamma; MDSC, myeloid-derived suppressor cell; NK, natural killer; PD-1, programmed death 1; PD-L1, programmed death ligand-1; TAM, tumor-associated macrophage; T_{eff}, effector T cell; T_{reg}, regulatory T cell.

Courtesy Georgina V. Long

IDO-inhibition + anti-PD-1

Promising efficacy in phase 1/2 study of IDOi + anti-PD1



BID, twice daily; MTD, maximally tolerated dose; PD-L1, programmed death ligand-1; Q3W, every 3 weeks.
Hamid O, et al. *Ann Oncol*. 2017;28(suppl 5):1214O.

MUNICH 2018 ESMO congress

Georgina V. Long

ECHO-202 / KEYNOTE-037

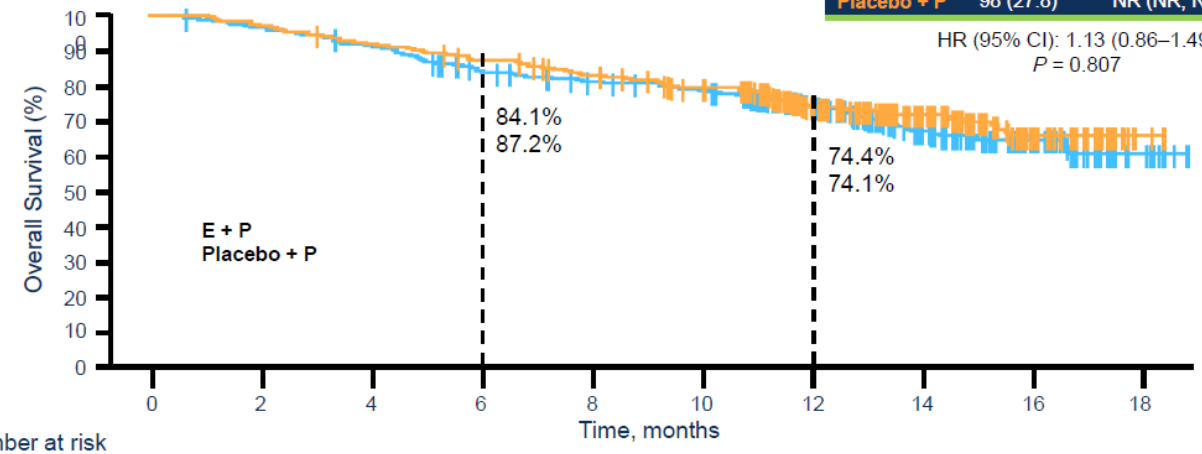
- Phase 1: Epacadostat 50, 100, or 300 mg PO BID + Pembrolizumab 200 mg IV Q3W
- MTD of epacadostat not reached
- Phase 2: Epacadostat 100 mg PO BID
- Phase 1/2 efficacy in treatment-naive melanoma:
  - ORR = 55%
  - Median PFS = 22.8 mo

Overall Survival

Fase 3

	Events, n (%)	Median OS, months (95% CI)
E + P	106 (29.9)	NR (NR, NR)
Placebo + P	98 (27.8)	NR (NR, NR)

HR (95% CI): 1.13 (0.86–1.49)
P = 0.807



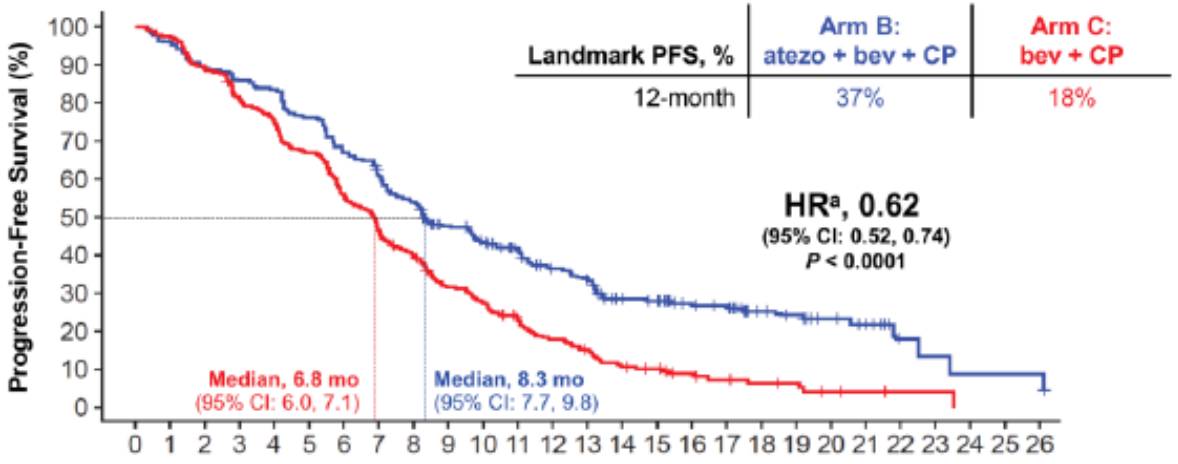
Number at risk

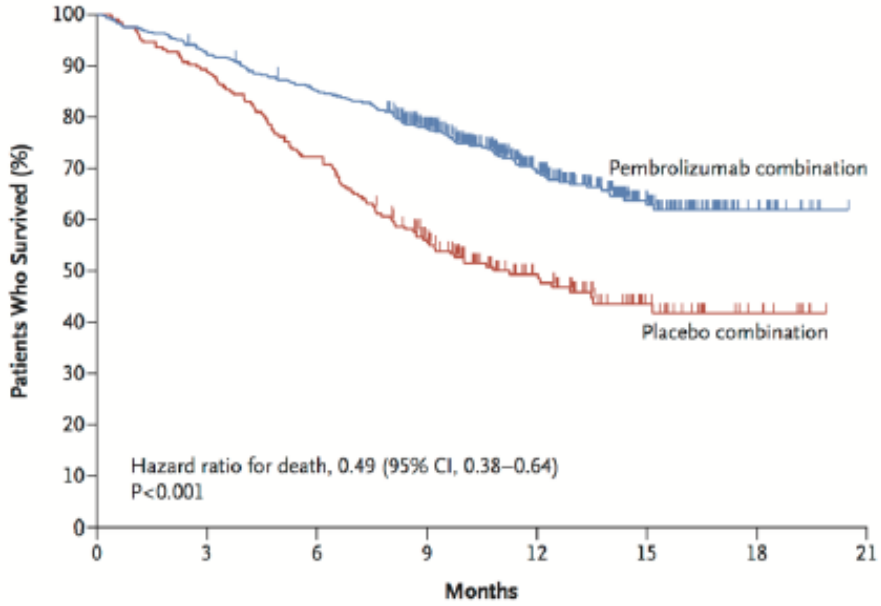
E + P	354	340	322	290	274	263	183	96	42	5
Placebo + P	352	342	323	304	285	263	186	115	43	2

CI, confidence interval; E, epacadostat; HR, hazard ratio; NR, not reached; OS, overall survival; P, pembrolizumab.

Frontline immunotherapy

Frontline combinations with chemo in non-squamous NSCLC





- Magnitude of benefit follows PD-L1 expression
- Squamous data : Keynote 407, IMPower 131

Ghandi et al. NEJM 2018

Frontline immunotherapy

Frontline combinations with chemo in TNBC

IMpassion130 study design

Key IMpassion130 eligibility criteria[a]:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented[b]
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

Stratification factors:

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])[c]

R 1:1

Atezo + nab-P arm:
Atezolizumab 840 mg IV
– On days 1 and 15 of 28-day cycle
+ *nab*-paclitaxel 100 mg/m² IV
– On days 1, 8 and 15 of 28-day cycle

Double blind; no crossover permitted

Plac + nab-P arm:
Placebo IV
– On days 1 and 15 of 28-day cycle
+ *nab*-paclitaxel 100 mg/m² IV
– On days 1, 8 and 15 of 28-day cycle

RECIST v1.1
PD or toxicity

- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

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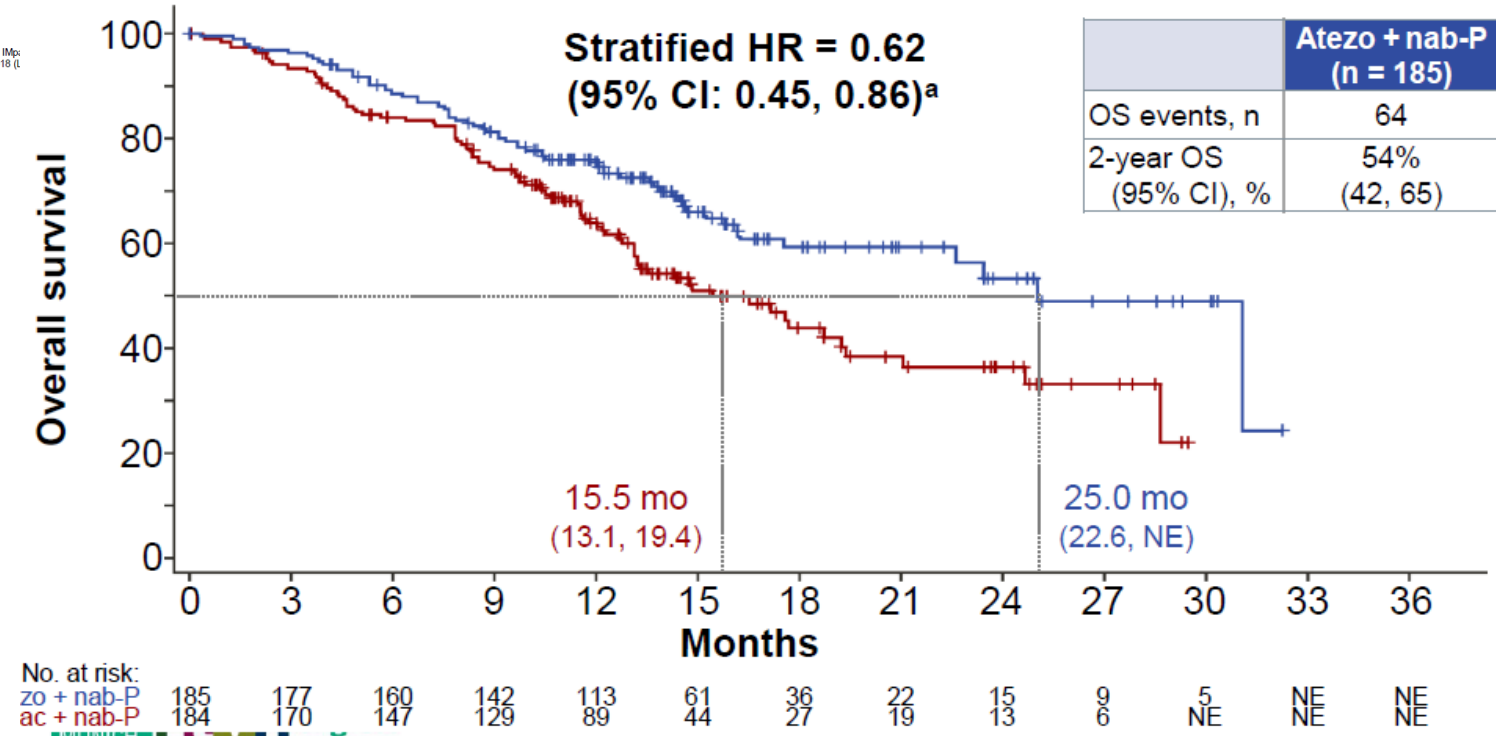
IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were investigator assessed (per RECIST v1.1).

Schmid P, et al. IMp
ESMO 2018 (L

Interim OS analysis: PD-L1+ population



	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
OS events, n	64	88
2-year OS (95% CI), %	54% (42, 65)	37% (26, 47)

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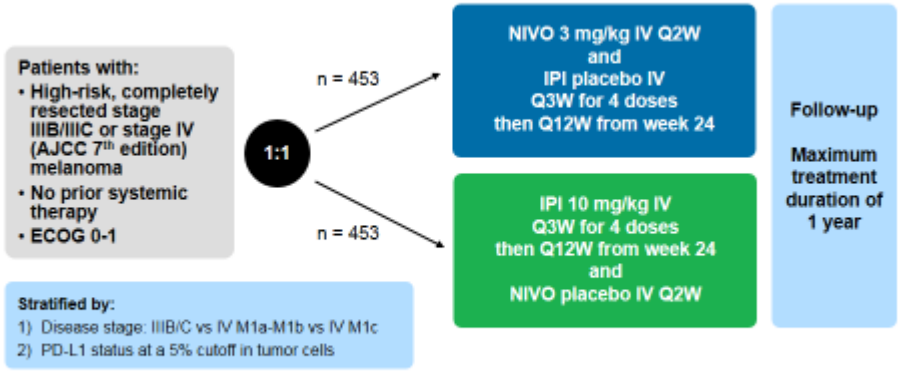
Data cutoff: 17 April 2018. Median OS durations (and 95% CI) are indicated on the plot. [a] Not formally tested.

Schmid P, et al. IMpassion130
ESMO 2018 (LBA1_PR)

Adjuvant immunotherapy

CheckMate 238: 24-Month Follow-Up

CheckMate 238: Study Design



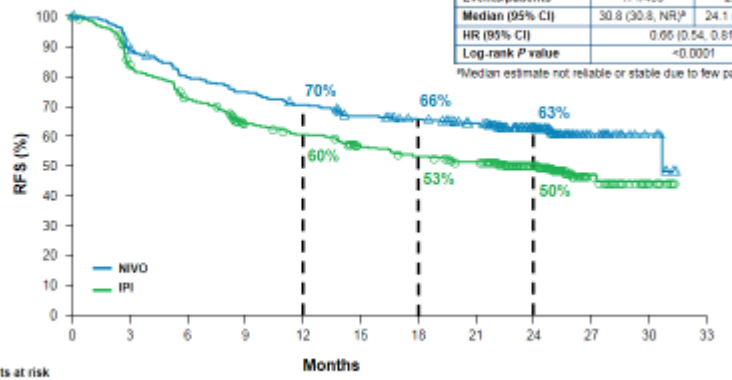
Enrollment period: March 30, 2015 to November 30, 2015

CheckMate 238: 24-Month Follow-Up

Primary Endpoint: RFS in All Patients

	NIVO	IPI
Events/patients	171/453	221/453
Median (95% CI)	30.8 (30.8, NR)[a]	24.1 (16.6, NR)
HR (95% CI)	0.65 (0.54, 0.81)	
Log-rank *P* value	<0.0001	

[a]Median estimate not reliable or stable due to few patients at risk.



Number of patients at risk

NIVO	453	394	353	331	311	291	280	264	205	28	7	0
IPI	453	363	314	270	251	230	216	204	149	23	5	0

CheckMate 238: 24-Month Follow-Up

Summary of Recurrence Events

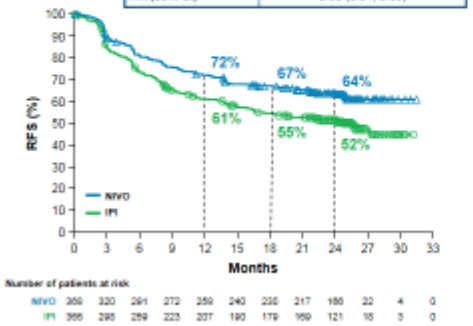
	NIVO (n = 453)	IPI (n = 453)
Events, n (%)	171 (38)	221 (49)
Recurrence	171 (38)	216 (48)
Disease at baseline	1 (<1)	2 (<1)
Local recurrence	31 (7)	46 (10)
Regional recurrence	35 (8)	36 (8)
Distant metastasis	97 (21)	128 (28)
New primary melanoma	7 (2)	4 (1)
Death	0	5 (1)

CheckMate 238: 24-Month Follow-Up

Subgroup Analysis of RFS: Disease Stage III and IV

Stage III

	NIVO	IPI
Events/patients	135/368	174/366
Median (95% CI)	NR	25.5 (16.6, NR)
HR (95% CI)	0.68 (0.54, 0.85)	



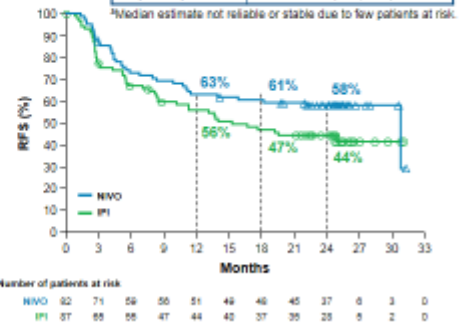
Number of patients at risk

NIVO	368	320	291	272	259	240	230	217	166	22	4	0
IPI	366	295	259	223	207	190	179	169	121	16	3	0

Stage IV

	NIVO	IPI
Events/patients	35/82	47/87
Median (95% CI)	30.8 (15.9, NR)[a]	15.4 (8.5, NR)
HR (95% CI)	0.68 (0.44, 1.06)	

[a]Median estimate not reliable or stable due to few patients at risk.

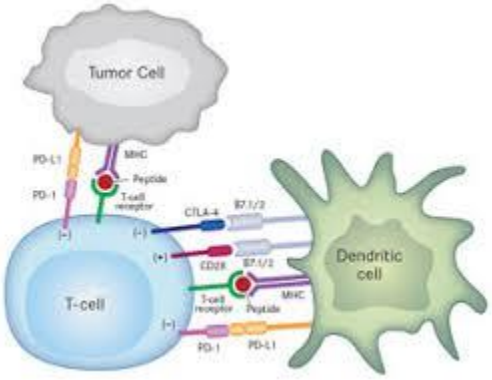


Number of patients at risk

NIVO	82	71	59	56	51	49	46	45	37	6	3	0
IPI	87	65	55	47	44	40	37	35	28	5	2	0

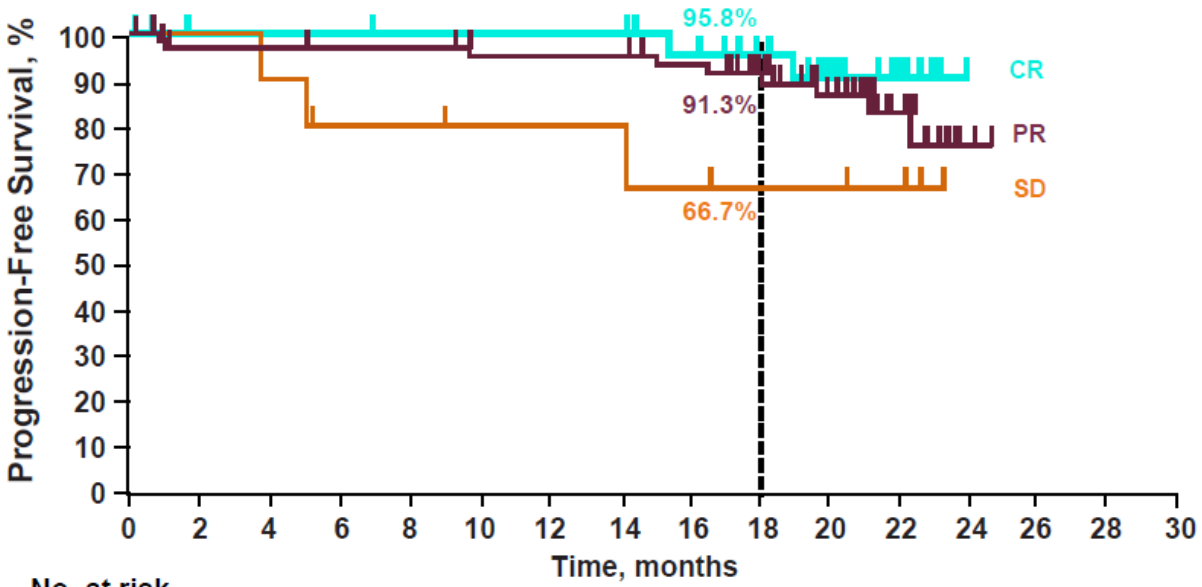
Weber et al NEJM 2017

- What is the right time for discontinuing immunotherapy?



I melanoma we have some evidence from long term follow up

PFS[a] in 103 Melanoma Patients Who Completed Protocol-Specified Time on KEYNOTE-006



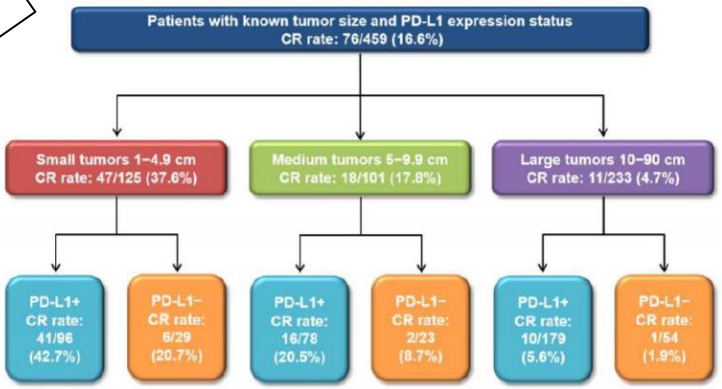
No. at risk

CR	28	27	27	27	26	26	26	26	23	19	15	6	1	0	0	0
PR	65	58	58	57	57	54	51	54	51	44	32	15	3	0	0	0
SD	10	10	9	7	7	6	6	6	5	4	4	3	0	0	0	0

[a]Per immune-related response criteria by investigator review; time is measured from last dose of pembrolizumab. Data cutoff: Dec 4, 2017 Long, G et al ASCO 2018.

Baseline parameters associated with CR

Keynote 001



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Robert et al , J Clin Oncol, 2017

What about patients who stop due to toxicity?

CheckMate-067: Follow-up in patients who stopped for toxicity

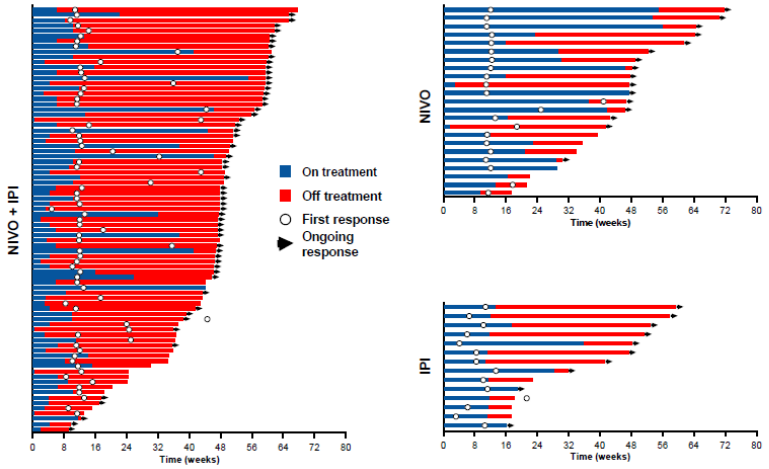
- 68% (81/120), 85% (23/27), and 30% (14/47) of patients who discontinued NIVO + IPI, NIVO, and IPI, respectively, due to drug-related toxicity, experienced a complete or partial response

	NIVO + IPI (N = 120)	NIVO (N = 27)	IPI (N=47)
Median time to response, months (range)[a]	2.8 (1.1–10.3)	2.8 (2.5–9.5)	2.8 (2.6–8.3)
Median duration of response, months (95% CI)[b]	13.1 (NR–NR)	NR (5.6–NR)	NR (1.4–NR)
Ongoing response among responders, n/N (%)[a]	56/81 (69)	16/23 (70)	10/14 (71)

[a]Minimum follow-up of 11 months from date of randomization
[b]Censored data (response ongoing)
NR = not reached

Larkin J et.al ESMO 2015

Time to and Durability of Response in Patients Who Discontinued Due to Toxicity



What about patients who stop for any reason?

Patient Analysis: Pooled Checkmate 067-069

All-treated patients on NIVO+IPI (N = 407)

30 (7.4%) remain on treatment
Median duration of treatment: 40.0 months (range: 38-45)

377 (92.6%) patients stopped treatment
Median duration of treatment: 2.4 months (range: 0-41)

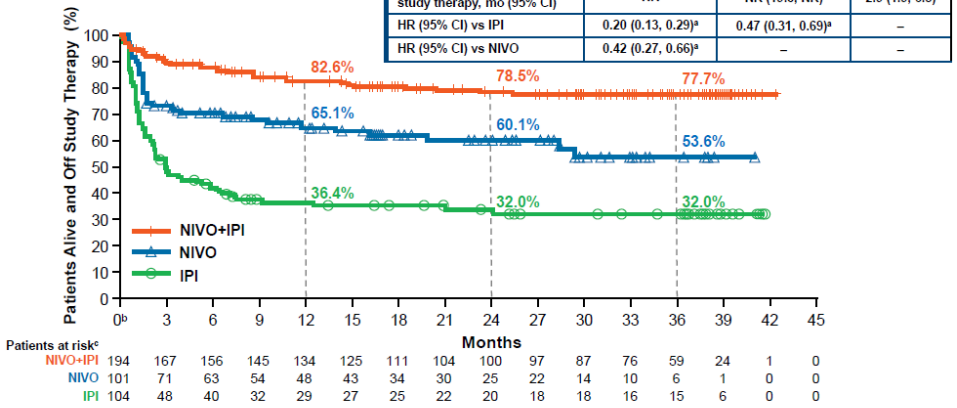
Reasons for discontinuation
- 177 (44%) Study drug toxicity
- 107 (26%) Disease progression
- 35 (9%) Patient request
- 24 (6%) AE unrelated to study drug
- 17 (4%) Maximum clinical benefit
- 4 (1%) Deaths
- 4 (1%) Withdrew consent
- 6 (2%) Other

- Median duration of follow-up was 37.5 months in the NIVO+IPI arm
- 55.0% of total NIVO+IPI patients are continuing follow-up

Postow, M et al SITC 2017

Patients Alive and Off Study Therapy at 3-Years: 069/067

	NIVO+IPI (n = 194)	NIVO (n = 101)	IPI (n = 104)
Median time alive and off study therapy, mo (95% CI)	NR	NR (19.8, NR)	2.9 (1.9, 6.5)
HR (95% CI) vs IPI	0.20 (0.13, 0.29)[a]	0.47 (0.31, 0.69)[a]	–
HR (95% CI) vs NIVO	0.42 (0.27, 0.66)[a]	–	–



[a]$P < 0.0001$; [b]Time "0" is defined as time from the last study dose date; [c]Includes all patients off therapy – both those with and without subsequent therapy

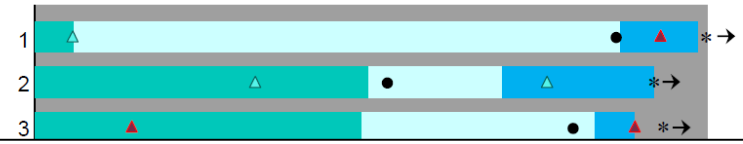
Postow, M et al SITC 2017

What happens if we retreat patients?

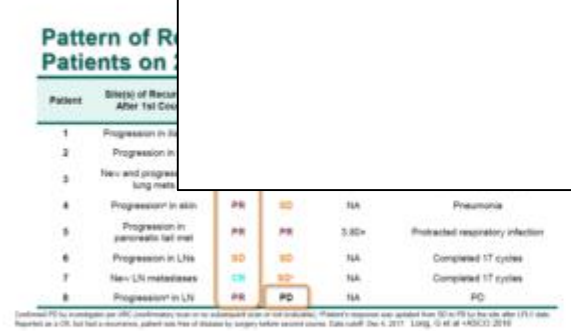
Pattern of Recurrence and Response in Patients on 2nd Course of Pembrolizumab

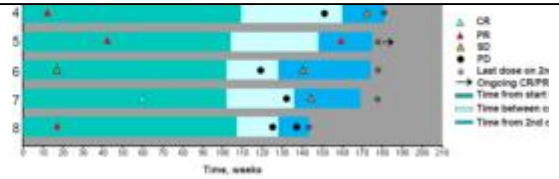
Patient	Site(s) of Recurrence After 1st Course	1st Course BOR	2nd Course BOR	2nd Course DOR, mo	Reason for 2nd Course Discontinuation
1	Progression in iliac LNs	CR	PR[b]	2.8+	Treatment ongoing
2	Progression in skin	CR	CR	7.63	Completed 17 cycles
3					
4					
5					
6					
7					
8					

Treatment Exposure and Duration of Response in Patients on 2nd Course of Pembro on -006

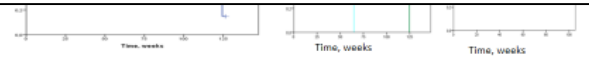


Indirect evidence that we should not treat melanoma patients with a CR or PR forever





- 108 patients (21%) stopped in absence of PD
  - 81 (16%) Patient/MD decision
  - 29 (6%)@AE



Total number of patients	Stopping upon PT/MD decision: 81 (100%)		Discontinuation due to AE: 29 (100%)	
ORR	Total	%	Total	%
CR	34	43	8	28
PR	31	39	13	45
SD	15	19	5	17
NE	0	0	2	7
RELAPSES	2	2.5	9	31
CR	1*	3	2	25
PR			6*	46
SD	1	7	2	25
NE			1	50
* Reintroduction of PD-1	1 CR → new CR		3 PR → 1CR, 1 PR and 1 not yet evaluated	
MEDIAN TIME	Weeks	Range	Weeks	Range
On treatment	64	8-122	27	0-103
Follow up after last dose	42	0-93	60	25-126
Time to relapse	12	8-15	23	7-48

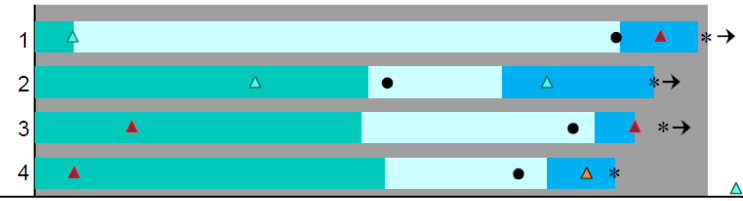
What happens if we retreat patients?

Pattern of Recurrence and Response in Patients on 2nd Course of Pembrolizumab

Patient	Site(s) of Recurrence After 1st Course	1st Course BOR	2nd Course BOR	2nd Course DOR, mo	Reason for 2nd Course Discontinuation
1	Progression in iliac LNs	CR	PR[b]	2.8+	Treatment ongoing
2	Progression in skin	CR	CR	7.63	Completed 17 cycles
3	New and progression[a] of lung mets	PR	PR[b]	0+	Treatment ongoing
4	Progression[a] in skin				
5	Progression in pancreatic tail met				
6	Progression in LNs				
7	New LN metastases				
8	Progression[a] in LN	PR	PD	NA	PD

[a]Confirmed PD by investigator per irRC (confirmatory scan or no subsequent scan or not evaluable). [b]Patient's response was updated from SD to PR by the site after LPLV date. Reported as a CR, but had a recurrence, patient was free of disease by surgery before second course. Data cutoff: Dec 4, 2017. Long, G et al +ASCO 2018

Treatment Exposure and Duration of Response in Patients on 2nd Course of Pembro on -006



on 2nd course
R/PR on 2nd course
start to end of 1st course
een courses
2nd course start to last scan

50 60 70 60 90 100 110 120 130 140 150 160 170 180 190 200 210

Time, weeks

When do we stop?

Real life outcome of advanced melanoma patients who discontinue pembrolizumab in the absence of disease progression

Yanina Jansen, Elisa A. Rozeman, Mamix Geukes Foppen, Lars Bastholt, Henrik Schmidt, Johannes v. Van Thienen, John B. A. G. Haanen, Leena Tiainen, Inge Marie Svane, Siru Päivikki Mäkelä, Ana Arance, Lise Hoejberg, Marta Nyakas, Oddbjorn Straume, Christian U. Blank, Bart Neyns

- 509 patients with advanced melanoma treated with PEMBRO outside of an interventional clinical trial at 9 European hospitals
- 40 patients (8%) PEMBRO ongoing
- 343 patients (67%) stopped @PD
- 108 patients (21%) stopped in absence of PD
  - 81 (16%) Patient/MD decision
  - 29 (6%)@AE

PFS from last dose to PD: AE vs Pt/MD decision

PFS from last dose to PD: according to BORR

Adverse event

Patient/physician choice

Time, weeks

Time, weeks

Time, weeks

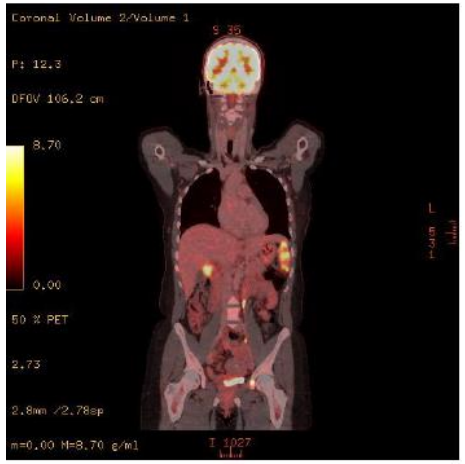
	Stopping upon PT/MD decision		Discontinuation due to AE	
Total number of patients	81 (100%)		29 (100%)	
ORR	Total	n	Total	n
CR	34	43	6	26
PR	31	39	13	45
SD	15	19	5	17
NE	0	0	2	7
RELAPSES	2	2.5	9	31
CR	1*	3	2	25
PR			6*	46
SD	1	7	2	28
NE			1	50
* Reintroduction of PD-1	1 CR → new CR		3 PR → 1CR, 1 PR and 1 not yet evaluated	
MEDIAN TIME	Weeks	Range	Weeks	Range
On treatment	64	8-122	27	0-103
Follow up after last dose	42	0-93	60	25-126
Time to relapse	12	8-15	23	7-48

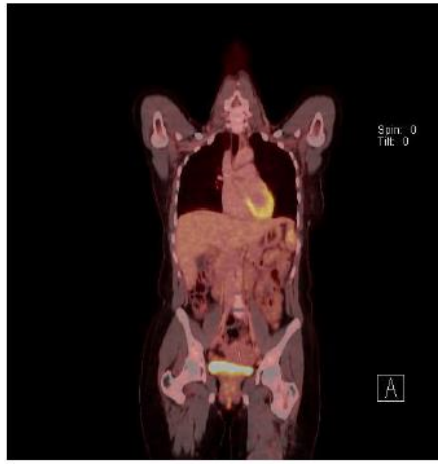
Can a PET-scan help to decide to stop therapy in melanoma?

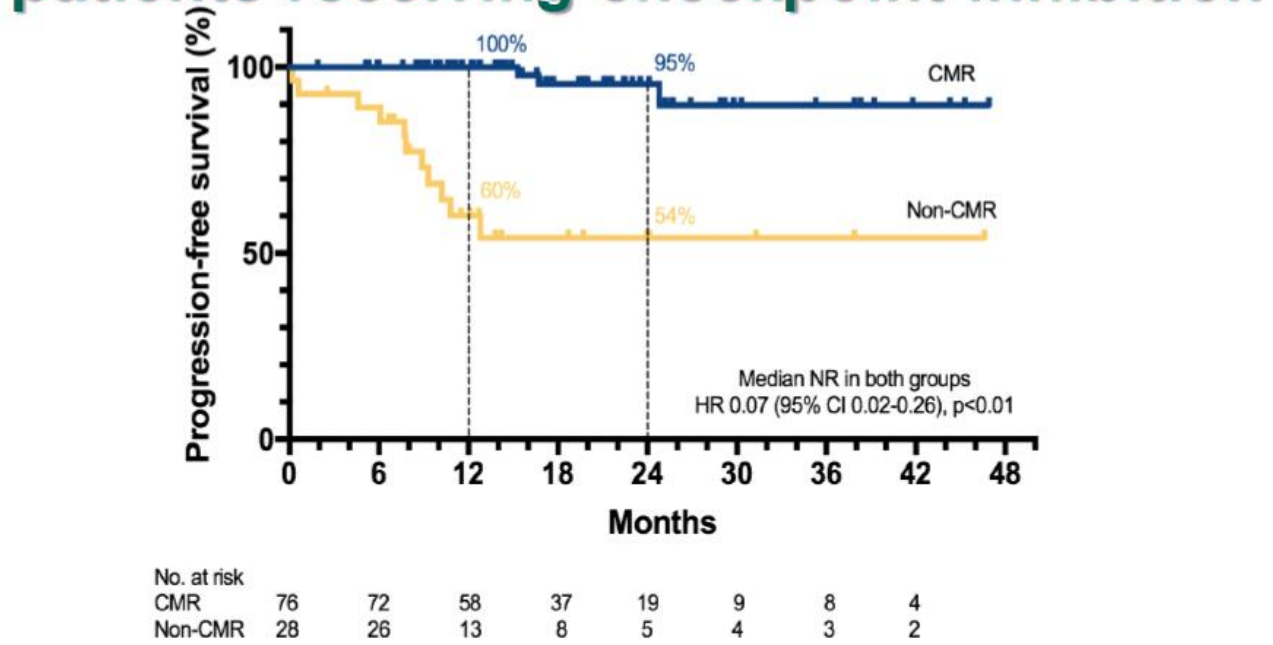
Methods

- PET at 1 year of treatment
- Response defined by EORTC criteria
- N = 104

- 28% RECIST CR
- 75% PET CMR







Melanoma Institute Australia

Utility of 1-year FDG-PET (PET) to determine outcomes from anti-PD-1 (PD1) based therapy in patients (pts) with metastatic melanoma (MM)

Aaron C. Tan[1,2], Louise Emmett[1,3,4], Serigne Lo[1], Victor Liu[3], Alexander D. Guminski[1,2,5], Georgina V. Long[1,2,5], Alexander M. Menzies[1,2,5]

[1]Melanoma Institute Australia and The University of Sydney; [2]Royal North Shore Hospital; [3]St Vincent's Hospital; [4]The University of New South Wales; [5]Mater Hospital

CONQUER CANCER™ THE ASCO FOUNDATION MERIT AWARD RECIPIENT

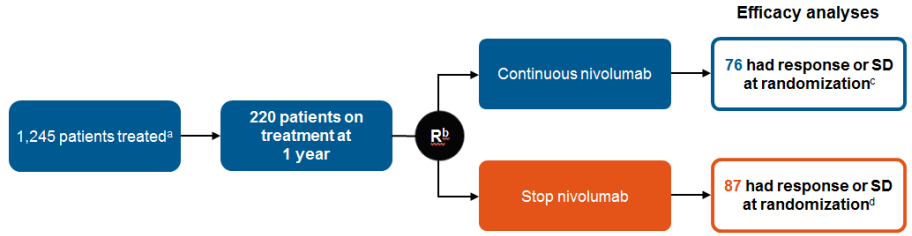
CheckMate 153: Randomized Results of Continuous vs 1-Year Fixed-Duration Nivolumab in Patients With Advanced Non-Small Cell Lung Cancer

David R. Spigel,[1*] Mihael McCleod,[2*] Maen A. Hussein,[3*] David M. Waterhouse,[4*] Lawrence Einhorn,[5] Leora Horn,[6] Ben Creelan,[7] Sunil Babu,[8*] Natasha B. Leighl,[9] Felix Couture,[10] Jason Chandler,[11*] Glenwood Goss,[12] George Keogh,[13*] Edward B. Garon,[14*] Kenneth B. Blankstein,[15*] Davey B. Daniel,[16*] Mohamed Mohamed,[17*] Ang Li,[18] Nivedita Aanur,[18] Robert Jotte[19*]

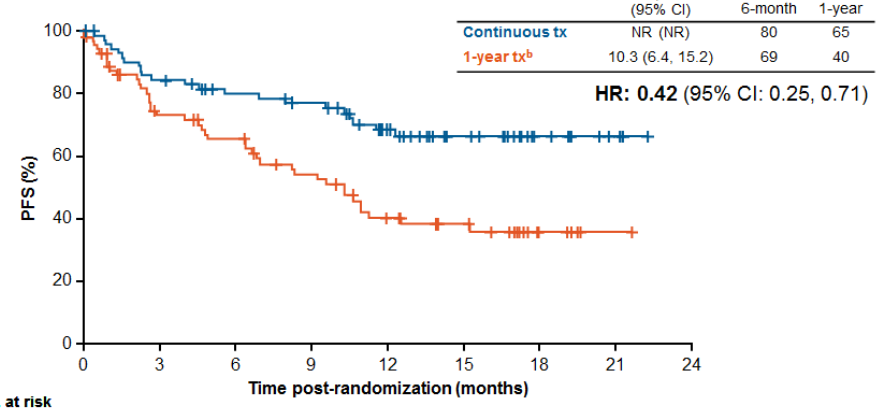
[1]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; [2]Florida Cancer Specialists, Cape Coral, FL, USA; [3]Florida Cancer Specialists, Leesburg, FL, USA; [4]OHC (Oncology Hematology Care, Inc), Cincinnati, OH, USA; [5]Indiana University, Indianapolis, IN, USA; [6]Vanderbilt University Medical Center, Nashville, TN, USA; [7]Moffitt Cancer Center, Tampa, FL, USA; [8]Fort Wayne Medical Oncology and Hematology, Fort Wayne, IN, USA; [9]The Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; [10]CISSS Chaudiéere-Appalaches, Levis, QC, Canada; [11]West Cancer Center, Memphis, TN, USA; [12]The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada; [13]Charleston Hematology Oncology Associates, Charleston, SC, USA; [14]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [15]Hunterdon Healthcare, Flemington, NJ, USA; [16]Tennessee Oncology, Chattanooga, TN, USA; [17]Cone Health Cancer Center at Wesley Long, Greensboro, NC, USA; [18]Bristol-Myers Squibb, Princeton, NJ, USA; [19]The US Oncology Network/Rocky Mountain Cancer Centers, Denver, CO, USA

*Immuno-Oncology Integrated Community Oncology Network (IO ICON) member

CheckMate 153: Continuous vs 1-Year Nivolumab
Patient Flow and Analysis Populations



CheckMate 153: Continuous vs 1-Year Nivolumab
PFS From Randomization[a]



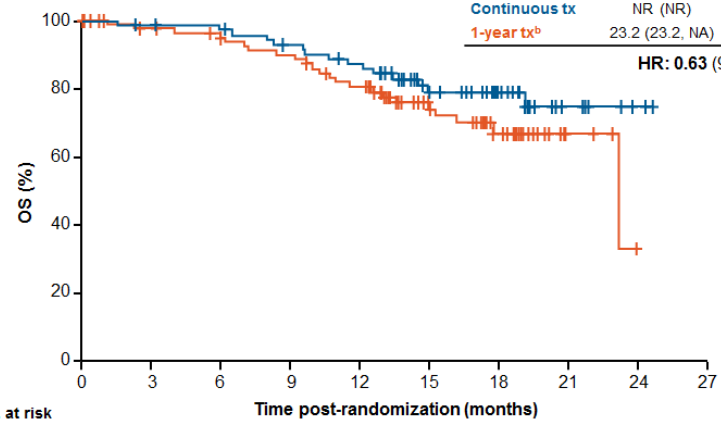
	Median, months (95% CI)	PFS rate, % 6-month	1-year
Continuous tx	NR (NR)	80	65
1-year tx[b]	10.3 (6.4, 15.2)	69	40

HR: 0.42 (95% CI: 0.25, 0.71)

No. at risk									
Continuous tx	76	60	53	49	35	22	10	3	0
1-year tx	87	50	43	33	21	16	5	1	0

[a]Patients who did not have PD at randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months
[b]With optional retreatment allowed at PD
NR = not reached; tx = treatment

CheckMate 153: Continuous vs 1-Year Nivolumab
OS From Randomization[a]



	Median, months (95% CI)	OS rate, % 6-month	1-year
Continuous tx	NR (NR)	97	88
1-year tx[b]	23.2 (23.2, NA)	95	81

HR: 0.63 (95% CI: 0.33, 1.20)

No. at risk										
Continuous tx	76	74	72	67	62	41	29	7	2	0
1-year tx	87	79	74	70	61	38	23	4	0	0

[a]Patients who did not have PD at randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months
[b]With optional retreatment allowed at PD

MADRID 2017 ESMO congress

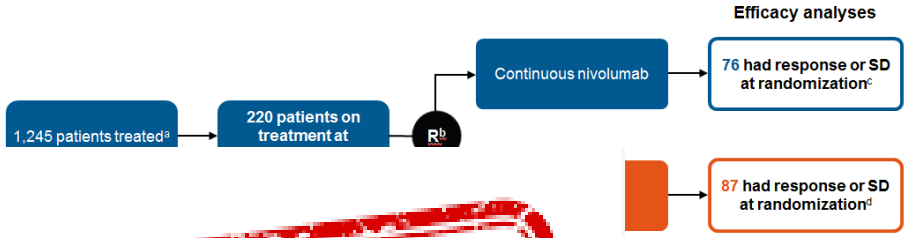
CheckMate 153: Randomized Results of Continuous vs 1-Year Fixed-Duration Nivolumab in Patients With Advanced Non-Small Cell Lung Cancer

David R. Spigel,[1*] Mihael McCleod,[2*] Maen A. Hussein,[3*] David M. Waterhouse,[4*] Lawrence Einhorn,[5] Leora Horn,[6] Ben Creelan,[7] Sunil Babu,[8*] Natasha B. Leighl,[9] Felix Couture,[10] Jason Chandler,[11*] Glenwood Goss,[12] George Keogh,[13*] Edward B. Garon,[14*] Kenneth B. Blankstein,[15*] Davey B. Daniel,[16*] Mohamed Mohamed,[17*] Ang Li,[18] Nivedita Aanur,[18] Robert Jotte[19*]

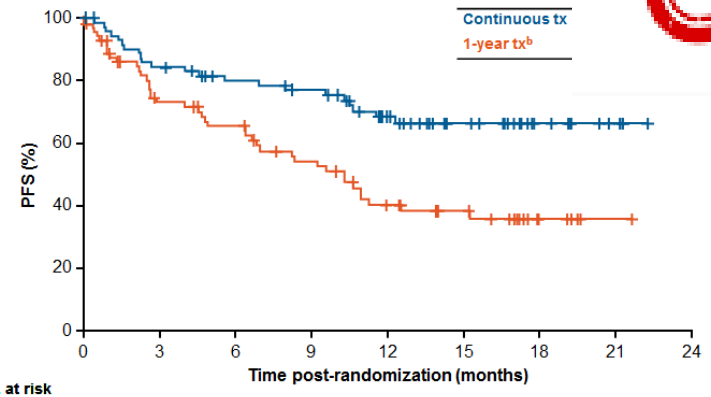
[1]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; [2]Florida Cancer Specialists, C Specialists, Leesburg, FL, USA; [4]OHC (Oncology Hematology Care, Inc), Cincinnati, OH, USA; [5]Indiana Univers University Medical Center, Nashville, TN, USA; [7]Moffitt Cancer Center, Tampa, FL, USA; [8]Fort Wayne Medical On USA; [9]The Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; [10]CISSS Chaudi [11]West Cancer Center, Memphis, TN, USA; [12]The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada; Associates, Charleston, SC, USA; [14]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [15]Hunter [16]Tennessee Oncology, Chattanooga, TN, USA; [17]Cone Health Cancer Center at Wesley Long, Greensboro Princeton, NJ, USA; [19]The US Oncology Network/Rocky Mountain Cancer Centers, Den

*Immuno-Oncology Integrated Community Oncology Network (IO ICON) member

CheckMate 153: Continuous vs 1-Year Nivolumab
Patient Flow and Analysis Populations



CheckMate 153: Continuous vs 1-Yea
PFS From Randomizat



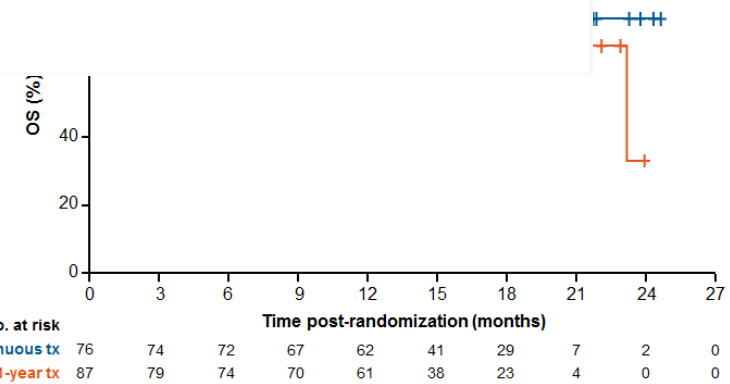
No. at risk									
Continuous tx	76	60	53	49	35	22	10	3	0
1-year tx	87	50	43	33	21	16	5	1	0

[a]Patients who did not have PD at randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months
[b]With optional retreatment allowed at PD
NR = not reached; tx = treatment

Nivolumab
ion[a]

Median, months (95% CI)	OS rate, %	
	6-month	1-year
NR (NR)	97	88
23.2 (23.2, NA)	95	81

HR: 0.63 (95% CI: 0.33, 1.20)



No. at risk										
Continuous tx	76	74	72	67	62	41	29	7	2	0
1-year tx	87	79	74	70	61	38	23	4	0	0

[a]Patients who did not have PD at randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months
[b]With optional retreatment allowed at PD

- How do we identify responders? ✓
- How do we increase response rates? ✓
- What is the right time for discontinuring immunotherapy ? ✓

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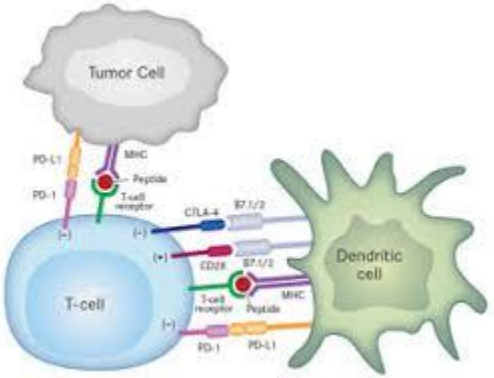
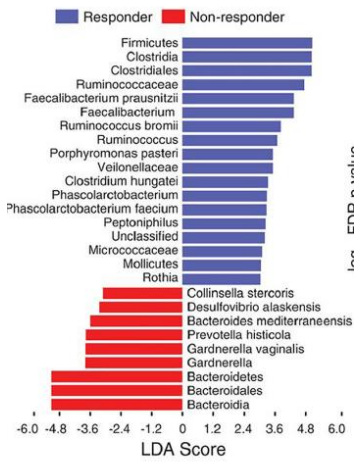
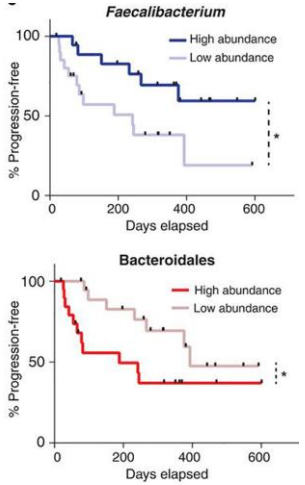


Challenges not discussed today





Role of microbiome

Cancer Research

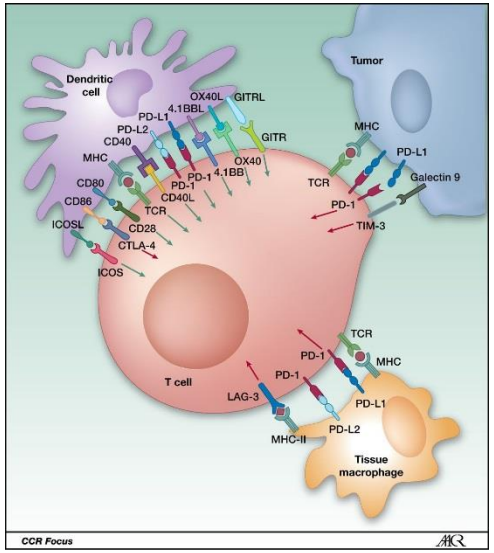
Clinical Research (Excluding Clinical Trials)

Abstract 5541: Clinical impact of hypothyroidism and PD-L1 SNPs in patients having non-small cell lung cancer treated with nivolumab

Tomoko Funazo, Hiroaki Ozasa, Takashi Nomizo, Takahiro Tsuji, Yuto Yasuda, Hironori Yoshida, Yuichi Sakamori, Hiroki Nagai, Toyohiro Hirai, and Young Hak Kim

DOI: 10.1158/1538-7445.AM2018-5541 Published July 2018

Predicting irAE's



Cancer treatment and 'financial toxicity'

Download audio show transcript

Monday 17 August 2015 5:50PM (view full episode)

Cancer treatments can produce all kinds of toxicities.

A relatively new term, though, is 'financial toxicity', the idea that the costs of treating cancer can be so severe they impact upon a patient's quality of life, becoming an adverse effect themselves.

In the United States, Yousuf Zafar has been taking a good long look at financial toxicity.

IMAGE: COULD OUT-OF-POCKET EXPENSES BE THEIR OWN KIND OF ADVERSE EFFECT? (RICARDO CORRAL - FLICKR/CC BY-NC-ND 2.0)

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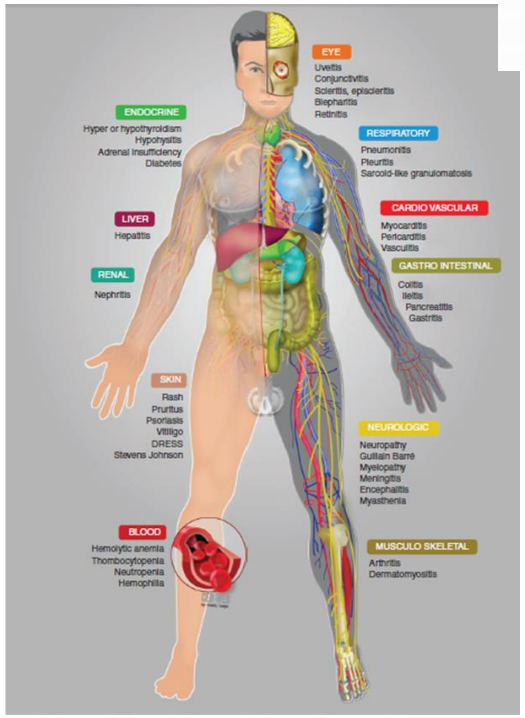


Future perspectives

Immunotherapy toxicity predicted by circulating cytokines

Severe and potentially life-threatening immune-related toxicities associated with checkpoint inhibitor immunotherapy could be effectively predicted and managed through the

98 samples were taken from the validation cohort (49 at baseline and 49 early during treatment).

The authors profiled the expression of 65 circulating cytokines to investigate

p=0·037) and 0·70 in early treatment (0·55–0·85, p=0·017).

Alexander Lyon (Imperial College London, UK) explained, "[This study] has identified a novel 11 cytokine

Can we predict irAE's?

who received immunotherapy at two centres in Australia—either anti-PD-1 monotherapy (pembrolizumab or nivolumab; n=40) or anti-PD-1 plus anti-CTLA-4 (ipilimumab; n=58). An independent validation cohort of 49 patients treated with anti-PD-1 plus anti-CTLA-4 was also included. 309 plasma samples were collected from the two discovery cohorts and analysed for cytokine expression (baseline sample for every patient and longitudinal samples throughout treatment) and

related toxicities at baseline and early during treatment. The expression of these 11 cytokines was integrated into a single toxicity score (CYTOX), and its predictive value was tested. In discovery cohort 2, ROC analysis showed that the area under the curve for CYTOX score to discriminate severe toxicity was 0·78 (95% CI 0·65–0·91, p=0·0009) at baseline and 0·77 (0·63–0·90, p=0·0014) in early treatment. In the independent validation cohort, these values were 0·68 at baseline (0·51–0·84,

and targeting these effective but toxic therapies to patients with the greatest benefit and the lowest risk of serious adverse events."

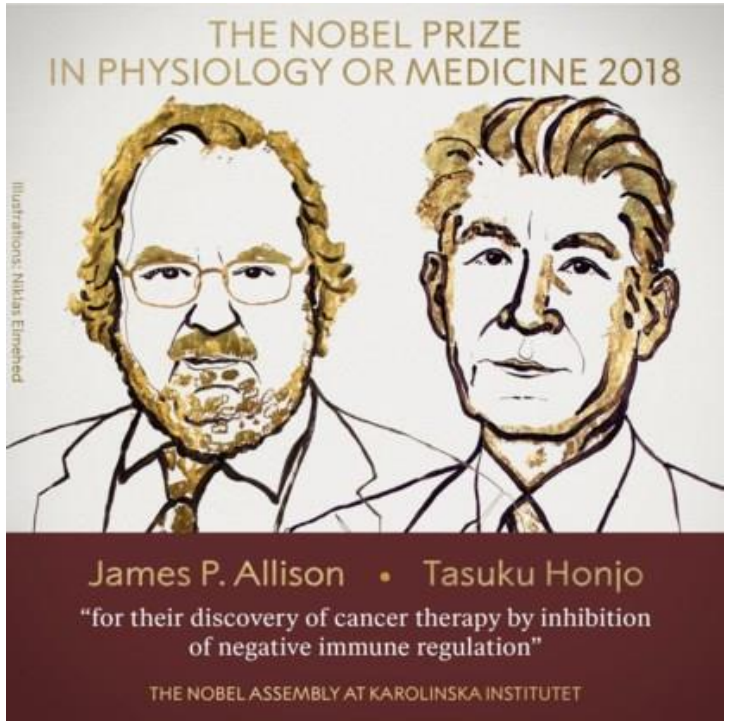
Niki Karachaliou (University Hospital Sagrat Cor, Barcelona, Spain) added, "Whether the CYTOX score can be easily used in daily clinical practice or whether it can apply to other immunotherapies than the combination of anti-PD-1 with anti-CTLA-4 remains to be defined."

Elizabeth Gourd

Lancet Oncol 2018

Published Online November 15, 2018 http://dx.doi.org/10.1016/S1470-2045(18)30855-6

For the study see Clin Cancer Res 2018; published online Nov 8. DOI:10.1158/1078-0432



Thank you for your attention!

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