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CHALLENGES WITH IMMUNE CHECKPOINT INHIBITORS

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DISCLOSURES

Details of the DOI for all authors are listed at the end of this presentation

METHODOLOGY

Literature review of selected topics regarding challenges with immune checkpoint inhibitors conducted on PubMed and Cochrane. Systematic reviews, other reviews, and other relevant publications selected for analysis. Abstracts on same topics from the American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) conferences were also included for analysis. Free internet search were also conducted to identify additional references. Research conducted between January and June 2018.

TOPICS

- Elderly population
- Brain metastasis
- Pseudoprogression and hyperprogression
- Patients with pre-existing immune-disease
- Steroids
- Gut microbiome, antibiotics and ICI
- Duration of therapy

ELDERLY AND IMMUNE CHECKPOINT INHIBITORS

SAFETY IN ELDERLY

Similar safety of ICI across different ages:

Alkharabsheh O, *et al.* An overview of the toxicities of checkpoint inhibitors in older patients with cancer, J Geriatr Oncol (2018)

Friedman CF, *et al.* Efficacy and safety of checkpoint blockade for treatment of advanced melanoma (mel) in patients (pts) age 80 and older (80+). J Clin Oncol 2016;34(15_suppl):10009

Older patients with more Hyperprogression disease

(19% *vs.* 5%; P = 0.018)

Champiat S. *et al.* Clin Cancer Res.2017 Apr 15;23(8):1920-1928

FDA SUBSET ANALYSIS OF THE SAFETY OF NIVOLUMAB IN ELDERLY PATIENTS WITH ADVANCED CANCERS

More adverse events with aging?

	Patients < 65 yrs (N=616) n%	Patients ≥ 65 yrs (N=414) n%	Patients ≥ 70 yrs (N=212) n%
Grade 1-2 Adverse Events	584 (94.8)	394 (95.2)	202 (95.3)
Grade 3-5 Adverse Events	360 (58.4)	259 (62.6)	152 (71.7)
Serious Adverse Events	313 (50.8)	242 (58.5)	123 (58.0)
All Adverse Events leading to Discontinuation	89 (14.4)	71 (17.1	42 (19.8)
AEs Requiring Treatment with Immune Modulating Medication	256 (41.5)	196 (47.3)	110 (51.9)
Select irAE's where immune modulating medication was initiated			
Diarrhea/colitis	15 (2.4)	17 (4.1)	11 (5.2)
Pneumonitis	23 (3.7)	8 (1.9)	5 (2.4)
Hepatitis	8 (1.3)	3 (0.7)	1 (0.5)
Nephritis and renal dysfunction	6 (1.0)	8 (1.9)	7 (3.3)
Rash	47 (7.6)	34 (8.2)	22 (10.4)

Singh H, *et al.* J Clin Oncol, 34, no. 15_suppl (May 20 2016) 10010. Reprinted with permission.

COMPARISON OF EFFICACY OF ICIS BETWEEN YOUNGER AND OLDER PATIENTS

A systematic review and meta-analysis

9 randomised clinical trials, 5265 patients; Controls: 2340; ICIs: 2925

Similar HRs for OS (P = 0.96) between subgroups of younger and older patients

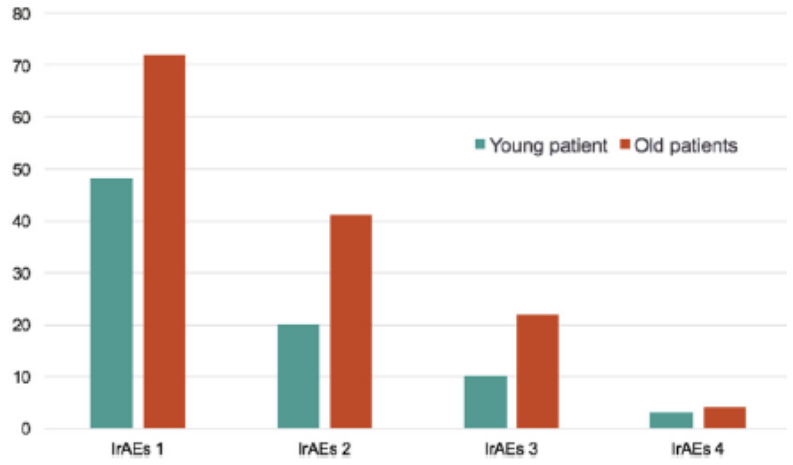
Hazard ratios for overall survival according to type of ICI and type of tumour				
Type of ICI		HR	95%CI	*P*
Anti-CTLA-4 mAb	4 trials			0.43†
	<65	0.82	0.71-0.95	0.009
	≥65	0.77	0.69-0.85	<0.001
Anti-PD-1 mAb	4 trials			0.50†
	<65	0.68	0.54-0.85	<0.001
	65-75	0.60	0.48-0.73	<0.001
	≥75	0.86	0.41-1.83	0.70
Type of tumour		HR	95%CI	*P*
Melanoma	4 trials			0.60†
	<65	0.66	0.50-0.88	<0.001
	≥65	0.72	0.62-0.84	<0.001
Others	4 trials			0.73†
	<65	0.75	0.64-0.88	<0.001
	≥65	0.79	0.62-0.99	0.04

Nishijima TF, *et al.* Cancer Treatment Reviews 45 (2016) 30-37

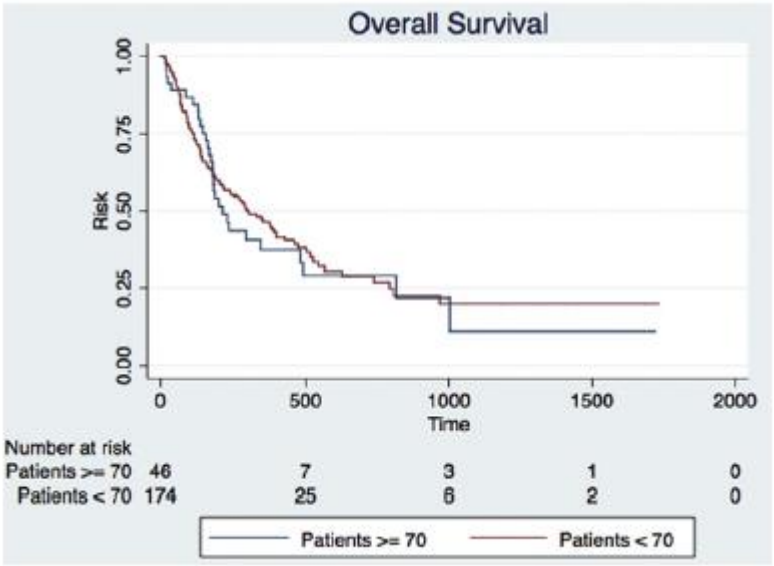
IMMUNOTHERAPY PHASE I TRIALS

In patients older than 70 years with advanced solid tumours

No statistical significance differences in severe toxicity (grade III and IV)
More grade I and II IrAEs in elderly



Median OS 7.1 mo in old patients *vs.* 9.8 mo in young patients
HR 0.92, 95% CI 0.61-1.39; p=0.77)



Description of IrAEs grade in old patients and young patients

IrAEs, Immune-related Adverse Events.

TREATING THE ELDERLY

With ICI real life experience from a large Brazilian centre

106 stage IV patients, average age 74.4 years old (65-90)

Primary sites: Lung, melanoma, urologic and colorectal

FRAILTY was the only predictive variable for risk of AE
OR 3.03 (95%CI 1.36 – 6.74; p 0.006)

Silva CC, J Clin Oncol 36, 2018 (suppl; abstr e15077).

ELDERLY AND ICI

Implication for clinical practice and research

Older and multi-morbidity patients under-represented in ICI clinical trials

Controversial safety data with elderly using ICI

The efficacy of ICI in elderly seems overall positive and comparable to younger patients

Age SHOULD NOT be a formal contra-indication for ICI

- But more vigilance during treatment advisable

Elderly/frailty-specific clinical trials with ICIs needed

- More studies with ICI including elderly population
- Validation of geriatric/frailty assessment tools before and during ICI
- Frailty *vs.* age influence on ICI results

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BRAIN METASTASIS AND IMMUNE CHECKPOINT INHIBITORS

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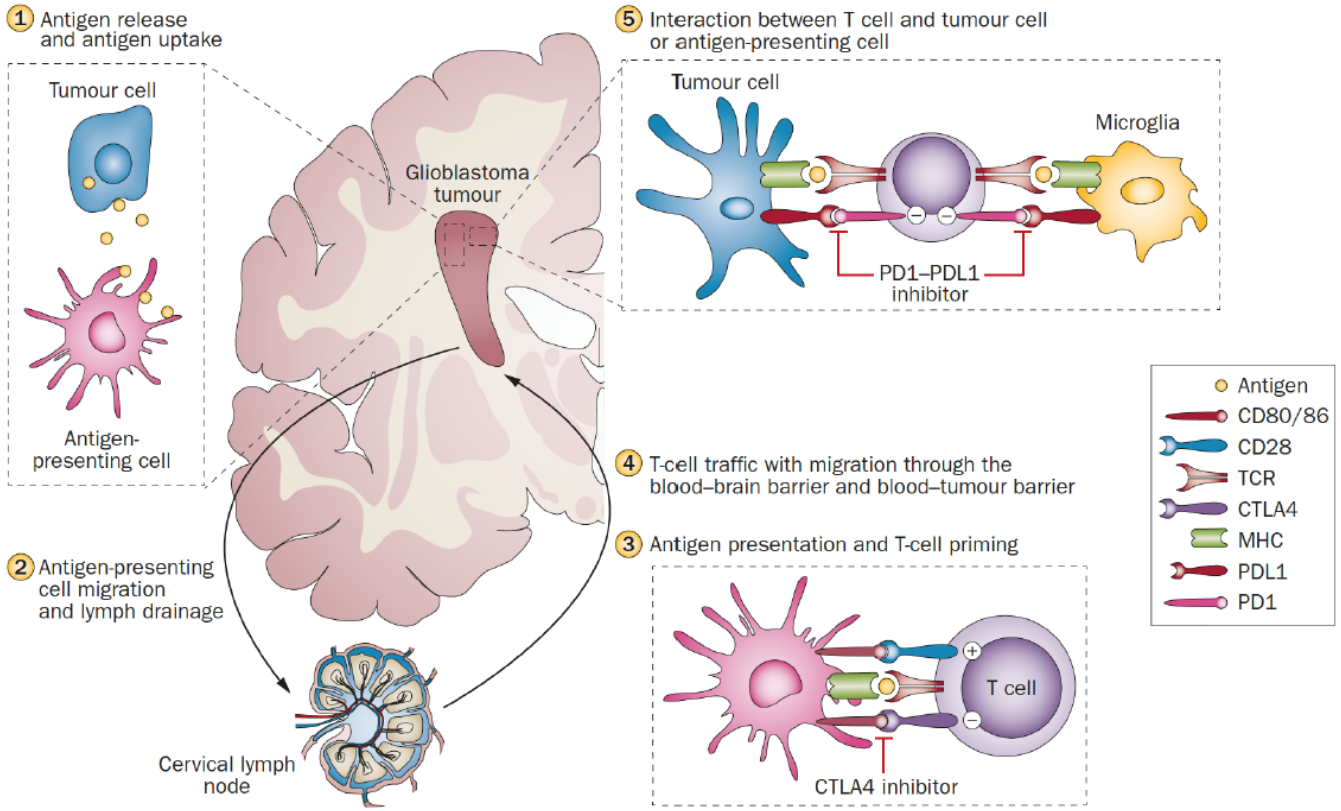
BRAIN TUMOURS AND IMMUNE SYSTEM

The immune cycle of glioblastoma



CANCER IMMUNOTHERAPY IN PATIENTS WITH BRAIN METASTASES

Author	Phase	Tumour type	Agent	Patients, n	Objective response rate (%)
Weber (2011)	II (Retrospective)	melanoma	ipi	12	17
Margolin (2012) cohort A	II	melanoma	ipi	51	16*
Margolin (2012) cohort B	II	melanoma	ipi	21	5*
Queirolo (2014)	EAP (Retrospective)	melanoma	ipi	146	12
Parakh (2017)	Real-world (Retrospective)	melanoma	nivo or pembro	66	21*
Goldberg (2016)	II	melanoma	pembro	18	22*
Goldberg (2016)	II	NSCLC	pembro	18	33*
Long (2017) Cohort B	II	melanoma	nivo	25	20*
Long (2017) Cohort C	II	melanoma	nivo	16	6*
Haanen (2016)	I	melanoma	nivo	10	50
Bidoli (2016)	EAP (Retrospective)	NSCLC	nivo	37	19*
Goldman (2016)	I	NSCLC	nivo	12	16*
Haanen (2016)	I	melanoma	nivo +ipi	10	50
Tawbi (2017)	II	melanoma	nivo +ipi	75	55*
Long (2017) Cohort A	II	melanoma	nivo +ipi	26	42*
EAP expanded access programme *Intracranial ORR					

Caponnetto S, *et al.* Cancer Immunol Immunother 2018;67(5):703–11.

CANCER IMMUNOTHERAPY IN PATIENTS WITH BRAIN METASTASES

- Some small studies showed intracranial responses in melanoma and lung metastases with ICI
- Better results on stable/ asymptomatic and/or previously untreated brain metastases
- Small studies analysis suggest a better response for ipi+nivo comparing with monotherapy in brain metastases

Caponnetto S, *et al.* Cancer Immunol Immunother. 2018 May;67(5):703-711.

EFFICACY OF ICI

In patients with brain metastasis from NSCLC, RCC, and melanoma

128 patients with Brain mets, median age 60.6 years

ICI efficacious in brain metastasis

	Primary Cancer	No. Patients	Estimated Median (months)	P-Value (Log-Rank Test)	1-year survival rate
OS from start of immunotherapy				.4041	
	RCC	15	Not reached		55.4% ± 13.9
	Melanoma	19	16.4		54.5% ± 11.9
	NSCLC	94	11.0		48.3% ± 11.4
PFS from start of Immunotherapy					
	RCC	15	5.9	.068	42.4% ± 13.5
	Melanoma	19	6.7		31.1% ± 11.5
	NSCLC	94	3.6		21.0% ± 8.9

Lauko A, *et al.* J Clin Oncol 36(5_suppl):214.

BRAIN METS AND ICI

Implication for clinical practice and research

Most trials excluded patients with brain mets due to their worse prognosis and steroids concomitant treatment

ICI showed efficacy and can be used in patients with brain mets

In melanoma brain mets, ipi+nivo seems to have better response, comparing with monotherapy in untreated patients

More studies with ICI in patients with brain metastasis needed

- Larger studies with ICI (mono and combo) in patients with brain mets
- Could patients under steroids (different doses? duration of treatment?) be treated with ICI for brain mets?
- Combination or sequence with radiotherapy?

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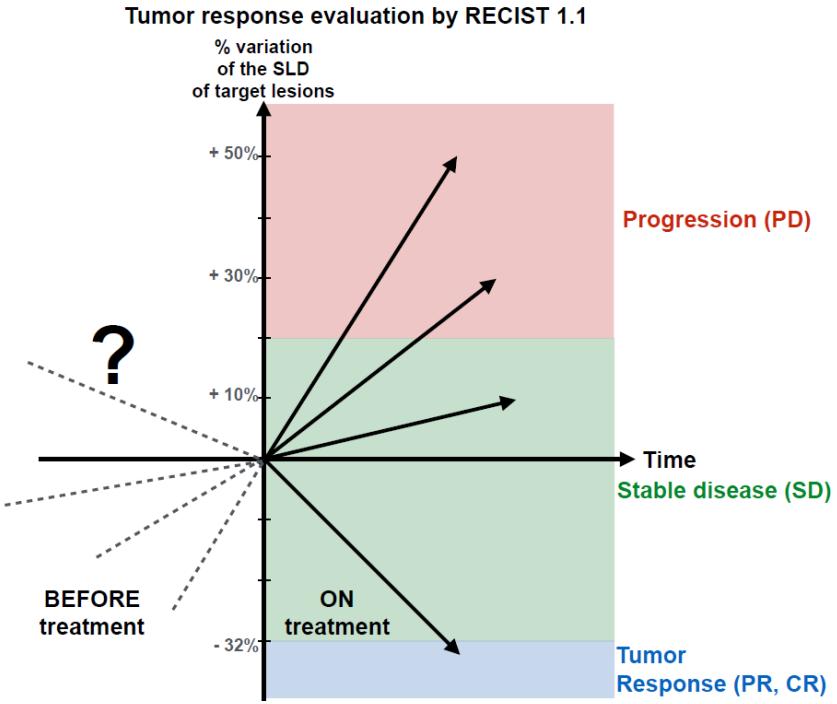
HYPERPROGRESSION AND PSEUDOPROGRESSION

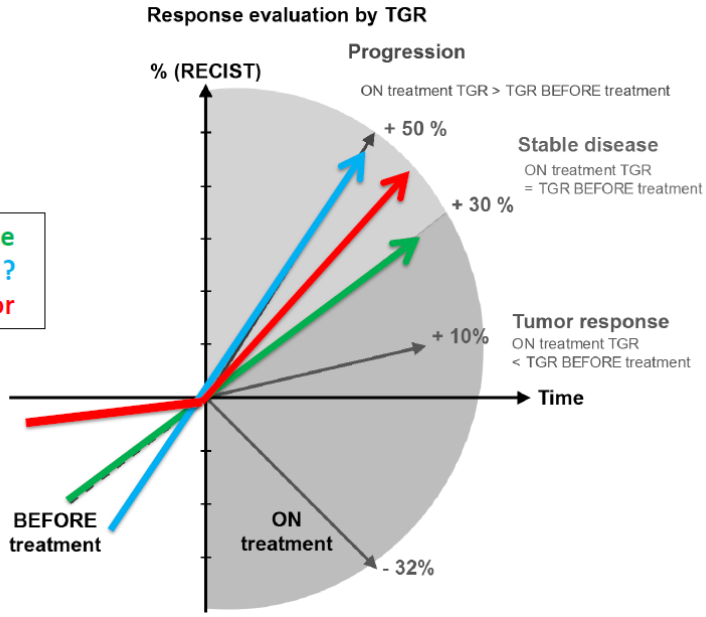
HYPERPROGRESSION AND PSEUDOPROGRESSION

- Hyperprogression is a rapid increase in tumour growth rate after starting a new treatment
- Pseudoprogression is an initial flare-up followed by tumour shrinkage after starting a new treatment (Saada-Bouzid E, *et al.* 2017)
- No consensus exists on the quantitative definition of hyperprogression or pseudoprogression with Immunotherapy
- A systematic review of 38 studies described 6% atypical responses on 151 of 2400 patients with solid tumours treated with anti-PD-1 (Queirolo P, *et al*. 2017)
- No systematic reviews yet published about hyperprogression and ICI

Changing radiological metrics for ICI progression evaluation?



Primary resistance
= Fast Progressor ?
≠ Hyperprogressor



TGR – Tumour Growth Rate

Champiat S. The issue of fast progression, ESMO Advanced Course on Unsolved questions in Immuno-Oncology, Amsterdam Feb 2018

HYPERPROGRESSIVE DISEASE

Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1

131 patients assessed retrospectively in different tumours

9% overall rate of hyperprogression (HP)

Older patients (≥65 ys) had more HP (19% *vs.* 5%; P=0.018)

8% patients not evaluated due to clinical progression before tumour evaluation and those with rapid tumour growth on new lesions not included - higher rates of HP?

HP independent of high tumour burden on baseline, previous treatments or histology

Champiat S. *et al*. Clin Cancer Res.2017 Apr 15;23(8):1920-1928.

HYPER/PSEUDOPROGRESSION IN NSCLC TUMOURS TREATED WITH ICI

- 242 patients, multicentre, retrospective French study

- **16% hyperprogression**
- **1.2% pseudoprogression**

- Results independent of tumour burden baseline, clinical, molecular, pathological characteristics, PD-L1 status

Ferrara R, *et al.* Annals of Oncology (2017) 28 (suppl_5): v460-v496. 10.1093/annonc/mdx380.

HYPER/PSEUDOPROGRESSION IN HEAD & NECK TUMOURS TREATED WITH ICI

- 34 patients, four French centres
- Hyperprogression defined as a TGKr* ≥ 2

- **29% hyperprogression**
- **0% pseudoprogression**

- Hyperprogression associated with shorter OS but non statistical significance (6.1 months *versus* 8.1 months, p=0.77)

*TGKr: tumour growth kinetics ratio (pre and post treatment)

Saâda-Bouzid E, *et al.* Annals of Oncology 2017;28(7):1605-1611.

PSEUDOPROGRESSION AND HYPERPROGRESSION

During ICI therapy for urothelial and kidney cancer

Review from clinical trials on atypical patterns of response on urothelial and renal cell carcinoma

Pseudoprogression (response beyond progression as surrogate):

- Urothelial cancer: 1.5 to 17%
- Renal cell carcinoma: 5 to 15%

Hyperprogression (HP):

- Urothelial cancer: 25% HP (2/8 patients, Champiat S, *et al.* 2017)
- No other urothelial or renal data

Soria F, *et al.* World J Urol. 2018 Mar 16, DOI: 10.1007/s00345-018-2264-0.

HYPERPROGRESSORS AFTER IMMUNOTHERAPY

Analysis of genomic alterations associated with accelerated growth rate

Tumours of 155 patients after ICI analysed by next generation sequencing

Hyperprogression disease (HP) defined as time-to treatment failure (TTF) <2 months, >50% increase in tumour burden, and >2-fold increase in progression pace

MDM2/MDM4 amplification

- 67% HP (4/6 patients); 100% TTF <2 months

EGFR alterations,

- 20% HP (2/10 patients); 80% TTF <2 months

TERT, PTEN, NF1 and NOTCH1 genes correlates with better prognosis

Kato S, *et al.* Clin Cancer Res. 2017;23(15):4242-4250.

HYPERPROGRESSION (HP) AND PSEUDOPROGRESSION (PP) DISEASES

Implication for clinical practice and research

Some patients worsen dramatically with ICI

Hyperprogression seems more frequent than pseudoprogression

Under rapid deterioration consider to stop ICI

If HP confirmed due to ICI effect, it should be managed as ICI severe toxicity

More studies needed to assess HP and PP with ICI

- Is HP influenced by ICI activity, or only consequence of disease behaviour?
- Are there risk factors and predictors of HP and PP?
  - Clinical, blood tests/biomarkers, radiology or genetic?
- Difference rates of HP and PP across different tumours and with different ICI treatments?
- International consensus on HP and PP definitions?

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AUTOIMMUNE DISEASES AND IMMUNE CHECKPOINT INHIBITORS

AUTOIMMUNE DISEASES (AID) AND CHECKPOINT INHIBITORS

- AID patients frequently excluded from ICI clinical trials due to possible higher toxicity rates (Calabrese L. *et al.* 2017)

- High frequency of cancer and concomitant autoimmune diseases
  - Lung 24,5%; Renal cancer 30% (El-Refai SM, *et al*. 2017)

- Few data assessing effectiveness and safety of ICI in patients with cancer and autoimmune disease

SAFETY OF PROGRAMMED DEATH–1 PATHWAY INHIBITORS

Among patients with non-small-cell lung cancer and pre-existing autoimmune disorders

56 patients with NSCLC and an autoimmune disease who received a PD-(L)1 inhibitor

Incidence of irAEs similar to reported in clinical trials without autoimmune disease patients

Characteristic	Patients
Flare of underlying AID	
Patients who did not develop AID flare	43 (77)
Patients who developed AID flare	13 (23)
Exacerbations among 13 patients with AID flare	17
Grade 1-2*	13 (87)
Grade 3-4	2 (13)
Grade unknown†	2
Treatment required for AID flare‡	
No treatment required	4
Supportive care§	7
Hydroxychloroquine‖	1
Topical or intra-articular corticosteroids	6
Systemic corticosteroids	4
PD-(L)1 inhibitor dosing during AID flare	
Continued	11
Temporarily discontinued	2
Permanently discontinued	0

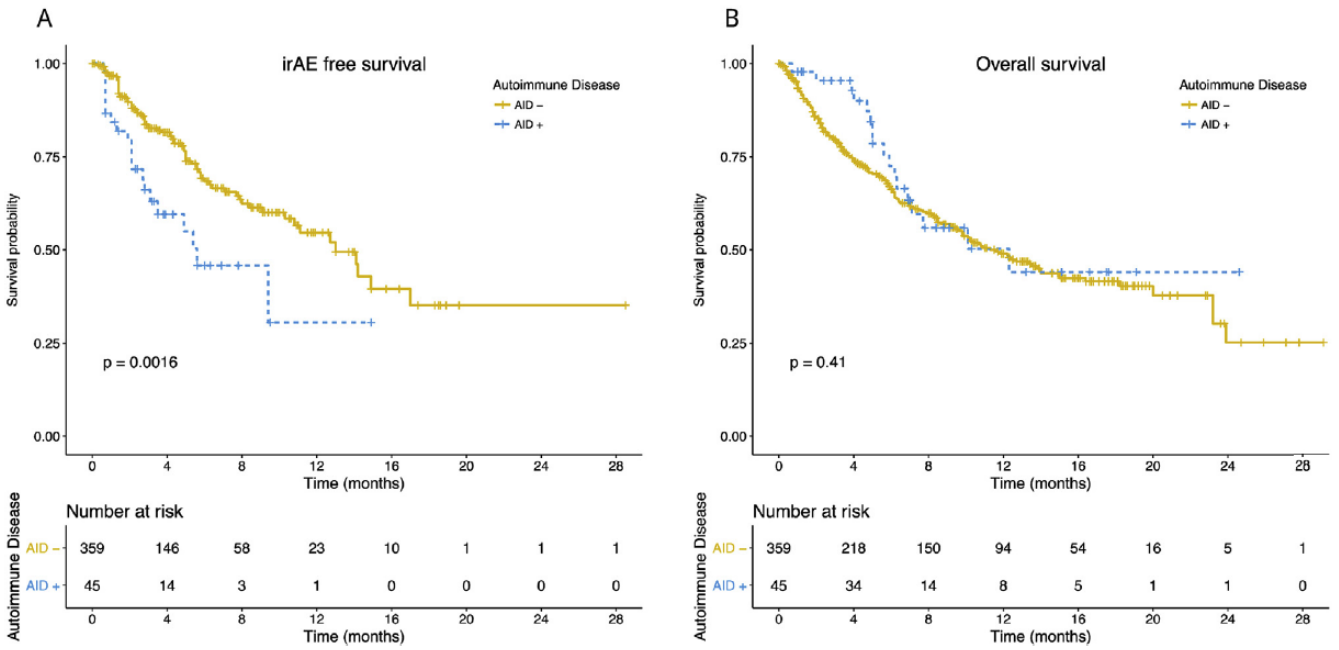
NOTE. Data are reported as No. or No. (%).

Leonardi GC, *et al.* J Clin Oncol 36:1905-1912. Reprinted with permission.

SAFETY AND EFFICACY OF ANTI-PROGRAMMED DEATH 1 ANTIBODIES

In patients with cancer and pre-existing autoimmune or inflammatory disease

More adverse events but similar overall survival



Reprinted from European journal of Cancer, 91, Danlos F-X, et al. Safety and efficacy of anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease. 21-29, Copyright 2018, with permission from Elsevier.

USE OF IMMUNE CHECKPOINT INHIBITORS

In the treatment of patients with cancer and pre-existing autoimmune disease: A systematic review

123 patients from 49 publications treated with ICI and previous autoimmune disease

Events	% (nº of patients)
Adverse events	75% (92)
Recovery from adverse event	90% (80)
Exacerbation of autoimmune disease	50% (61)
De novo irAEs	34% (31)
ICI discontinuation	17% (21)
Death	4% (5)

Adapted from: Abdel-Wahab N, *et al.* Ann Intern Med. 2018;168:121-130.

ICI-RELATED ADVERSE EVENTS REPORTED IN PATIENTS WITH AUTOIMMUNE DISEASE

Variable	Patients, n	Adverse Event, n (%)* Any	Exacerbation of Autoimmune Disease	De novo irAE
Status of autoimmune disease at start of CPI therapy†				
Active	49	33(67)	23 (47)	16 (33)
Inactive or stable	57	43 (75)	30 (53)	14 (25)
Receiving any therapy for autoimmune disease at start of CPI therapy‡				
Yes	44	26 (59)	17 (39)	10 (23)
No	57	47 (83)	33 (58)	20 (35)
Receiving immunosuppressive therapy for autoimmune disease at start of CPI therapy				
Yes	27	18 (67)	13 (48)	5 (19)
No	74	55 (74)	37 (50)	25 (34)
CPI used				
Ipilimumab	55	36 (66)	20 (36)	23 (42)
Anti-PD-1 or anti-PD-L1 agent	65	53 (82)	40 (62)	17 (26)
Combination of ipilimumab and nivolumab	3	3 (100)	1 (33)	2 (67)

CPI = checkpoint inhibitor; irAE = immune-related adverse event; PD-1 = programmed cell death 1; PD-L1 = programmed cell death ligand-1.
*Percentages are rounded to the nearest whole number
†Reported in 106 patients
‡Reported in 101 patients

Abdel-Wahab N, *et al.* Ann Intern Med. 2018;168:121-130.

AUTOIMMUNE DISEASES AND CHECKPOINT INHIBITORS

Implications for clinical practice and research

Patients with autoimmune disease at higher risk of immune-related adverse events, but frequently manageable

Autoimmune disease SHOULD NOT be a formal contra-indication for ICI

- Careful discussion with patients before starting ICI treatment
- Close vigilance during treatment should be implemented
- Multidisciplinary management might be needed
- AID treatment could be maintained during treatment with ICI

More studies with AID and ICI needed

- Prospective trials (including observational) should include more AID patients

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STEROIDS AND CHECKPOINT INHIBITORS

STEROIDS AND IMMUNE SYSTEM

- ICI trials excluded patients with steroids treatment due to risk of less efficacy or higher toxicity
- Dexametasone increases expression of CTLA-4 during T cell activation (Xia *et al*, 1999)
- Dexametasone suppresses the function of activated T lymphocytes by enhancing expression of PD-1, inhibition of IL-2, IFN-γ, TNF-α and induction T cells apoptosis (Xing *et al*, 2015)
- In patients treated with pembrolizumab and heavily immunosuppressive treatment, CD4+ and CD8+ lymphocytes still demonstrate proliferative capacity and immunological activity (Walker *et al*, 2017)

CONCOMITANT USE OF CORTICOSTEROIDS AND IMMUNE CHECKPOINT INHIBITORS

In patients with haematologic or solid neoplasms: A systematic review

8 in 10 studies did not identify any differences in outcomes

2 in 10 studies identified differences between ICI alone and ICI with steroids… but…

- Study power not tailored to find statistic differences
- Details about differences on aggressiveness of disease not provided
- NO steroids dose threshold objectively measured

Not enough data to conclude less ICI efficacy with steroids

No clinical studies exploring this interaction as primary objective

Garant A, *et al.* Critical Reviews in Oncology / Hematology 120 (2017) 86–92.

EFFECT OF PRETREATMENT STEROIDS

On the development of immune related adverse events

0% (0/17) patients receiving corticosteroids prior to starting immunotherapy experienced treatment-limiting irAEs

Pre-treatment steroids seems NOT to be associated with increase in disease progression or death

Treatment-Limiting Adverse Events-n (%)					
	Immune	Infection or Comorbidity	Disease Progression or Death	Ongoing Treatment	Total
On steroids when immunotherapy initiated?	Yes	0 (0)	8 (47.1)	2 (11.8)	17 (100)
	No	29 (19.9)	71 (48.6)	27 (18.5)	146 (100)
	Total	29 (17.8)	79 (48.4)	29 (17.8)	163 (100)

Margiotta P, *et al.* J Clin Oncol 36, 2018 (suppl; abstr e15095).

DELETERIOUS EFFECT OF BASELINE STEROIDS

On efficacy of PD-(L)1 blockade in patients with NSCLC

640 PD-(L)1 naive patients with advanced NSCLC from 2 centres

14% (90/640) received ≥10 mg/qd steroids at the start of PD-(L)1 blockade

Baseline steroid ≥10 mg of prednisone associated with poorer outcome in NSCLC patients treated with PD-(L)1 blockade

	Progression Free Survival		Overall Survival		Best Overall Response		
Institution	HR	p-value	HR	p-value	+steroids	No/low steroids	p-value
MSKCC	1.9	<0.01	2.7	<0.01	6%	19%	0.02
GRCC	1.6	0.04	2.5	<0.01	8%	18%	0.2

Arbour KC, et al. J Clin Oncol 36, 2018 (suppl; abstr 9003).

STEROIDS AND ICI

Implication for clinical practice and research

Many patients need steroids before, at starting, during or even after ICI treatment due to comorbidities, for treatment or toxicity management

Controversial evidence on the (less) benefit of ICI with steroids

ICI toxicity management with steroids should follow clinical guidelines (ESMO, NCCN, SITC…)

Other clinical use of steroids with ICI should be considered under careful vigilance

Further studies are important to tackle this frequent clinical challenge

- Does steroids reduce effectiveness of ICI?
- Any steroids dose threshold for such influence?

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GUT MICROBIOTA, ANTIBIOTICS AND TUMOUR RESPONSE TO IMMUNOTHERAPY

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ESMO

GUT MICROBIOTA, ANTIBIOTICS AND TUMOUR RESPONSE TO IMMUNOTHERAPY

- Gut microbiota important for human host (Ming Yi, *et al*. 2018)
  - Defensive (infections, inflammatory diseases, cancer, etc...)
  - Regulation of host immune system
  - Metabolism, absorption of nutrients and homeostasis

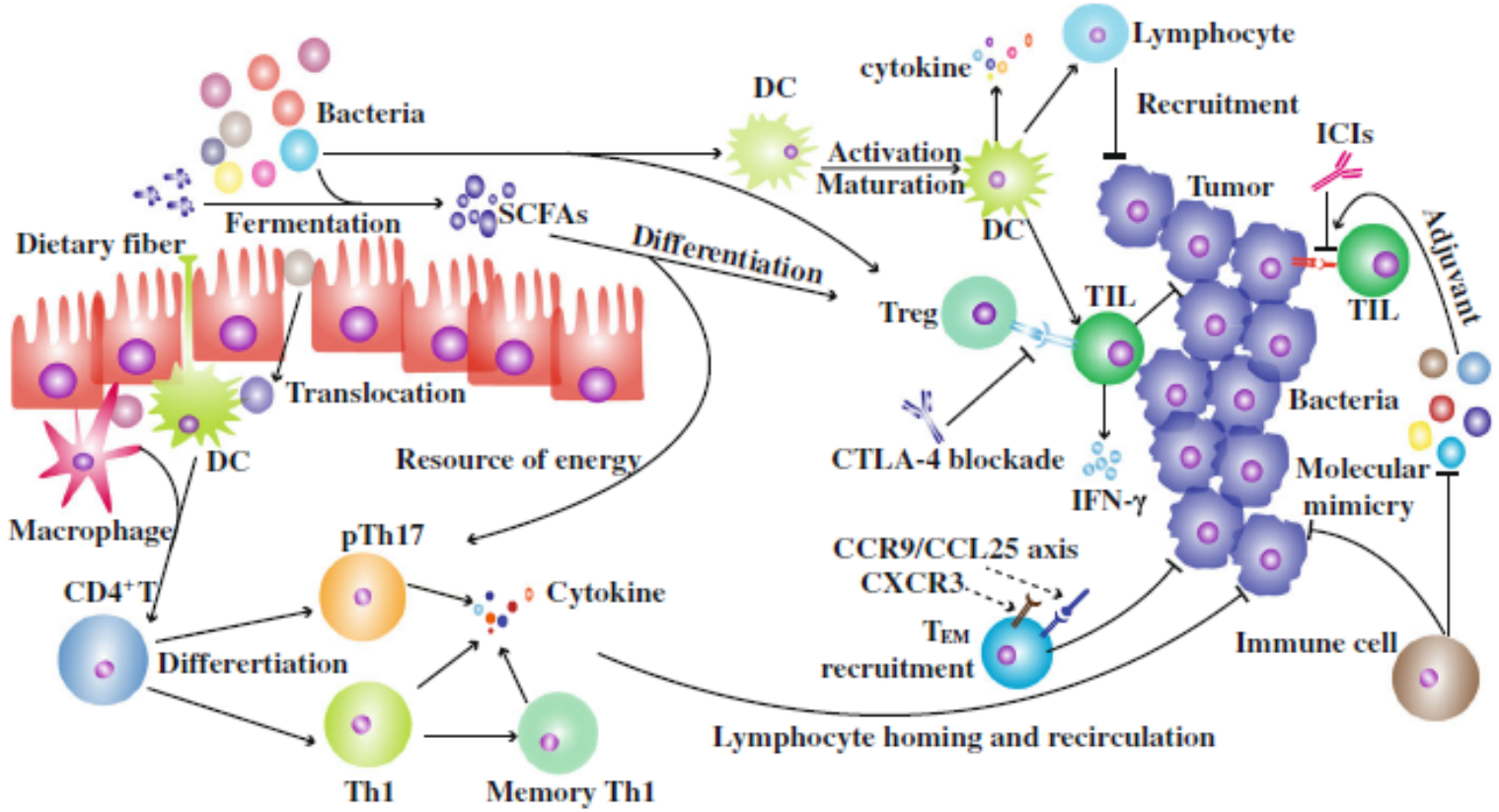
- Antibiotics can change microbiota ecosystem – **Dysbiosis**

- **Dysbiosis** is associated with different immune-mediated diseases such as chronic inflammatory and **cancer**

GUT MICROBIOTA CAN INFLUENCE IMMUNOTHERAPY EFFICACY

Patient population	Antineoplastic treatment	Observations	Conclusions
Immunotherapy			
249 patients with advanced-stage cancers (140 with NSCLC, 67 with RCC, and 42 with urothelial carcinoma)	Immunotherapy with anti-PD-1 or anti-PD-L1 mAbs	• Patients prescribed antibiotics within 2 months before or 1 month after the first injection of anti-PD-1 or anti-PD-L1 mAbs had shorter PFS (3.5 months versus 4.1 months; $P=0.017$) and OS (11.5 months versus 20.6 months; $P<0.001$) durations • Metagenomic analyses revealed that *Akkermansia muciniphila* was enriched in responders	• Antibiotic prescription is associated with decreased response to ICB (association remained significant after multivariate analyses adjusted for known prognostic risk factors) • *A. muciniphila* is associated with response to PD-1 blockade
43 patients with metastatic melanoma	Immunotherapy with anti-PD-1 mAb	16S rRNA analysis revealed that enrichment of *Faecalibacterium* spp. in baseline faecal samples was correlated with a better clinical outcome at 6 months ($P<0.01$) and increased densities of $CD8^+$ T cells in the tumour microenvironment	Proof of concept demonstrated in mice: the higher abundance of *Faecalibacterium* spp. in germ-free mice transplanted with faecal samples from responders versus nonresponders confirmed that the gut microbiota dictates the outcome of therapy
42 patients with metastatic melanoma	Immunotherapy with either anti-PD-1 or anti-CTLA-4 mAbs	Therapeutic benefit was correlated with a high abundance of *Bifidobacterium longum*, *Collinsella aerofaciens*, and *Enterococcus faecium*; *A. muciniphila* was present exclusively in responders	In germ-free mice, FMT of samples from patients with a response to ICB improved responsiveness to anti-PD-L1 antibodies in a T cell-dependent manner, suggesting that the bacteria have a direct role in dictating therapeutic outcomes
74 patients with advanced-stage NSCLC	Immunotherapy with anti-PD-1 mAb (nivolumab)	Prescription of antibiotics within 3 months before or during nivolumab treatment did not affect PFS; OS was not evaluated	In NSCLC, PFS after ICB was not influenced by antibiotics treatment
Two cohorts of patients with metastatic melanoma ($n=26$ and 39)	Immunotherapy with anti-CTLA-4 (ipilimumab) and/or anti-PD-1 (nivolumab) mAbs	• 16S rRNA cluster analysis revealed that patients with faeces enriched for *Faecalibacterium* spp. and Firmicutes had longer PFS durations • Responders to ipilimumab plus nivolumab or nivolumab alone had faeces that was enriched for *Faecalibacterium prausnitzii* and *Dorea formicigenerans*, respectively	• Gut microbiota composition correlated with clinical outcome • Only 4 and 3 patients in these cohorts had recently received antibiotics; therefore, studies on the influence of antibiotic-related dysbiosis were inconclusive

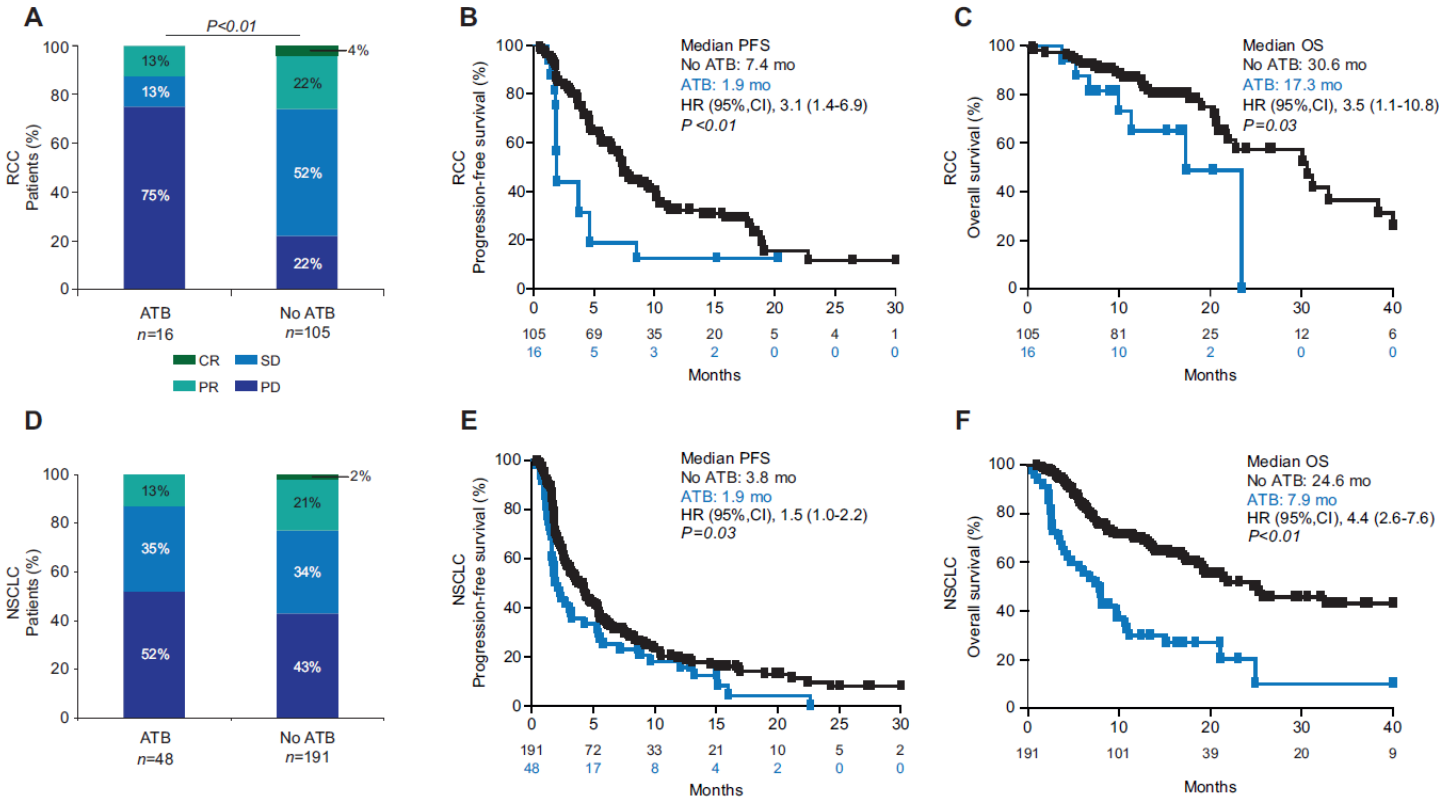
POTENTIAL MECHANISM OF GUT MICROBIOME REGULATING ICIS EFFICACY



Source: Ming Yi, *et al.* J Hematol Oncol 2018;11:47; reproduced under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

NEGATIVE ASSOCIATION OF ANTIBIOTICS

On clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer



Derosa L, *et al.* Annals of Oncology 2018, 29(6):1437-1444. By permission of Oxford University Press, on behalf of the European Society for Medical Oncology (ESMO).

ANTIBIOTIC USE AND OVERALL SURVIVAL

In lung cancer patients receiving nivolumab

109 lung cancer patients who received nivolumab

- 80% received ATB (ATB+) and 20% did not (ATB-)

Group	1-year OS (%)	Median OS (95% CI) (months) Log rank p = 0.0002	HR (95% CI)	p- value
ATB-	62.0	17.2 (8.8- 17.2)	0.29 (0.15- 0.58)	0.0004
ATB+	24.3	5.4 (3.1- 7.7)	-	-

Decreased OS in ATB+ group

- Due to antibiotic (and dysbiosis)-induced resistance to immunotherapy?

ATB, antibiotic

Adapted from: Do TP, *et al.* J Clin Oncol 36, 2018 (suppl; abstr e15109).

GUT MICROBIOME COMPOSITION TO PREDICT (NON) RESISTANCE

In renal cell carcinoma (RCC) patients on nivolumab

69 RCC patients, treated with Nivolumab, faecal samples evaluated by whole genome sequencing (WGS)

Primary resistance (PR) or non-PR based on RECIST (outcome 6 months PFS)

ICI-resistant mice compensated with faecal microbiota transplantation (FMT) from non-PR patients or with commensals identified by WGS

All patients: 27 (39%) PR and 42 (61%) non-PR

With antibiotics: 8 (73%) PR and 3 (27%) non-PR (p=0.01)

Specific gut related to best responses and/or PFS

- *Akkermansia muciniphila* and *Bacteroides salyersiae* more abundant in non-PR
- *B. salyersiae* or *A. muciniphila* could restore the efficacy of ICI improving by a 43% the prevalence of non-PR

Derosa L, et al. J Clin Oncol 36, 2018 (suppl; abstr 4519).

GUT MICROBIOTA, ANTIBIOTICS AND TUMOUR RESPONSE TO IMMUNOTHERAPY

Implication for clinical practice and research

Gut dysbiosis and antibiotics could affect ICI efficacy by mechanisms still poorly understood

More studies needed to assess relationship between antibiotics, gut microbiota and ICI efficacy

- How does dysbiosis and/or antibiotics influence ICI efficacy?
- Modulating gut microbiota in humans will change ICI efficacy?
- Does infection/immune-system-status itself (and not antibiotics) influence ICI efficacy?

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DURATION OF ICI TREATMENT

- Approved duration of treatment with ICIs followed clinical trials design

- **Duration of treatment can be different?**
  - To reduce immune related adverse events
  - To reduce the very high cost of treatment

STOPPING ICI AFTER COMPLETE RESPONSE (CR)?

- Retrospective review from 2 institutions
- 24 complete responders with nivolumab or pembrolizumab

Median time to CR: 10 months pembrolizumab, 17 months nivolumab

Median time off therapy*: 8 months nivolumab, 2-7 months pembrolizumab**

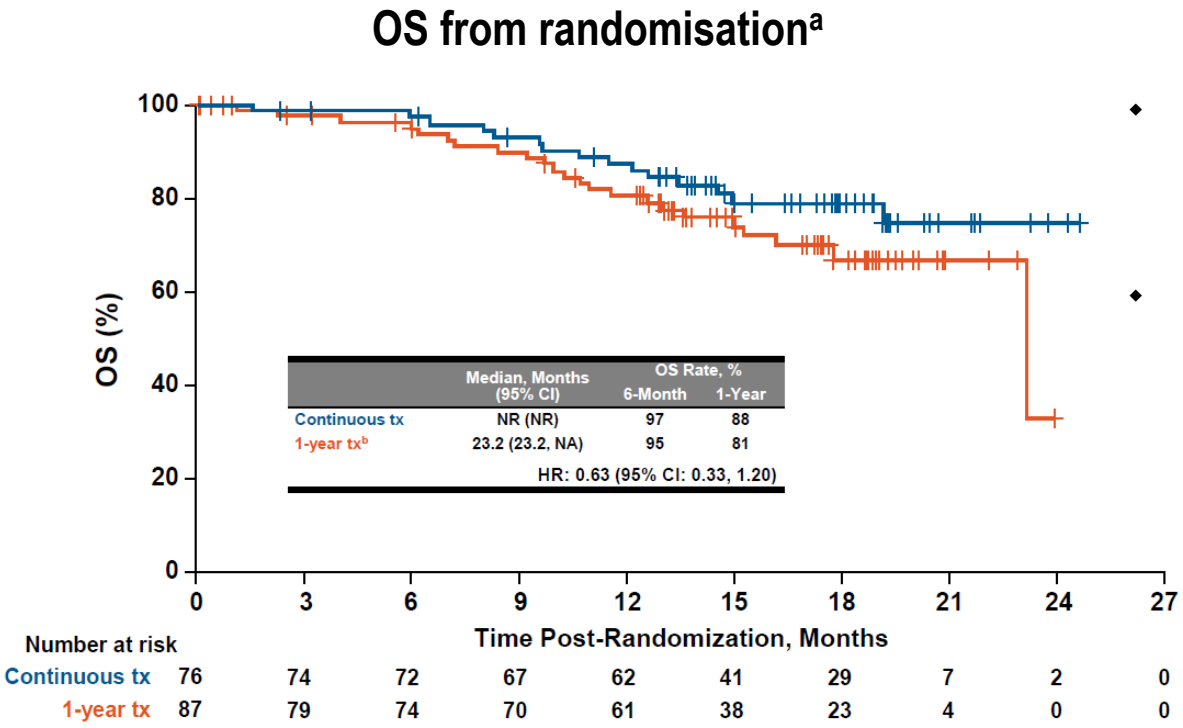
- **23/24 patients maintained response**
- **1/24 relapse and successfully re-induced**

* After complete response

**Two different programmes to access pembrolizumab with median time off therapy after CR of 2 months and 7 months respectively

Atkinson VG, Annals of Oncology, Volume 27, Issue suppl_6, 1 October 2016, 1116P.

ONE YEAR NIVOLUMAB IN NSCLC? - CHECKMATE 153



- OS showing a trend favoring continuous nivolumab (HR = 0.63 (95% CI: 0.33, 1.20)
- But more mature data needed

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

Spigel DR, *et al.* Ann Oncol 2017;28(Suppl5): Abstract 1297O. Presented at ESMO 2017. Courtesy of Prof DR Spigel

DURABLE COMPLETE RESPONSE AFTER DISCONTINUATION OF PEMBROLIZUMAB

In Patients with Metastatic Melanoma

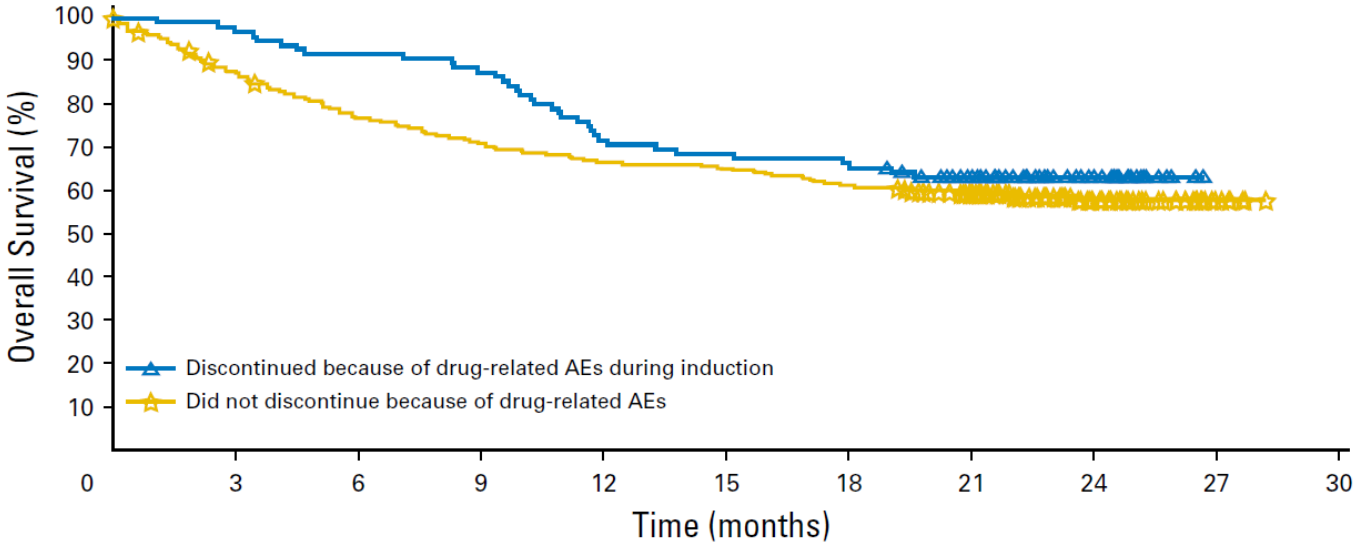
- 105 Melanoma patients with complete response (CR)
  - median follow-up 43 months
  - 67 patients discontinued pembrolizumab after CR

- 24-months disease-free survival from time of CR
  - **90.9% in all 105 patients with CR**
  - **89.9% in the 67 patients who discontinued treatment**

Robert C, *et al.* J Clin Oncol 36:1668-1674

DISCONTINUATION OF NIVO+IPI

During induction phase in advanced melanoma, does not affect efficacy



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

LONG-TERM OUTCOMES

In patients after discontinuation of PD1/PDL1 inhibitors

20 patients with disease control* and discontinuation of ICI, with median 11 cycles of treatment

8 in 8 (100%) in melanoma group had disease control after a median follow-up of 9 months

8 in 12 (67%) in non-melanoma group had disease control after a median follow-up of 10 months

*Disease control included stable disease, partial and complete response.

Myint Z, *et al.* J Clin Oncol 36, 2018 (suppl; abstr e15086)

DURATION OF TREATMENT WITH ICI

Implication for clinical practice and research

Duration of treatment with ICI should follow approved recommendations and clinical guidelines

Early interruption could be considered, but under careful discussion and agreement with patient and close vigilance

More studies needed on larger real world populations

- Could we stop earlier ICI with partial response/stable disease?
- Does less administrations of ICIs affect long-term response?
- Differences across different tumours and with different ICI treatments?

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THANK YOU!

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DISCLOSURES

Luís Castelo-Branco has reported no conflicts of interest

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