Immunotherapy in specific clinical situation (HIV, auto-immune diseases, elderly, organs transplants,brain metastases,…)

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Disclosures

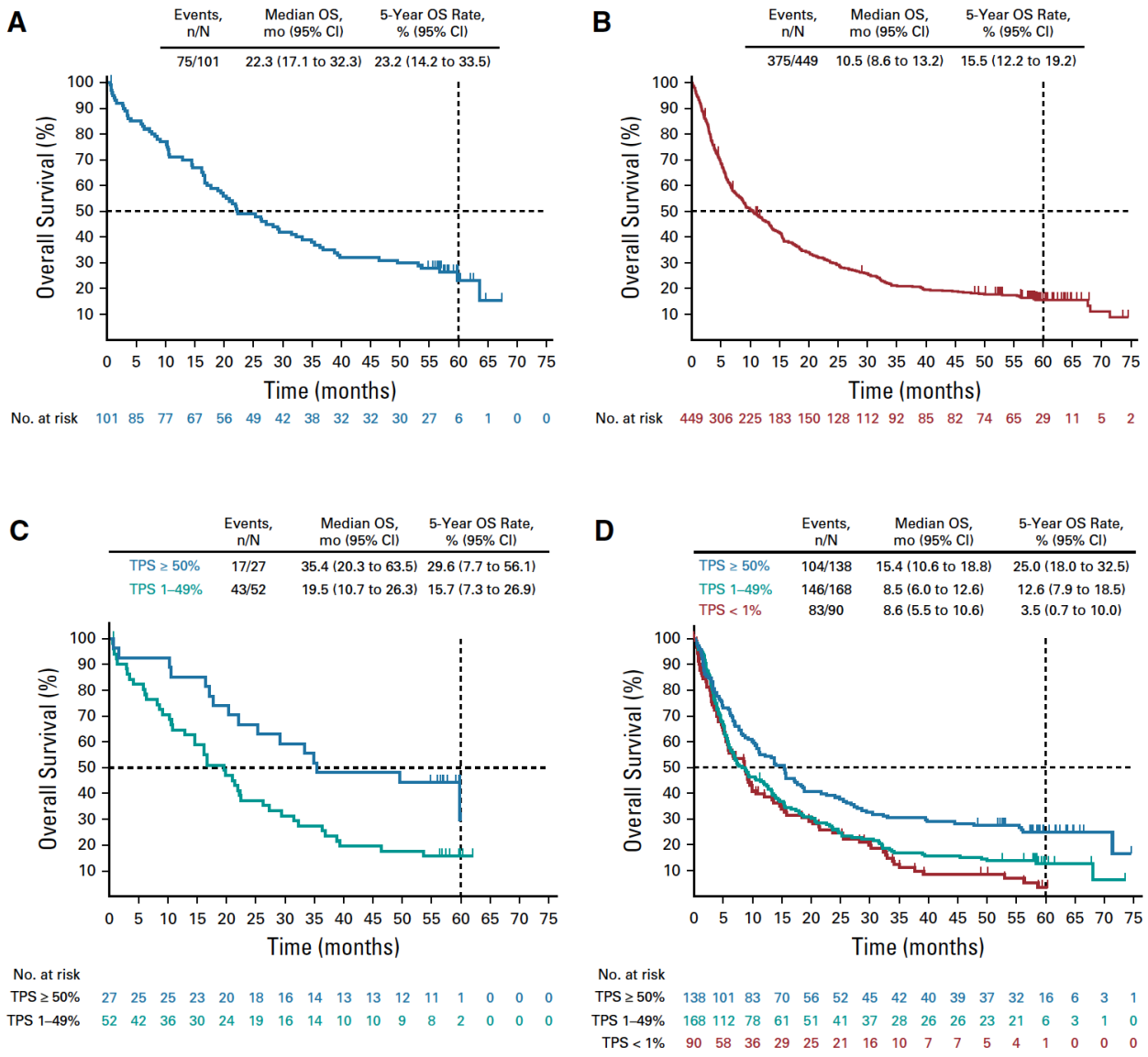
- None
- Interpretation bias of the literature related to my field of interest (Lung cancer)

Discussion plan : ICI and “excluded patients”

- General considerations
- Autoimmune disease (AID)
- HIV
- Organs Transplants
- Brain Metastasis
- Elderly
- …

Potential long term benefit of ICI

Five-Year Overall Survival for Patients With Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study

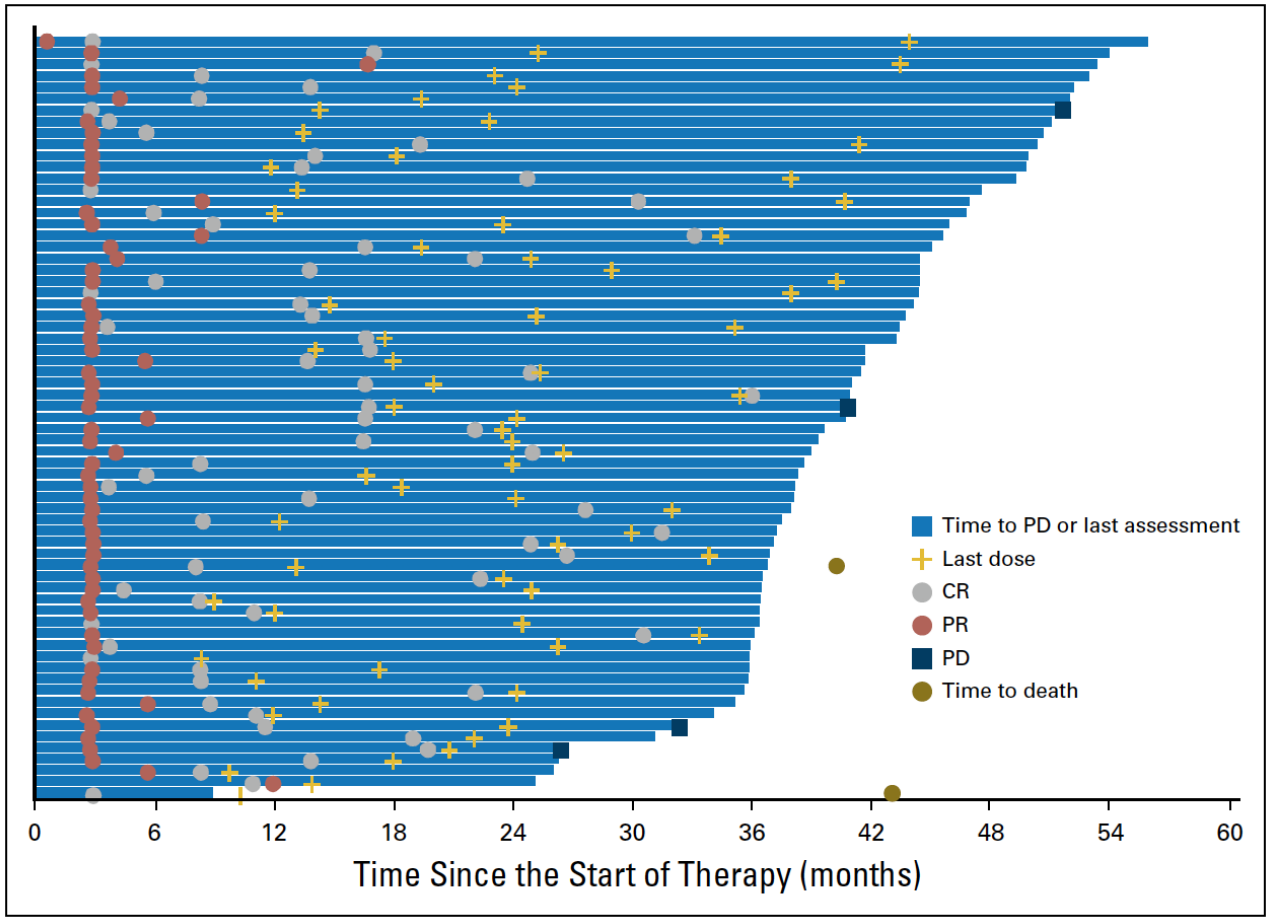


Garon E.B. J Clin Oncol, 2019

Durable complete response after treatment cessation

- Response can be durable after treatment cessation
- Response can be achieved quickly
- Lack of reproducible predictive biomarker (efficacy and safety)

Durable Complete Response After Discontinuation of Pembrolizumab in Patients With Metastatic Melanoma



Robert C. JCO , 2018

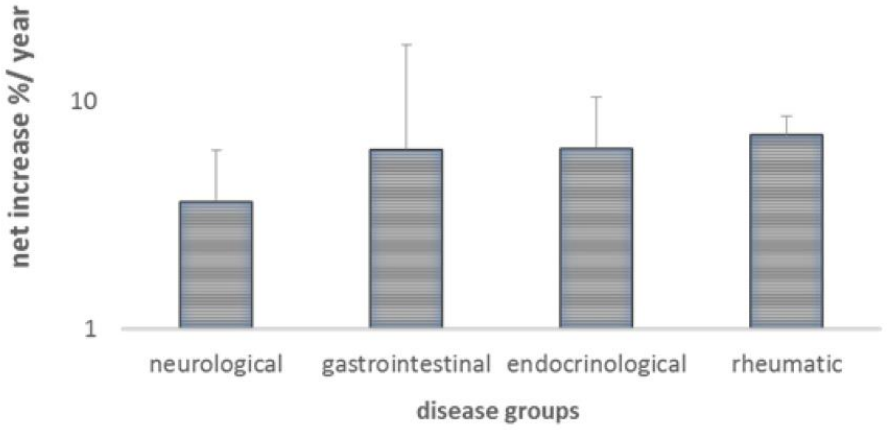
Discussion plan : ICI and “excluded patients”

- General consideration
- Autoimmune disease (AID)
- HIV
- Organs Transplants
- Brain Metastasis
- Elderly
- …

AID and cancer: Incidence

- Higher incidence of cancer (1)
  - Chronic inflammation
  - Immunosuppression
  - Shared environmental factors
  - …
- Global world incidence is increasing (2)

1985-2015



- AID as paraneoplastic syndrome (3)
  - Wide variety
  - Could be occult or not identified as such

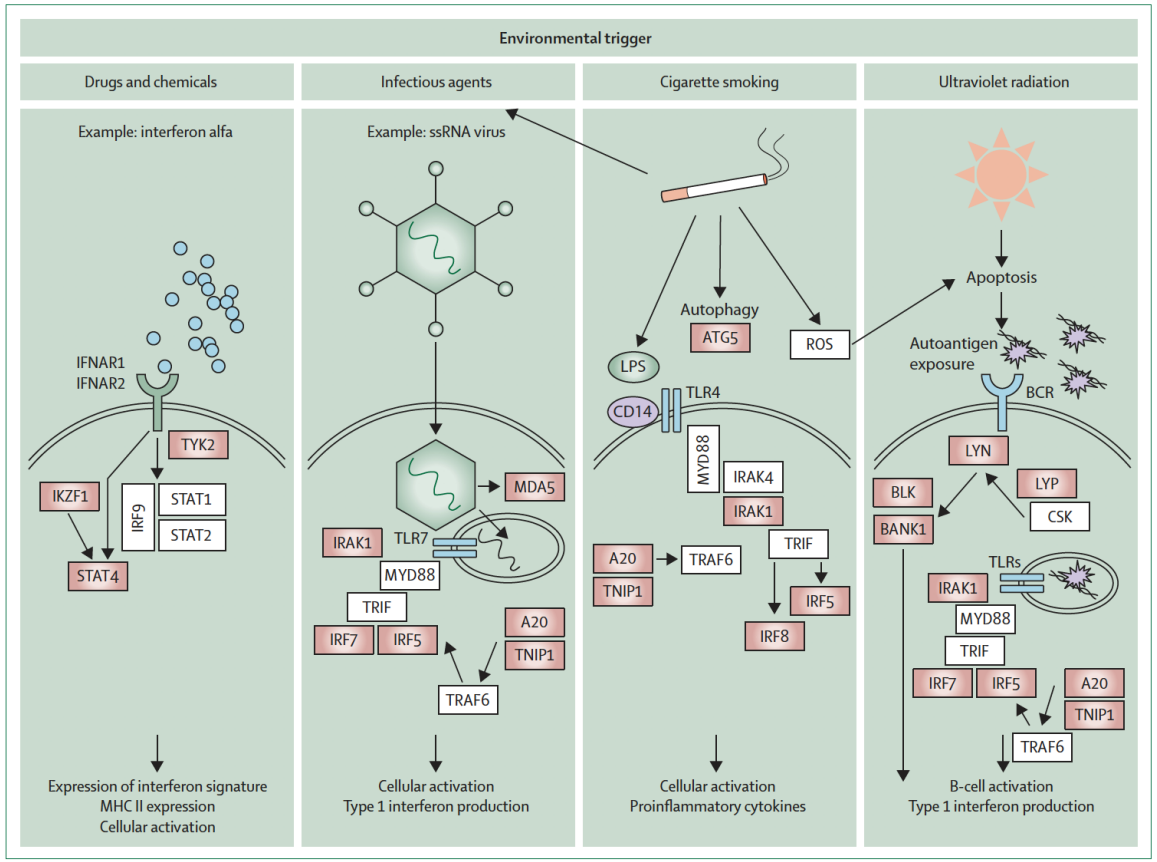
Lung cancer patients aged 65 years or older
SEER Data base 1992 -2009
210 509 patients with lung cancer. (4)

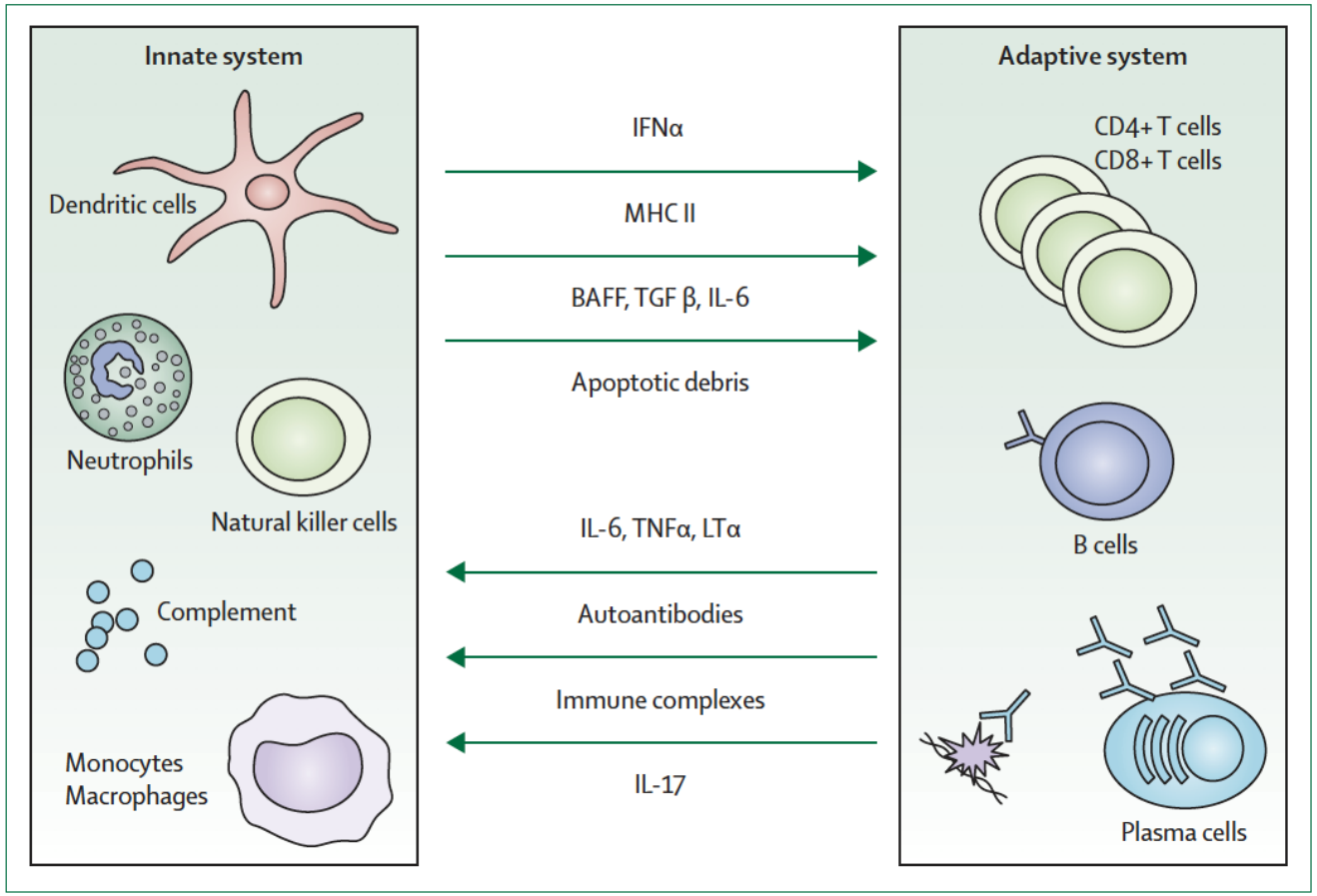
Autoimmune Disease	Prevalence, %
Rheumatoid arthritis	5.9
Psoriasis	2.8
Polymyalgia rheumatic	1.8
Addison disease	1.0
Systemic lupus erythematosus	0.9
Ulcerative colitis	0.8
Giant cell arteritis	0.8
Sicca syndrome	0.6
Regional enteritis	0.5
Ménière disease, unspecified	0.5
Total (any autoimmune disease)	13.5

1. Beyaert R. Mol Cancer, 2013
2. Lerner A. IJCD, 2015
3. Sculier C. Lung cancer, 2017
4. Khan S.A . Jama oncol, 2016

AID immunopathogenic mechanisms

Genetic predisposition





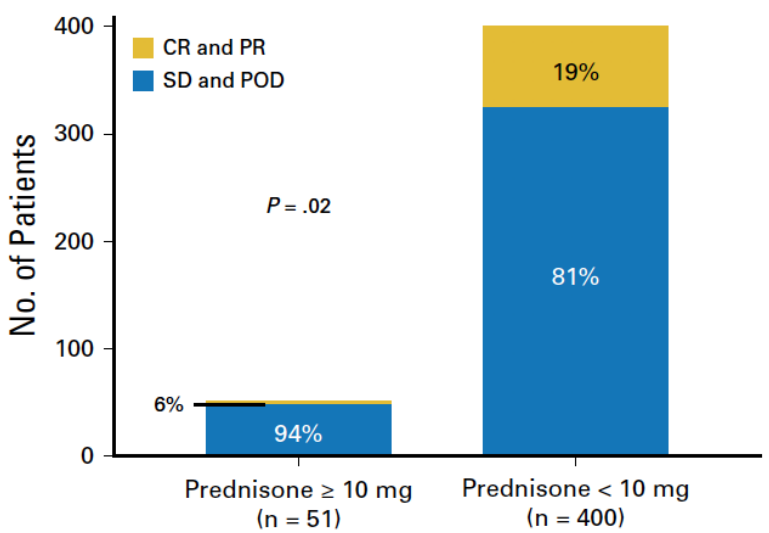
Imbalance between Immune Surveillance and Tolerance
Sustained inflammatory cascade

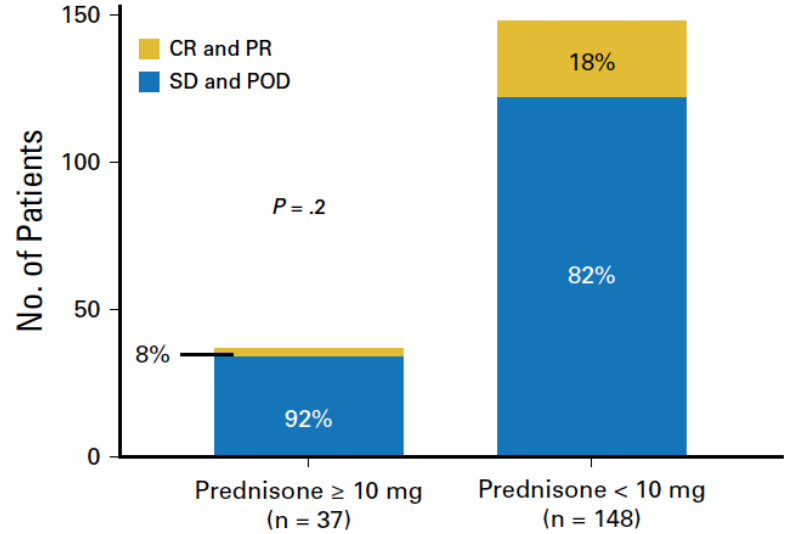
Wahren-Herlenius M. Lancet , 2013

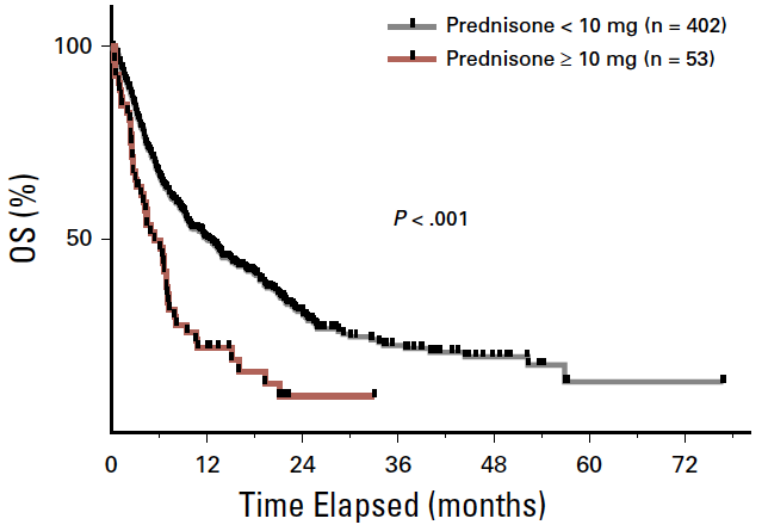
AID : Immuno-suppression (IS) and ICI efficacy

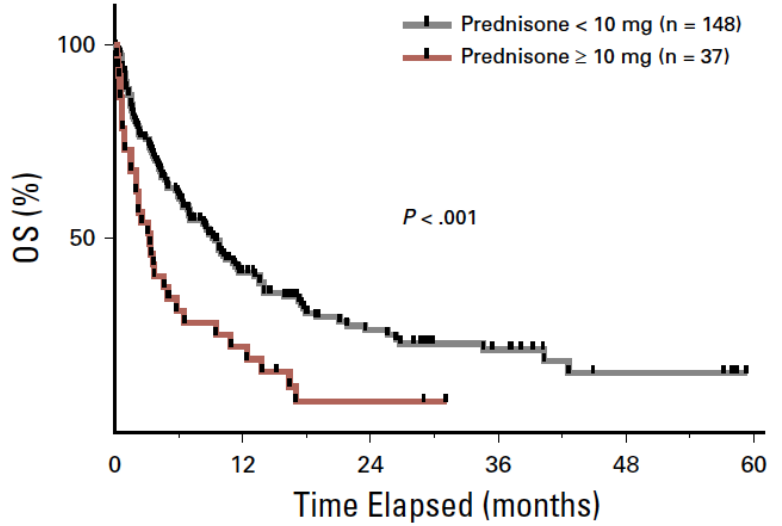
Impact of Baseline Steroids on Efficacy of Programmed Cell Death-1 and Programmed Death-Ligand 1 Blockade in Patients With Non–Small-Cell Lung Cancer

Retrospective pooled analysis
Memorial Sloan Kettering Cancer Center
and Gustave Roussy Cancer Center





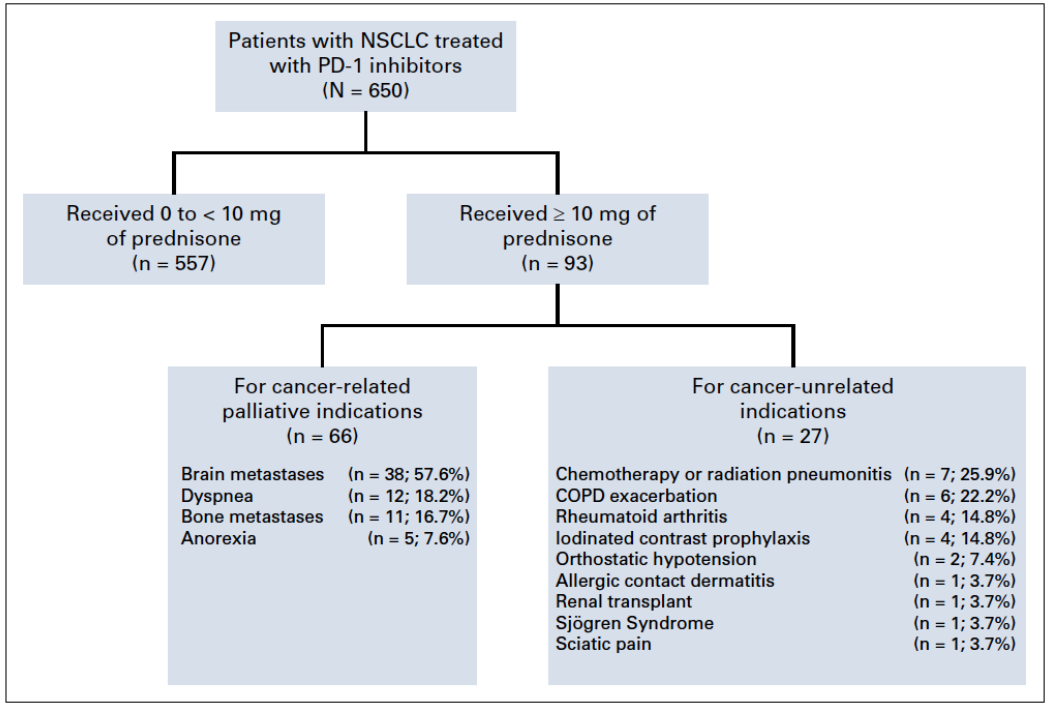


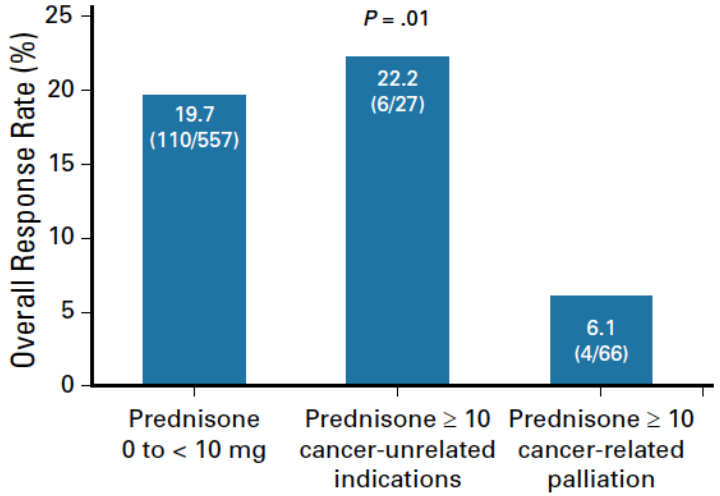


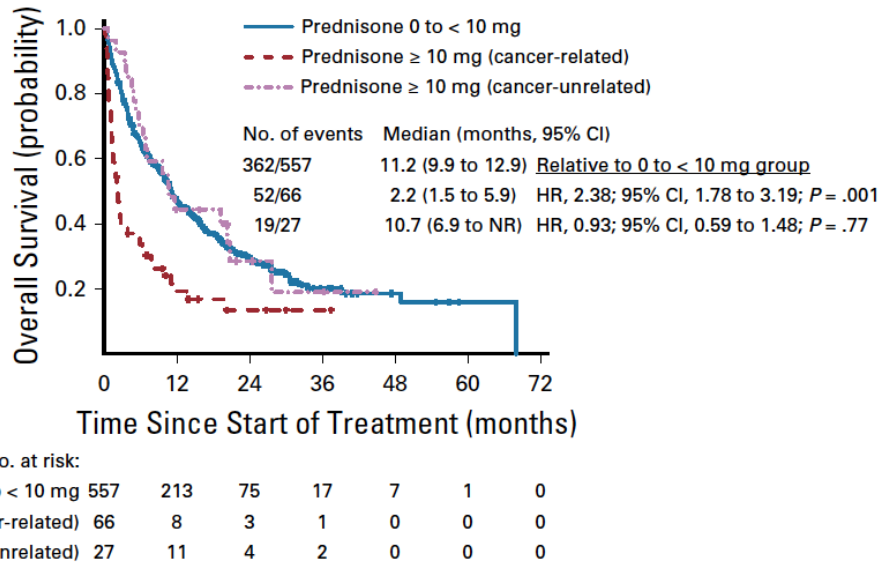
Arbour K.C. J Clin Oncol, 2018

Steroids for related or unrelated cancer indications

Immune Checkpoint Inhibitor Outcomes for Patients With Non–Small-Cell Lung Cancer Receiving Baseline Corticosteroids for Palliative Versus Nonpalliative Indications







Ricciuti B. J Clin Oncol, 2019

Auto immunity and cancer really a bad thing ?

Antineural and Antinuclear Autoantibodies of Prognostic Relevance in Non-Small Cell Lung Cancer ?

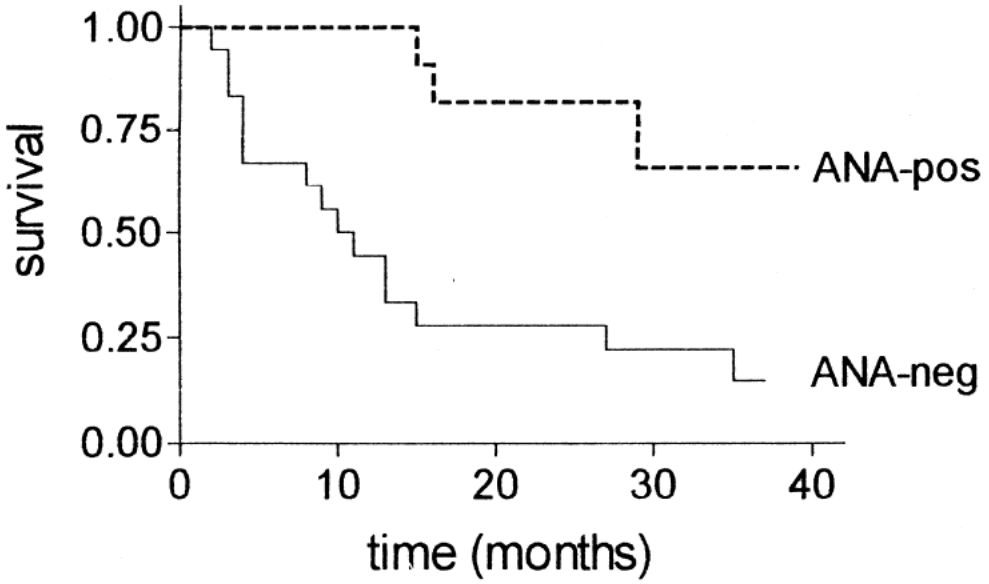
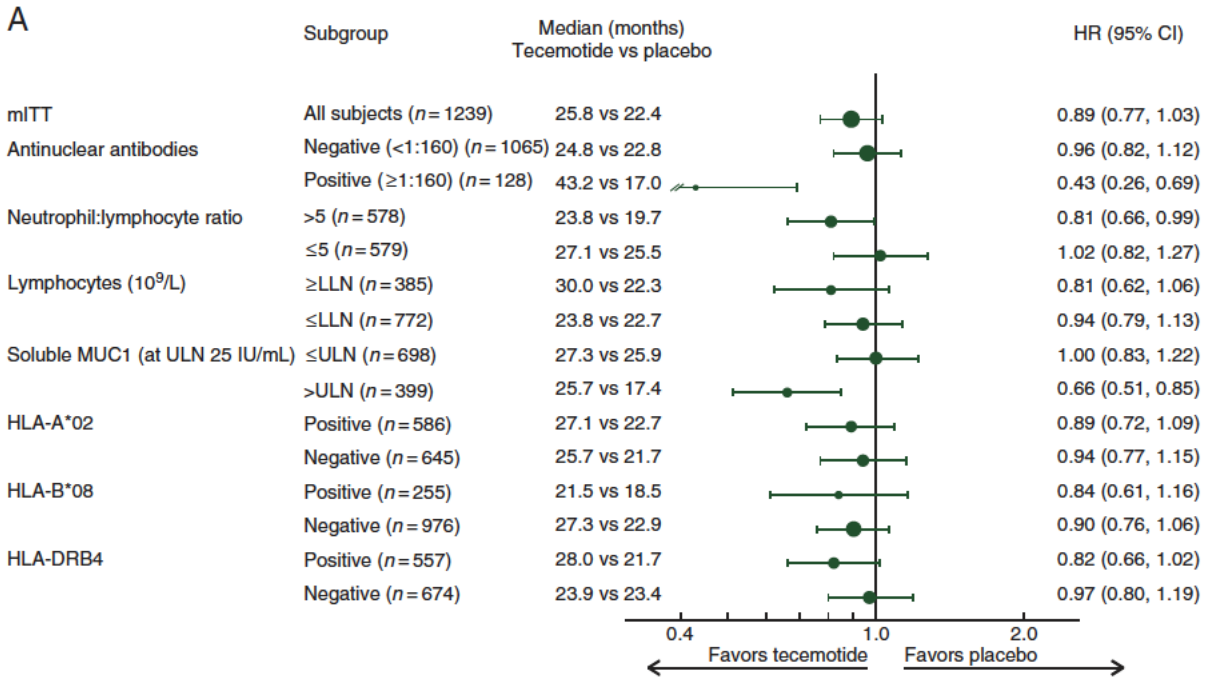


Fig 5. Survival functions of stage III patients grouped by ANA finding presented as Kaplan-Meier plots. Log-rank test showed a significantly better prognosis of the ANA-positive stage III patients (p = 0.0025).

Blaes F. Ann Thorac surg 2000; 69: 254-8

Tecemotide in unresectable stage III non-small-cell lung cancer in the phase III START study: updated overall survival and biomarker analyses



Mitchell P. Ann of Oncol , 2015

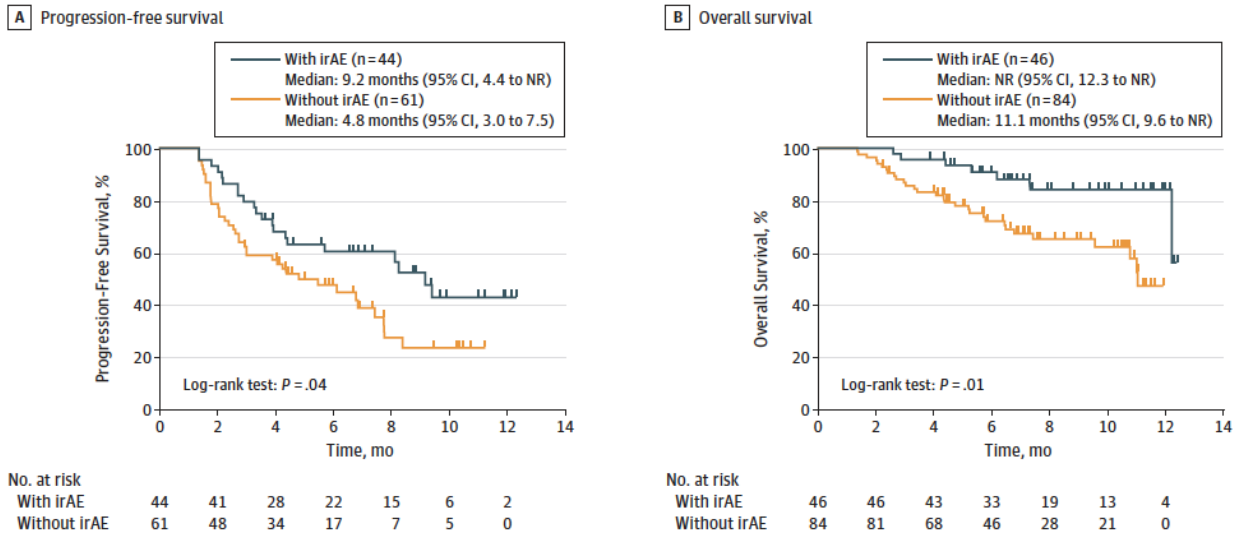
IrAEs and Outcome: Favourable Relationship?

JAMA Oncology | Brief Report

Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non–Small-Cell Lung Cancer

Koji Haratani, MD; Hidetoshi Hayashi, MD, PhD; Yasutaka Chiba, PhD; Keita Kudo, MD, PhD; Kimio Yonesaka, MD, PhD; Ryoji Kato, MD; Hiroyasu Kaneda, MD, PhD; Yoshikazu Hasegawa, MD, PhD; Kaoru Tanaka, MD, PhD; Masayuki Takeda, MD, PhD; Kazuhiko Nakagawa, MD, PhD

Figure. Analysis of Survival for Patients With or Without irAEs



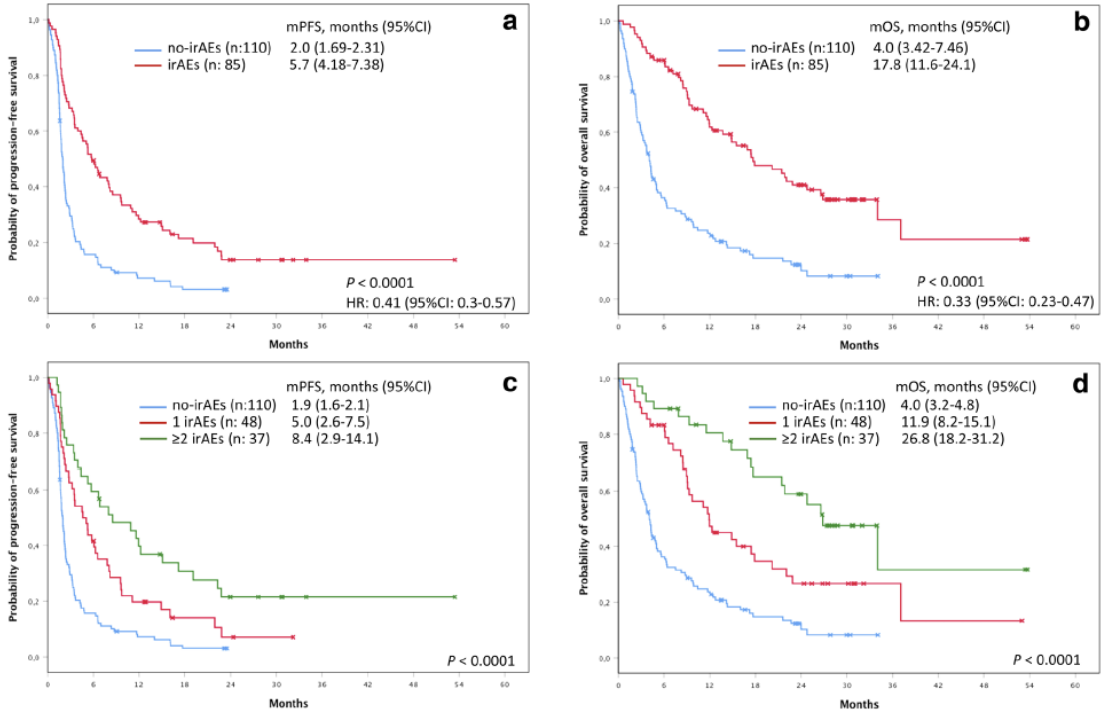
Kaplan-Meier curves with 6-week landmark analysis for (A) progression-free survival (B) and overall survival in patients with or without irAEs. irAEs indicates immune-related adverse events; NR, not reached.

IrAEs all grade

Ricciuti B. J Clin Cancer Res, 2019

Impact of immune-related adverse events on survival in patients with advanced non-small cell lung cancer treated with nivolumab: long-term outcomes from a multi-institutional analysis

Biagio Ricciuti[1,4] · Carlo Genova[2] · Andrea De Giglio[1] · Maria Bassanelli[3] · Maria Giovanna Dal Bello[2] · Giulio Metro[1] · Marta Brambilla[1] · Sara Baglivo[1] · Francesco Grossi[2] · Rita Chiari[1]



IrAEs that required intensive monitoring or treatment with immunosuppressive agents or endocrine therapy.

Haratani K. Jama oncol, 2017

AID and ICI : Which Data

- Toxicity :
  - Flare of AID ?
  - Outcome of AID ?
  - Other irAEs?
- Efficacy
  - RR ?
  - PFS ?
  - OS ?
  - Discontinuation rate (DR)?

AID and ICI : Case Series (ORR, Flare, irAEs, DR)

Table 2. Retrospective Case Series Evaluating ICI Use in Patients With AID

Study	N[a]	Tumor	ICI	AID	Treatment for AID[b]	ORR	AID Flare Rate[c]	irAE Rate[d]	Rate of Permanent Discontinuation Due to Toxicity[e]
Tison et al[40]	112	Melanoma (59%) NSCLC (35%) Other (6%)	PD-1/PD-L1 in 85% of patients	Ps/PsA, RA, IBD, SA, SLE, PMR/TA	22%	Melanoma: 48% NSCLC: 54%	33-43% 14-45% 42% Gr 3/4: 13%	38% Gr 3–5: 16% 10-27%	Not stated 4-12%
Leonardi et al[41]	56	NSCLC	PD-1/PD-L1	RA, PMR/TA, Scleroderma, Ps/PsA, Thyroiditis, IBD, MG, MS	20%	22%	14-45% 23% Gr 3/4: 4%	38% Gr 3/4: 10% 10-27%	14% 5-8%
Menzies et al[42]	52	Melanoma	PD-1	RA, PMR, SS, ITP, Ps, IBD, GBS, MG, Thyroiditis, SLE	38%	33%	33-43% 38% Gr 3/4: 6%	29% Gr 3/4: 10% 13-23%	12% 4-12%
Danlos et al[43]	45	Melanoma (80%) NSCLC (13%) Other (7%)	PD-1	Vitiligo, Ps/PsA, Thyroiditis, RA, ITP, SA, MS, MG, PMR, PAN, Sarcoidosis, T1 DM	16%	38%	14-45% 24%	22% 10-27%	9% 4-12%
Johnson et al[44]	29	Melanoma	Ipilimumab	RA, Ps, Thyroiditis, MS, IBD, SLE, Sarcoidosis	41%	21%	19% 24%	31% Gr 3–5: 31% 28%	Not stated 16%
Gutzmer et al[45]	19	Melanoma	PD-1	Ps/PsA, RA, Vasculitis, PMR, SA, Sarcoidosis, IBD, GBS, MS, MG, Thyroiditis	32%	32%	33-43% 42%	16% 13-23%	0% 4-12%
Richter et al[46]	16	Melanoma NSCLC NHL	PD-1 (69%) Ipilimumab (31%)	RA, PMR, Sarcoidosis, SLE, Vasculitis	44%	Not stated	6%	38% Gr 3/4: 25% 10-27% 28 %	31% 4-16%
Lee et al[47]	8	Melanoma	Ipilimumab	RA	87.5%	50%	19% 75% Gr 3/4: 25%	50% Gr 3/4: 50% 28 %	62.5% 16%

Kennedy L.C. JNCCN, 2019

AID and ICI : Individual Data

- AID type
- AID Active or not (I -?)
- ICI type
- IS or not
- Flare
- irAEs

- Cancer type
- IS type
- Line of treatment
- Treatment cessation / How many cycles?
- Outcome of AID
- Outcome of the cancer (Cancer Related ✝)

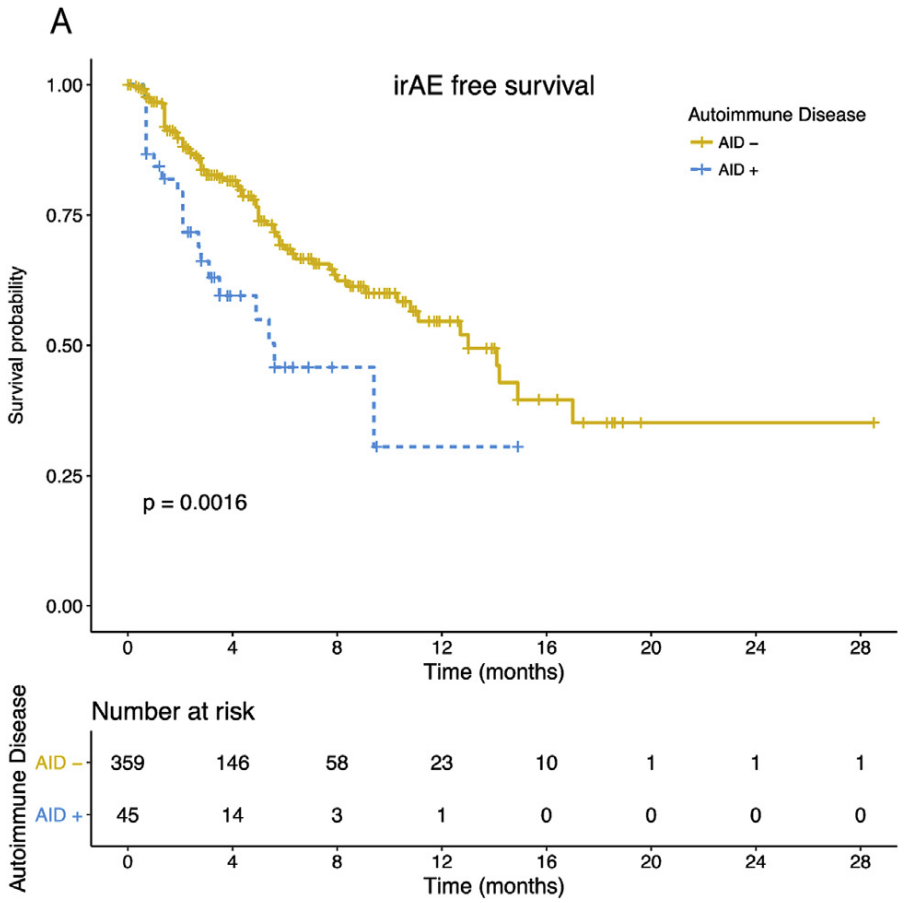
Preexisting Autoimmune Disease	CPI Used	Patients, *n*	Active Preexisting Autoimmune Disease/Reported Cases, *n/N*	Receiving Treatment for Autoimmune Disease/Reported Cases, *n/N*	Adverse Events, *n*		
					Any	Exacerbation of Autoimmune Disease	De No irA
All patients	–	123	49/106	44/101	92	61	42
Psoriatic arthritis and/or psoriasis	Ipilimumab	4	4/4	2/4	3	1	3
	Nivolumab or pembrolizumab	23	3/20	2/21	21	20	4
	Atezolizumab	1	0/1	0/1	1	1	0
	All	28	7/25	4/26	25	22	7
Rheumatoid arthritis	Ipilimumab	15	13/15	5/7	13	9	7
	Nivolumab or pembrolizumab	5	2/4	3/3	2	1	1
	All	20	15/19	8/10	15	10	8
Autoimmune thyroid disease	Ipilimumab*	4	0/3	1/3	2	0	2
	Nivolumab or pembrolizumab	6	5/5	5/5	2	2	0
	Combination of ipilimumab and nivolumab	1	NR	NR	1	0	1
	All	11	5/8	6/8	5	2	3
Ulcerative colitis†	Ipilimumab	6	3/5	1/3	3	3	1
	Nivolumab or pembrolizumab	2	1/1	1/1	2	2	0
	All	8	4/6	2/4	5	5	1
Crohn disease	Ipilimumab	4	1/4	2/4	2	0	2
	Pembrolizumab	1	0/1	0/1‡	1	1	0
	All	5	1/5	2/5	3	1	2
Multiple sclerosis§	Ipilimumab	5	2/4	2/4	2	2	1
	Nivolumab	1	0/1	0/1	0	0	0
	All	6	2/5	2/5	2	2	1
Sarcoidosis	Ipilimumab	3	1/3	2/3	3	2	1
	Nivolumab	2	0/2	0/2	2	1	1
	All	5	1/5	2/5	5	3	2
Myasthenia gravis	Nivolumab or pembrolizumab	4	1/4	4/4	4	3	1
Eosinophilic granulomatosis with polyangiitis‖	Ipilimumab	1	0/1	1/1	1	0	1
	Pembrolizumab	1	1/1	1/1	0	0	0
	All	2	1/2	2/2	1	0	1
Inflammatory arthritis	Ipilimumab	1	1/1	1/1	1	1	1
	Anti-PD-1 (unspecified)	1	NR	0/1	1	1	1
	All	2	1/1	1/2	2	2	2
Psoriasis and autoimmune thyroid disease	Ipilimumab	1	1/1	0/1	1	0	1
	Pembrolizumab	1	NR	NR	1	0	1
	All	2	1/1	0/1	2	0	2
Spondyloarthropathy	Anti-PD-1 (unspecified)	1	0/1	0/1	1	0	1
	Nivolumab	1	0/1	0/1	1	1	0
	All	2	0/2	0/2	2	1	1
Systemic lupus erythematosus	Ipilimumab	2	1/2	2/2	0	0	0
Vitiligo	Anti-PD-1 (unspecified)	2	NR	0/2	2	0	2
Ankylosing spondylitis	Ipilimumab and nivolumab	1	NR	0/1	1	0	1
Ankylosing spondylitis and psoriasis	Pembrolizumab	1	1/1	1/1	0	0	0
Behçet disease	Ipilimumab	1	1/1	NR	1	0	1
Celiac disease	Ipilimumab	1	0/1	0/1	0	0	0
Cold agglutinin	Anti-PD-1 (unspecified)	1	NR	0/1	1	1	0
Crohn disease and sarcoidosis	Nivolumab	1	0/1	0/1	1	0	1
Crohn disease and psoriasis	Pembrolizumab	1	0/1	0/1	1	1	0
Granulomatosis with polyangiitis (sinus-limited)	Combination of ipilimumab and nivolumab	1	1/1	1/1	1	1	0
Guillain-Barrè syndrome	Pembrolizumab	1	0/1	0/1	1	0	1
Idiopathic thrombocytopenic purpura	Nivolumab	1	0/1	0/1	1	1	0
IgA nephropathy¶	Ipilimumab	1	0/1	1/1	0	0	0
IgM nephropathy	Pembrolizumab	1	0/1	1/1	1	0	1
Melanoma-associated retinopathy	Pembrolizumab	1	1/1	0/1	1	1	0
Melanoma-associated retinopathy and vitiligo	Ipilimumab	1	1/1	1/1	1	1	0
Myositis	Pembrolizumab	1	0/1	0/1	1	1	0
Polymyalgia rheumatica	Nivolumab	1	1/1	1/1	1	1	0
Rheumatoid arthritis and polymyalgia rheumatica	Ipilimumab	1	1/1	1/1	1	1	0
Rheumatoid arthritis and myasthenia gravis	Pembrolizumab	1	0/1	0/1	1	1	0
Reactive arthritis	Ipilimumab	1	0/1	0/1	0	0	0
Rheumatic fever	Ipilimumab	1	0/1	0/1	0	0	0
Seronegative rheumatoid spondyloarthritis and autoimmune thyroid disease	Nivolumab	1	1/1	1/1	1	0	1
Sjögren syndrome	Ipilimumab	1	0/1	0/1	1	0	1
Type 1 diabetes	Nivolumab	1	NR	1/1	1	0	1
Transverse myelitis	Ipilimumab	1	1/1	0/1	1	0	1

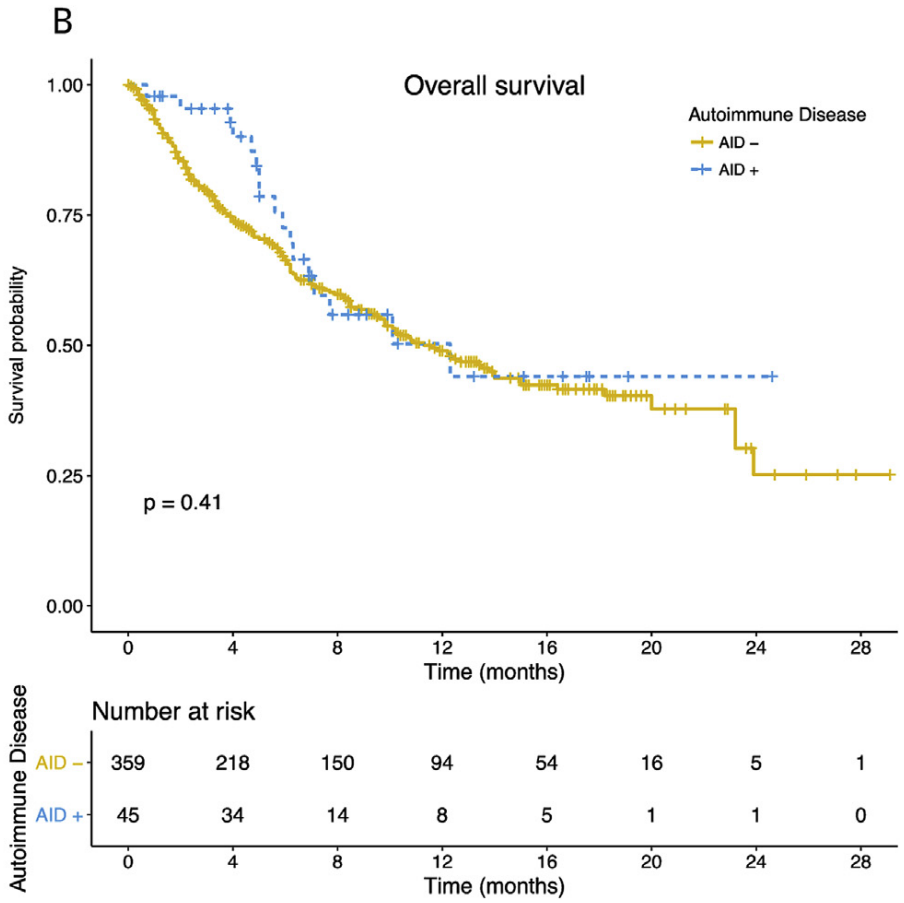
Abdel-Wahab N. Ann of Inter Med, 2018

AID and ICI: OS ?

Safety and efficacy of anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease

REISAMIC: French Prospective registry of grade ≥ 2 irAEs
AID n= 45





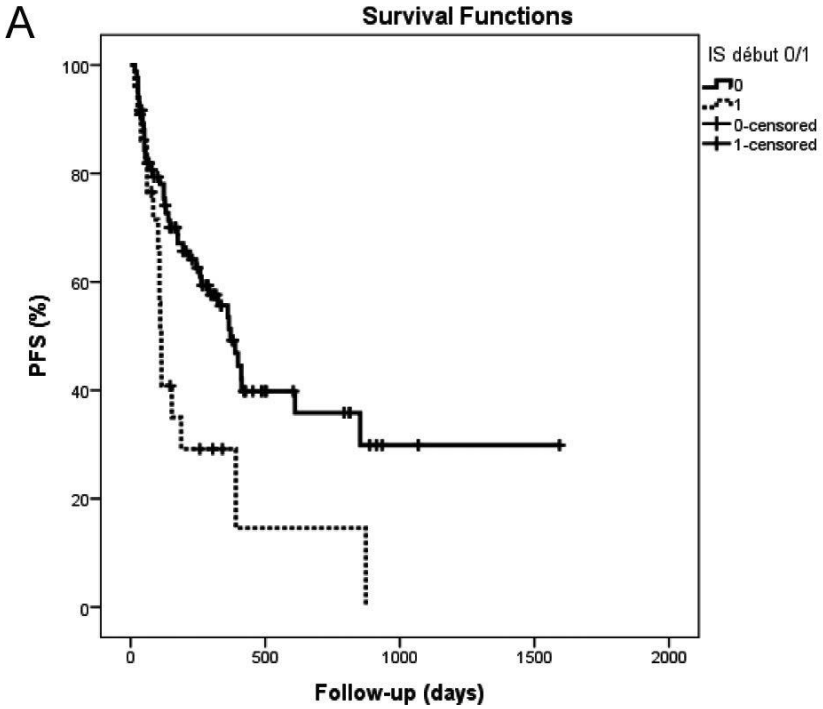
Danlos F. EJC,2018

AID and ICI : PFS / OS by IS status

Safety and Efficacy of Immune Checkpoint Inhibitors in Patients With Cancer and Preexisting Autoimmune Disease: A Nationwide, Multicenter Cohort Study

Retrospective cohort
N= 112
Mostly melanoma and lung cancer
Mostly Anti PD-1/ PDL-1

A



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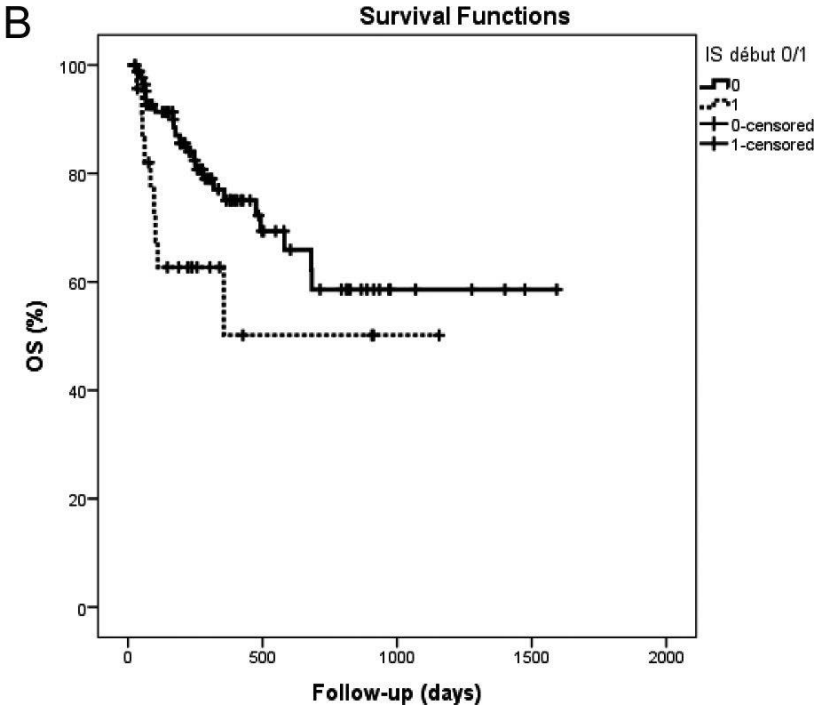
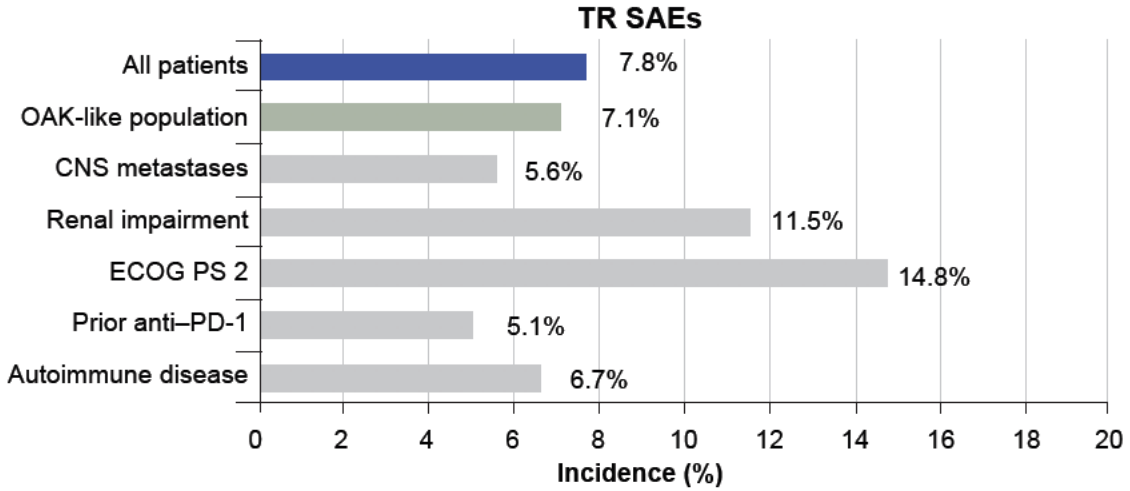


Tison A. Arthr and Rheumatol, 2019

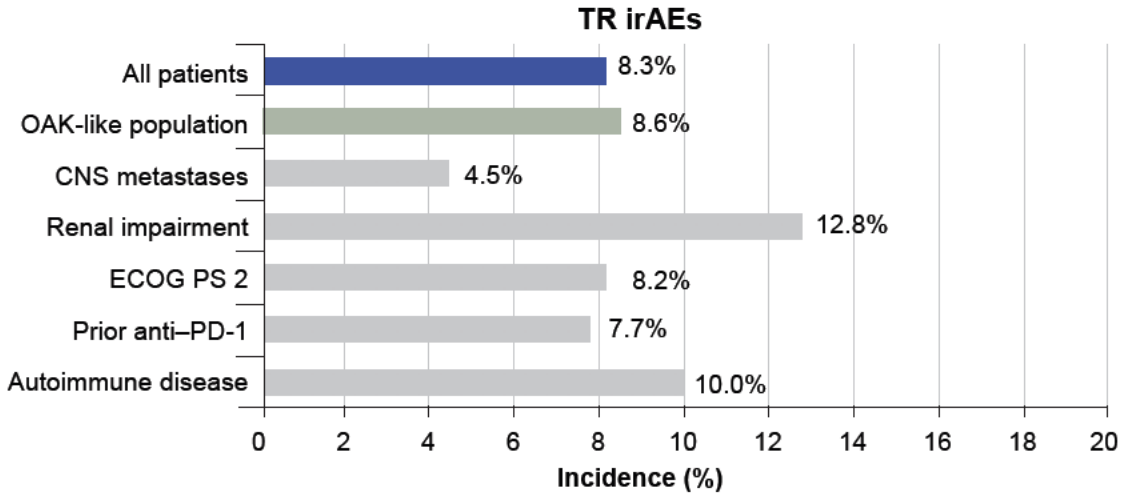
AID and ICI : Prospective Clinical Trial Data

TAIL is a prospective Phase III/IV, open-label, multicenter study evaluating the safety and efficacy of **atezolizumab** monotherapy in patients with **previously** treated advanced **NSCLC** n= 615

- OAK like (n = 406)
  +
- Prior treatment with checkpoint inhibitors
- Untreated asymptomatic CNS metastases
- Autoimmune disease n= 30
- ECOG PS of 2
- Active or chronic hepatitis B/C viral (HBV/HCV) infections
- Renal impairment



DR : 16 versus 4.7%



Ardizzoni A. ESMO 2019

AID and ICI : Prospective Clinical Trial Data

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Table 4. Efficacy in All Patients and Key Subgroups

Patient Subgroup	n	CR, n (%)	PR, n (%)	ORR (95% CI), %	mPFS (95% CI), mo	OS events, n	mOS (95% CI), mo
All patients	615	3 (0.5)	65 (10.6)	11.1 (8.7, 13.8)	2.7 (2.1, 2.8)	312	11.1 (8.9, 12.9)
OAK-like population	406	3 (0.7)	52 (12.8)	13.5 (10.4, 17.3)	2.8 (2.7, 3.9)	181	13.7 (11.6, 15.5)
CNS metastases	89	0	5 (5.6)	5.6 (1.8, 12.6)	1.4 (1.3, 1.5)	58	5.1 (4.1, 8.5)
Renal impairment	78	0	9 (11.5)	11.5 (5.4, 20.8)	3.1 (2.6, 5.2)	38	13.0 (8.5, 17.0)
ECOG PS 2	61	0	2 (3.3)	3.3 (0.4, 11.3)	1.7 (1.4, 2.8)	46	3.5 (1.9, 5.1)
Prior anti–PD-1 therapy	39	0	1 (2.6)	2.6 (0.1, 13.5)	1.6 (1.3, 2.9)	23	6.2 (3.5, 15.0)
Autoimmune disease	30	0	3 (10.0)	10.0 (2.1, 26.5)	2.9 (1.4, 4.2)	18	10.1 (6.5, 14.1)

CR, complete response; mPFS, median progression-free survival; PR, partial response.

Ardizzoni A. ESMO 2019

AID and ICI: Clinical Trial Data

Safety and efficacy of **atezolizumab** in patients with autoimmune disease: subgroup analysis of the **SAUL** study in locally advanced/metastatic **urinary tract carcinoma**

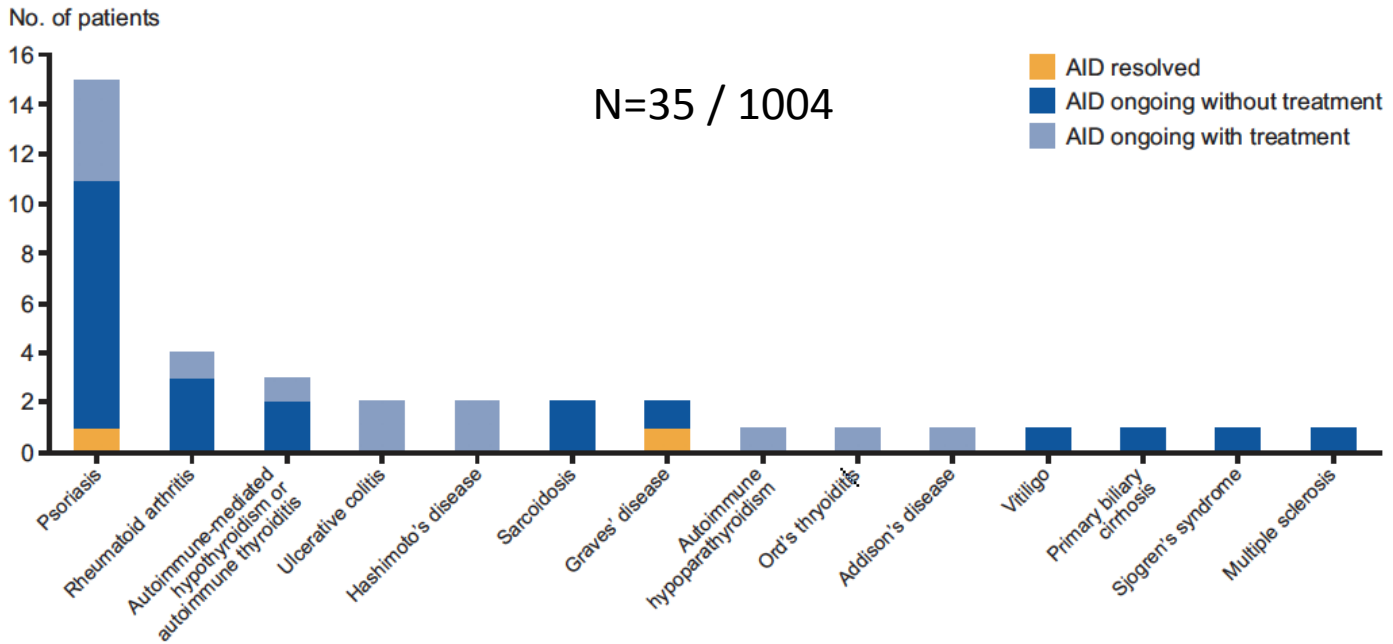
Patients with locally advanced/metastatic urothelial or non-urothelial carcinoma of the urinary tract, including the following populations ineligible for IMvigor211[5]:

- ECOG PS 2
- Progression on prior non-platinum treatment
- Creatinine clearance ≥15 mL/min
- Treated asymptomatic CNS metastases
- Steroid treatment ongoing at baseline
- Stable controlled AID
- HIV-positive status

→ **Atezolizumab 1200 mg IV q3w until loss of clinical benefit, unacceptable toxicity, patient or investigator decision to withdraw from therapy or death**

Primary endpoint:
- Safety

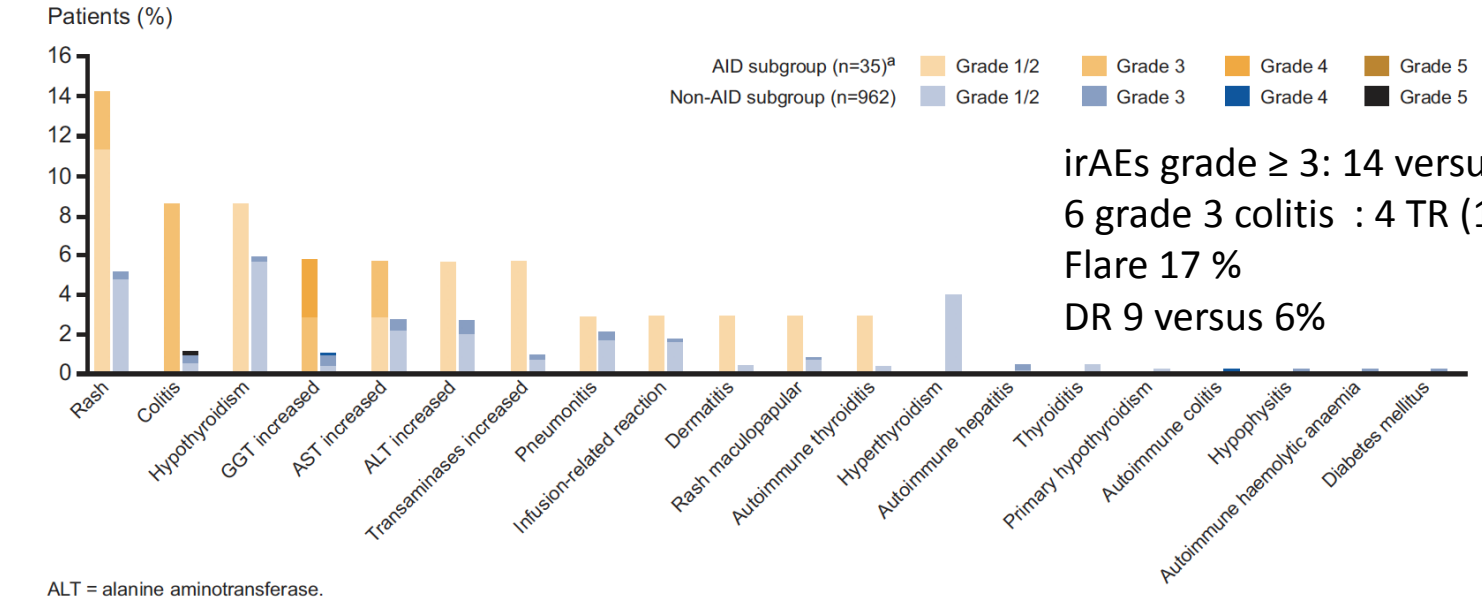
Secondary endpoints:
- OS
- PFS
- ORR
- DCR
- Duration of response



Loriot Y. Asco 2019

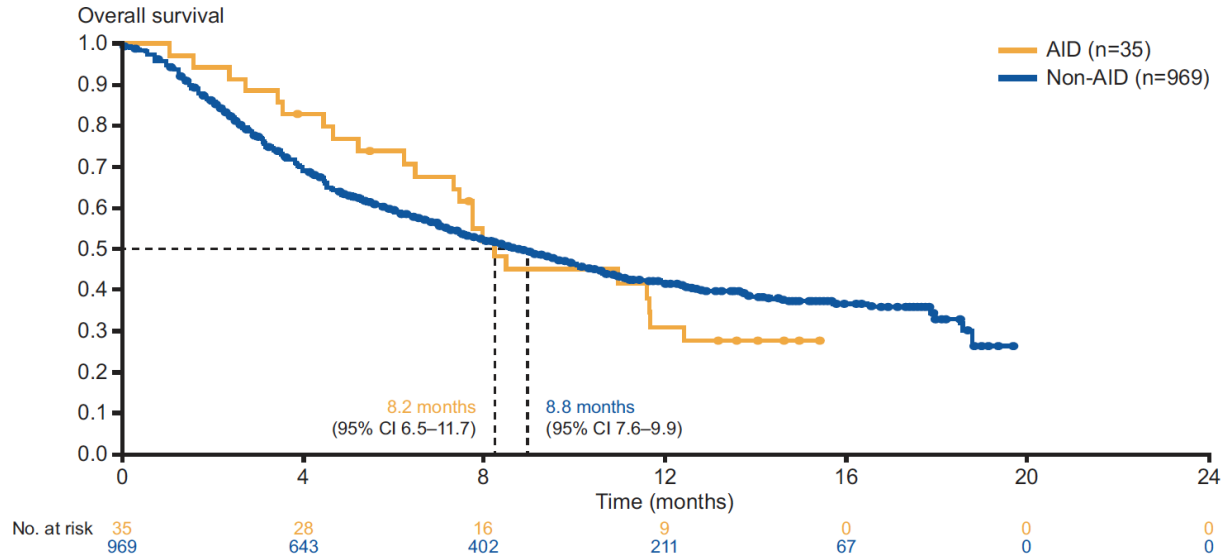
AID and ICI: Clinical Trial Data

Safety and efficacy of atezolizumab in patients with autoimmune disease: subgroup analysis of the **SAUL** study in locally advanced/metastatic urinary tract carcinoma



irAEs grade ≥ 3: 14 versus 6 %
6 grade 3 colitis : 4 TR (1 flare)
Flare 17 %
DR 9 versus 6%

ALT = alanine aminotransferase.
[a]2.8% = 1 patient, 5.7% = 2 patients, 8.5% = 3 patients.



Loriot Y. Asco 2019

AID and ICI : key messages

- Evidence : AID patients were excluded from randomised CT and the level of evidence is based on case series (mostly retrospective) and some phase IV ”real world “ , with numerous limitations : size, heterogeneity (AID, T,..) lack of reporting information (Line, AID and cancer outcomes,..)
  - AID incidence is increasing and prevalence in cancer is not so rare
  - AID are heterogenous diseases (type ? , active ? , IS?)
  - Safety :
    - Flare : manageable, frequent , grade 3/4 4-25% , caution RA and ipilimumab.
    - irAEs : manageable , slightly more frequent, earlier
    - Discontinuation rate : more frequent
  - Efficacy:
    - ORR similar
    - PFS/ OS :
      - similar as non AID’s population
      - Lower in case of IS
  - Ongoing phase 1 helpful?
  - Need for a wide international register

AID and ICI: Recommendations

ICIs May Be Considered
1. Consult with appropriate autoimmune subspecialist
2. Low level of or no immunosuppression with good control of underlying autoimmune disorder
3. Patient informed consent

Avoid ICIs
1. Autoimmune neurologic or neuromuscular disease
2. Life-threatening autoimmune disease
3. Patients with poor control of autoimmune disease OR requiring high doses of immunosuppressants for control

=> To put in perspective with the expected beneficial effect of ICI

Kennedy L.C. JNCCN, 2019

Discussion plan

- Autoimmune disease(AID) and ICI
- HIV
- Organs Transplants
- Brain Metastasis
- Elderly
- …

HIV and cancer: Considerations

- 1.8 million people newly infected in 2017 (2018 Belgium 882)
- ART are effective leading to near normal life expectancy
- Persistence of virus integrated CD4 + T cells lead to chronic inflammation
- Incidence of cancer remain elevated and for some is more frequent in this population (1)

Cancer	Estimated No. of Cases/Yr in the United States among Persons with AIDS†	SIR after Combination ART in the United States‡	Role of Immunosuppression from HIV Infection	Etiologic Virus	Other Causative Factors
AIDS-defining					
Non-Hodgkin's lymphoma	1194	11.5	++ to ++++ for different types	EBV§	
Kaposi's sarcoma	765	498.1	+++	KSHV	
Cervical cancer	106	3.2	+	HPV	Tobacco
Non–AIDS-defining					
Lung cancer	376	2.0	+	?	Smoking, pulmonary infections
Anal cancer	313	19.1	+	HPV	
Hodgkin's lymphoma	179	7.7	++	EBV	
Oral cavity and pharyngeal cancer	100	1.6¶	0 to + for different types	HPV	Tobacco, alcohol
Hepatocellular carcinoma	117	3.2	0 or +	HBV, HCV	Alcohol, other hepatic insults
Vulvar cancer	15	9.4	+	HPV	
Penile cancer	13	5.3	+	HPV	

- Lung cancer is the leading cause of cancer related deaths in patient receiving ART
- 2017 ,a phase 1 (BMS anti-PDL-1compound) showed no unexpected safety signal and appeared to enhance HIV-1–specific immunity (2)

1. Longo D.L. NEJM , 2018
2. Gay C.L . J Infect Dis , 2017

HIV and ICI : Case Series / Systematic Review

Safety and Efficacy of Immune Checkpoint Inhibitor Therapy in Patients With HIV Infection and Advanced-Stage Cancer
A Systematic Review

Table 2. Select Studies of Immune Checkpoint Inhibitor Therapy in Patients With Advanced-Stage Cancer

Source	Sample Size	Study Type	Tumor Type (No.)	ICI Therapy (No.)	Adverse Events (No.)	HIV Load	CD4 Cell Count	Best Response
Ostios-Garcia et al,[20] 2018	7	Retrospective case series	NSCLC (7)	Pembrolizumab (5), nivolumab (2)	Grade 1 arthralgia (1), grade 1 fatigue (1), grade 1 headache (1), grade 1 chest pain (1), grade 2 arthralgia (2)	Remained suppressed[a]	Stable[b]	Stable disease (2), PR (3), PD (2)
Samri et al[28] 2017	12	Retrospective case series	NSCLC (12)	Nivolumab (12)	Grade 1 hepatitis (1), hypereosinophilia (1)	Remained suppressed[c]	Stable	Stable disease (4), PR (3), PD (5)
Heppt et al,[17] 2017	10	Retrospective case series	Melanoma (9), Merkle cell carcinoma (1)	Nivolumab (1), pembrolizumab (3), ipilimumab (3), ipilimumab plus nivolumab (3)	Grade 1 pneumonitis (1), grade 1 fatigue (1)	Remained suppressed	Stable[d]	PR (1), CR (2), PD (6), NR (1)
Park et al,[27] 2018	8	Retrospective case series	HNSCC (3), melanoma (2), cutaneous SCC (2), SCC (1)	Anti-PD-1 (7), ipilimumab plus nivolumab (1)	Anti-PD-1, grade 1 fatigue (4), grade 1 rash (2); ipilimumab plus nivolumab, grade 3 hepatitis (1)	Remained suppressed	Upward trend[e]	PR (4), CR (1), PD (2), NR (1)
Galanina et al,[26] 2018	8	Retrospective case series	Kaposi sarcoma (8)	Nivolumab (8)	No grade ≥2 toxic effects reported[f]	Pretreatment median (range): 20.5 /mL (0-116 706 mL); posttreatment median (range): 64 /mL (0-1 390 000 mL)	Upward trend (mean increase by 80.5 /μL)	PR (4), CR (1), stable disease (3)
Uldrick,[29] 2017	21	Prospective clinical trial	Primary effusion lymphoma (2), Kaposi sarcoma (1), diffuse large B-cell lymphoma (1), anal cancer (5), head and neck (5), SCC (1), NSCLC (2), HCC (1), transitional cell carcinoma (1), pancreatic cancer (1), cholangiocarcinoma (1)	Pembrolizumab (21)	Most treatment-emergent AEs were grades 1-2 (93%),[g] immune-related AEs, grade 1 hypothyroidism (2), grade 1 ALT increase (1), grade 1 joint stiffness (1), grade 1 pneumonitis (1), grade 2 pneumonitis (2), grade 2 hypothyroidism (4), grade 3 ALT increase (1)	Remained suppressed	Upward trend	NR

HIV Load stable to upward trend
CD4 cell count stable
irAEs : 9%
No unexpected safety signal

Cook M.R. Jama Oncol, 2019

HIV and ICI : Case series / Systematic review

Safety and Efficacy of Immune Checkpoint Inhibitor Therapy in Patients With HIV Infection and Advanced-Stage Cancer
A Systematic Review

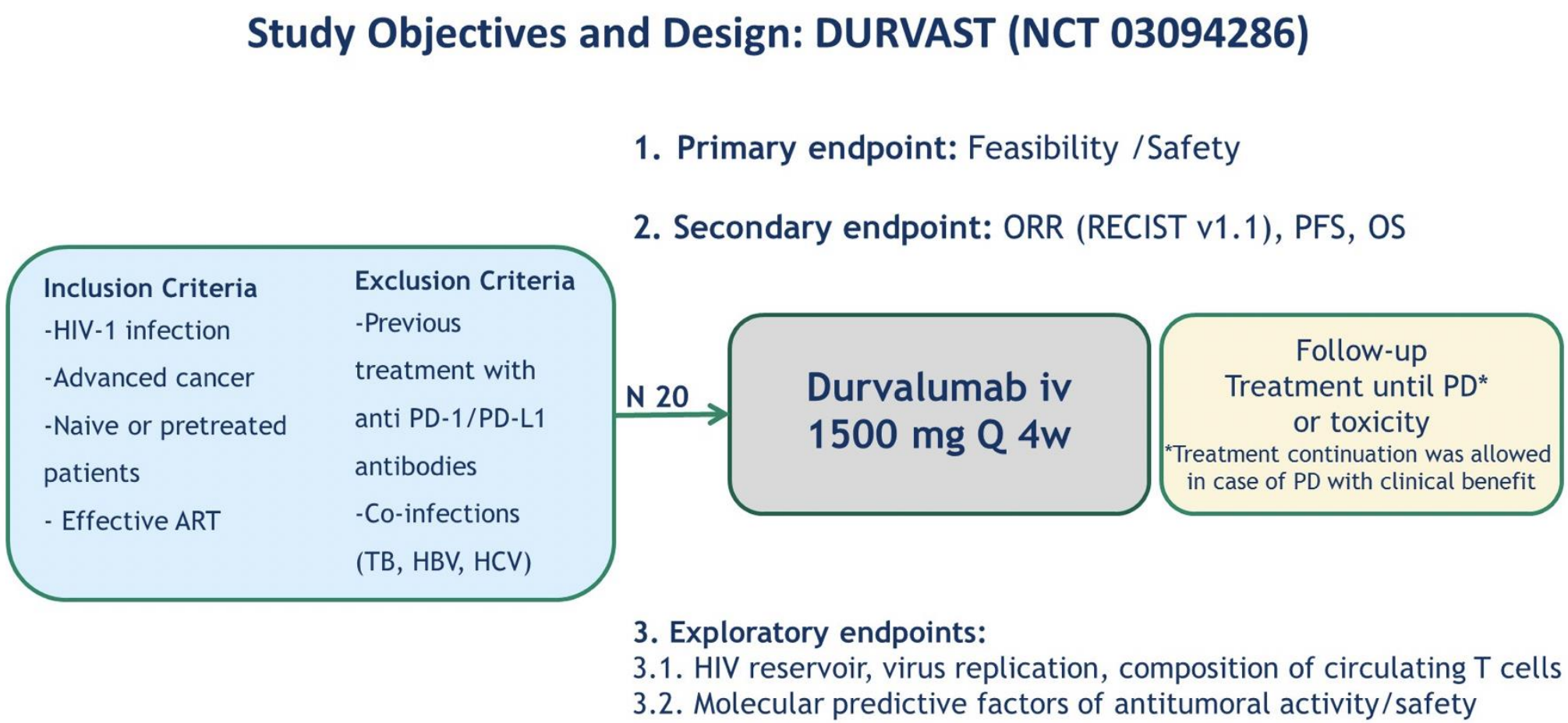
Table 3. Objective Response Rates per Disease Type

Disease Type	No. of Patients With Known Response	Patients With Previous Systemic Treatment, No. (%)	Response (No. of Patients)	ORR, %[a]
NSCLC	23	19 (83)	CR (1), PR (6), stable disease (8), PD (8)	30
Melanoma	11	5 (45)	CR (1), PR (2), PD (8)	27
Kaposi sarcoma	8	Unknown[b]	CR (1), PR (4), PD (3)	63
Classic Hodgkin lymphoma	2	2 (100)	CR (1), PR (1)	NA
Merkel cell carcinoma	1	1 (100)	CR (1)	NA

Similar efficacy

Cook M.R. Jama Oncol, 2019

HIV and ICI: Clinical Trial



Gonzalez-Coa M. ASCO, 2019

HIV and ICI: DURVAST trial

Baseline characteristics

	n= 20
Age, median (range), y	54 (30-73)
Male sex, n (%)	16 (80%)
ECOG PS 0-1, n (%)	19 (95%)
Non smokers, n (%)	2 (10%)
Number of previous lines, median (range)	1 (0-3)
0, n (%)	8 (40%)
1, n (%)	8 (40%)
≥2, n (%)	4 (20%)
Tumor type, n (%)	
NSCLC Non Squamous	11 (55%)
NSCLC Squamous	3 (15%)
SCLC	1 (5%)
Melanoma	2 (10%)
Anal carcinoma	2 (10%)
Bladder carcinoma	1 (5%)
PD-L1 (TPS%)*, n (%)	
Negative (<1%)	11 (55%)
Low (1-49%)	1 (5%)
High (>50%)	3 (15%)

	n=20
HIV group transmission, n (%)	
IDU	8 (40%)
MSM	6 (30%)
Heterosexual	4 (20%)
Unknown	2 (10%)
Duration of HIV infection years, median (range)	16 (3-32.9)
Duration of ART years, median (range)	10 (2-20)
Plasma viral load (pVL) ≤50 copies of HIV RNA/ml	20 (100%)
Basal CD4 count , cells per mm3, n (%)	
100-199	1 (5%)
200-350	8 (40%)
>350	11 (55%)
ART therapy, n (%)	
NRTIs + INSTI	14 (70%)
NRTIs + NNRTIs	6 (30%)

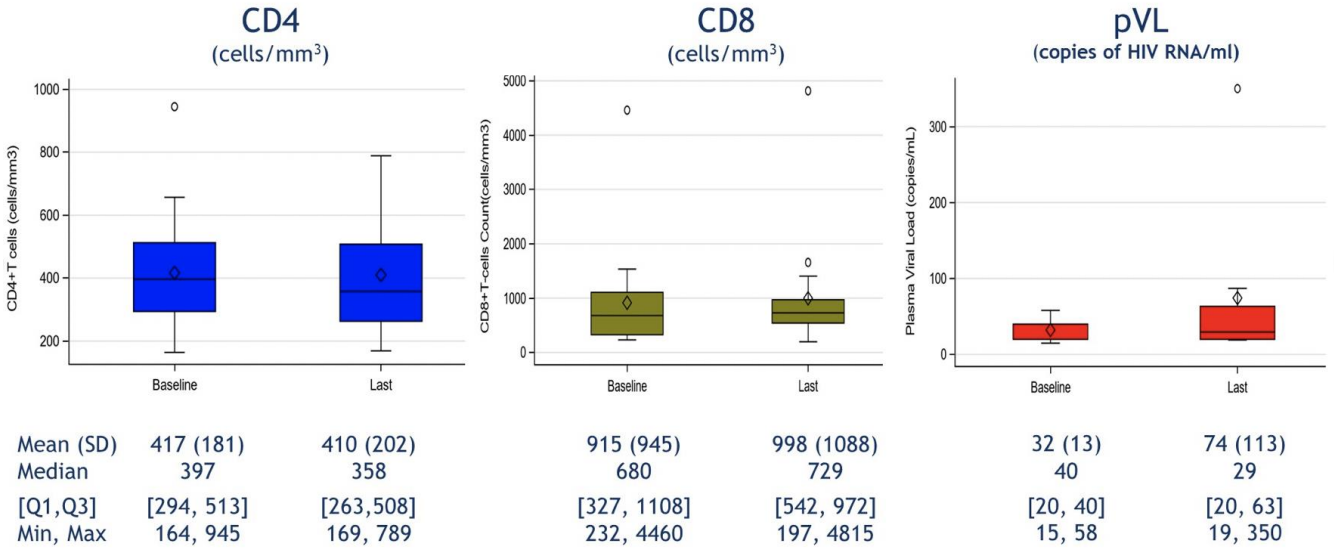
Gonzalez-Coa M. ASCO, 2019

HIV and ICI: DURVAST trial

Adverse Events (AEs)

Non-Drug related AEs, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any	23 (75%)	10 (50%)	1 (5%)	1 (5%)	2 (10%)
Respiratory infection	1 (5%)	1 (5%)	1 (5%)	0	1 (5%)
Neurological	0	0	0	0	1 (5%)
Arterial ischemia	0	0	0	1 (5%)	0
Hypotension	0	3 (15%)	0	0	0
Fever	2 (10%)	2 (10%)	0	0	0
Arthromyalgia	11 (55%)	2 (10%)	0	0	0
Asthenia	9 (45%)	2 (10%)	0	0	0
Nausea-vomiting	5 (25%)	0	0	0	0
Constipation	2 (10%)	1 (5%)	0	0	0
Disphagia	2 (10%)	1 (5%)	0	0	0
Diarrhoea	2 (10%)	2 (10%)	0	0	0
Skin AEs	3 (15%)	0	0	0	0
Neutropenia	0	1 (5%)	0	0	0

T cell count and plasma viral load

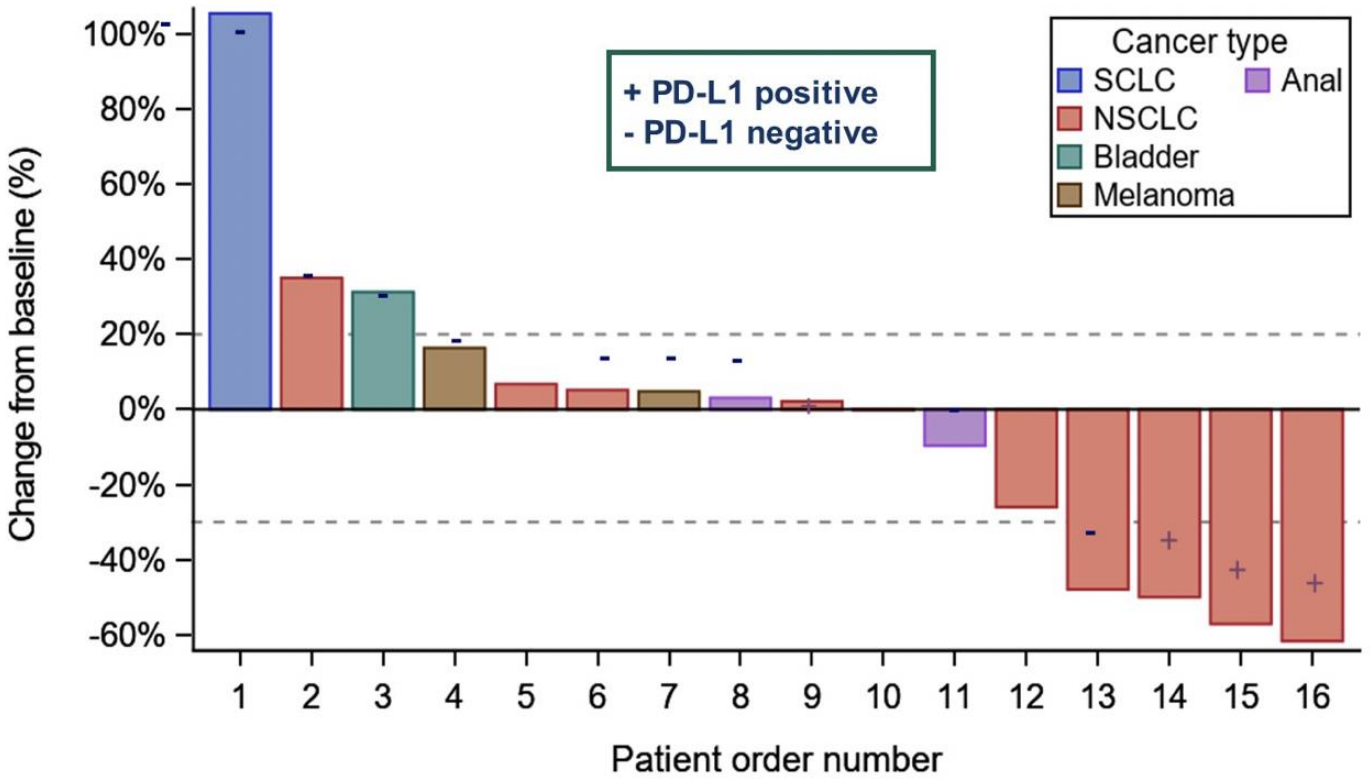


	CD4 Baseline	CD4 Last	CD8 Baseline	CD8 Last	pVL Baseline	pVL Last
Mean (SD)	417 (181)	410 (202)	915 (945)	998 (1088)	32 (13)	74 (113)
Median	397	358	680	729	40	29
[Q1,Q3]	[294, 513]	[263,508]	[327, 1108]	[542, 972]	[20, 40]	[20, 63]
Min, Max	164, 945	169, 789	232, 4460	197, 4815	15, 58	19, 350

Gonzalez-Coa M. ASCO, 2019

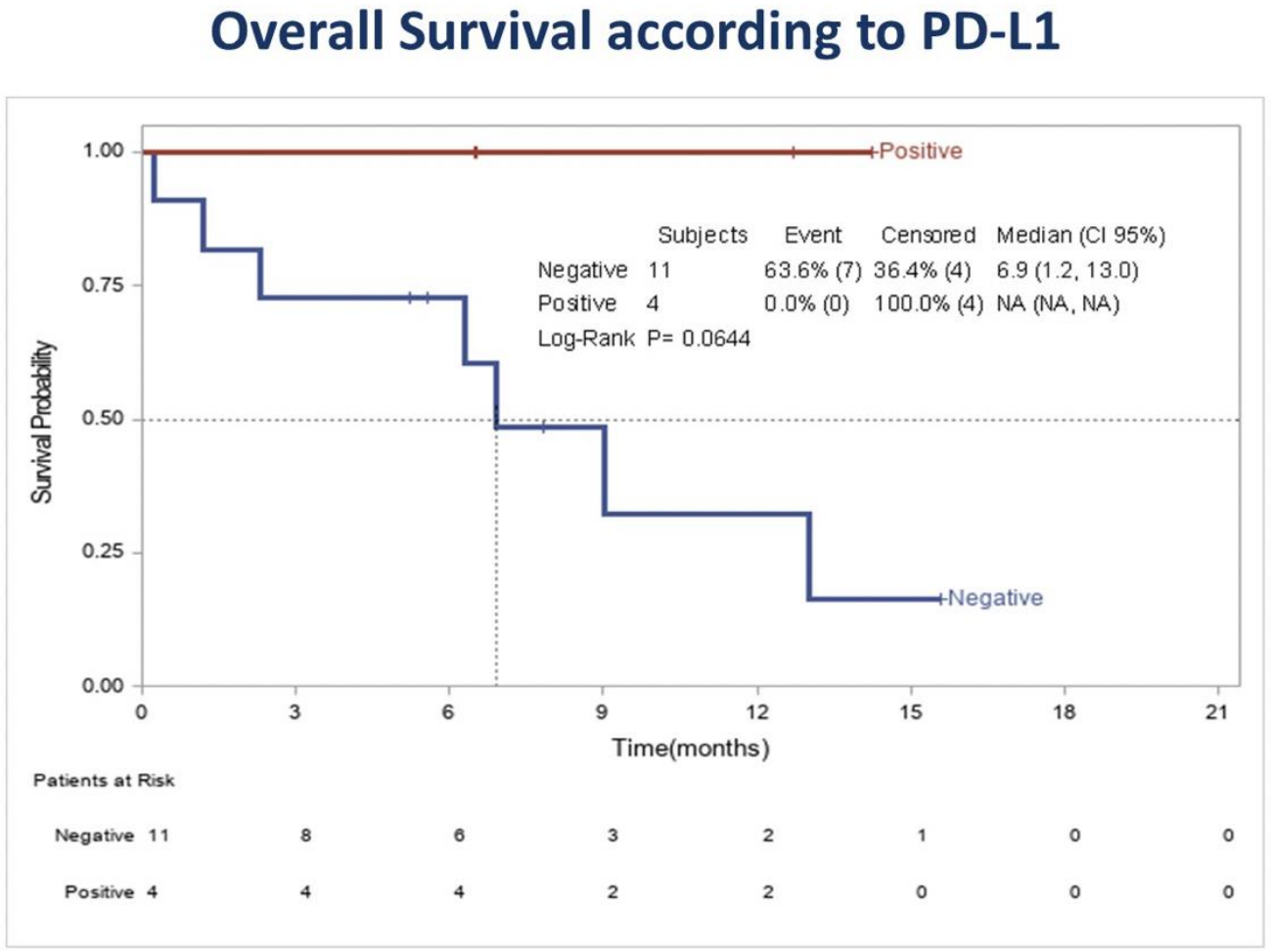
HIV and ICI: DURVAST trial

Response	All (n=20)
PR, n (%)	4 (20%)
SD, n (%)	5 (25%)
DCR, n (%)	8 (40%)
PD, n (%)	11 (55%)
RECIST	7 (35%)
NE	4 (20%)
DOR, months median (range)	6.5 (3.5-17 +)



Gonzalez-Coa M. ASCO, 2019

HIV and ICI: DURVAST trial



Gonzalez-Coa M. ASCO, 2019

HIV and ICI : Key messages / recommendations

- Evidence : Case series , systematic review and phase II
- For ART treated patient with controlled viral load and count of CD-4 over 100/ mm^3
  - ICI seems to be safe
    - No new signal
    - CD4 T cells count at least stable
    - Viral load stable
  - Similar efficacy in NSCLC

Discussion plan : ICI and “excluded patients”

- Autoimmune disease(AID)
- HIV
- Organs Transplants
- Brain Metastasis
- Elderly
- …

Organs transplants (OT): considerations

- OT and risk of cancer
  - Immunosuppression (organ rejection)
  - Aging of this population
  - Grafting in the context of Tumor (relapse)
- OT number doubled between 2003 and 2017 : 56.263 => 102.664 (1)

1. www.transplant-observatory.org

OT and ICI : Case series and systematic review

- Two recent systematic review (1,2)
- Complexity of the data and interpretation
  - Heterogeneity
    - Which transplant and for which reason
    - Which immunosuppression
    - Which Cancer
    - Which ICI
- Data of importance
  - Safety
    - Organ Rejection (OR) rate
      - Organ failure ?
      - irAE ?
      - decrease of immunosuppression ?
      - Leading to death ?
  - Efficacy under immunosuppression ?

1. De Bruyn P. Cur Op Oncol, 2019
2. Fisher J. J Am Acad Dermatol, 2019

OT and ICI : Systematic review

Table 1. Patient characteristics

Characteristics	Total	Liver transplant	Kidney transplant
Organ transplant	48	19	29
Tumor type			
Cutaneous melanoma	27	7	20
Uveal melanoma	3	1	2
NSCLC	3	1	2
HCC	10	10	0
cSCC	3	0	3
ADCD	1	0	1
UC	1	0	1
Immunotherapy			
Nivolumab	18	10	8
Pembrolizumab	12	5	7
Ipilimumab	11	3	8
Ipilimumab/nivolumab	4	0	4
Ipilimumab/pembrolizumab	3	1	2
Organ transplant outcome			
Organ preservation	28	12	16
Organ rejection with organ failure	15	5	10
Organ rejection without organ failure	5	2	3
Antitumor response/final outcome			
CR	3	2	1
PR	12	2	10
SD	2	0	2
Disease control rate	17	4	13
PD	22	8	14
Death from organ failure before evaluation	4	4	0
UK	5	3	2

ADCD, adenocarcinoma of the duodenum; CR, complete response; cSCC, cutaneous squamous-cell carcinoma; HCC, hepatocellular carcinoma; NSCLC, nonsmall cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; UC, urothelial carcinoma; UK, unknown.

- Wide heterogeneity and few reports => Descriptive data
- Efficacy :
  - Global DCR 35 %
  - Liver transplant DCR 21%, recurrent HCC 0% !
  - Kidney transplant DCR 45 %
- Safety
  - Liver transplant
    - OR rate : 37 %
    - Organ failure rate : 26%
    - OR rate leading to death : 21 %
  - Kidney transplant
    - OR rate : 49 %
    - Organ failure rate : 34%
- 10 patients with DCR and no graft rejection
- Data by ICI (safety / efficacy) : insufficient to conclude
- Data by Immunosuppression type and dosage : insufficient to conclude

De Bruyn P. Cur Op Oncol, 2019

OT and ICI : key message

- Evidence from Case series / systematic review
  - Frequent OR leading to failure
    - Ability to compensate ? (liver / heart/ lung)
  - DCR without OR observed despite ongoing immunosuppression => need for understanding underlying mechanisms
  - Decision should be taken considering the expected beneficial effect of ICI
    - liver transplant and ICI use in the context of recurrent HCC : no benefit
  - Need for a multidisciplinary team
  - Need for wide register

Discussion plan : ICI and CT “excluded patients”

- Autoimmune disease(AID)
- HIV
- Organs Transplants
- Brain Metastasis
- Elderly
- …

Brain M+ and ICI: Considerations

- High frequency : M+ NSCLC up to 40 % , Melanoma up to 50%
- Specific Tumor microenvironment
- Underrepresented in pivotal trials
  - Discrepancy between trials
- Brain metastasis categories
  - Treated
  - Untreated (Active)
    - Stable without corticosteroids
    - Stable with corticosteroids
    - Symptomatic
- Concurrent RT and ICI ?

Brain M+ and ICI: Clinical Trials

Ref.	Phase	Histology	ICI / Brain M+ categories	N	Brain DCR % / Extracranial DCR %	Brain ORR % / Extracranial DCR %	AE grade ≥ 3 % / AE neuro * grade ≥ 3 %	OS
Margolin, Lancet oncol, 2012	II (subpop)	Melanoma	Nivo / Asympto Nivo /Sympto controlled CS	51 21	24 vs 28 10 vs 5	16 vs 14 5 vs 5	NR/ 4 NR/ 0	OS 12 m : 31% OS 12 m : 12%
Tawbi,NEJM,2018	II	Melanoma	Nivo + Ipi untreat.	94	58 vs 56	50 vs 50	55 / 7	OS 12 m : 81%
Long, Lancet Oncol,2018	II r	Melanoma	Nivo+ Ipi asympto untreat. Nivo Asympto untreat. Nivo sympto	36 27 16	57 vs 60 21 vs 31 19 vs 33	46 vs 57 21 vs 29 6 vs 25	63 /6 16 / 0 13 / 19	OS 12 m: 60% OS 12m : 60% OS 12m: 30 %
Golberg, Lancet Oncol, 2016 JCO , 2018 (OS)	II	Melanoma NSCLC	Pembro Asympto untreat Pembro Asympto untreat	18 18	NR	22 vs 22 33 vs 33	6 / 6 10 / 10	OS 2 Y : 31%
Flippot, JCO, 2019 (subgroup)	II	RCC	Nivo untreated Nivo treated asympto	39 34	50 vs 51	12 (< 10mm) vs 21	10 / 12 15 / NR	OS 12m : 66.7% OS 12m: 58.8%

* AE nervous system : headache , dizziness

- Observations from phase II
  - Brain M+ versus extracranial M+ : same range of efficacy
  - No specific / new safety signal
  - Lower control rate (IC and EC) and lower OS of symptomatic metastasis (CS?)

Brain M+ and ICI: register retrospective analysis

- ORR
  - BM + : 20.6%
  - BM - : 22.7%
- DCR
  - BM+ : 43%
  - BM- : 52 % (p: 0.024)
- Active BM :
  - 13 % CS > 10mg/d prednisolone
  - IC ORR : 27 %, IC DCR : 60.3%
  - Brain PD (Active vs Stable)
    - 54,2% vs 30% (p< 0.001)

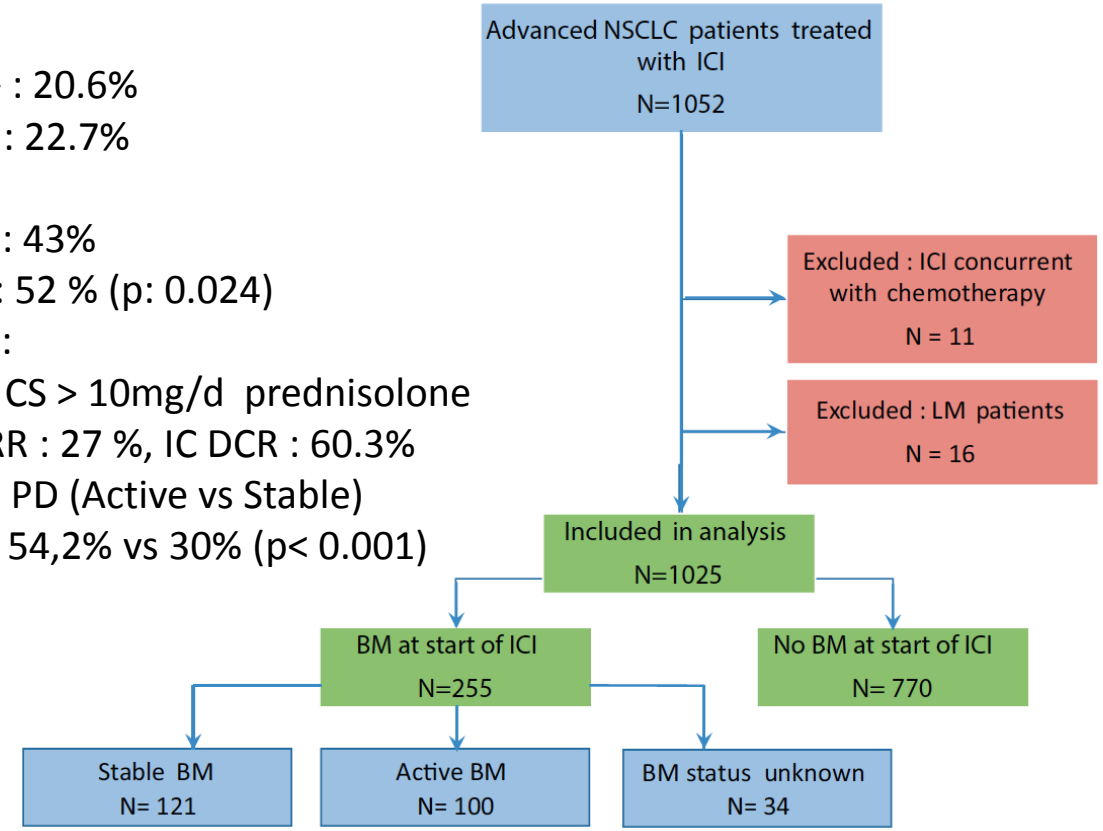
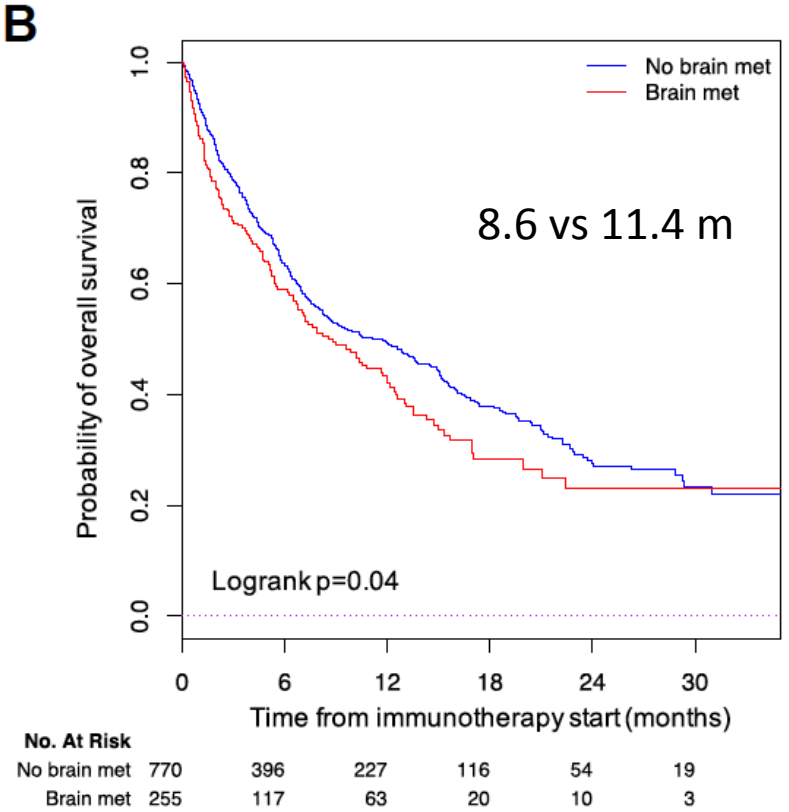


Figure 1. CONSORT diagram: patient inclusion. ICI: immune checkpoint inhibitor; LM: leptomeningeal metastasis; BM: brain metastasis.



- Stable BM : Cranial irradiation within 3 months before starting ICI is associated with a superior OS (HR = 0.52 , p:0.04)

Hendriks L. JTO, 2019

Brain M+ and ICI: “Concurrent” Stereotactic RS (SRS)

Effectiveness and safety of “real” concurrent stereotactic radiotherapy and immunotherapy in metastatic solid tumors: a systematic review

Salvatore Trapani[a], Moana Manicone[b], Angelica Sikokis[a], Nunziata D’Abbiero[b], Francesco Salaroli[b], Giovanni Ceccon[b], Sebastiano Buti[a,*]

[a] Medical Oncology Unit, University Hospital of Parma, Parma, Italy
[b] Radiotherapy Unit, University Hospital of Parma, Italy

(1)

Brain SRS : 10 case series and 1 phase 1 study
Mostly melanoma

- Data suggest that concurrent SRS and ICI seem to be safe and effective.
  - Radionecrosis range 8.7-16.7 % , comparable SRS alone 9% at 1Y, 18% at 2Y (2)

- Concurrent (versus non concurrent) administration of SRS and immunotherapy leads to better outcomes in terms of response and survival, without increasing toxicity

1. Trapani S. Crit Rev in Oncol, 2019
2. Minniti. G. J Neurooncol, 2014

Brain metastasis and ICI: Key message

- Evidence from phase II and register
  - ORR similar than Extracranial
  - Symptomatic BM worse outcome
  - BM active experienced more PD
  - Irradiated Stable BM within three Months do better
  - Concurrent SRS is safe and leads to better outcome then non-concurrent

Discussion plan : ICI and CT “excluded patients”

- Autoimmune disease(AID)
- HIV
- Organs Transplants
- Brain Metastasis
- Elderly
- …

Elderly and ICI : Considerations

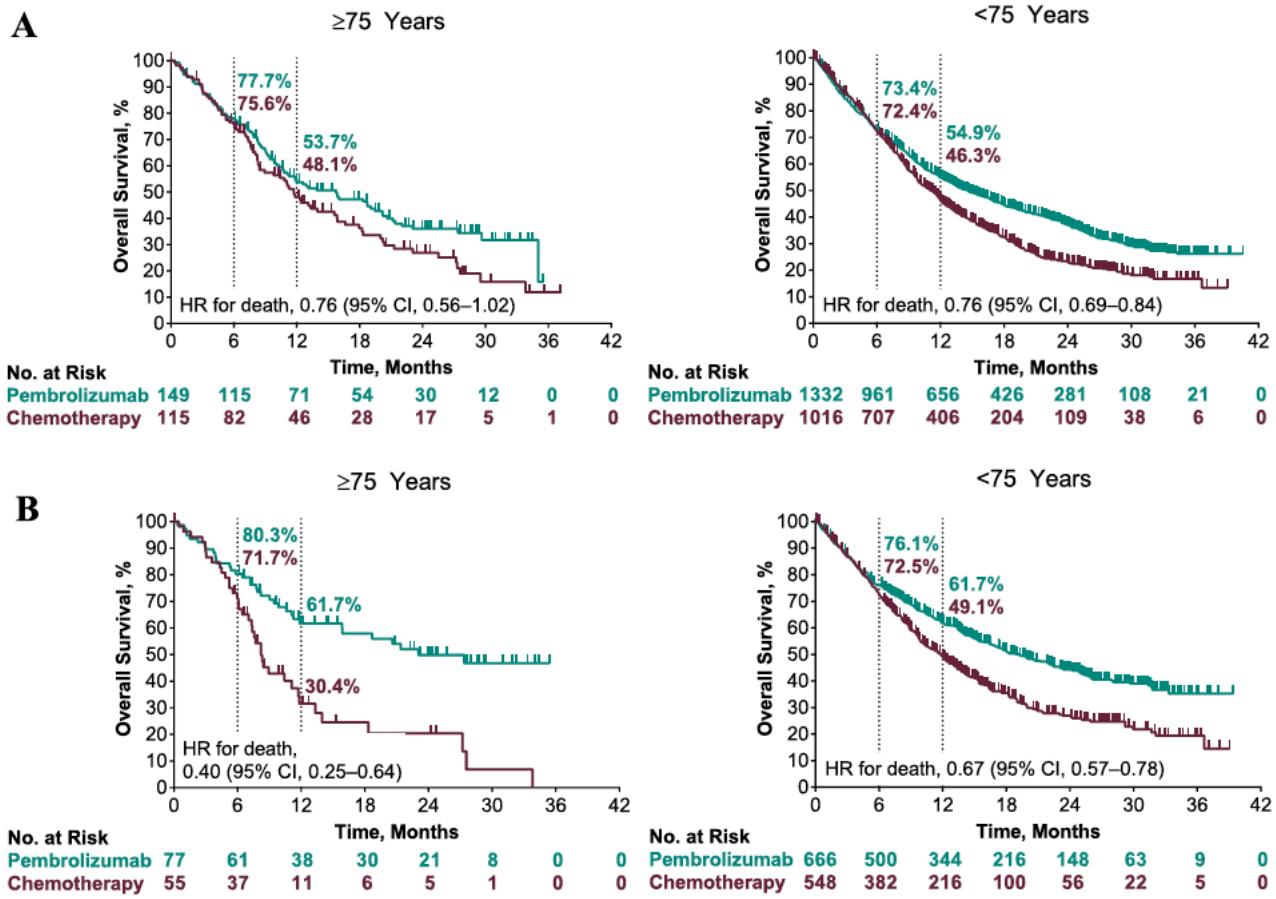
- Elderly ?
  - Age was is older: 65, 70, 75 ?
  - Disability, Frailty, Comorbidity
    - Which scale ? G8 , PS ?
- 2035 : due to aging it ‘s estimated and projected that 67 % of newly diagnosed cancer will be over 65 (2012 : 57%) (1)
- “Immunosenescence” or “aging-associated immune remodeling »

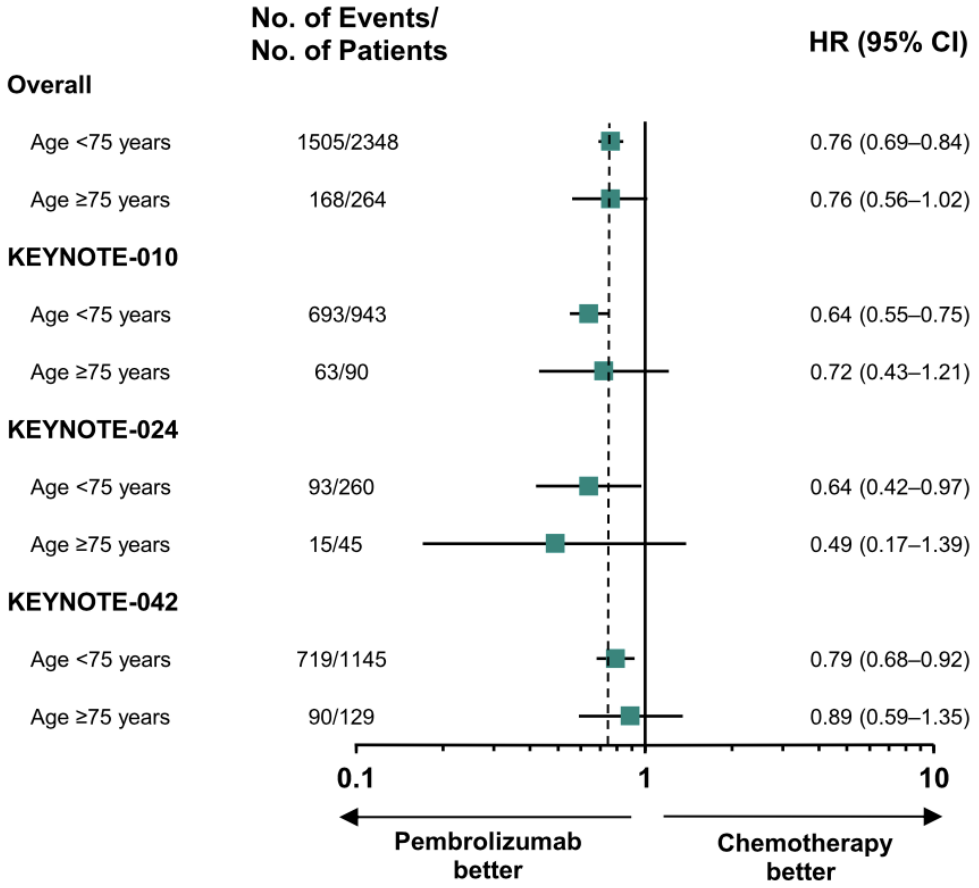
1. Pilleron S et al. Int J Cancer, 2019

Elderly and ICI: Clinical Trial

- Safety (≥ 75 vs < 75 y)
  - AE ≥ 3 : 24 vs 17 %
  - AE grade 5 0 vs 0.3%
  - irAEs ≥ 3 : 9.4 vs 7.1 %

Safety and efficacy of pembrolizumab monotherapy in elderly patients with PD-L1–positive advanced non–small-cell lung cancer: Pooled analysis from the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 studies





Noasaki K. Lung Cancer, 2019

Elderly and ICI: meta analysis

Table 1 Characteristics of included studies. Abbreviations: NSCLC (non-small lung cancer); S-NSCLC (squamous non-small lung cancer); NS-NSCLC (non-squamous non-small lung cancer); RCC (renal cell cancer); H&N (head & neck); NR (not reported); Q (every); W (weeks)

	Study Name	Drug	Phase	Malignancy	First line	Arm 1	Arm 2	Arm 3	Patient' number	Age median	Age range	Age mean	n (%) < 65 y	n (%) ≥ 65 y
Rittmeyer 2016 [33]	OAK	Atezolizumab	3	NSCLC	N	Atezolizumab 1200 mg Q 3 W	Docetaxel 75 mg/m^2 Q 3 W		850	64	33–85	63	453 (53)	397 (47)
Fehrenbacher 2016 [26, 34]	POPLAR	Atezolizumab	2	NSCLC	N	Atezolizumab 1200 mg Q 3 W	Docetaxel 75 mg/m^2 Q 3 W		287	62	36–84	61.5	174 (61)	113 (39)
Brahmer 2015 [5]	Checkmate-017	Nivolumab	3	S-NSCLC	N	Nivolumab 3 mg/kg Q 2 W	Docetaxel 75 mg/m^2 Q 3 W		272	63	39–85	63	152 (56)	120 (44)
Borghaei 2015 [6]	Checkmate-057	Nivolumab	3	NS-NSCLC	N	Nivolumab 3 mg/kg Q 2 W	Docetaxel 75 mg/m^2 Q 3 W		582	62	21–85	NR	339 (58)	243 (42)
Motzer 2015 [4]	Checkmate-025	Nivolumab	3	RCC	N	Nivolumab 3 mg/kg Q 2 W	Everolimus 10 mg daily		821	62	18–88	61.3	497 (61)	324 (39)
Robert 01–2015 [29]	Checkmate-066	Nivolumab	3	Melanoma	Y	Nivolumab 3 mg/kg Q 2 W	Dacarbazine 1000 mg/m^2 Q 3 W		418	65	18–87	62.7	200 (48)	218 (52)
Ferris 2016 [2]	Checkmate-141	Nivolumab	3	H&N	N	Nivolumab 3 mg/kg Q 2 W	Chemotherapy		361	60	28–83	59.1	248 (69)	113 (31)
Herbst 2016 [8]	Keynote-010	Pembrolizumab	2/3	NSCLC	N	Pembrolizmab 2 mg/kg Q 3 W	Pembrolizumab 10 mg/kg Q 3 W	Docetaxel 75 mg/m^2 Q 3 W	1033	NR	NR	62	604 (58)	429 (42)
Robert 06–2015 [9]	Keynote-006	Pembrolizumab	3	Melanoma	N	Pembrolizumab 10 mg/kg Q 2 W	Pembrolizumab 10 mg/kg Q 3 W	Ipilimumab 3 mg/kg Q 3 W	834	NR	NR	60.3	467 (56)	367 (44)

Table 2 Summary of HR for OS by Age

Age	HR (95% CI)
Age < 65 years	0.68 (0.61 to 0.75)
Age ≥ 65 years	0.64 (0.54 to 0.76)

Table 3 Summary of HR for PFS by Age

Age	HR (95% CI)
Age < 65 years	0.73 (0.61 to 0.88)
Age ≥ 65 years	0.74 (0.60 to 0.92)

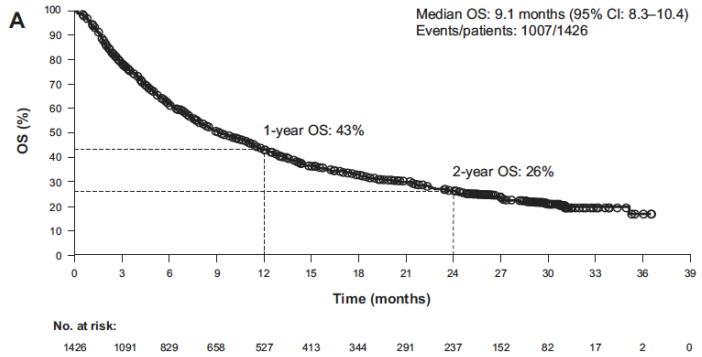
Elias R. J for Immunoth, 2018

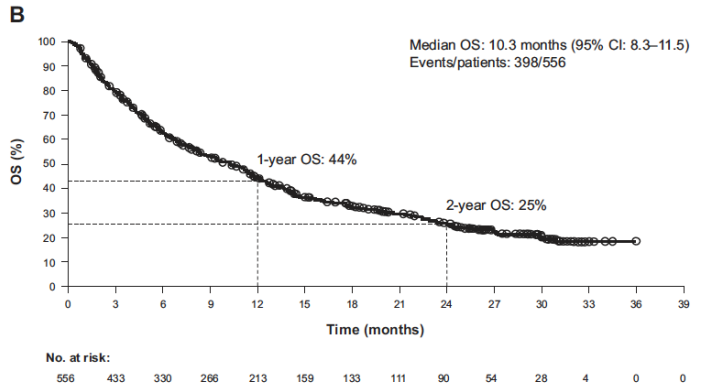
Elderly and ICI : age ≥ 70 and PS 2

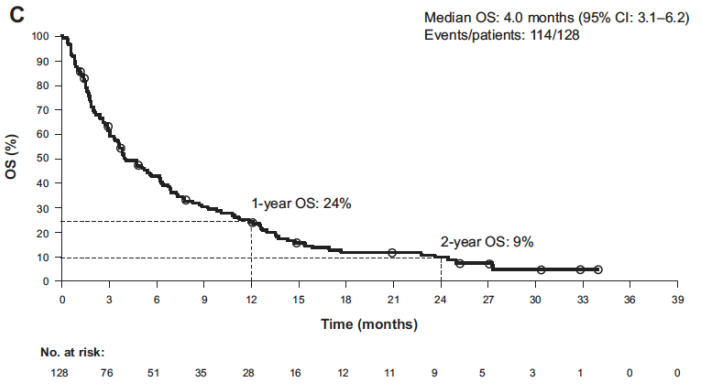
Safety, Efficacy, and Patient-Reported Health-Related Quality of Life and Symptom Burden with Nivolumab in Patients with Advanced Non-Small Cell Lung Cancer, Including Patients Aged 70 Years or Older with Poor Performance Status (CheckMate 153)

Phase III /IV previously treated
N all : 1426 (PS 2 : 128)
N ≥ 70 : 556 patients (PS 2 : 63)

	All	≥ 70	PS 2
OS m	9.1	10.3	4
2Y OS	26 %	25 %	9
AE grade ≥ 3	6 %	6 %	9 %







Spigel D, JTO, 2019

Elderly and ICI: Belgian Real World Data

Real life safety and effectiveness of nivolumab in older patients with non-small cell lung cancer: results from the Belgian compassionate use program

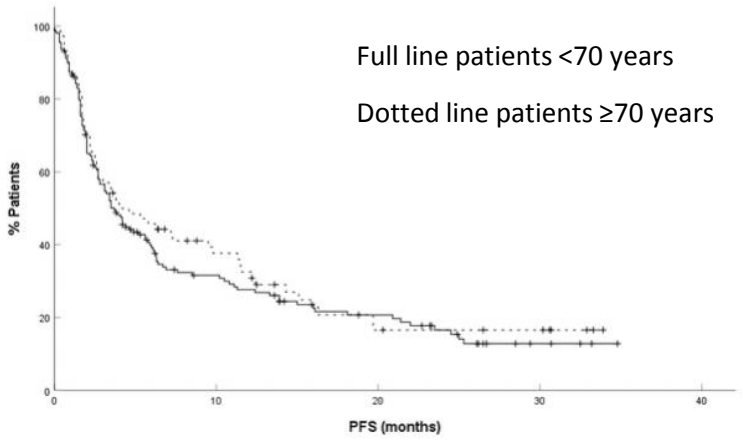
All patients (N=324)	Patients <70 (N=216)	Patients ≥70 (N=108)	Patients ECOG-PS 0-1 (N=224)	Patients ECOG ≥ 2 (N=87)

- Patients characteristics well balanced in both groups
- No difference in Safety
- No difference in OS and PFS by age
- Lower OS and PFS for PS ≥ 2

Joris S. Journal of Geriatric Oncology, accepted

Elderly and ICI: Belgian Real world data

Figure 1a: Progression Free Survival



Full line patients <70 years

Dotted line patients ≥70 years

Figure 1b: Overall Survival

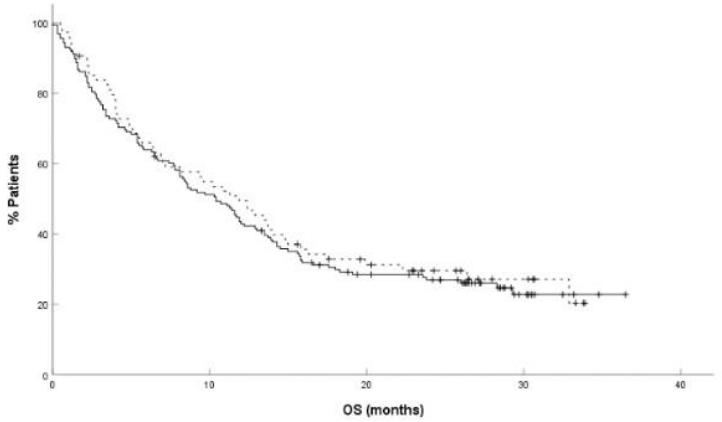
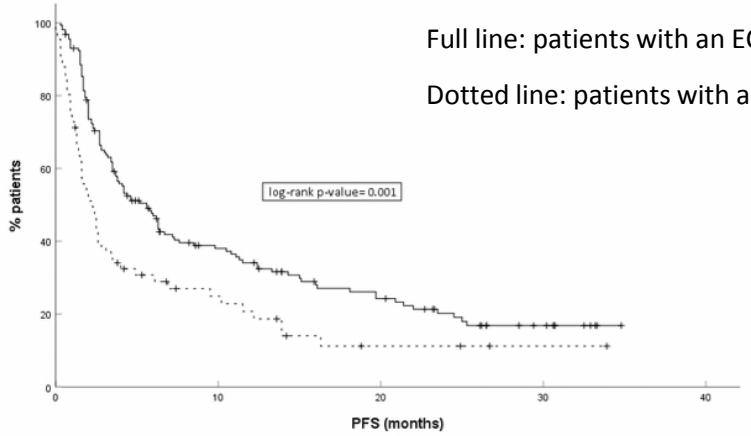


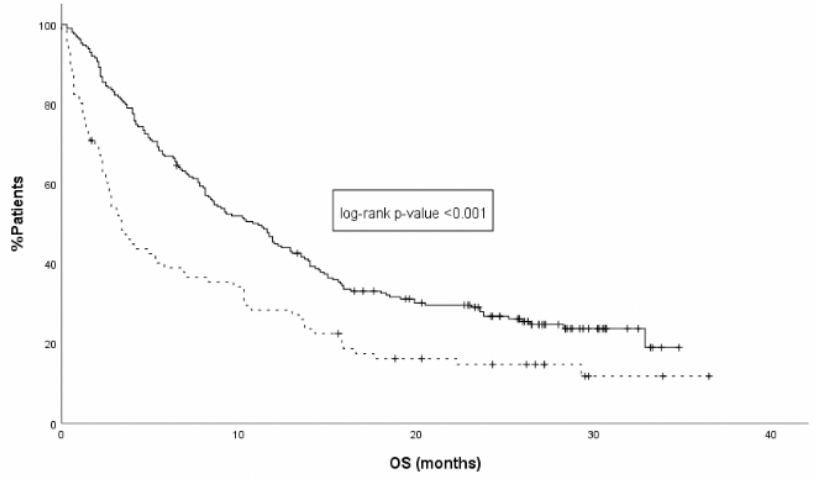
Figure 2a: Progression Free survival



Full line: patients with an ECOG-PS 0-1

Dotted line: patients with an ECOG-PS ≥2

Figure 2b: Overall survival



Joris S. Journal of Geriatric Oncology, accepted

Elderly and ICI : Key messages

- Evidence from meta analysis and real world data
  - Similar efficacy
  - Similar toxicity , no new signal
  - PS 2 : Lower benefit without more toxicity
- Need more prospective trial ?
  - other performance scale?

Thank you for your attention

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