Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Immune Checkpoint Inhibitors in Cancer Patients with Autoimmune Diseases

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Disclosures

- National Institute of Health (K01AI163412)
- Advisory Board/Consultant: ChemoCentryx
- I will be discussing non-FDA approved indications during my presentation

Many questions to answer

- Can we quantify the risk of adverse events
- Can we predict which patients are more likely to develop adverse events
- Can we prevent these adverse events
- How we can optimally manage adverse events
- Availability of clinical decision support tools
- Availability of clinical trials

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Many questions to answer

Can we quantify the risk of adverse events

Annals of Internal Medicine REVIEW

Use of Immune Checkpoint Inhibitors in the Treatment of Patients With Cancer and Preexisting Autoimmune Disease

A Systematic Review

Noha Abdel-Wahab, MD, PhD; Mohsin Shah, MD; Maria A. Lopez-Olivo, MD, PhD; and Maria E. Suarez-Almazor, MD, PhD

- 123 ICI-treated patients with preexisting AIDs in 49 publication
- A broad spectrum of AIDs, mostly PsO and/or PsA, RA, AIT and IBD
- **75% had adverse events**
  - **41% flares of preexisting AIDs**
  - **25% de novo irAEs** (mostly colitis, hypophysitis)
  - **9% both**
  - **No differences were observed in patients with active versus inactive disease**
  - **Patients receiving immunosuppression at ICI initiation seemed to have fewer adverse events**
- **62% were managed with corticosteroids**, 16% required other immunosuppressive therapies
- Adverse events **improved in more than half of patients** without ICI discontinuation (**only 17% discontinued ICI**)
- **Three patients (2.4%) died** because of adverse events

- **Median time to flare was 5.1 week (range 1.4-20 weeks)**
- New onset irAEs and/or Flare in specific AID categories:
  - **PsO/PsA ---- 89%** (n=25/28)
  - **RA ---- 75%** (n=15/20)
  - **IBD ---- 62%** (n=8/13)
  - **AIT---- 45%** (n=5/11)
  - **MS ---- 33%** (n=2/6)
  - **MG ---- 100%** (n=4)
  - **Sarcoidosis ---- 100%** (n=5)

Autoimmunity Reviews 19 (2020) 102687

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Immune checkpoint inhibitors therapies in patients with cancer and preexisting autoimmune diseases: A meta-analysis of observational studies

Wenhui Xie [a], Hong Huang [a], Shiyu Xiao [b], Yong Fan [a], Xuerong Deng [a], Zhuoli Zhang [a,*]

- 619 ICI-treated patients with preexisting AIDs in 14 studies (until August 2019)
- A broad spectrum of AIDs, mostly RA, PsO and/or PsA, AIT and IBD
- 0%-57% had active disease, 14%-73% were receiving immunosuppressants at ICI initiation
- **Pooled incidence rate of any adverse event - 60%** (95% CI 52% to 68%)
- Pooled incidence of ORR- 30% (95% CI 22% to 39%)
    - Median PFS ranged from 3 to 14.4 months
- **Patients receiving immunosuppression compared to those without**
    - **Similar flare risk** (RR = 1.08, 95%CI 0.72–1.62)
    - **Lower ORR** (RR = 0.58, 95%CI 0.26–1.33)
    - Median OS ranged from 10.5 to 22.5 months

- **AID flares - 35%** (95% CI 29% to 41%)
    - Grade 1-2 (80%, 95% CI 74%-86%)
    - **RA ---- 53%**
    - **PsO/PsA ---- 42%**
    - **AIT---- 42%**
    - **IBD---- 34%**

- **De novo irAEs - 33%** (95% CI 24% to 42%)
    - Grade 1-2 (68%, 95% CI 58%-78%)
    - Colitis, thyroiditis, hypophysitis were the most common

Open access Original research
Journal for ImmunoTherapy of Cancer

Increased rates of immunosuppressive treatment and hospitalization after checkpoint inhibitor therapy in cancer patients with autoimmune disease

David Andrew Bender ,[1] Samuel P Heilbroner,[1] Tony J C Wang,[1,2] Catherine A Shu,[2,3] Brigham Hyde,[4] Catherine Spina,[1,2] Simon K Cheng[1,2]

- 284 ICI-treated patients with AIDs & 3230 patients without AIDs
- Cancer types were melanoma and lung
- Patients with AIDs were more likely to receive oral prednisone after ICI (16.7% vs 8.6%, p=0.0048)
- **Patients with AIDs were more likely to receive IV methylprednisolone after ICI (8.4% vs, 3.7% p=0.0012)**
- **Melanoma patients with AIDs were more likely to be hospitalized within 180 days after ICI (24.1% vs 5.8%, RR = 4.2, p<0.0001)**

- Rates of corticosteroids & hospitalization following ICI therapy was **not uniform across AID categories**
  - IV methylprednisolone – 60% of IPF
  - **Hospitalization – 50%-60% in patients with UC, SS, RA and MG**
- **85.4%** of patients with AIDs did not receive the same ICI agent after hospitalization

Annals of Internal Medicine ORIGINAL RESEARCH

Safety and Efficacy of Checkpoint Inhibition in Patients With Melanoma and Preexisting Autoimmune Disease

A Cohort Study

Monique K. van der Kooij, MD; Karijn P.M. Suijkerbuijk, MD, PhD; Maureen J.B. Aarts, MD, PhD; Franchette W.P.J. van den Berkmortel, MD, PhD; Christian U. Blank, MD, PhD; Marye J. Boers-Sonderen, MD, PhD; Jesper van Breeschoten, MSc; Alfonsus J.M. van den Eertwegh, MD, PhD; Jan Willem B. de Groot, MD, PhD; John B.A.G. Haanen, MD, PhD; Geke A.P. Hospers, MD, PhD; Djura Piersma, MD, PhD; Rozemarijn S. van Rijn, MD, PhD; Albert J. ten Tije, MD, PhD; Astrid A.M. van der Veldt, MD, PhD; Gerard Vreugdenhil, MD, PhD; Michiel C.T. van Zeijl, MD; Michel W.J.M Wouters, MD, PhD; Olaf M. Dekkers, MD, PhD; and Ellen Kapiteijn, MD, PhD

- 228 ICI-treated melanoma patients with AIDs & 2546 patients without AIDs
- **Incidence of ≥ grade 3 irAEs was similar in patients with AIDs versus without AIDs**
  - In anti-CTLA-4 treated patients: 30% vs. 30%
  - In anti-PD-1 treated patients: 17% vs. 13%
  - In ICI combination treated patients: 44% vs. 48%
- **Objective response rate was similar in patients with AIDs versus without AIDs**
  - In anti-CTLA-4 treated patients: 10% vs. 16%
  - In anti-PD-1 treated patients: 40% vs. 44%
  - In ICI combination treated patients: 39% vs. 43%
- **Survival did not differ between patients with AIDs versus without AIDs**
  - Median 13 months vs. 14 months

- **Patients with IBD were more prone to anti-PD1 colitis** (19%) vs. those with other AIDs (3%) and vs. those without AID (2%)

- **Anti-PD-1 discontinuation was more frequent in patients with AIDs** (17%) vs. without AIDs (9%)

ASCO
Journal of Clinical Oncology
576 Volume 38, Issue 6

Immune Checkpoint Inhibitor Therapy in Patien With Preexisting Inflammatory Bowel Disease

Hamzah Abu-Sbeih, MD[1]; David M. Faleck, MD[2]; Biagio Ricciuti, MD[3,4]; Robin B. Mendelsohn, MD[2]; Abdul R. Naqash, MD[5]; Justine V. Cohen, DO[6,7]; Maclean C. Sellers, MD, PhD[6,7]; Aanika Balaji, MD[8]; Guy Ben-Betzalel, MD[9]; Ibraheim Hajir, MBChB[1C] Jiajia Zhang, MD, MPH[8]; Mark M. Awad, MD, PhD[4]; Giulia C. Leonardi, MD[4,11]; Douglas B. Johnson, MD, MSCI[12]; David J. Pinato, MD, MRes, MRCP, PhD[13]; Dwight H. Owen, MD, MS[14]; Sarah A. Weiss, MD[15]; Giuseppe Lamberti, MD[16]; Mark P. Lythgoe, MPharm, MBBS[13]; Lisa Manuzzi, MD[16]; Christina Arnold, MD[14]; Wei Qiao, PhD[1]; Jarushka Naidoo, MBBCh[8]; Gal Markel, MD, PhD[9]; Nick Powell, PhD, MBChB[10]; Sai-Ching J. Yeung, MD[1]; Elad Sharon, MD, MPH[17]; Michael Dougan, MD, PhD[6,7]; and Yinghong Wang, MD, PhD[1]

- 102 ICI-treated patients with preexisting IBD (50% each with UC or CD)
- 83% received anti-PD1/PD-L1 & 10% combination ICI
- Median time from last active IBD episode to ICI initiation was **5 years**
- **42%** were not receiving treatment for IBD
- **GI adverse events occurred in 41% after a median of 62 days compared to 11% in patients without IBD (P <0.001)**
  - **Grade 3 or 4 diarrhea in 21%**
- **Four patients (4%) had colonic perforation**, 2 of whom required surgery
- **No GI adverse event-related deaths**

- **Anti-CTLA-4 therapy & IBD involving the colon showed tendency for an increased risk of GI adverse events**

Unpublished Data

A multicenter cohort study of 133 patients with preexisting AIDs treated with ICI combination or single agent ICI

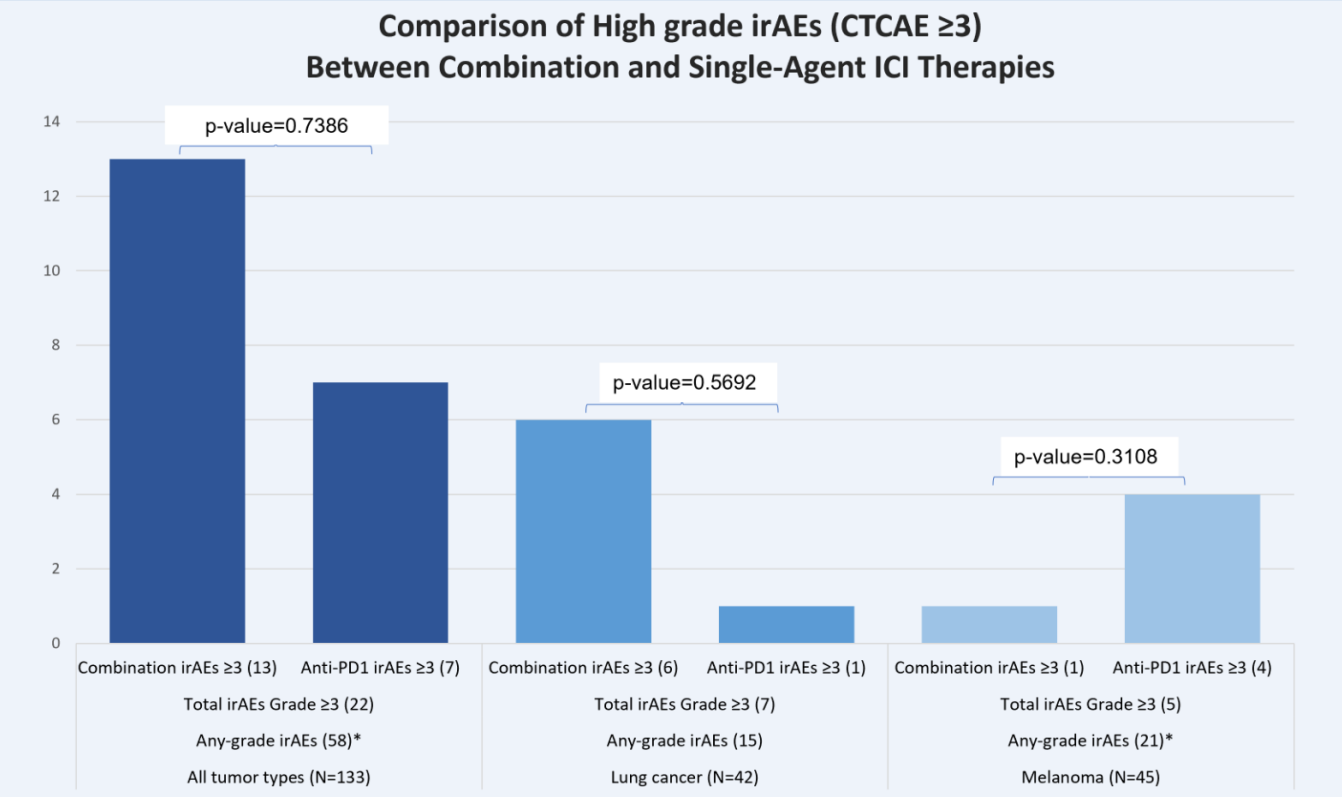
- **64 treated with combination ICI & 69 treated with single-agent anti-PD1**
- Cancer types were mainly melanoma (34%) and lung (32%)
- 95% had inactive AIDs & 21% were receiving immunomodulating therapies at ICI initiation

Preexisting autoimmune diseases	irAE, N (%)			Flare, N (%)		
	Combination	Single	P-value	Combination	Single	P-value
Total	38(59)	22(32)	0.0015	20(31)	25(36)	0.544
Dermatologic	**11(65)**	**2(14)**	**0.0046**	**6(35)**	**5(36)**	**0.980**
Psoriasis/Psoriatic Arthritis	11(65)	1(8)	0.0046	6(35)	5(38)	0.980
Vitiligo	-	1(100)		-	0(0)	-
Rheumatologic	**10(53)**	**4(22)**	**0.0566**	**7(37)**	**8(44)**	**0.637**
Rheumatoid arthritis	4(36)	3(21)	0.6564	3(27)	8(57)	0.135
Polymyalgia rheumatica	2(67)	-		2(67)	-	-
Systemic lupus erythematosus	1(100)	0(0)	0.3333	0(0)	0(0)	0.333
Sarcoidosis	2(100)	0(0)	0.3333	0(0)	0(0)	0.333
Scleroderma/CREST	1(50)	1(100)	0.3333	2(100)	0(0)	0.333
Gastrointestinal	**3(43)**	**3(33)**	**1.0000**	**3(43)**	**0(0)**	**0.062**
Crohn's disease	1(33)	0(0)	1.0000	2(67)	0(0)	0.400
Ulcerative colitis	2(67)	2(50)	1.0000	1(33)	0(0)	0.428
Celiac disease	0(0)	1(33)	1.0000	0(0)	0(0)	1.000
Endocrine	**8(89)**	**6(46)**	**0.0743**	**1(11)**	**4(31)**	**0.360**
Graves' disease	3(75)	0(0)	0.1429	1(25)	0(0)	1.000
Hashimoto's thyroiditis	4(100)	6(67)	0.4965	0(0)	4(44)	0.228
Type I diabetes	1(100)	-	-	0(0)	-	-
Neurologic	**0(0)**	**2(50)**	**1.0000**	**1(100)**	**1(25)**	**0.400**
Multiple Sclerosis	0(0)	-	-	1(100)	-	-
Guillian-Barre syndrome	-	1(50)	-	-	0(0)	-
Myasthenia Gravis	-	1(50)	-	-	1(50)	-
Hematologic	**2(50)**	**0(0)**	**1.0000**	**0(0)**	**0(0)**	**1.000**
Autoimmune hemolytic anemia	2(100)	-	-	0(0)	-	-
Immune thrombocytopenic	0(0)	0(0)	1.0000	0(0)	0(0)	1.000
More than 1 AID	**4(57)**	**5(50)**	**1.0000**	**2(29)**	**7(70)**	**0.153**
Autoimmune Disease status at initiation of checkpoint inhibitor						
Inactive	34(58)	22(33)	0.0052	18(31)	23(34)	0.647
Active	4(80)	0(0)	0.1429	2(40)	2(100)	0.428
Autoimmune Disease treatment at initiation of checkpoint inhibitor						
Off treatment	26(59)	9(27)	0.0055	12(27)	8(24)	0.764
On treatment	12(60)	13(36)	0.0849	8(40)	17(47)	0.602
On systemic immunomodulators	3(33)	4(21)	0.6465	5(56)	11(58)	0.907

Unpublished Data

A multicenter cohort study of 133 patients with preexisting AIDs treated with ICI combination or single agent ICI

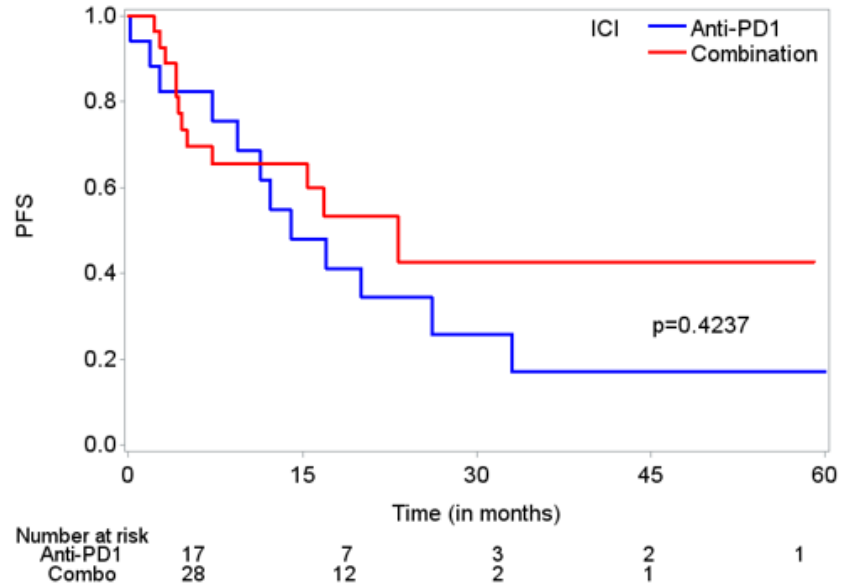
- **High grade toxicities were equivalent in both groups** (39.5% vs 35%, p=0.7386)
- **No treatment-related deaths** were observed



Unpublished Data

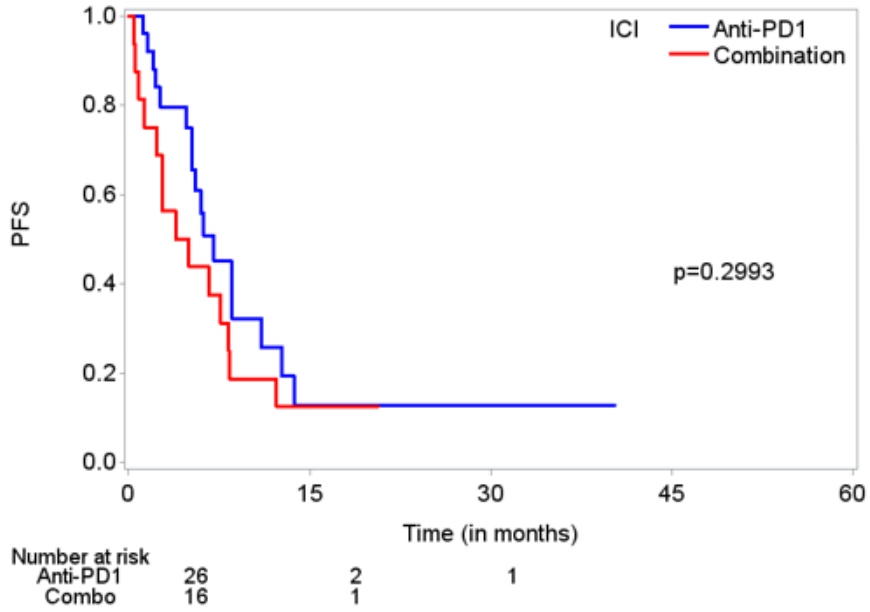
A multicenter cohort study of 133 patients with preexisting AIDs treated with ICI combination or single agent ICI

Progression Free Survival in Melanoma Patients treated with ICI Combination vs. Single-agent anti-PD-1



Immunotherapy agent	Median PFS (95% CI)
Anti-PD1	14.0 months (7.3-26.2)
Combination	23.2 months (5.0 – not estimated)

Progression Free Survival in Lung Cancer Patients treated with ICI Combination vs. Single-agent anti-PD-1

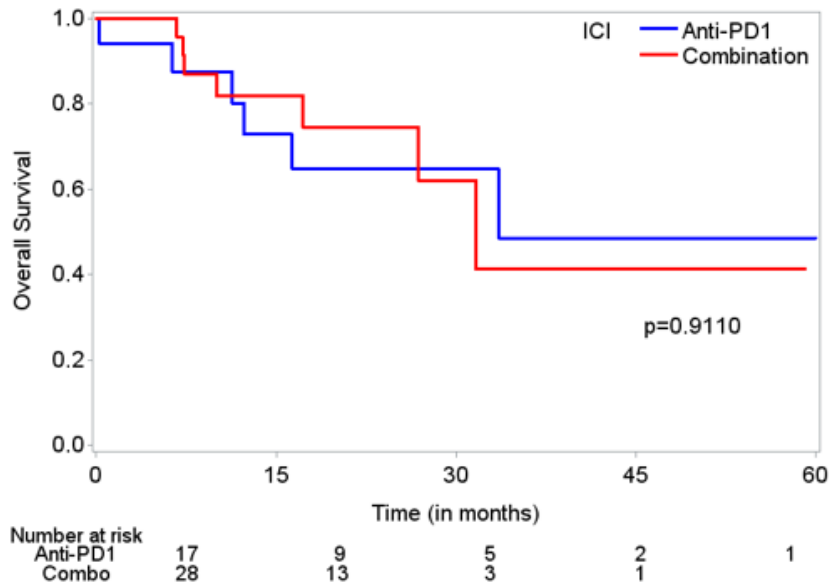


Immunotherapy agent	Median PFS (95% CI)
Anti-PD1	7.1 months (5.2-11.0)
Combination	4.4 months (1.3-8.3)

Unpublished Data

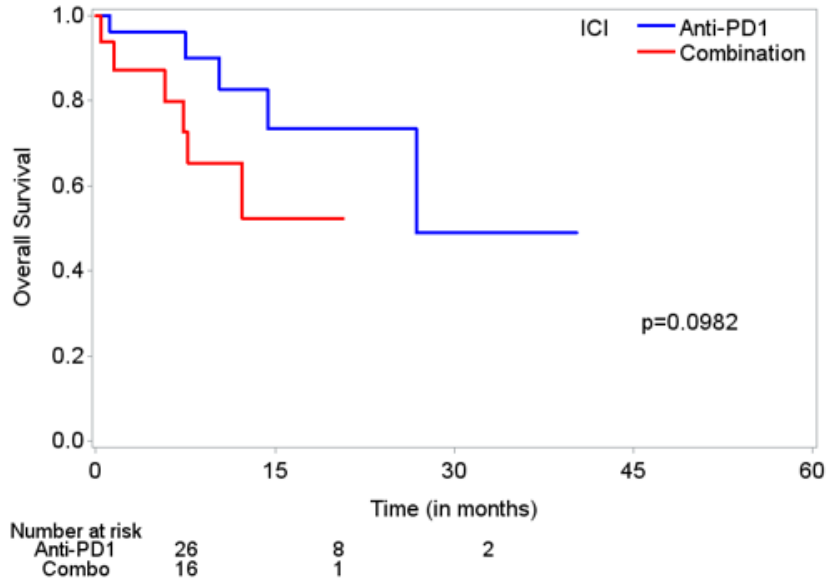
A multicenter cohort study of 133 patients with preexisting AIDs treated with ICI combination or single agent ICI

Overall Survival in Melanoma Patients treated with ICI Combination vs. Single-agent anti-PD-1



Immunotherapy agent	Median OS (95% CI)
Anti-PD1	33.5 months (11.3- not estimated)
Combination	31.6 months (17.2 – not estimated)

Overall Survival in Lung Cancer Patients treated with ICI Combination vs. Single-agent anti-PD-1



Immunotherapy agent	Median OS (95% CI)
Anti-PD1	26.8 months (14.4 – not estimated)
Combination	No reached (5.7- not estimated)

Many questions to answer

Can we quantify the risk of adverse events

- **About 30-40% of patients with AIDs** will experience flare and similar percentage may experience de novo irAEs
- **Patients with AIDs tend to require more corticosteroid and increased hospitalization**, potentially indicating higher AEs compared to patients without AIDs
- Preliminary results show the **rate of AEs may not be significantly different between combination ICI and single agent anti-PD1** for patients with AIDs

Many questions to answer

Can we predict which patients are more likely to develop adverse events

Supportive Care in Cancer (2021) 29:7747–7753
https://doi.org/10.1007/s00520-021-06359-7

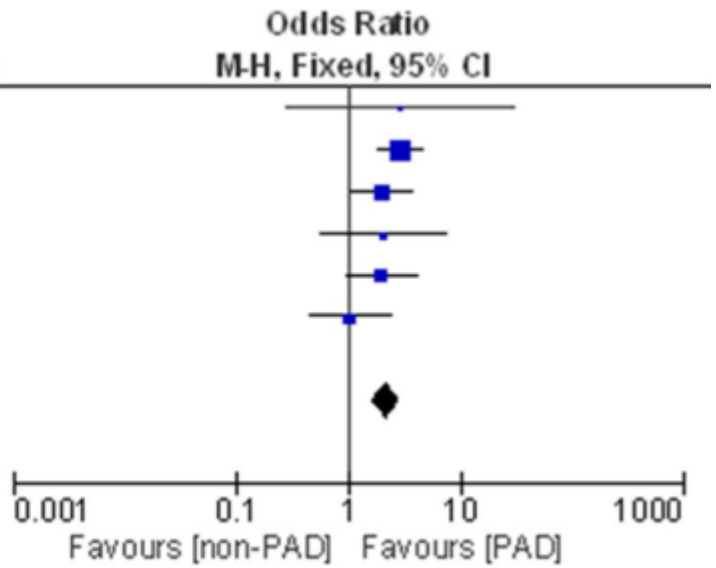
ORIGINAL ARTICLE

Preexisting autoimmune disease is a risk factor for immune-related adverse events: a meta-analysis

Atsushi Yamaguchi[1,2] · Yoshitaka Saito[1] · Keisuke Okamoto[1] · Katsuya Narumi[2] · Ayako Furugen[2] · Yoh Takekuma[1] · Mitsuru Sugawara[1,3] · Masaki Kobayashi[2,4]

Study or Subgroup	PAD Events	PAD Total	non-PAD Events	non-PAD Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bair 2019	3	4	25	49	1.6%	2.88 [0.28, 29.64]
Cortellini 2019	56	85	266	666	34.6%	2.90 [1.81, 4.67]
Danlos 2018	20	45	102	352	21.6%	1.96 [1.04, 3.69]
Kartolo 2018	8	12	33	66	5.7%	2.00 [0.55, 7.29]
Loriot 2020	24	35	506	962	18.8%	1.97 [0.95, 4.06]
Schadendorf 2019	17	25	664	983	17.7%	1.02 [0.44, 2.39]
Total (95% CI)		**206**		**3078**	**100.0%**	**2.14 [1.58, 2.89]**
Total events	128		1596			

Heterogeneity: Chi² = 4.70, df = 5 (P = 0.45); I² = 0%
Test for overall effect: Z = 4.94 (P < 0.00001)



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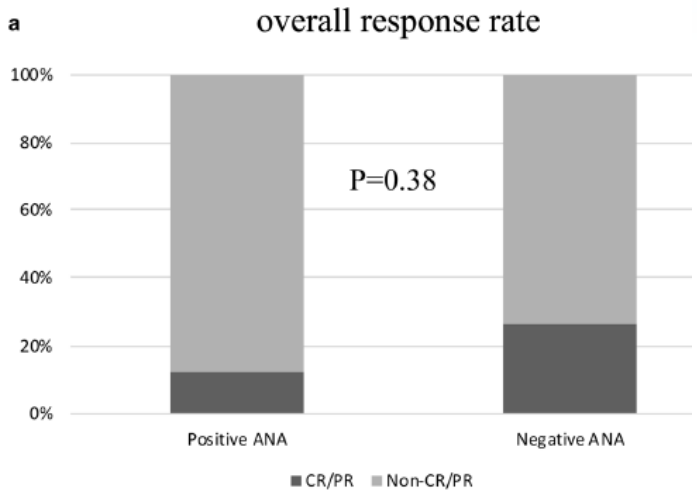
Clinical and Translational Oncology (2020) 22:919–927
https://doi.org/10.1007/s12094-019-02214-8

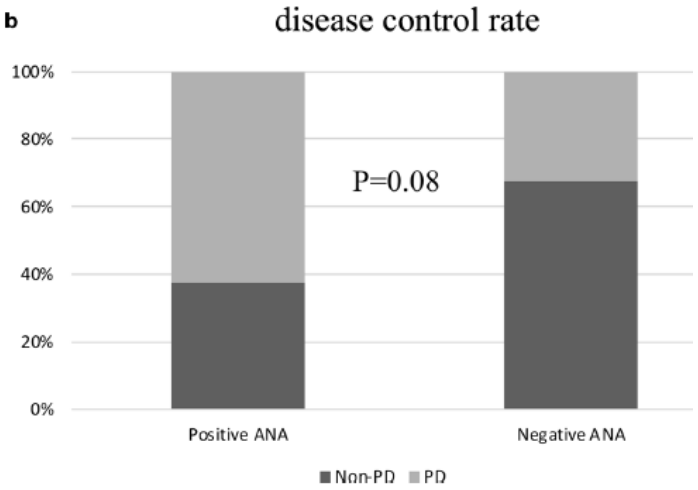
RESEARCH ARTICLE

Safety and efficacy of PD-1/PD-L1 blockade in patients with preexisting antinuclear antibodies

T. Sakakida[1] · T. Ishikawa[1,2] · Y. Chihara[2,3] · S. Harita[3] · J. Uchino[3] · Y. Tabuchi[2,10] · S. Komori[4] · J. Asai[4] · T. Narukawa[5] · A. Arai[6] · H. Tsunezuka[7] · T. Kosuga[8] · H. Konishi[8] · M. Moriguchi[1] · H. Yasuda[1] · F. Hongo[5] · M. Inoue[7] · S. Hirano[6] · O. Ukimura[5] · Y. Itoh[1] · T. Taguchi[2,9] · K. Takayama[3]

	Positive ANA $N=9$	Negative ANA $N=182$	*P* value
Total of irAEs	4	69	0.69
Thyroid Dysfunction	1 (Gr2: $N=1$)	27 (Gr1: $N=12$, Gr2: $N=15$)	0.76
Cutaneous disorders	2 (Gr1: $N=1$, Gr2: $N=1$)	33 (Gr1: $N=31$, Gr2: $N=2$)	0.76
Interstitial pneumonitis	1 (Gr2: $N=1$)	11 (Gr1: $N=5$, Gr2: $N=5$, Gr3: $N=1$)	0.54
Colitis	2 (Gr1: $N=1$, Gr2: $N=1$)	3 (Gr2: $N=2$, Gr3: $N=1$)	0.0002
Hypophysitis	1 (Gr3: $N=1$)	5 (Gr2: $N=2$, Gr3: $N=3$)	0.16
Diabetes	0	3 (Gr4: $N=3$)	0.70





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Lung Cancer 130 (2019) 5–9

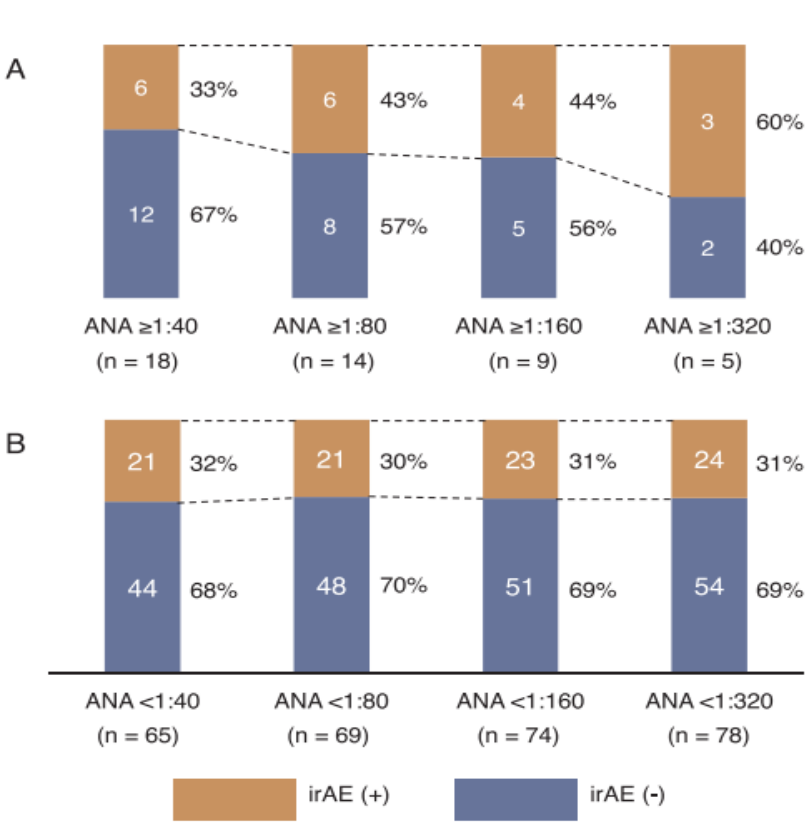
Contents lists available at ScienceDirect

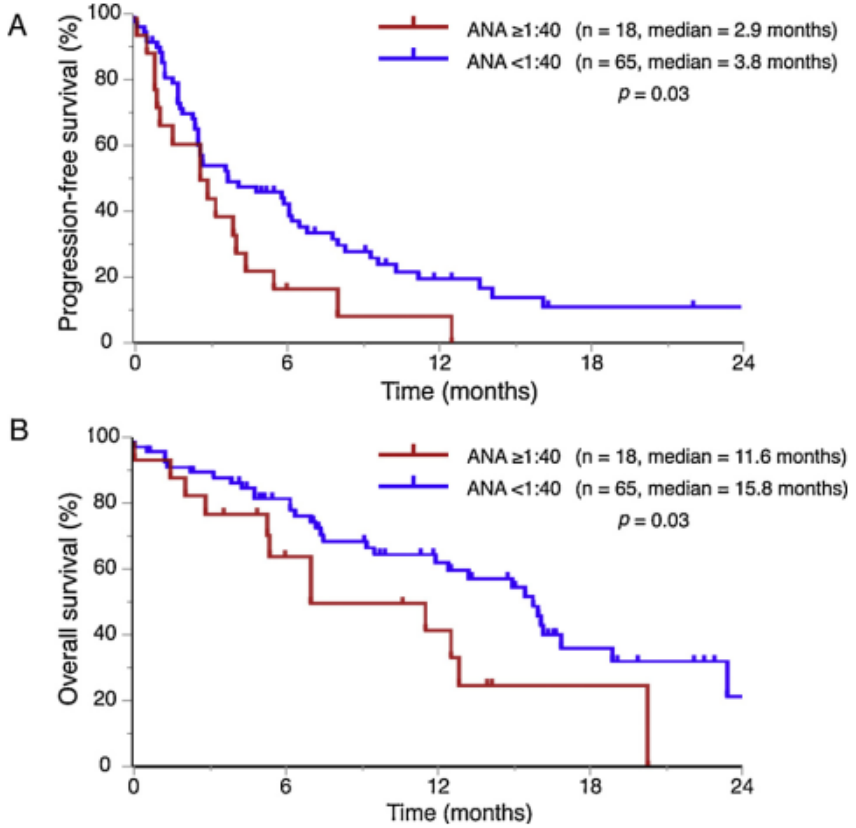
Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Safety and efficacy of PD-1 inhibitors in non–small cell lung cancer patients positive for antinuclear antibodies

Yasuto Yoneshima[a], Kentaro Tanaka[a], Yoshimasa Shiraishi[a], Kojiro Hata[b], Hiroyuki Watanabe[b], Taishi Harada[c], Kohei Otsubo[a], Eiji Iwama[a], Hiroyuki Inoue[a,d], Satohiro Masuda[b], Yoichi Nakanishi[a,d], Isamu Okamoto[a,*]





Open access Original research
Journal for ImmunoTherapy of Cancer

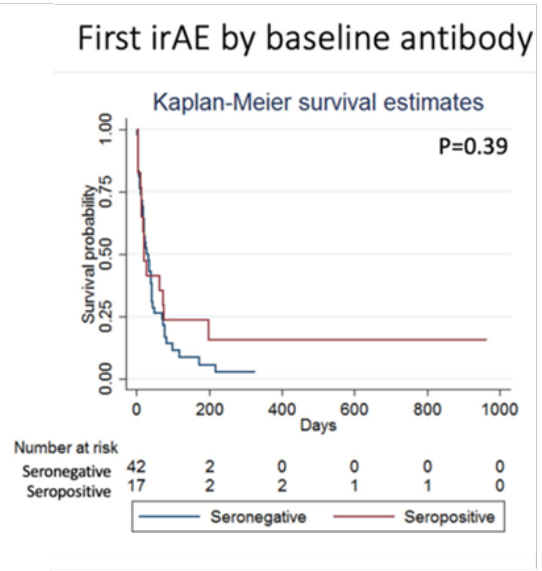
Lower baseline autoantibody levels are associated with immune-related adverse events from immune checkpoint inhibition

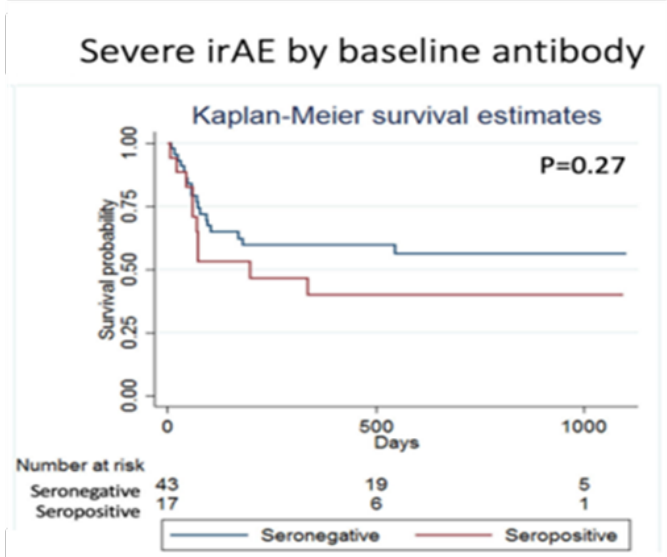
Nilasha Ghosh [1], Michael Postow [2], Chengsong Zhu,[3] Deanna Jannat-Khah,[1] Quan-Zhen Li,[3] Greg Vitone,[4] Karmela K Chan,[1] Anne R Bass[1]

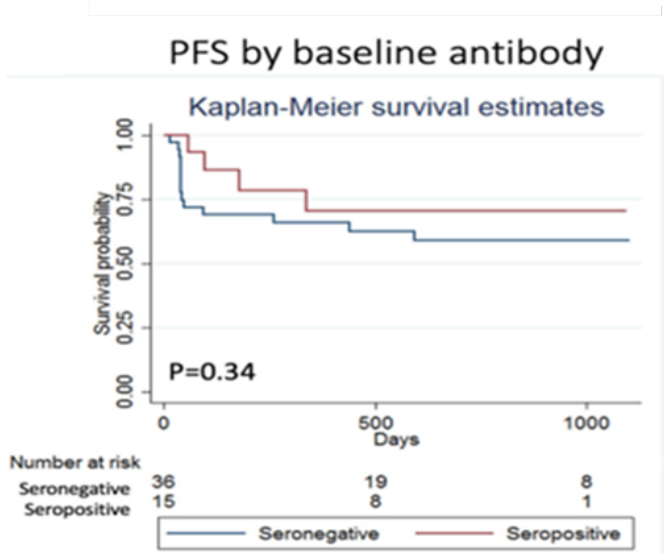
- 60 Melanoma patients receiving ICI combination
- Microarray autoantigen panel (120 autoantibodies, both IgG and IgM, associated with CTDs and with irAEs in prior literature)

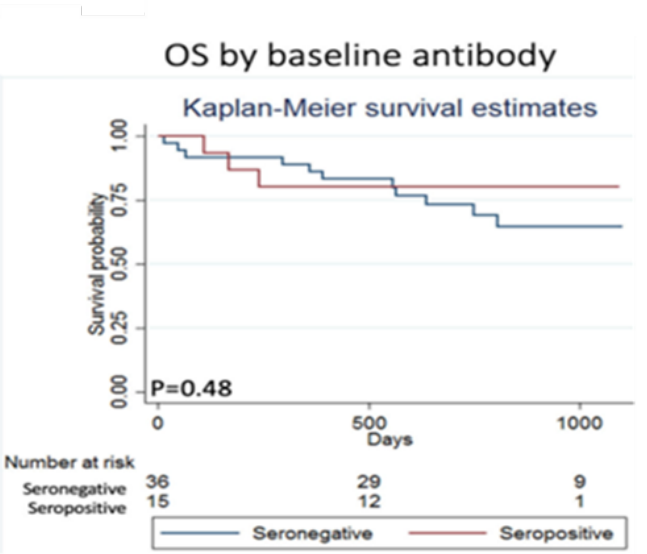
Category	Expected	Diarrhea/colitis	Hepatitis	Thyroid	Arthritis/arthralgia	Rash/pruritis	Sicca	Endo	Myocarditis	Myalgia
Low	**8(13.33%)**	3 (14.27%)	4 (18.18%)	2(14.29%)	0 (0.00%)	4(17.39%)	2 (25.0%)	1 (5.88%)	1(33.33%)	3 (37.5%)
Slightly	**27(45.00%)**	12(57.14%)	12(54.55%)	8 (57.14%)	4 (66.67%)	10 (43.38%)	4(50.0%)	10 (58.82%)	1(33.33%)	3 (37.5%)
Modelate	**12 (20.00%)**	5 (23.81%)	3 (13.64%)	2(14.29%)	0 (0.00%)	3 (13.04%)	1(12.5%)	3 (17.65%)	1(33.33%)	1(12.5%)
High	**13(21.67%)**	1(4.76%)	3(13.64%)	2(14.29%)	2(33.33)	6 (26.09%)	1(12.5%)	3 (17.65%)	0 (0.00%)	1(12.5%)

- **No autoantibodies were identified as being predictive of specific events**









- **Considering ANA, RF and CCP autoantibodies, there were no significant differences between the seropositive and seronegative patients in irAE development, severity, timing, or survival**

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Many questions to answer

Can we predict which patients are more likely to develop adverse events

- **At this point, the answer is NO**
  - **Patients with ANA positivity had more colitis in one study**
  - **Another study showed lower baseline AB levels is associated with irAEs and perhaps it is the change in AB levels that predict irAEs**
- **Larger high-powered prospective studies still needed**

Many questions to answer

Can we prevent these adverse events

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ASCO special articles

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

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Autoimmune Disease

Patients with pre-existing ADs are often not offered therapy with ICPis out of concern for exacerbation of symptoms and typically have been excluded from clinical trials involving these agents. However, data suggest that they may be safely treated.[251-253] A 2016 systematic review of case reports of patients with pre-existing ADs treated with ICPis found that only 41% of patients experienced an exacerbation of their pre-existing AD, despite 46% having active disease upon ICPi initiation.[288] Among 112 patients with pre-existing ADs in a 2019 retrospective cohort study, 70 patients (71%) experienced AD and/or other irAE(s), with pre-existing AD flare occurring in 53 patients (47%) and/or other irAE(s) in 47 patients (42%). There was a need for immunosuppressive therapy in 48 patients (43%) and permanent discontinuation of ICPi in 24 patients (21%). For patients requiring immunosuppressive therapy before initiating ICPi, the mPFS was shorter (3.8 months *v* 12 months; $P = .006$).[254]

A proposal for a selective immunosuppressive strategy for patients with ADs includes two steps for controlling ADs when using ICPi: (1) Rotation phase: discontinuation of all nonselective immunosuppressants and replacement with the most appropriate selective immunosuppression and assess for the stability of AD 2-4 weeks before the start of concomitant ICPi treatment, if timing allows based on the pace of cancer growth and urgency of treatment; 2. Maintenance phase: simultaneous selective immunosuppression and ICPis during the entire immunotherapy period.[255]

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
ANNALS OF ONCOLOGY driving innovation in oncology

REVIEW

Autoimmune diseases and immune-checkpoint inhibitors for cancer therapy: review of the literature and personalized risk-based prevention strategy

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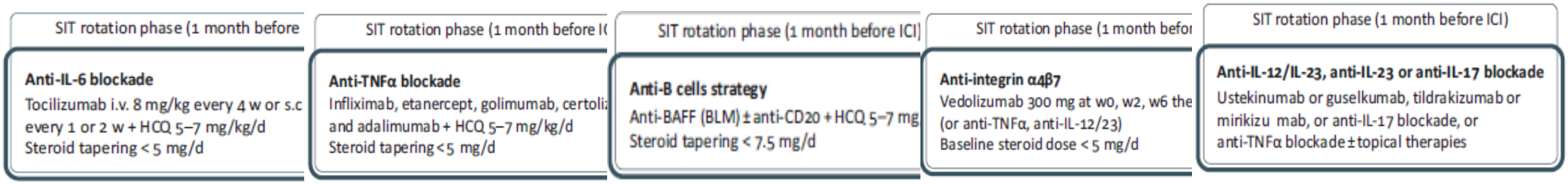

Giant cell arteritis & Polymyalgia Rheumatica & Rheumatoid arthritis

Spondyloarthritis & Systemic granulomatous disease

Systemic lupus erythematosus & Sjögren's syndrome

Inflammatory bowel diseases

Psoriasis

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Many questions to answer

Can we prevent these adverse events

- **Prevention strategy has been suggested adapted from treatment recommendations for primary AIDs**
- **Clinical trials are needed to compare treatment options and evaluate their impact on tumor immunity in this special cancer population with AIDs**

Many questions to answer

How we can optimally manage adverse events

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Unpublished Data

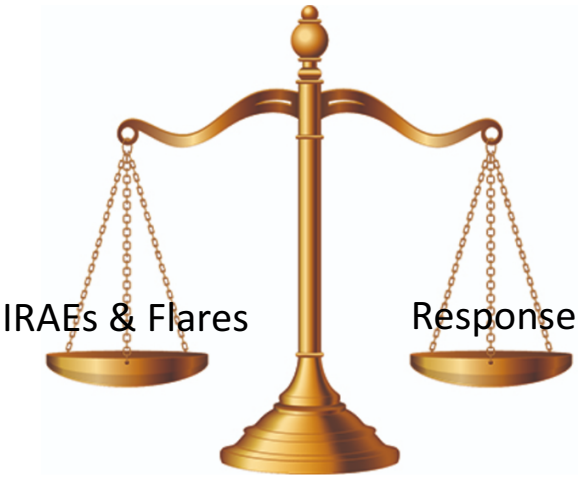
Meta-analysis of 72 observational studies through June 2021: preliminary data on 2790 patients with preexisting AIDs

- **Median time to onset of any adverse event ranged from 30 days to 24 months**

- Pooled incidence rate of:
  - Any adverse event - 47% (range 0% to 86%)
  - AIDs flares - 36% (range 0% to 85%)
  - De novo irAEs - 24% (range 0% to 75%)
  - **Corticosteroids use for management of adverse events - 34% (range 3% to 85%)**
  - **ICI discontinuation - 18%** (range 3% to 79%)
  - **Death from any reason - 10%** (95% CI 3% to 20%)
  - Additional analyses still ongoing

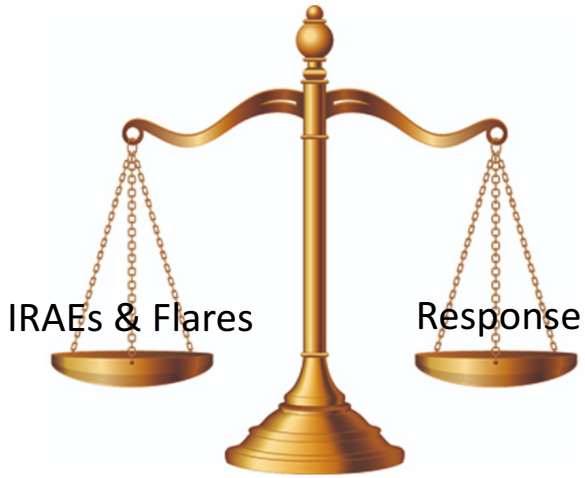
Towards targeted therapies for adverse events **WHY?**

- Published guidelines endorse for corticosteroids as a first-line therapy for adverse events
- Studies from melanoma and NSCLC patients treated with ICIs have shown that the use of **prednisone ≥ 10 mg/day led to detrimental cancer outcome and worsen survival**
- Patients treated with **corticosteroids within the first two months after ICI initiation had shorter PFS and OS** as compared to those who received corticosteroids later
- **Targeted therapies could be more safe and preferable to corticosteroids especially for patients with AIDs who require chronic treatment**



Cytokine inhibitors as targeted therapies for adverse events

Known vs Unknown



- Cytokine inhibitors are approved for management of AIDs that involve multiple organs
  - **Efficacy of individual cytokine inhibitors for various ICI related organ-specific toxicities is unclear**
  - **Deep understanding of pathogenesis and similarities/differences in immunohistopathological findings of various organ-specific toxicities is needed**

- Published guidelines recommend cytokine inhibitors for refractory irAEs and upfront to prevent flares of preexisting AIDs
  - Reduce duration of symptoms and hospitalization due to irAEs
  - **Impact on ICI tumor immunity & survival is unclear**
  - **Potential treatment-related adverse events added to irAEs**

Unpublished Data

Interleukin-6 blockade abrogates immunotherapy toxicity and promotes tumor immunity

- We used a multi-disciplinary approach to study the role of IL-6/Th17 axis in ICI-related autoimmunity and tumor immunity
  - Nanostring gene expression profiling in colitis-irAE and normal colon biopsies (n=23), and tumor biopsies from ICI-treated melanoma patients (n=22)
  - We evaluated the effect of IL-6 blockade on autoimmunity and ICI-therapeutic activity in murine models
  - A retrospective study to evaluate the safety and efficacy of IL-6 receptor (IL-6R) blockade for ICI-related AEs management (n=31)
- **Conclusion: Targeting IL-6(R) could be an effective approach to mitigate autoimmunity while maintain and possibly boost tumor immunity**

Yared Hailemichael, PhD

Daniel Johnson, MD

Adi Diab, MD

Unpublished Data

A multicenter cohort study of 95 patients treated with anti-IL6R : preliminary data on 22 patients with preexisting AIDs

- Cancer types were primarily melanoma (50%), genitourinary cancer (32%), and lung cancer (9%)
- 86% received single-agent anti-PD-1 and 9% received nivolumab plus ipilimumab
- Median duration of follow-up since ICI initiation 23 months
- **77 % of patients received corticosteroids as first-line therapy, and 45% received disease-modifying antirheumatic drugs (DMARDs) without improvement**

Preexisting AIDs	ICI-induced adverse Event treated with anti-IL-6
Rheumatoid arthritis (n=14)	Flare of rheumatoid arthritis (n=14)
Psoriasis/Psoriatic arthritis (n=4)	MG/myositis (n=1) Polymyalgia Rheumatica (n=1) Psoriatic arthritis flare (n=1) New-onset psoriatic arthritis (n=1)
Undifferentiated arthritis (n=2)	Rheumatoid-like arthritis
Polymyalgia Rheumatica (n=1)	Rheumatoid-like arthritis
Sjogren's syndrome (n=1)	Rheumatoid-like arthritis

Unpublished Data

A multicenter cohort study of 95 patients treated with anti-IL6R : preliminary data on 22 patients with preexisting AIDs

Primary Outcome

- **77% had irAEs improvement after a median of 3 months**
  - Of 12 evaluable with arthritis-irAE, the median CDAI score was 30 and dropped to 8
- The median **CRP level was 77.4 mg/L and dropped to 3.5 mg/L** within 10 weeks
- **Three patients (13%)** stopped IL-6R blockade due to side effects **(2 had psoriasis exacerbation, 1 recurrent infection)**

Secondary Outcome

- **54% continued their ICI therapy**
- **Median duration of concomitant therapy was 8 months (1 to 38 months)**
- In 10 melanoma patients with AIDs, the ORR was **50% prior** and **50% after** treatment

ORR	Before anti-IL6	ORR	After anti-IL6
CR	1	CR	3
PR	4	PR	2
PD	3	PD	3
SD	2	SD	2
Total	**10**	**Total**	**10**

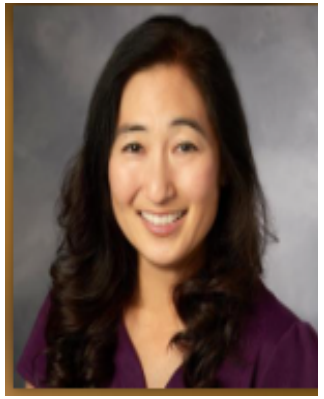
- **No mortality because of adverse events**

Ongoing Study

Measuring Impact of Steroid-Sparing immunomodulators within ImmunoONcology ⟶ MISSION

- Determine the impact of SSIs used for irAEs management on cancer outcome
- Determine the impact of maintenance SSIs used for pre-existing autoimmune diseases, transplant recipients or irAEs prophylaxis on cancer outcome

Pankti Reid, MD, MPH



Tamiko Katsumoto, MD

Namrata Singh, MD, MSCI, FACP

Ongoing Trials for Management/Prevention of Adverse events: NCI Clinical Trials Database Search in April 2022

Ongoing clinical trials	Trial ID	Status
Infliximab or Vedolizumab in Treating Immune Checkpoint Inhibitor-Related Colitis in Patients With Genitourinary Cancer or Melanoma	NCT04407247	Recruiting
TNF-Inhibitor as Immune Checkpoint Inhibitor for Advanced MELanoma	NCT03293784	Active, not recruiting
Study of **Rituximab or Tocilizumab** for Patients With Steroid-Dependent Immune-Related Adverse Events (irAEs)	NCT04375228	Recruiting
Checkpoint Inhibitor Induced Colitis and Arthritis -Immunomodulation With **IL-6 Blockade** and Exploration of Disease Mechanisms (COLAR)	NCT03601611	Completed
Tocilizumab, Ipilimumab, and Nivolumab for the Treatment of Advanced Melanoma, Non-Small Cell Lung Cancer, or Urothelial Carcinoma	NCT04940299	Recruiting
A Phase II Study of the Interleukin-6 Receptor Inhibitor **Tocilizumab** in Combination With Ipilimumab and Nivolumab in Patients With Unresectable Stage III or Stage IV Melanoma	NCT03999749	Recruiting
Atezolizumab With or Without **Tocilizumab** in Treating Men With Prostate Cancer Before Radical Prostatectomy	NCT03821246	Recruiting
A Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatment Combinations in Patients With Advanced Liver Cancers (Morpheus-Liver) * **Multiple combination regimens including Tocilizumab + ICI therapy**	NCT04524871	Recruiting
A Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatment Combinations in Patients With Metastatic or Inoperable Locally Advanced Triple-Negative Breast Cancer * **Multiple combination regimens including Tocilizumab + ICI therapy**	NCT03424005	Recruiting
A Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatments and Combinations in Patients With Urothelial Carcinoma (MORPHEUS-UC) * **Multiple combination regimens including Tocilizumab + ICI therapy**	NCT03869190	Recruiting
Tofacitinib for the Treatment of Refractory Immune-related Colitis From Checkpoint Inhibitor Therapy- TRICK Study	NCT04768504	Recruiting
Treatment Efficacy of Corticosteroids, **Mycophenolate Mofetil and Tacrolimus** in Patients With Immune Related Hepatitis (I-HEP)	NCT04810156	Not yet recruiting
Role of Gut Microbiome and Fecal Transplant on Medication-Induced GI Complications in Patients With Cancer	NCT03819296	Recruiting
Fecal Microbiota Transplantation in Treating Immune-Checkpoint Inhibitor Induced-Diarrhea or Colitis in Genitourinary Cancer Patients	NCT04038619	Recruiting

Many questions to answer

How we can optimally manage adverse events

- **Corticosteroids remain the 1st line treatment option as recommended by the current guidelines**
- **Cytokine inhibitors are promising as targeted therapies for adverse events**
- **Clinical trials are needed in patients with preexisting AIDs who require chronic therapy**

Many questions to answer

Availability of clinical decision support tools

- **As of now, the answer is NO. But it is expected to have one in the near future**

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Ongoing Study

Improving decision-making in patients with cancer and pre-existing autoimmune disease considering immune checkpoint inhibition

ClinicalTrials.gov Identifier: NCT04751396

Recruitment Status : Not yet recruiting
First Posted : February 12, 2021
Last Update Posted : March 10, 2021

The specific aims are:

1. Evaluate the benefits and risks of immune checkpoint inhibitors in patients with cancer and pre-existing autoimmune disease
2. Develop a multicomponent shared decision-making tool for cancer patients with autoimmune disease considering treatment with immune checkpoint inhibitors
3. Evaluate the tool which will be appropriate for low-literacy populations, and will be tailored to patients' individual characteristics

Maria Lopez-Olivo, MD, PhD

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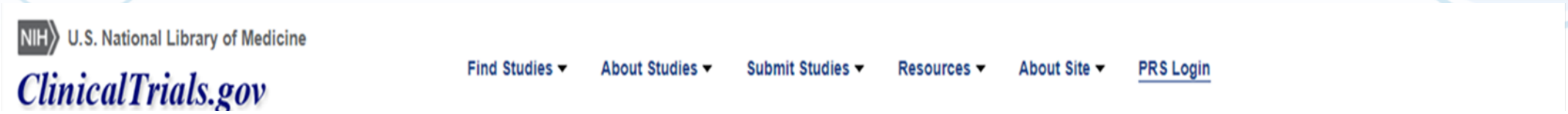
CA237619

Many questions to answer

Availability of clinical trials

- **Currently, we have two active clinical trials for patients with cancer and AIDs**



Nivolumab in Patients With Advanced Non-Small Cell Lung Cancer and Pre-existing Autoimmune Disease

Primary Outcome

- Dose-limiting toxicity (1st 6 weeks after cycle 1)
  - Cohort 1: RA, Psoriasis, DM, GCA/PMR, and SLE
  - Cohort 2: US, CD, and MS

ClinicalTrials.gov Identifier: NCT03656627

Recruitment Status : Active, not recruiting
First Posted : September 4, 2018
Last Update Posted : June 18, 2021

Secondary Objectives

- Evaluate the overall response rate
- Evaluate progression free survival
- Evaluate overall survival

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Nivolumab in Treating Patients With Autoimmune Disorders and Advanced, Metastatic, or Unresectable Cancer

Primary Objective

- **Assess the safety of nivolumab in patients with varying severity of autoimmune diseases**
  - RA, SLE, DM, SSc, IBD, MS, SS, others

Secondary Objectives

- **Evaluate the efficacy of nivolumab**
- **Evaluate impact of nivolumab on AIDs severity indices**
- **Propose dosing recommendation of nivolumab based on AIDs severity**
- **Identify predictive biomarkers of response, resistance, and toxicity**

ClinicalTrials.gov Identifier: NCT03816345

Recruitment Status : Recruiting
First Posted : January 25, 2019
Last Update Posted : September 20, 2021

See **Contacts and Locations**

Take home Messages

- About one-third of patients with AIDs tend to experience AIDs flare following ICI therapy
- Combination ICI may not be necessary to avoid for patients with AIDs but efficacy benefit is unclear in this patient population
- No definitive AID characteristics or biomarkers can effectively predict which patients with AIDs are more likely to develop adverse events
- Targeted therapies may be safer and preferable to nonspecific immunosuppression by systemic corticosteroids
- Ongoing studies to evaluate the impact of agents used to treat AIDs on tumor outcome and the needs of patients with AIDs considering ICI therapy
- Active clinical trials evaluating nivolumab use for patients with AIDs

Multidisciplinary discussion between oncologists & organ-disease specialists is needed to effectively manage each individual patient with AID