Immunotherapy in Special Patient Populations

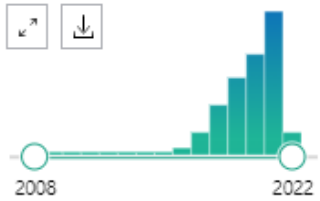
Michael Morse, MD, MHS
Medical Oncology
Duke University Health System

Topics: Immune Checkpoint Inhibitors in:

- Autoimmune disorders
- Organ transplants
- Chronic viral infections
- Concurrent immunosuppressants
- Patients receiving PPI or antibiotics
- Organ dysfunction
- Pregnancy
- Brain metastases
- Pediatric
- Elderly
- COVID-19

ICB in patients with pre-existing autoimmune disease

- Excluded from clinical trials so minimal clinical trial data
- Rapid increase in publications on this topic



- Many case reports of Rx with ICB in patients with autoimmune dz
- Series and reviews on individual autoimmune diseases
  - E.g., Halle BR, et al. Immune checkpoint inhibitors in patients with pre-existing psoriasis: safety and efficacy. J Immunother Cancer. 2021;9:e003066.
- Real world evidence/Cohort studies for ICB across autoimmune diseases
  - Fountzilas E, et al. Real-world safety and efficacy data of immunotherapy in patients with cancer and autoimmune disease: the experience of the Hellenic Cooperative Oncology Group. Cancer Immunol Immunother. 2022 Feb;71(2):327-337.
  - Tison A, et al. Safety and Efficacy of Immune Checkpoint Inhibitors in Patients With Cancer and Preexisting Autoimmune Disease: A Nationwide, Multicenter Cohort Study. Arthritis Rheumatol. 2019;71:2100-2111.
- Systematic reviews for ICB across autoimmune diseases
  - Abdel-Wahab, *Ann Intern Med.* 2018;168(2):121-130

Systematic Review

- N = 123 patients
- Most had metastatic melanoma.
- Preexisting autoimmune diseases : psoriasis and/or psoriatic arthritis, rheumatoid arthritis, autoimmune thyroid disease, ulcerative colitis, Crohn disease, multiple sclerosis, myasthenia gravis, and sarcoidosis.
- 83.5% received prior treatment for their autoimmune disease
- 46.2% had active autoimmune disease with ongoing symptoms
- 43.6% were receiving concomitant treatment (corticosteroids, synthetic or biologic disease-modifying antirheumatic drugs, or other immunosuppressants) at initiation of CPI therapy.

Abdel-Wahab, *Ann Intern Med.* 2018;168(2):121-130

Outcome of patients with pre-existing autoimmune dz

- 1/2 had exacerbation of prior autoimmune disease
  - Generally the same manifestations as those occurring before CPI therapy.
- > 1/3 experienced de novo irAEs
  - colitis and hypophysitis the most common
- No differences in frequency of AEs in patients with active vs inactive preexisting autoimmune dz
- Fewer AEs in those receiving immunosuppressive therapy at initiation of CPI therapy
- Ipilimumab associated with more de novo irAEs; anti–PD-1/PD-L1 agents had more disease flares
- Most AEs were treated with corticosteroids; 16% required other immunosuppressive tx
- AEs improved in more than half of cases without the need to discontinue CPI therapy.
- Death from a serious adverse event was reported in 2.4% of patients.
  - Suggest that irAEs may be more severe in patients with concomitant autoimmune disease.

Abdel-Wahab, *Ann Intern Med.* 2018;168(2):121-130

French Multicenter Cohort Study

- Adults with preexisting autoimmune disease who were receiving ICIs
  - Psoriasis (n = 31), rheumatoid arthritis (n = 20), and IBD (n = 14).
  - Twenty-four patients (22%) receiving immunosuppressive therapy at ICI initiation.
- Autoimmune disease flare and/or other IRAE(s) in 79 patients (71%)
  - Flare of preexisting autoimmune disease in 53 patients (47%)
  - Other IRAE(s) in 47 patients (42%),
  - Need for immunosuppressive therapy in 48 patients (43%)
  - Permanent discontinuation of ICI in 24 patients (21%).
- PFS shorter in patients receiving immunosuppressive therapy at ICI initiation (3.8 v 12 mo
- PFS shorter in patients who experienced a flare of preexisting autoimmune disease or other IRAE,
  - Trend toward better survival in the subgroup without immunosuppressant use or ICI discontinuation.

Arthritis Rheumatol. 2019 Dec;71(12):2100-2111.

Use of ICB in allo-HSCT

Literature review

Ijaz, Biol Blood Marrow Transplant, 25 (2019), pp. 94-99

Most common indication for CPI use: Hodgkin lymphoma.

CPIs: ipilimumab, nivolumab, and pembrolizumab

	aGVHD	cGVHD	Death due to GVHD	ORR/CR/PR
CPI pre-allo-HSCT (n= 107)	56%	29%	11%	68/47/21%
CPI post-allo-HSCT For relapse (n= 176)	14%	9%	7%	54/33/21%

GVHD incidence associated with ICB administered post allo-HSCT is higher if previous GVHD (55%) vs first episode of GVHS (30%) (*Blood. 2017 Jul 13; 130(2):221-228.; Blood. 2018 Jul 5; 132(1):9-16*).

Graft Versus Host Disease Associated with ICI: A Pharmacovigilance Study and Systematic Literature Review

- Pharmacovigilance analysis of cases of GVHD associated with ICI in allo-transplant patients
  - 93 cases of GVHD associated with ICI (61.8% men, median age 38y).
  - Cases were mostly associated with nivolumab (53/93, 57.0%), pembrolizumab (23/93, 24.7%) and ipilimumab (12/93, 12.9%) monotherapies.
  - GVHD events occurred after 1 [1; 5.5] injection of ICI, with a time to onset of 35 [IQR = 14; 176] days.
  - Immediate subsequent mortality after GVHD was 24/93, 25.8%.
  - No significant difference in mortality depending on the molecule (p = 0.41) or the combination regimen (combined vs. monotherapy, p = 0.60).
  - Previous h/o GVHD present in 11/18.

Nguyen, Front Pharmacol. 2021 Feb 5;11:619649.

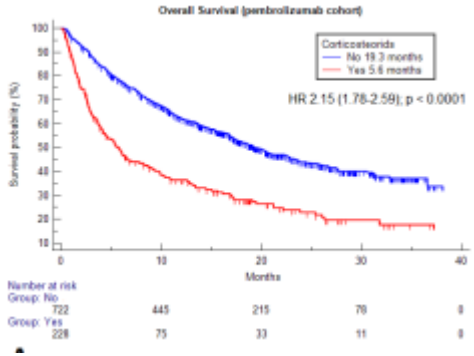
Solid Organ Transplant recipients receiving ICB for malignancy

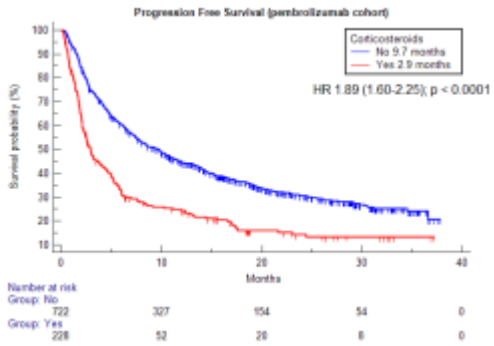
- Pooled analysis (n=64 cases from literature) of organ transplant after ICI
- Allograft rejection rate: 41% (renal: 44%, liver: 39%, cardiac: 20%) (71% organ failure)
  - typically occurred at 1-2 doses;
  - High rate of rejection if treated only with low dose pred (75%); lower rate of rejection with tacrolimus (10%)
- Graft rejection: lower with ipi (23%) vs 48-54% (nivo), 39% (pembro).
- ORR: 36% (nivo 26%, pembro 53%)
- ORR for single agent immunosuppressive (IS): 46% vs 29% (combined IS)

Oncologist. 2020 Jun;25(6):505-514.

Chronic immunosuppressants

- "Responses may be less frequent in patients receiving high-dose steroids or other disease-modifying therapies (15%) than in those not requiring these agents (44%)" (Reported in Cancer 2017;123:1904-11)
- Lower OS and PFS for NSCLC receiving steroids who start pembrolizumab





J Immunother Cancer. 2021 Apr;9(4):e002421

ICB in HIV + patients with malignancy

- Systematic review (n=73 patients)
  - 62: anti-PD-1 therapy; 6: anti-CTLA-4, 4: anti-PD-1/CTLA-4; 1: sequential ipilimumab and nivolumab therapy
  - Well-tolerated (≥grade 3 IRAE: 8.6%.
  - HIV remained suppressed in 26 of the 28 (93%) with undetectable HIV load.
  - CD4 cell counts increased (mean [SD] change, 12.3 [28.5] /µL).
  - Objective response rates were 30% for non-small cell lung cancer, 27% for melanoma, and 63% for Kaposi sarcoma.

JAMA Oncol . 2019 Jul 1;5(7):1049-1054

ICB in the "elderly"

- Pooled analysis: borderline significant OS benefit for ICIs vs no ICIs arms (HR = 0.84, 95% CI 0.7–1; *P* = 0.05) in particular in 1st line trials with HR = 0.77 (95%CI 0.61–0.96; *P* = 0.02) (Cancer Immunology, Immunotherapy 2021;70:1777–1780)
- Meta-analysis: OS benefit with ICIs was significant in both younger and older patients (cut-off age of 65-70 years). (Cancer Treat Rev. 2016 Apr;45:30-7.
- Meta-analysis: ICI therapy improves OS in both younger and older patients with advanced cancers (magnitude of improvement does not depend on age) (J Geriatr Oncol. 2020 Apr;11(3):508-514.)

ICB in pediatrics

- ACCELERATE and European Medicines Agency Paediatric Strategy Forum for medicinal product development of checkpoint inhibitors for use in combination therapy in paediatric patients.
  - High rate of activity of monotherapy checkpoint inhibitors, including complete responses, in Hodgkin lymphoma and hypermutant tumours.
  - Very limited activity of checkpoint inhibitors as single agents in other paediatric tumours (overall response rate–2.8% with Hodgkin's lymphoma excluded).
    - Tumour-associated leucocytes of most paediatric tumours contain few T cells,
    - PD-L1 expression is absent in the majority of tumours (except Hodgkin lymphoma)
    - Contain higher proportions of myeloid cells (macrophages and MDSC)
  - Except for hypermutation, there is no other predictive biomarker.
  - There is no benefit to children to be included in new monotherapy trials of other checkpoint inhibitors with the same mechanism of action unless there is more scientific knowledge.

Pearson ADJ, Eur J Cancer. 2020 Mar;127:52-66.

ICB in organ dysfunction

- No specific contraindication to ICB exists for patients with renal, hepatic, or cardiac dysfunction
  - These patients have been largely excluded from clinical trials
- 27 patients with organ dysfunction (Kanz, J Immunother Cancer. 2016 Oct 18;4:60)
  - Organ dysfunction was defined as cardiac (left ventricular ejection fraction ≤45 %), renal (creatinine ≥2 mg/dL or GFR ≤30 ml/min) or hepatic dysfunction (evidence of cirrhosis on imaging or AST, ALT or bilirubin ≥3x ULN).
  - Worsening organ dysfunction requiring hospitalization or dose delays occurred in 8 patients (30 %) although in most cases this was thought not-drug related and resolved with supportive care.
  - RR: 15%

ICB in brain metastases: general statements

- Lung cancer: To date only data provided by non-small-cell lung cancer subtypes are available (low level of evidence). Central response rate on these patients is estimated to be lower than primary site (ORR 17–20%) (low level of evidence).
- Renal cell carcinoma: Only data for clear cell subtypes are available. Responses are achievable only in a very limited number of patients with mono-site small (<1 cm) metastases (very low level of evidence).
- Melanoma: Combination between ICIs seems to be the best treatment strategy in patients with melanoma related brain metastases (BMs) (high level of evidence).
- Other malignancies: Limited data about clinical efficacy on BMs are available. This also includes solid malignancies with high CNS metastases rate (breast cancer and small-cell lung cancer).
- Breast cancer: Breast cancer BM had a lower immune contexture c/w melanoma and NSCLC
- Radiation therapy & ICIs: Recent randomized trials show limited efficacy of the abscopal effect (low level of evidence).
- Combinations between ICIs and stereotactic radiosurgery or WBI are under assessment

Nunno V, Immunotherapy. 2021 Apr;13(5):419-432.

ICB in pregnancy

- PD1/PD-L1 interactions plays a key role in maintaining fetal tolerance;
- Placenta with high PD-L1 expression
- Animal studies: anti-PD1/PD-L1 increased the risks of spontaneous abortions
- Anti-PD1 agents are categorized as pregnancy category D* by the Food and Drug Administration
- Ipilimumab is pregnancy category C*

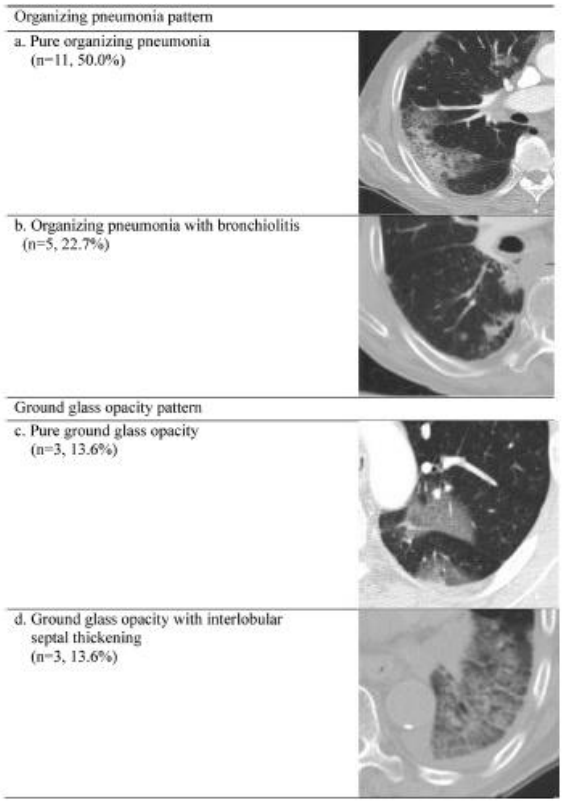
- * C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
- *D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

ICB in COVID-19

- "Current evidence does not support the notion that ICB therapy worsens complications from COVID-19, and we conclude that it supports the continued use of ICB therapy during the COVID-19 pandemic " (Garassino and Ribas, Cancer Immunol Res 2021;XX:XX–XX)
- Use of extended dosing interval did not lead to an increase of clinically relevant toxicities resulting in dose reduction and/or treatment discontinuation (Lung Cancer. 2021 Dec 24:S1525-7304(21)00305-3.)
- In a cohort of patients vaccinated while on ICB, irAEs were similar overall but 5/19 vaccinated within 72 hr before/after IO developed irAE (within 1-17 days) (Cancer Immunol Immunother. 2021 Dec 23;1-6.)

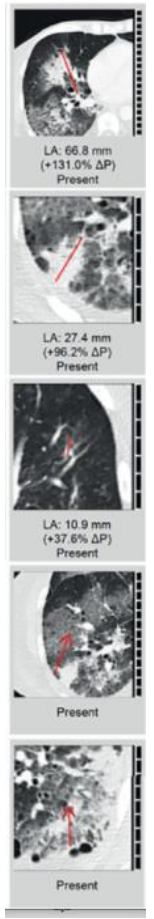
Immune related pneumonitis and COVID-19

Pt with ICB-Related pneum onitis



Cho JY, Lung Cancer. 2018 Nov;125:150-156.

Pt with COVID-19 (C_T 17) And who recently Initiated pembrolizumab For NSCLC



Is it possible to distinguish the two?

Mellinghoff, Front. Immunol., 20 December 2021

Summary

- Most “special” patient groups can be safely treated with ICB
- Exception: pregnancy (category C or D) and some organ transplants