# **Common Misunderstandings with Immune Checkpoint Inhibitors**

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### Questions

- Safety and effectiveness of influenza vaccine
- Antibiotic use and response
- PPI use and response
- Clinical pearls for ICI-induced colitis
- Triple M syndrome: myocarditis, myasthenia gravis and myositis
- Clinical pearls for steroid management used to treat immune-related adverse effects

# Immune Checkpoint Inhibitor (ICI) Therapy

- Cancer treatment strategies directed at improving the host immune response to cancer and which target immune checkpoint molecules
- Immune-related adverse events (irAE): Adverse events that occur via the activation of a patient's immune system that can occur in any tissue, organ, or system

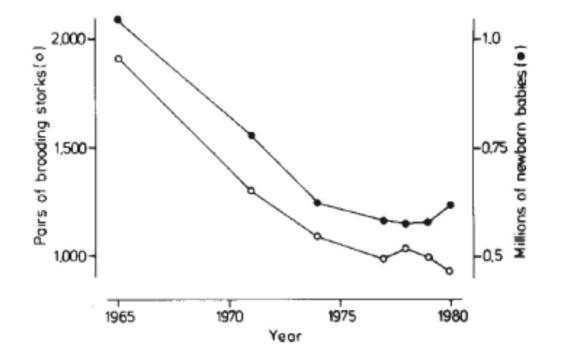
# **Clinically Available Immune Checkpoint Inhibitors**

#### **FDA** approved Indications

- Melanoma
- Non-small cell lung
- Head and neck cancer
- Urothelial carcinoma
- Hodgkin's lymphoma
- PMBC lymphoma
- Merkel cell carcinoma
- Cervical carcinoma
- Endometrial carcinoma
- Gastric or GEJ carcinoma
- Cutaneous squamous cell
- Small cell lung carcinoma
- Hepatocellular carcinoma
- Triple-negative breast carcinoma
- MSI-H and dMMR, TMB high

Anti-PD-1	Anti-PD-L1	Anti-CTLA4
Cemiplimab Nivolumab Pembrolizumab	Atezolizumab Avelumab Durvalumab	Ipilimumab

### **Cause versus Correlation: The Theory of the Stork**



SIES, H. A new parameter for sex education. Nature 332, 495 (1988). https://doi.org/10.1038/332495a0

# Vaccines and ICI therapy

- Early clinical trials disallowed vaccination while on study
- Small study from Switzerland described unexpectedly high rate of irAE's.
- Larger retrospective review from MSKCC-Chong et al. (2019)
  - N= 370 patients on ICI vaccinated for influenza
  - No increase in irAE's over previously published irAE rates
- Gopalakrishnan et al, 2018
  - N= 534 patients with various cancer types
  - Vaccinated and unvaccinated pts (37.4 v. 42.6, p = 0.067) developed equal rates of irAEs
  - Unvaccinated patients were more likely to be admitted for influenza related complications (62.4% 23.2 %, p = 0.032)
- Wijn et al, 2018
  - N= 127 patients with lung cancer receiving nivolumab
  - No increase in irAE in patients vaccinated for influenza on ICI

Chong CR, et al.. Clin Infect Dis. 2020 Jan 2;70(2):193-199. doi: 10.1093/cid/ciz202; Gopalakrishnan, R., et al. (2018). Journal of Clinical Oncology, 36(15\_suppl), 3053. https://doi.org/10.1200/JCO.2018.36.15\_suppl.3053; Wijn DH, et al. Eur J Cancer. 2018 Nov;104:182-187. doi: 10.1016/j.ejca.2018.09.012.

# Influenza Vaccine Effective

- Bayle et al., 2020 demonstrated high rate of seroconversion during 2018/2019 flu season
  - N= 30 patients
    - 25 with non-small cell lung cancer
    - 5 with urothelial cancer
  - Single, standard dose of subcutaneous influenza vaccine
  - 7 days (+/-2) after the last administration of therapy with immune checkpoint inhibitors
  - 42 post-vaccination: Seroprotective rates of 57-71% against H1N1 and H3N2

Bayle A, Khettab M, Lucibello F, et al. Immunogenicity and safety of influenza vaccination in cancer patients receiving checkpoint inhibitors targeting PD-1 or PD-11. Annals of Oncology; Published online 14 March 2020. DOI: https://doi.org/10.1016/j.annonc.2020.03.290; Gopalakrishnan, R, Johnson, D. B., York, S., Neuss, M. N., Osterman, T. J., Chism, D. D., Ancell, K. K. Mayer, I. A., Abramson, V. G., Levy, M. A., Wyman, K. Gilbert, J., Reddy, N., Morgan, D. S., Rathmell, K., & Horn, L. (2018). Impact of the influenza vaccination on cancer patients undergoing therapy with immune checkpoint inhibitors (ICI). Journal of Clinical Oncology, 36(15\_suppl), 3053. https://doi.org/10.1200/JCO.2018.36.

## Administer Flu Vaccine? Yes

- Inactivated influenza generally considered safe and effective
- Currently no data on other vaccines
- Generally recommended not to administer live-attenuated vaccines immediately before, during or immediately after ICI therapy.

**Antibiotics and ICI therapy** 

Do antibiotics affect outcomes from ICI therapy?

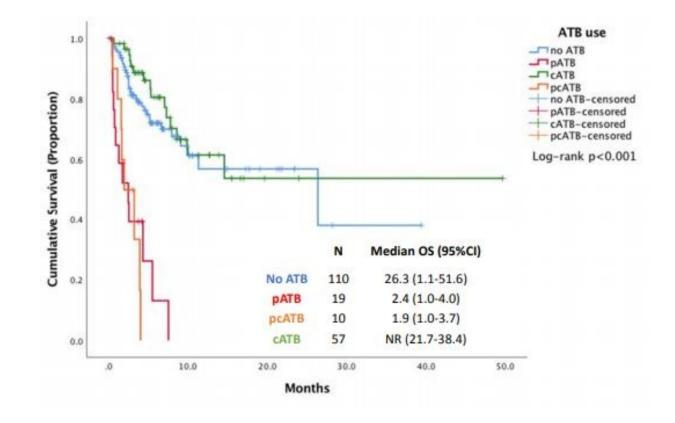
Short Answer is: YES

# **Antibiotics and ICI therapy**

Pinato et al. (2019)

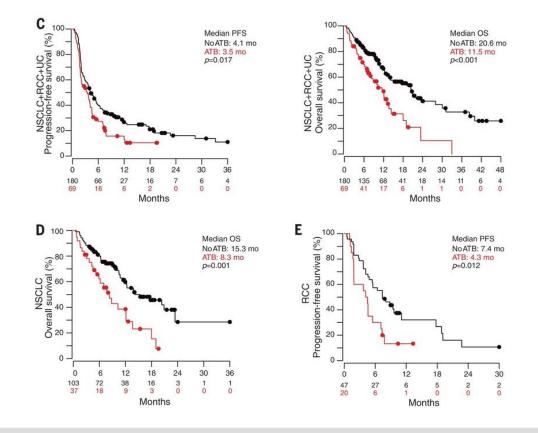
- Prospective, multicenter cohort study
- 195 patients (137 male)
- NSCLC (119) melanoma (38) other (39)
- Disseminated disease (165-84%)
- Looked at both pre-treatment antibiotic use (<30 days prior to ICI initiation) and concurrent antibiotic use

#### **Antibiotic Use Associated with Decreased Survival**



Pinato DJ, Howlett S, Ottaviani D, et al. Association of prior antibiotic treatment with survival and response to immune checkpoint inhibitor therapy in patients with cancer. Published online September 12, 2019. JAMA Oncol. doi:10.1001/jamaoncol.2019.2785

#### Antibiotic Use Associated with Decreased PFS and OS



Bertrand Routy et al. Science 2018;359:91-97

### Meta-analysis of Antibiotic Use on ICI- Decreased PFS and OS

- 19 eligible studies (including the Pinato and Routy studies)
- 2,740 cancer patients treated with ICIs
- Antibiotic use negatively associated with OS in cancer patients (HR = 2.37; 95% CI = 2.05–2.75; P < .001)</li>
- Antibiotic use associated with significantly reduced PFS in patients treated with ICIs (HR = 1.84; 95% CI = 1.49–2.26; P < .001; I2 = 56.2%)</li>

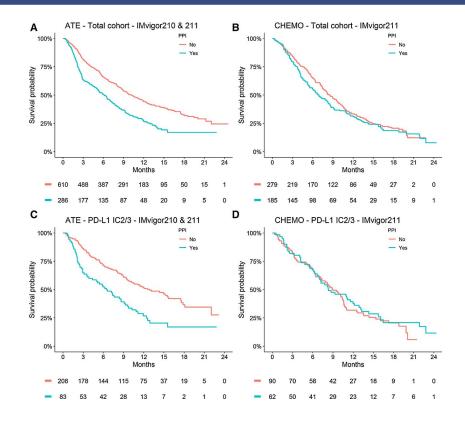
Study	HR (95% CI)	Weight ?
Zhao (2019)	2.86 (1.30, 6.25)	3.53
Hakozaki (2019)	2.02 (0.70, 5.83)	1.94
Elkrief (2019)	2.00 (0.83, 4.76)	2.85
Agarwal (2019)	1.93 (1.09, 3.42)	6.66
Schett (2019)	2.80 (1.70, 4.50)	9.19
Rounis (2019)	4.60 (1.70, 12.00)	2.28
Pinato (2019)	3.40 (1.90, 6.10)	6.40
Routy NSCLC (2018)	- 2.31 (1.40, 3.83)	8.60
Routy UC (2018)	2.27 (0.86, 5.98)	2.32
Tinsley (2018)	1.72 (0.94, 3.16)	5.92
Sen (2018)	2.00 (1.20, 3.30)	8.51
Lalani (2018)	1.47 (0.76, 2.84)	5.01
Kim (2018)	1.93 (1.20, 3.00)	10.37
Huemer (2018)	• 4.29 (1.08, 16.98)	1.15
Do (2018)	3.44 (1.72, 6.67)	4.74
Derosa RCC (2018)	2.10 (0.90, 5.00)	2.96
Derosa NSCLC (2018)	- 2.50 (1.60, 3.70)	12.39
Ahmed (2018)	2.90 (1.10, 8.10)	2.18
Thompson (2017)	3.50 (1.49, 8.21)	2.99
Overall (I-squared = 0.0%, p = 0.851)	2.37 (2.05, 2.75)	100.00
0.0589 1 Study	17	
	HR (95% CI)	Weight %
Zhao (2019)	3.45 (1.79, 6.67)	5.32
Hakozaki (2019)	2.03 (1.03, 3.99)	5.16
Elkrief (2019)	3.13 (1.20, 7.69)	3.50
Schett (2019)	2.20 (1.50, 3.40)	7.83
Rounis (2019)	2.76 (1.80, 6.40)	5.53
Routy NSCLC (2018)	0.89 (0.58, 1.34)	7.72
Routy UC (2018)	1.97 (0.91, 4.23)	4.47
Tinsley (2018)	1.37 (0.76, 2.45)	5.97
Swami (2018)	4.06 (1.78, 9.25)	4.10
Sen (2018)	1.20 (0.80, 2.10)	7.02
Lalani (2018)	2.03 (1.25, 3.30)	6.99
Huemer (2018)	2.50 (1.08, 5.78)	4.01
Derosa RCC (2018)	- 2.20 (1.30, 3.30)	7.20
Derosa NSCLC (2018)	1.30 (0.90, 1.80)	8.55
Ahmed (2018)	- 1.60 (0.84, 3.03)	5.46
		5.64
Thompson (2017)	2.50 (1.56, 5.41)	
Kaderbhai (2017)	0.89 (0.47, 1.68)	5.50
Overall (I-squared = 56.2%, p = 0.002)	1.84 (1.49, 2.26)	100.00
NOTE: Weights are from random effects analysis		
0.108 1	9.25	

Huang, X. Z., Gao, P., Song, Y. X., Xu, Y., Sun, J. X., Chen, X. W., Zhao, J. H., & Wang, Z. N. (2019). Antibiotic use and the efficacy of immune checkpoint inhibitors in cancer patients: a pooled analysis of 2740 cancer patients. Oncoimmunology, 8(12), e1665973. https://doi.org/10.1080/2162402X.2019.1665973

### **PPIs and ICI**

- PPIs cause significant changes to the gut microbiome, which plays an important role in regulating immune function
- Altered gut microbiome could negatively impact the efficacy of immune checkpoint inhibitors
- · Emerging data shows an association with PPI use and decreased PFS with ICI
- Until this is further investigated, H2 blockers recommended first line for GI ppx with steroid use

#### PPIs Associated with Decreased Survival in IMvigor 210 and 211



Ashley M. Hopkins et al. Clin Cancer Res 2020;26:5487-5493

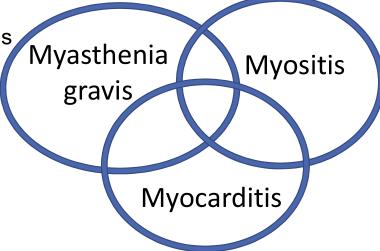
# **Clinical Pearls Regarding ICI-induced Colitis**

- Can Budesonide Be Used To Prevent ICI-Induced Colitis?
  - Phase II double-blinded trial investigated prophylactic budesonide in patients with melanoma receiving ipilimumab
  - Dose: budesonide 9 mg/d
  - Results: No decrease in risk of developing grade ≥ 2 diarrhea
- Best Practice for Treatment of ICI-Induced Colitis
  - Once patients have improvement of symptoms to grade 0 or 1-taper of steroids should occur over at least 1 month
  - Beware of rebound diarrhea!
  - If patients have been started on budesonide in addition to systemic steroids, start tapering the prednisone FIRST.
  - Do NOT administer antidiarrheals in patients with ≥ Grade 2 diarrhea as this may cause toxic megacolon and/or perforation.
    - And it usually is not effective
  - If no response to steroids in 3 days, infliximab 5 mg/kg week 0, 2, 6 or vedolizumab 300 mg IV week 0, 2, 6

Weber J, Thompson JA, Hamid O, et al: A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic buesonide in patients with unresectable stage III or IV melanoma. Clin Cancer Res 15:5591-5598, 2009; NCCn Guidelines v1. 2020 Management of Immune Checkpoint Inhibitor Related Toxicities

# Triple "M" Syndrome

- Immune induced myocarditis, myositis and myasthenia gravis are rare but potentially severe complications
- Myasthenia gravis, myositis and myocarditis may occur together. If you find/suspect one, send the work up for all 3.
- Symptoms:
  - Fatigue, weakness, frequently with ocular or bulbar symptoms
  - May have respiratory symptoms
  - May have chest pain
  - Muscle pain/weakness
- Early detection is key



Brahmer, J. et al. Journal of Clinical Oncology. 2018. Oliveira, K et. al. Neurology. 2020

#### **Case Study**

- Patient was seen in oncology clinic 3 days later with right eye ptosis and worsening difficulty swallowing, he was also unable to hold his head up
- Initial laboratory values:
  - CK 3772
  - Troponin 1937
  - BNP 1019
  - AST 304
  - ALT 374
- ECG showed ST-elevation anterior leads and ST depression in lateral leads

# What is likely diagnosis?

- 1. Myositis
- 2. Acute MI
- 3. Myocarditis
- 4. Myasthenia gravis
- 5. Hepatitis
- 6. All of the above

#### **Case Study**

- Additional labs confirmed myositis, and myocarditis. MG was ruled out.
- Patient was treated with solumedrol 1000mg and IVIG x 5 days.
- Patient clinically improved and was discharged on high dose steroids.

# **General Principles Of Steroid Management**

- DO NOT use short course pulse steroid course (e.g. methylprednisolone dose packs)
- Once irAE is resolved to grade 1 or baseline, taper steroids over at least one month-many need longer steroid taper
- Beware of emerging irAEs during steroid tapers.
- Closely monitor diabetics (or those at risk) for steroid-induced hyperglycemia
- Consider PJP prophylaxis for high-dose prolonged steroid course (e.g >20 mg prednisone for 4 weeks).
- Instruct patient to take with food, generally in the am
- GI prophylaxis (e.g., H2 blocker); avoid PPI if possible

#### Summary

- Is it ok for patients on immune checkpoint inhibitors to receive the flu vaccine?
  - Yes!
- Should we be giving antibiotics to cancer patients receiving immune checkpoint inhibitors?
  - Judiciously- For antibiotic resistance and for microbiome interaction with ICI
- Should we prescribe PPIs to cancer patients receiving immune checkpoint inhibitors?
  - Unnecessary prescription of PPIs should be avoided in patients who are receiving immune checkpoint inhibitors
- Should you prescribe loperamide to help with your patient's ICI-induced diarrhea/colitis?
  - For Grade ≥ 2, No. Doesn't usually help and could lead to toxic megacolon or perforation
- Myasthenia gravis, myositis and myocarditis may occur together.
  - If you find/suspect one, send the work-up for all 3.