Immunotherapy:
T-cell checkpoint blockade:
What should we expect?

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Disclosures

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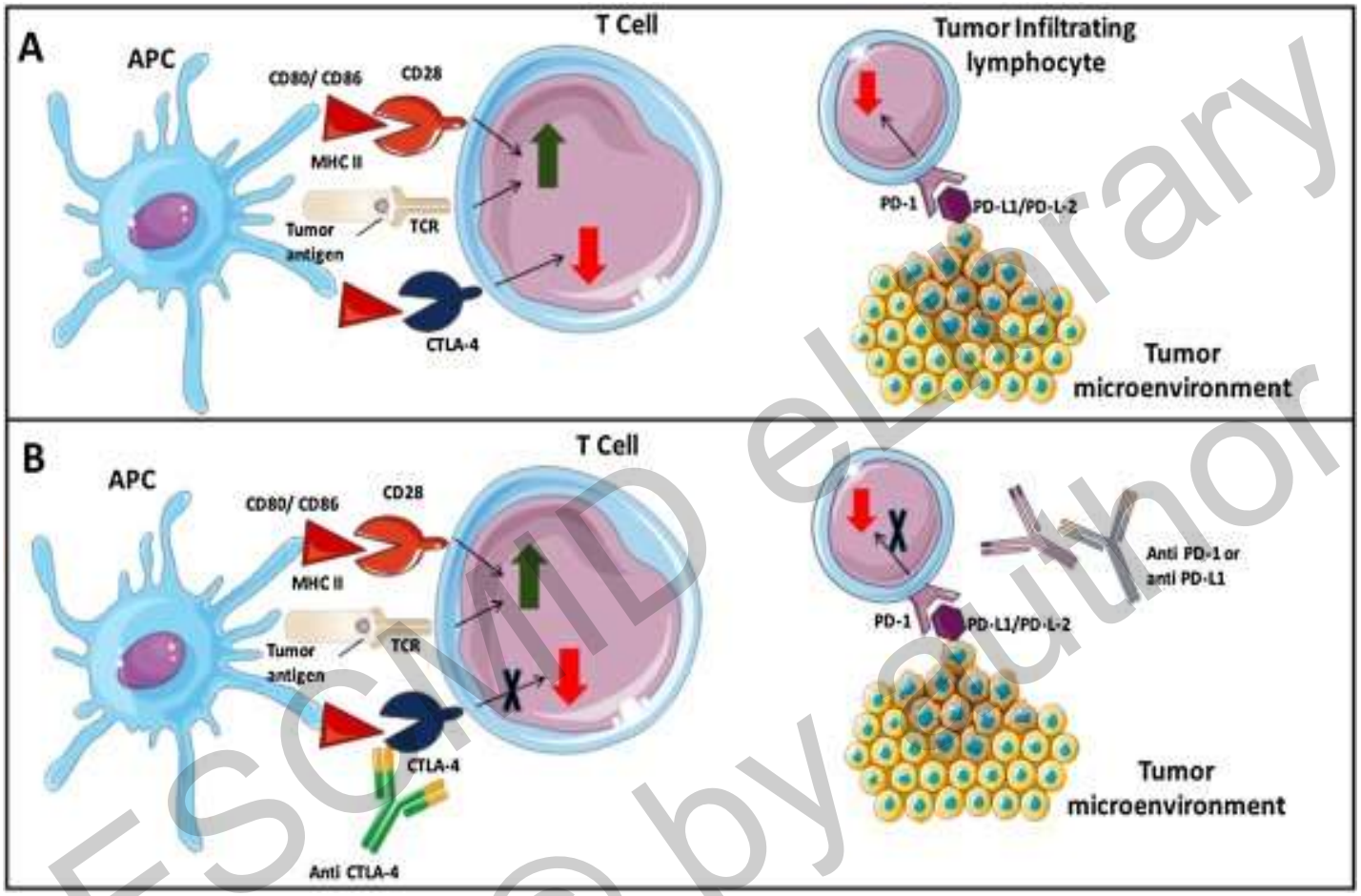
  - Cidara, Inc
  - Amplyx, Inc

* Last 12 months

Outline

- Mechanisms of action of CPIs
- Role in modern oncology armamentarium
- CPIs and infection risk
- Bacterial
  - Viral
  - Bacterial/Parasitic
  - Fungal
- Infections in patients treated for CPI-immune AEs
- Future questions

Check point inhibitors: A revolution in modern oncology



Schematic representation of immune checkpoint blockade by targeted mAbs. A 'Two signal model' of T cell activation. Antigen-presenting cells (APC) display tumor specific antigens on their surface by MHC-II molecules, recognized by T cell receptor (TCR). A second signal, mediated by CD28 binding to B7 costimulatory molecules (such as CD80 or CD86) is required for full activation. CTLA-4 is up-regulated shortly after T-cell activation, down-regulating the immune response to maintain tolerance. PD-1 is expressed by tumor infiltrating lymphocytes (TILs) after antigen exposure, and its interaction with its ligands results in T cells inhibition in the tumor microenvironment. **B.** Antibodies targeting these immune checkpoints, such as ipilimumab (anti CTLA-4) or nivolumab (anti PD-1) block the inhibitory signal, thus markedly enhancing the immune response to the tumor.

Diesendruck Y & Benhar I
Drug Res Updates 2017

Established class of agents in modern oncology treatments

Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.*

Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	Melanoma, non–small-cell lung cancer, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma

* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.

Postow MA et al. NEJM 2018

Accelerating FDA Approval of Checkpoint Inhibitors (20+ approvals in 8 years)

Cancer type/Therapy	Ipilimumab (YEVROY) (CTLA-4i)	Pembrolizumab (KEYTRUDA) (PD-1i)	Nivolumab (OPTIVO) (PD-1i)	Atezolizumab (TECENTRIQ) (PD-L1i)	Avelumab (BAVENCIO) (PD-L1i)	Durvalumab (IMFINZI) (PD-L1i)
Metastatic melanoma	2011	2014, 2015	2014, 2015 (Nivo + IPI)			
Squamous cell lung cancer (NSCLC)			2015			
Non-squamous non-small cell lung cancer (NSCLC)		2017				
Non-small cell lung cancer (NSCLC)		2015, 2016	2015	2016		
Renal cell cancer			2015			
Squamous cell carcinoma of the head and neck (SCCHN)		2016	2016			
Urothelial carcinoma		2017	2017	2016	2017	2017
Hodgkin lymphoma			2016			
Colorectal cancer		2017				
Merkel cell carcinoma					2017	

CPIs and acute and chronic viral infections

- Persistent viral Ag exposure->T cell exhaustion during *chronic* viral infections such as HCV, HBV, LCMV, HIV
- Unclear if checkpoint ligands lead to T-cell exhaustion in *acute* infections
- Most evidence is preclinical, focusing on virus-specific *ex vivo* T cells responses following PD-1 blockade
- In vivo efficacy remains circumstantial
- PD-1 expression might play a role in the establishment of chronicity of a transient viral infection
  - PD-1 upregulates CD8 T cells infected with influenza--> delayed viral clearance

Dyck L& Mills KHG. Eur J immunology 2017

CPIs and bacterial and parasitic infections

- PD-1 associated T cell exhaustion and impaired parasite clearance during *chronic* infections by *Schistosoma mansoni, Fasciola hepatica, Leishmania donovani, L mexicana, Toxoplasma gondii, Plasmodium falciparum* and PD-1 blockade restores responses and increases clearance (CD4-mediated increased INF-gamma)
- Most evidence is preclinical, focusing on parasite - specific T cells responses following PD-1 blockade
- Beneficial role of PD-1 blockade in clearance of *Helicobacter pylori* infection?

Dyck L& Mills KHG. Eur J immunology 2017

CPIs and intracellular pathogens

- The role of PD-1/PD-1 L pathway in MTB is controversial (mice, limited human studies)
- Concern (preclinical data) that immune checkpoint blockade may impair the expansion of T-cells repertoire, therefore predisposing treated patients to specific *intracellula*r infections, such as tuberculosis and listeriosis

Lazar-Molnar E, Chen B, Sweeney KA, et al. Programmed death-1 (PD-1)- deficient mice are extraordinarily sensitive to tuberculosis. Proc Natl Acad Sci USA 2010;107:13402–7.
Seo SK, Jeong HY, Park SG, et al. Blockade of endogenous B7-H1 suppresses antibacterial protection after primary Listeria monocytogenes infection. Immunology 2008; 123:90–9.
Rowe JH, Johanns TM, Ertelt JM, Way SS. PDL-1 blockade impedes T cell expansion and protective immunity primed by attenuated Listeria monocytogenes. J Immunol 2008; 180:7553–7

Additional concern: CPIs and reactivation of latent TB

- Several case reports
- Rapid onset (within the first 3 months of PD-1/PD-1 L blockade), in the absence of corticosteroids
- IRIS like phenomenon via boosting of MTB-specific T cells?

Rederlman-Sidi G et al. CMI 2018
Lee JJ et al. Act Oncol 2016
Picchi H et al. CMI 2016
Chu YC et al. J Thorac Oncol 2017

CPIs are broadly active against fungal infections controlled by T-cell effector functions

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- Barrios, CS, Johnson, BD, Henderson, JD Jr, Fink, JN, Kelly, KJ, and Kurup, VP. Enhanced expression of CTLA-4 and concurrent downregulation of CD28 on lung cells of mice exposed to *Aspergillus* antigen. J Allergy Clin Immunol. 2005; 115: pS258
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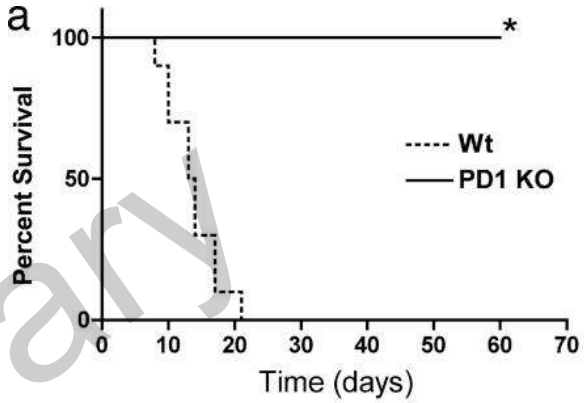
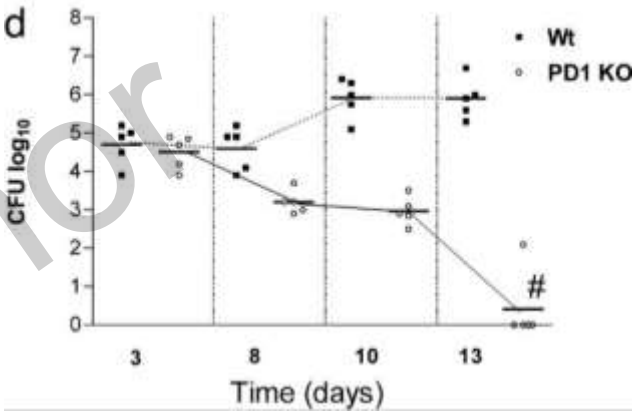
- **Daver N, Kontoyiannis DP. Checkpoint inhibitors and aspergillosis in AML: the double hit hypothesis. Lancet Oncol 2017.**

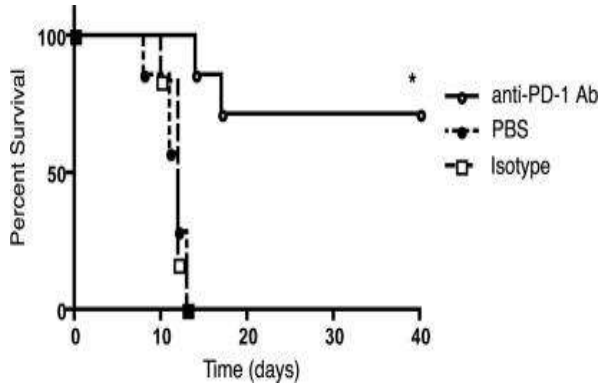
The PD-1/PD-L costimulatory pathway critically affects host resistance to the pathogenic fungus *Histoplasma capsulatum*



Lázár-Molnár E[1], Gácser A, Freeman GJ, Almo SC, Nathenson SG, Nosanchuk JD.
The PD-1/PD-L costimulatory pathway critically affects host resistance to the pathogenic fungus Histoplasma capsulatum. Proc Natl Acad Sci U S A.



- **In a lethal model of histoplasmosis, all PD-1-deficient mice survived infection, whereas the wild-type mice died with disseminated disease.**
- **PD 1-L expression on macrophages and splenocytes was up-regulated during infection, and macrophages from infected mice inhibited in vitro T cell activation.**
- **Antibody blocking of PD-1 significantly increased survival of lethally infected wild-type mice.**
- **PD-1/PD-L pathway has a key role in the regulation of antifungal immunity, suggesting that manipulation of this pathway represents a strategy of immunotherapy for histoplasmosis.**



T cells from patients with *Candida* sepsis display a suppressive immunophenotype

Spec A et al. Crit Care 2016

- 20 pts with candidemia, 16 non-septic critically ill pts with no evidence of bacterial or fungal infection were controls.
- T cells were analyzed via flow cytometry for cellular activation and for expression of positive and negative co-stimulatory molecules
- Compared to control patients, CD8 T cells from patients with candidemia had evidence of cellular activation as indicated by increased CD69 expression, while CD4 T cells had decreased expression of the major positive co-stimulatory molecule CD28.
- CD4 and CD8 T cells from patients with *candidemia* expressed markers typical of **T cell exhaustion** as indicated by either increased percentages for programmed cell death 1 (PD-1) or its ligand (PD-L1).

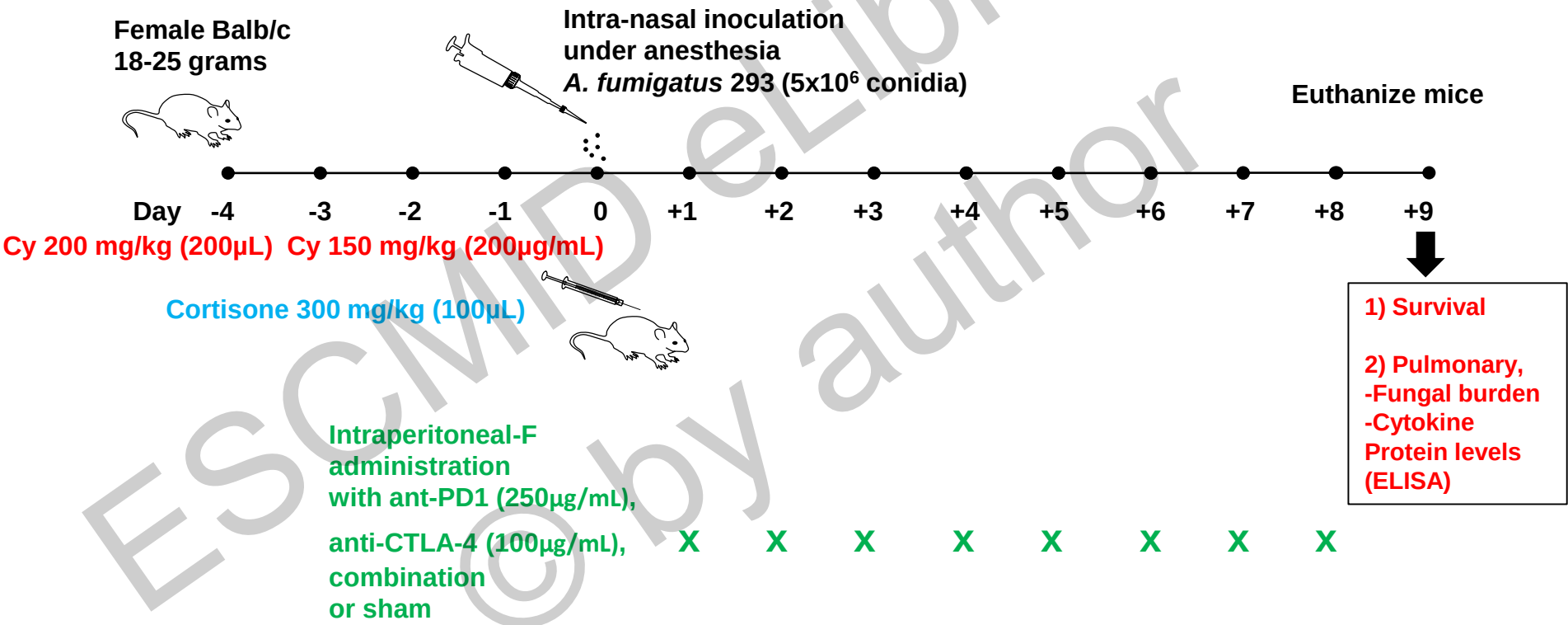
Blockade of the negative co-stimulatory molecules PD-1 and CTLA-4 improves survival in primary and secondary fungal sepsis.

Chang KC, et al. Crit Care. 2013

The ability of anti-PD-1 and anti-programmed cell death ligand-1 (anti-PD-L1) antagonistic antibodies to improve survival and reverse sepsis-induced immunosuppression in two mouse models of fungal sepsis (primary fungal sepsis and secondary fungal sepsis occurring after sub-lethal cecal ligation and puncture - CLP), was investigated.

- The administered anti-PD-1 and anti-PD-L1 antibodies were highly effective at improving survival in primary and secondary fungal sepsis.
- Both antibodies reversed sepsis-induced suppression of interferon gamma and increased expression of MHC II on antigen presenting cells.
- Blockade of cytotoxic T-lymphocyte antigen-4 (CTLA-4), a second negative co-stimulatory molecule that is up-regulated in sepsis and acts like PD-1 to suppress T cell function, also improved survival in fungal sepsis.

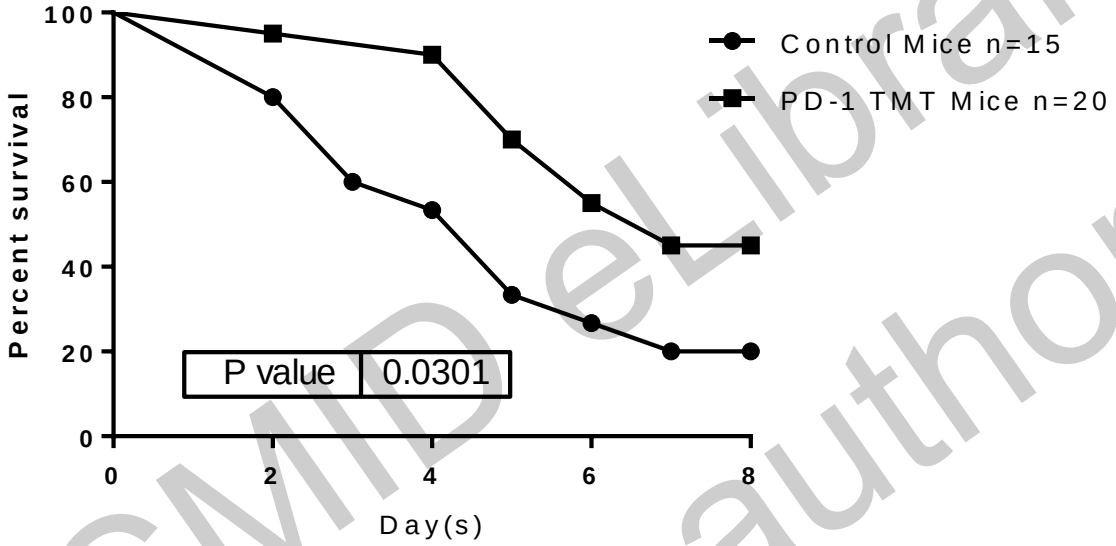
Studying CP blockade in a murine model invasive pulmonary aspergillosis



Cy-Cyclophosphamide

Robinson P…Kontoyiannis DP. *unpublished*

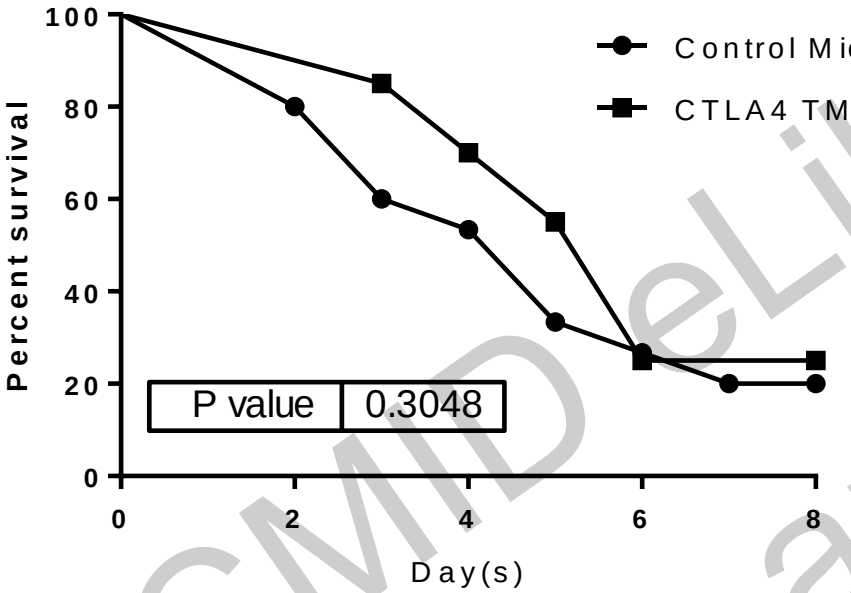
Survival differences between non treatment infected mice (control) vs. PD-1 treatment of infected mice



Robinson P… Kontoyiannis DP. *Unpublished*

BUT

No survival differences between non treatment infected mice (control) vs. CTLA treatment of infected mice



? Lack of efficacy

? Efficacy but increased immune injury

Robinson P… Kontoyiannis DP, *unpublished*

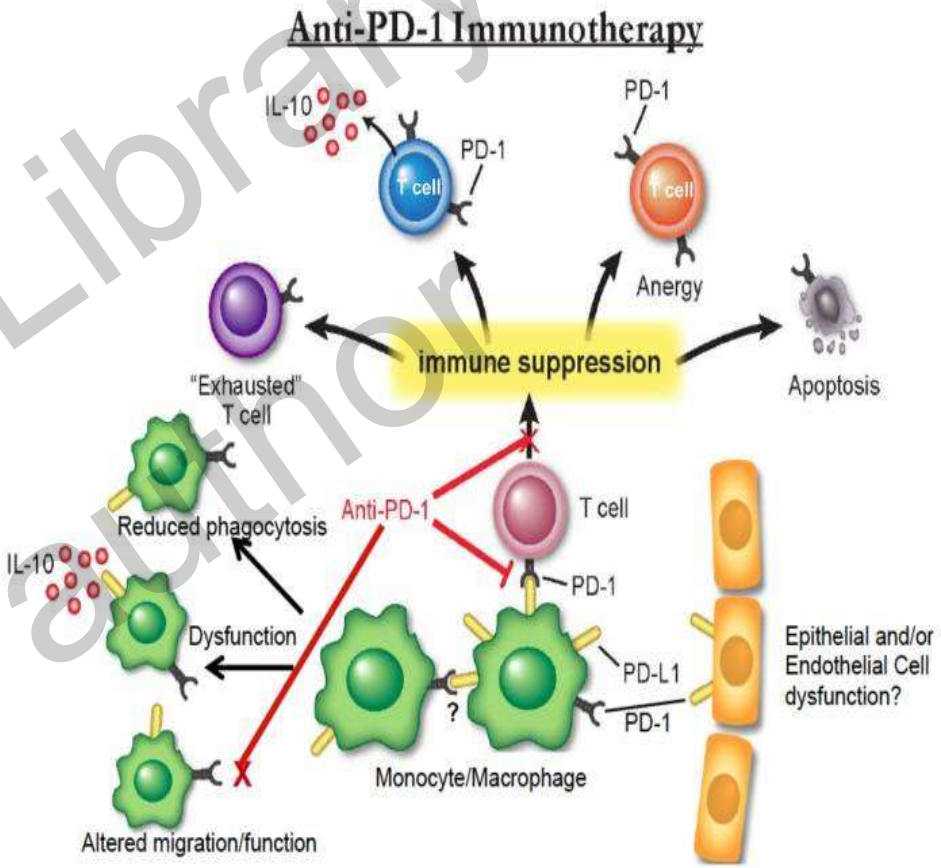
Potentially adjunctive treatment for refractory/resistant fungal infections? A case report

- Immunocompetent host, severe mucormycosis following trauma
- Refractory infection despite surgery, lipoAMB+POSA
- Low absolute lymphocyte count, low monocyte HLA-DR expression, and increased expression of programmed death-1 (PD-1) on T-cells
- Immunoadjuvant therapy with interferon-γ (100 μg X3/wk for 5 doses) starting on d28, followed by a single 250 mg dose of nivolumab on d 30.
- Subsequent immunological examinations showed increases in absolute lymphocyte count, monocyte HLA-DR expression, and CD8 T-cells, and decreased T-cell PD-1 expression
- Pt improved slowly, and repeat CT scans showed no residual infection, D/C from ICU d 80.

Grimaldi D et al. Lancet ID 2017

Anti-PD-1 immunotherapy proposed for sepsis

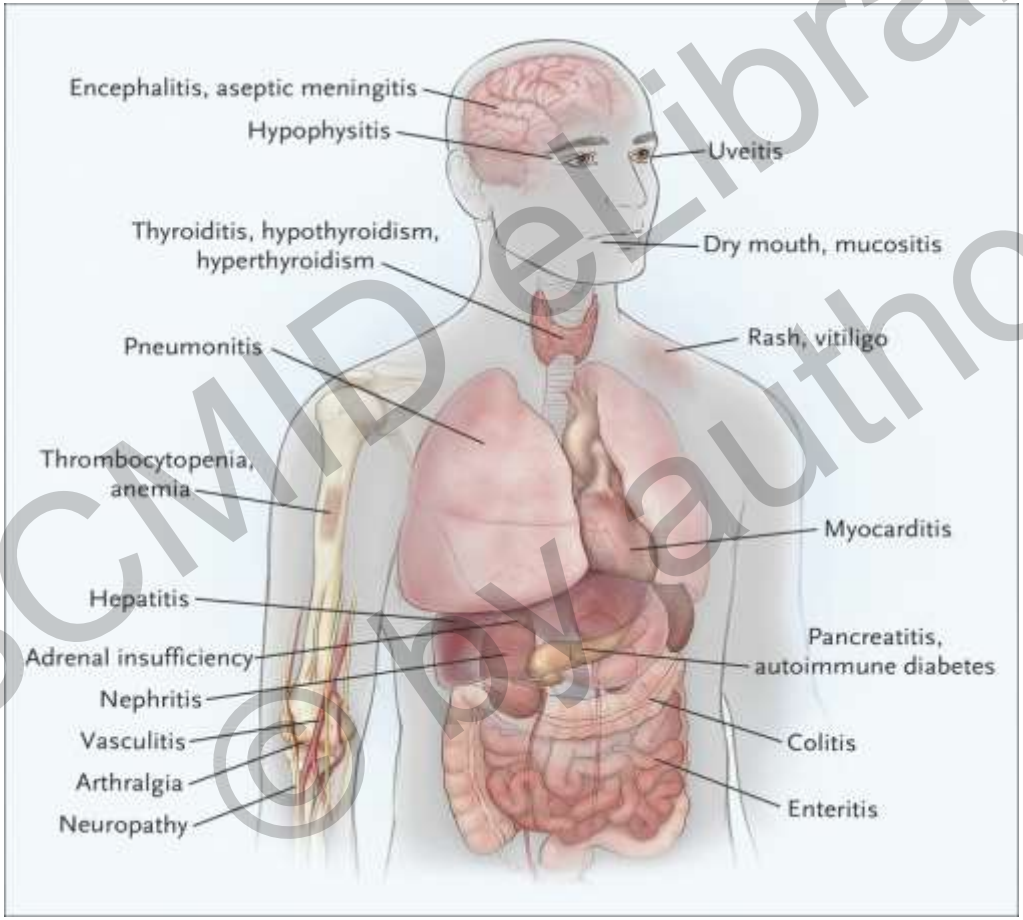
- Increasing preclinical evidence (from animal sepsis models and patient samples suggest that certain cytokines (IL-7), IL-15, GM-CSF), as well as co-inhibitory molecule blockade, such PD-1 and (PD-L1 are up-regulated on monocytes, macrophages, and T lymphocytes during sepsis.
- PD-L1 has also been shown to be increased on epithelial and endothelial cell populations in septic animal models, and may play a role in barrier function
- A phase I clinical trial of nivolumab (safety, PKs) in the treatment of severe sepsis /septic shock is ongoing (NCT02960854).



Hutchins NA et al. Trends Mol Med 2014

But…..

Frequent, often severe, and pleiotropic immune-related adverse effects associated with CPIs



Treatment: long term glucocorticosteroids and TNF inhibition (e.g., Infliximab) for GC-refractory cases

Postow MA & Hellmann MD. NEJM 2018

Opportunistic infections in patients treated for immune related AEs due to CPIs with

- Retrospective study of 740 patients with *melanoma* at MSKCC (2010-2014) who received immune checkpoint inhibitors.
- Serious infection occurred in 54 patients (7.3%)
  - Fungal in 6 (PJP in 3, IPA in 2), viral 5, pneumonias in 13
- Average time to infection: 135d, 80% within 6 months
- Risk factors for serious infections: corticosteroids (OR 7.71; and use of infliximab (OR, 4.74)
- Use of a combination of ipilimumab and nivolumab was associated with increased risk of serious infection, whereas use of pembrolizumab was inversely associated

Del Castillo M et al. CID 2016, Kyi C et al. J immunother Cancer 2014, Arriola E et al. Onco-Immunology 2015, Uslu U et al. J Immunother 2015, Redelman-Sidi G et al. CMI 2018

Screening and prevention measures-1#

- Preferred time point: Before checkpoint inhibitor initiation
- Assess for prior history or high risk of TB, hepatitis B/C, endemic fungal infections (histoplasmosis, coccidioidiomycosis)
- Screening all patients with T-spot, HBsAg, HBsAb, HBcAb, HCAb, CMV antibody, Toxoplasma IgG, IgM
- *Specific screening with work-up of immune-related adverse events:*
  - Colitis: Stool sample for stool culture, C diff toxin, O&P, Blood for CMV PCR
  - Pneumonitis: Blood sample for CMV PCR, *Aspergillus* galactomannan (AML)
  - Histoplasmosis and coccidiodiodomycosis serology if h/o or high risk of endemic fungal infections
  - Infectious disease and pulmonology consult

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Screening and prevention measures-2#

- General prevention:
  - Encourage up-to-date with inactive vaccines, ie., flu shots, pneumococcal vaccine
  - Avoid live vaccines during checkpoint inhibitors therapy, especially during immunosuppression for immune-related adverse events
- All patients started on high dose steroids (*daily dose ≥ 20mg/day of prednisone or equivalent or anticipated cumulative dose ≥ 360mg of prednisone or equivalent*)
  - PJP prophylaxis:
    - (if no sulfa allergy), Bactrim DS 1 tab PO BID,
    - Sulfa allergy: Atovaquone 1500mg PO/d or Dapsone 100mg PO/dy
  - HSV prevention: Valtrex 500mg PO daily

Screening and prevention measures-3#

- General prevention:
  - Antifungal prophylaxis*: Posaconazole tablet 300mg /d
  - Duration of antimicrobial prophylaxis:
    - During immunosuppressive therapy and continue for 4 weeks after the last dose of immunosuppressants.

* In hematologic cancers

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Some future questions-1

- How we evaluate best epidemiology in the new era?
  - RCT excluded cancer patients with active infections!
- Need post marketing studies
- How study the full range of CPI effects on the immune system?
  - Human studies
  - Murine studies
- Can we risk stratify for infections in patients treated for CPI-immune AEs?
- Clinical score cards?
  - Immuno-genetics?
  - Microbiome/mycobiome
  - Need for prophylaxis in certain subgroups?
- Viral infections or vaccinations as triggers of CPI-immune AEs (e.g, pneumonitis)
- Risk for infection when CPIs are combined with epigenetic agents, Mab, cytotoxic drugs

Some future questions-2

- Best treatment strategies of OIs developing post CPI-immune AEs, or in the setting of restarting or changing CPIs
- Natural history of OIs in patients receiving various CPIs
- Is the a role CPIs in the setting of treatment of specific (viral or fungal) difficult to treat infections?
  - *PML*
  - *Refractory onychomycosis*
- Synergy of CPIs with anti-infective drugs that have adjunct immuno-potentiating action (e.g., echinocandins)
- CPIs and IRIS-like manifestations
- Infections in CPI treated patients as function of underlying disease (e.g., solid tumor vs leukemia)
- *Early efforts for "guidelines"* (Redelman-Sidi G et al. CMI 2018, Brahmer JR et al. JCO 2018) *but we need many more quality data!*

Conclusions

- “Game changing” new drugs in the oncology treatment
- Intriguing, mostly protecting effects, mainly based on preclinical studies
- OIs associated with immunosuppression treatment of CPIs-immune AEs
- ? Potential for IRIS
- CPIs and infection risk: A mixed bug, new exciting “niche” area for investigation

Thank you!
(and see you
In Athens!)

For more information:
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