ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

Workshop

Managing comorbidities & concomitant medications

Mars, floor 1

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Moderated by
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Mercury number IOBE18NP04371-10
Date of preparation: December 2018

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Some examples/ protocols with immunotherapy – exclusion criteria

Bristol-Myers Squibb

Autoimmune disease: clinical trial exclusion criteria

- Protocol I. Active or prior documented autoimmune disease within the past 24 months. Please note:
  - patients with vitiligo, Graves disease, or psoriasis not requiring systemic treatment (within the past 24 months) are not excluded.
- Protocol II. Active autoimmune disease that required systemic treatment in the past (i.e. with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Please note:
  - patients who have not required systemic treatment in the past 2 years should discuss their case with medical monitor to determine eligibility
  - patients with hyper/hypothyroidism, vitiligo, controlled asthma, Type I diabetes, Graves' disease, or Hashimoto's disease are eligible to participate
  - replacement and symptomatic therapies (e.g. levothyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) are not considered a form of systemic treatment and are allowed

References

Brain metastasis: clinical trial exclusion criteria

- Protocol I. Have symptomatic central nervous system (CNS) malignancy or metastasis (screening not required). Patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids greater than 10 mg per day of prednisone or equivalent, and their disease is asymptomatic and radiographically stable for at least 60 days
- Protocol II. Known active CNS metastases and/or carcinomatous meningitis. Please note:
  - Patients with previously treated brain metastases may participate provided that they are stable (without evidence of progression by imaging for at least 28 days before the first dose of study drug and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases or CNS edema, and have not required steroids for at least seven days before the first dose of study drug

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Organ dysfunction and transplant patients

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General remarks

- **Clinical trials**: patients with baseline (multiple) organ dysfunctions and organ transplanted patients are excluded
- Safety? Efficacy in these patients?
- In patients who have received organ transplants, the PD-1 and CTLA-4 pathways are vital down regulators of autoimmunity by restricting T-cell activation, thus activation of these pathways by immune checkpoint inhibition may enhance organ transplant rejection
- Patients who receive organ transplants also require constant chronic immunosuppression

Chae et al. Cancer Treat Rev 2018;63:116–121.

Kanz et al. – organ dysfunction

- A multicenter retrospective analysis of patients with solid tumors and baseline **organ dysfunction** AND R/ with CPI
- Renal insufficiency (GFR ≤ 30 ml/min or creatinine ≥ 2 mg/dl)
  cardiac dysfunction (LEVF ≤ 45 %)
  hepatic dysfunction(AST, ALT or bilirubin > 3 × upper limit of normal or evidence of cirrhosis on imaging)
- No significant increase in irAE-incidence
- Deteriorating organ dysfunction occurred infrequently and spontaneously resolved with supportive care
- Anti-PD-1 administration can be considered in patients with organ dysfunction

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPI, checkpoint inhibitor; GFR, glomerular filtration rate; irAE, immune-related adverse event; LEVF, Left ventricular ejection fraction.
Kanz et al. Immunother Cancer 2016;4:60.

Herz et al. – chronic kidney failure

- Four case reports
- Patients with chronic kidney failure
- R/ with ICI: anti-CTLA-4 or anti-PD1
- None of these patients experienced deteriorated kidney function during treatment
- No kidney toxicity was observed

ICI, immune checkpoint inhibitors.
Herz et al. Eur J Cancer. 2016;67:66–72.

Kittai et al. Chae et al.– transplant patients

- In one report, 4/12 patients treated with ICI experienced organ rejection
- Transplant rejection was experienced by 1/6 patients treated with anti-CTLA4 versus 4/8 patients treated with anti-PD1
- Is anti-CTLA4 safer?
- Only cases
- Excluded from trials

Kittai et al. J Immunother 2017;40:7:277–281.

Daste et al. Nishijima et al. – elderly

- Elderly patients suffer from more comorbidity
- Tolerance of immunotherapy in elderly patients is rather similar compared to younger patients
- A 2016 systematic review and meta-analysis (> 5000 pts) by Nishijima et al. compared ICI efficacy in younger and elderly patients (cut-off 65–70 years) and observed that PFS and OS was consistently higher in both groups (except for 4 trials PD-1 inhibition in elderly patients, showing no OS benefit)
- Trials in elderly needed

OS, overall survival; PFS, progression-free survival;.

1. Daste et al. Eur J Cancer 2017;82:155–166. Nishijima TF et al. Cancer Treat Rev 2016;45:30–7.

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ICI in patients under chronic immunosuppression or autoimmune diseases

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Abdel-Wahab et al.

- A meta-analysis: 49 case reports of cancer patients (N = 123) with auto-immune diseases and treated with ICI
- 50% had autoimmune disease exacerbation
- 34% had de novo irAEs, with colitis and hypophysitis reported as the most frequent AE (9% each)
- No permanent discontinuation

Abdel-Wahab et al. Ann Intern Med 2018;1682:121–130.

Leonardi GC et al.

- Retrospective analysis of 46 NSCLC (stage IIIb/IV) patients with autoimmune disease + anti-PD-1
- Upregulation AI-related symptoms during ICI were rather uncommon
- Only 17% of patients experienced exacerbation of their AI-status
- 26% of patients developed one or more irAEs non-associated to their autoimmune disease, but no Grade 3 or 4 irAEs were reported
- 3 patients had to permanently discontinue anti-PD-1 treatment due to an irAE

NSCLC, non-small cell lung cancer.
Leonardi GC et al. J Clin Oncol 2018;36:19:1905–1912.

Menzies et al.

- 52 melanoma pts with autoimmune disease + CPI
  38 % flare / 29 % other irAEs
- An increase of immune toxicity during anti-PD-1 treatment in melanoma patients with active autoimmune disease
- However, these toxicities were perceived as mild, easily manageable under adequate corticosteroid treatment, and did not require therapy discontinuation
- Above all, significant clinical response rates were achieved
  RR 33 %

Menzies et al. Ann Oncol 2017;28:2:368–76.

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HIV

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General remarks

- Skepticism exists concerning ICI in cancer patients with chronic infectious diseases as many studies suggested these could alter immune checkpoint molecules functioning
- This was first noted in chronic Hepatitis B infection, which induced CTLA-4 gene polymorphisms
- Multiple in vitro and in vivo studies provided evidence that interactions occurred between HIV-infections and immune checkpoint molecules such as PD-1, PD-L1, CTLA-4, TIM-3, LAG-3 and TIGIT
- In fact, PD-1, TIM-3 and LAG-3 are markers of T cell exhaustion and are measured before antiretroviral therapy, they can be used to predict time of viremia rebound

Marra et al. The Open AIDS Journal, 2017;11:91–100.

Ostios-Garcia L et al. HIV and NSCLC

- HIV patients with metastatic NSCLC
- These patients received anti-PD-1 nivolumab (n = 2) or pembrolizumab (n = 5)
- Antiretroviral therapy was continued during treatment
- A partial response was noted in 3/7 patients
- No Grade 3 or 4 irAE were observed
- Immune reconstitution inflammatory syndrome was not observed

HIV, human immunodeficiency virus.
Ostios-Garcia L et al, J Thorac Oncol 2018;13:7:1037–42.

Tomsitz D et al. / Wightman F et al. HIV and melanoma

- A 76-year old male, HIV-positive patient
  - Consecutively treated with ipilimumab and nivolumab for M+ melanoma
  - The viral load stayed below the limit of detection and CD4+ levels remained stable during the entire treatment with ICI until an event of autoimmune leukopenia occurred
- HIV reservoir in a HIV-positive patient with metastatic melanoma on ART (antiretroviral therapy). Treatment with ipilimumab induced alterations in the number and phenotype of CD4+ T cells: increase of CD4+ T cells after each infusion
  - after the first dose of ipilimumab unspliced cell-associated HIV RNA concentrations increased, and decline in plasma HIV RNA

ART, antiretroviral therapy.
Tomsitz D et al. J Eur Acad Dermatol Venereol 2018;32:1:e26–e28

Rai R et al. HIV and solid cancers

- A multicenter retrospective study
  - analyzed ICI treatment in HIV positive patients with different types of malignancies
  - 8 HIV-positive patients
  - patients experienced no loss in viral control during treatments with anti-PD-(L)1 agents

Rai R et al. Annals of Oncology 2017;28:5(Suppl.).

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Hepatitis B and C

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Hepatitis

- There have been reports of ICI-treated patients with chronic Hepatitis B and C who benefited from ICI treatment and who did not experience any immune-mediated hepatitis
- Initially, patients with chronic liver diseases or liver transplants were systematically excluded from every ICI-based clinical trial, therefore the literature about this patient subgroup remains limited
- Indeed, hepatocellular carcinoma (HCC) is an indication that has gained interest when it comes to ICI-treatment, suggesting that eventually more patients with underlying liver disease will be treated with immunotherapy

HCC, hepatocellular carcinoma.
Rai R et al. Annals of Oncology 2017;28:5(Suppl.).

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Brain metastasis and ICI treatment

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Lung cancer – brain metastasis

- The checkmate 057 trial compared treatment with docetaxel or nivolumab in previously-treated NSCLC with brain metastasis (BM)
  - No OS benefit of nivolumab over docetaxel (HR: 1.04, 95% CI: 0.62–1.76)
- The OAK study compared atezolizumab with docetaxel in platinum-failed patients with advanced/metastatic NSCLC including supra-tentorial metastatic patients
  - an increased median OS of atezolizumab over docetaxel was noted (HR: 0.54, 95% CI: 0.31–0.94)
- Both ICI did have a manageable safety profile that was comparable to prior studies and also comparable to the safety profile of docetaxel

BM, brain metastasis.
Borghaei et al. N Engl J Med 2015;373:1627–39

Renal cell cancer– brain mets (NIVOREN)

- Albiges et al. performed a prospective analysis (NIVOREN) of response to nivolumab in BM renal cell carcinoma(RCC)- a subset of the patients included in this real life trial (73 pts- lesions 11 mm, no ss, no edema, no cortico's
  - This was the first study that included RCC-patients with pre-treated and non-pre-treated BM
  - Nivolumab efficiency was more favorable in BM patient without prior local treatment compared to pre-treated patients, and most patients in the latter group required local treatment due to disease progression
  - The six month progression-free survival was 44.8% in previously treated patients in comparison to 24.5% in non-treated patients / only RR of 11.8 %

RCC, renal cell carcinoma.
Albidges et al, ASCO 2018.

Melanoma– brain mets

- Patients with asymptomatic, previously-untreated BM were administered the combination of ipilimumab/nivolumab or nivolumab monotherapy (3 arm trial)
- Eventually, a 46% intracranial response rate was observed with the combination ipilimumab/nivolumab (asymptomatic not pretreated patients) - 17% CR intracranial
- **Thus, nivolumab combined with ipilimumab should be considered as a first-line therapy for patients with asymptomatic untreated brain metastases.**

Chapman PB et al. Lancet Oncol 2018;19:5:589–91.

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Influenza vaccination

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Negative report

- An observational study from Läubli et al. included 23 lung cancer patients in Switzerland, and investigated the safety and vaccine-induced immunity during ICI treatment
- Overall irAE frequency was 52%, and 26% were Grade 3/4 irAEs, which was significantly higher than published safety data from other clinical trials with anti-PD-(L)1 inhibitors
- One should remain skeptical about results as this was a small cohort of 23 patient and no randomization occurred

Läubli et al. J ImmunoTherapy Cancer 2018:6:40.

Positive report

- Wijn et al performed a cohort study on 123 lung cancer patients under treatment with anti-PD-1 (nivolumab) and compared irAE-incidence in influenza-vaccinated lung cancer patients versus non-vaccinated lung cancer patients
- This study concluded that ICI treatment did not increase the incidence of (serious) irAEs
- There were also no significant differences regarding tumor response, treatment outcome or discontinuation rate

Wijn et al. Eur J Cancer 2018;104:182–187.

Positive report

- A large retrospective study of ICI-treated cancer patients (N = 534) from Gopalakrishnan et al.
- Influenza vaccination is safe
  - Vaccination reduces the amount of hospitalization from flu-related and immune-related adverse events.
- This study also stated that OS may increase with influenza vaccination

Gopalakrishnan R et al. ASCO 2018.

BvP ION statement

- **Influenza vaccination remains indicated in cancer patients, even under therapy with immune checkpoint inhibitors. Close monitoring for immune-related toxicity must of course be further maintained.**
- **We recommend vaccination at least one week before administration of ICI therapy to allow for resolution of possible vaccine-induced flu-like syndrome.**
- **Out of precaution, we would however advise against vaccination during an episode of immune-related toxicity under immune checkpoint inhibition, or in patients in the recovery phase of such episode (i.e. as long as there is a need for systemic steroids or other immunosuppressive medication to control the immune-related toxicity).**

Gopalakrishnan R et al. ASCO 2018.

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Closing remarks

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Refreshment break

Lounge, floor 0

Please make you way to your second workshop room at 18.55

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