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Challenges in PD-1/PD-L1 HBV Trials

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Potential AND Challenges with PD-1 Targeting Therapies

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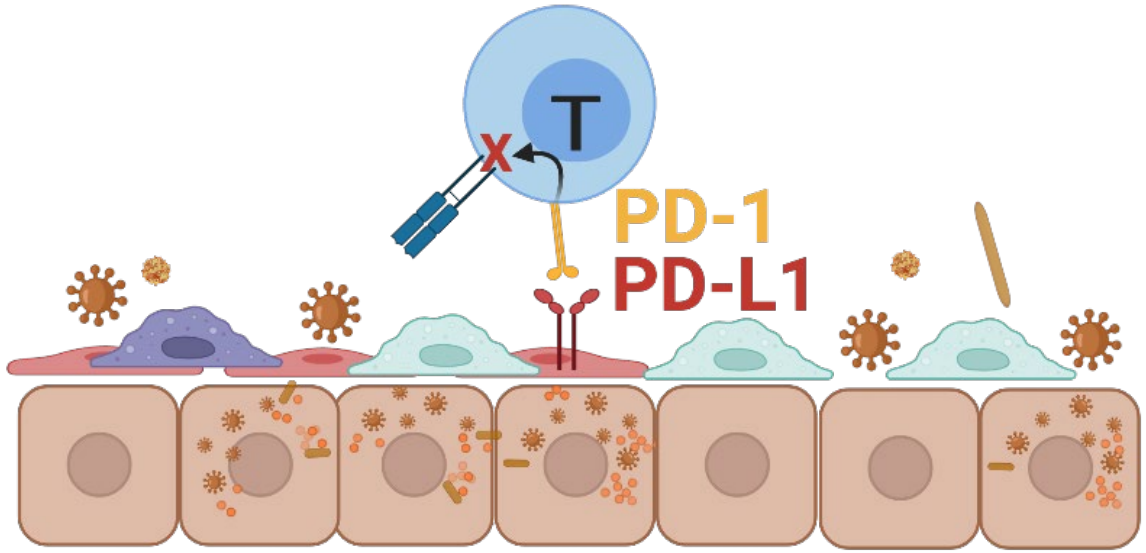
- Immunotherapy targeting the PD-1 axis has the potential to restore HBV-specific T & B cell magnitude and function

Release the brakes

- **Block inhibitory receptor function**
- **PD-1-PD-L1 interaction**
  - **PD-1 suppresses T cell receptor signaling**
  - **reduced cytokine production**
  - **reduced killing**
  - **reduced proliferation**



Potential AND Challenges with PD-1 Targeting Therapies

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- Many sponsors are progressing drugs targeting PD-1/PD-L1 for immune restoration
  - Inclusion/exclusion criteria have been very conservative for safety reasons
  - Consequence = high screen fail rate

- Many immune-related adverse events (IrAEs) documented in clinical trials where therapies were 2nd or 3rd line

Propose to review or harmonize inclusion/exclusion criteria to maintain safety and decrease screen fail rates

Questions and Considerations

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Question	Consideration
What is the real world incidence of IrAEs in PD-1 monotherapy in patients that are generally healthy, or at least 1st line treatment?	Much of the data are based on early clinical trials of late-stage cancer patients with multiple morbidities/frailty
What IrAEs should be prioritized?	Most are reversible by steroids.
Should we focus on irreversible IrAEs?	Thyroiditis:What is the general prevalence of chronic HBV patients on thyroid replacement therapy? What is the risk of death with PD-1 monotherapy?
Are there actual predictors of IrAEs? Any validated evidence that auto-antibodies actually serve as a predictor?	Auto-antibodies are a significant exclusion factor in HBV studies Not seen as valuable in oncology
Does a liver targeting checkpoint inhibitor carry the same risk of IrAE as that of an infused mAb?	Should liver targeted drugs or small molecules use different criteria?

Maximize room for “blips” in standard virology biomarkers

- Trials may include patients on NUC
- Setting exclusion at the limit of detection within X months excludes patients that would rationally be considered eligible
  - exclusion < 20 U/mL HBV DNA
  - patient = 27 U/mL HBV DNA with past 6 months
- HBV DNA: does upper limit matter?
  - If on NUC, do we allow for blips (ie < 100 U/mL)?
- ALT: does elevated ALT impact risk? Efficacy?
  - Is the underlying cause of elevated ALT important?

Open Discussion