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# Checkpoint Inhibitors in HBV Clinical Development

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# Potential AND Challenges with PD-1 Targeting Therapies

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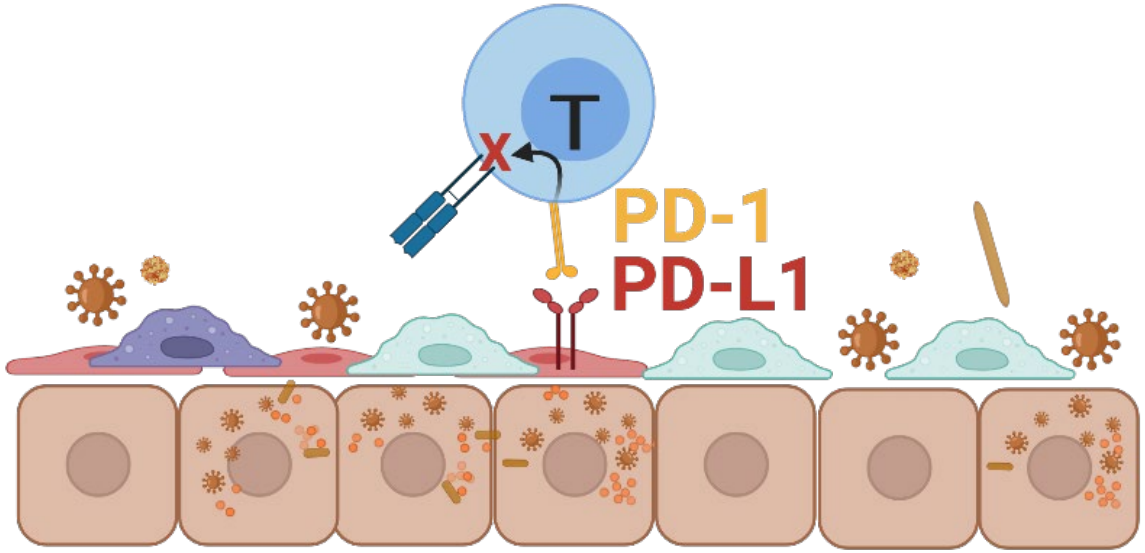
- Immunotherapy targeting the PD-1 axis has the potential to restore HBV-specific T & B cell magnitude and function
- Realistically, only a portion of CHB patients will respond to checkpoint blockade

**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**



# Working Group

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- HBV Forum convened a discussion October 2023 to identify major questions around checkpoint inhibitors in CHB patients

  Can we identify patients who will benefit from checkpoint inhibitor therapy before safety becomes an issue, and enrich for responders?

  Will CHB patients display a similar risk-benefit profile to cancer patients?
  very different population

  Are there reliable (experimental) approaches from oncology to predict response/IrAE during PD-1 therapy?
  Are these being tested pro/retrospectively in clinical trial samples?

# Key Themes of Working Group Discussion

# 1. Identifying Responders

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- Multiple, small studies are testing PD-1/PD-L1 inhibitors
- No single early-stage trial will enroll enough patients to answer previous questions
- Propose an **HBV Forum Database** (collate public data from checkpoint inhibitor studies presented at EASL & AASLD, similar to Biomarkers Database Working Group)
  - Response rate
  - Target: PD-1 or PD-L1
  - Dosing schedule and amounts
  - Mode: systemically delivered antibody, ASO, siRNA, small molecule.
  - Patient demographics: responders & IrAEs
  - HBV stage: responders & IrAEs
  - Combination therapies
  - Treatment algorithm to assess 1st,2nd or 3rd line use?
  - Age/time since HBV diagnosis

# 2. Benefit-Risk Assessment

- Consensus that the benefit-risk assessment for checkpoint inhibitor therapy will differ between oncology patients vs. CHB patients
  - IrAEs can occur in any organ system, with the median onset usually within 2–16 weeks from the commencement of therapy, depending on the organ system involved (Weber)

- Further emphasizes the need to identify the HBV subpopulations most likely to benefit from checkpoint inhibitor therapy

# 3. Key Learnings from Oncology

- Propose to review oncology literature to understand predictors of IrAEs among cancer patients receiving PD-1/PD-L1 therapies
  - Assess to what extent these findings are applicable to CHB patients

- Oncology resources:
  - Excellent meta-analyses available over time
  - QoL/PRO also should be considered

# Xu C, et al. Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis. BMJ. 2018 Nov 8;363

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Table 2

Effect of treatment on each specific grade 1-5 adverse event. Values are odds ratios* unless stated otherwise

| Group | Fatigue | Pruritus | Rash | Diarrhoea | Colitis | Nausea | Vomiting | ALT increased | AST increased | Pneumonitis | CRE increased | Hypothyroidism | Hyperthyroidism |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | 26 | 24 | 24 | 27 | 16 | 26 | 19 | 16 | 16 | 14 | 10 | 19 | 14 |
| No of patients | 13 641 | 12 371 | 12 371 | 14 139 | 8729 | 13 641 | 9761 | 7666 | 7666 | 6855 | 4585 | 9252 | 7562 |
| Nivolumab as control | | | | | | | | | | | | | |
| Ipilimumab | 1.14 | 0.48 | 0.69 | *0.42* | *0.17* | 0.75 | 0.43 | 0.63 | 0.68 | 1.02 | 0.33 | 2.68 | *2.58* |
| Tremelimumab | 0.84 | 0.55 | 0.24 | *0.15* | 0.99 | 0.61 | 0.52 | NA | NA | NA | NA | 1.49 | 0.72 |
| Pembrolizumab | 1.22 | 0.82 | 0.87 | 0.93 | 0.66 | 0.88 | 1.09 | 0.47 | 0.49 | 0.37 | 1.85 | 0.96 | 1.12 |
| Atezolizumab | 1.26 | 1.21 | 1.13 | 1.28 | NA | 0.61 | 0.49 | NA | NA | 0.58 | NA | 0.67 | NA |
| Two ICI drugs | 0.95 | 0.43 | 0.47 | *0.29* | *0.13* | 0.48 | 0.29 | *0.12* | *0.15* | 0.24 | 0.10 | 0.73 | *0.32* |
| One ICI drug with conventional therapy | *0.55* | 0.79 | 0.47 | *0.31* | 0.24 | *0.23* | *0.28* | 0.49 | 0.72 | 0.19 | 0.71 | 3.73 | 1.53 |
| Conventional therapy | *0.70* | *4.76* | *2.19* | 0.76 | *4.80* | *0.31* | *0.38* | 1.58 | 1.86 | 2.26 | 1.14 | *15.69* | *7.58* |

ALT=alanine transaminase; AST=aspartate transaminase; CRE=blood creatinine; ICI=immune checkpoint inhibitor; NA=not applicable.

# Unveiling Immune-Related Adverse Events (irAEs) and Symptom Burden in Melanoma Patients on Adjuvant Immune Checkpoint Inhibitors (ICIs)

Abstract ID: 444

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## BACKGROUND

- ICIs are used in the adjuvant/neoadjuvant setting for melanoma, but challenges persist regarding irAEs and their long-term impact on quality of life (QOL).
- Existing data from clinical trials are limited to highly selected populations and predetermined endpoints, failing to capture real-world experiences and symptom variability.
- The pathogenesis of irAEs and associated symptoms remains poorly understood.
- This prospective study (NCT04990726) aims to investigate irAEs, symptom burden, and immune/genetic biomarkers in adjuvant/neoadjuvant ICI-treated melanoma patients (pts) in real-world settings to understand the full impact of ICI therapy in melanoma patients receiving regular clinical care.

## METHODS

- 240 pts with surgically resectable stage II/III/IV melanoma initiating adjuvant/neoadjuvant ICIs, without prior systemic therapy or autoimmune diseases, will be enrolled. 35 pts undergoing active surveillance will serve as a comparative reference.
- Clinical assessments, patient-reported outcomes (PROs), and blood collection occur at baseline, months 1, 3, 6, 12, 18, 24, and at time of irAEs. Real-time symptom reporting is facilitated through mobile technology.

**Self-reported PROs**

- Quality of life (EORTC QOL-C30)
- Fatigue (FACIT v4)
- Depression (DASS-21)
- Sleep disorders (PROMIS-SD and SRI)
  - Questionnaires are sent via REDCap
    - Regularly scheduled
    - Self-initiated via mobile technology
  - Social work team notified if questionnaire responses indicate depression, or emotional difficulties

**Longitudinal immune profiling**

- PBMC flow cytometry
- Serum cytokines/chemokines
- Genotyping
- Proteomic analysis
- Gene expression profiling
- TCR sequencing
- Other Inflammatory Biomarkers (Differential WBCs, high-sensitivity CRP, ESR)

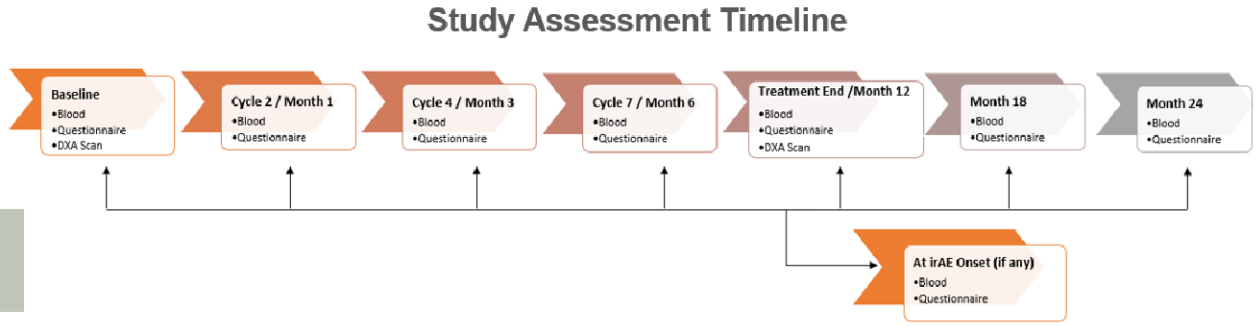
- **Specific aims**: **1)** To determine the incidence, clinical phenotypes, timing, and severity of irAEs in melanoma patients from the initiation of adjuvant ICI therapy through 2 years of follow-up; **2)** To longitudinally assess PROs in those patients, compared to patients with similar disease stage on surveillance; **3)** To longitudinally characterize patient immune signatures from the initiation of adjuvant ICI through 2 years of follow-up and evaluate their association with irAEs, symptom burden, and QOL

## IOTOX STUDY DESIGN (NCT04990726)

**Melanoma Cohort 1 (n=240)**
Patients initiating standard of care adjuvant anti-PD1

**Melanoma Cohort 2 (n=35)**
Patients opt for active surveillance after resection

**Assessments**
- irAEs
- Self-reported PROs
- Longitudinal immune profiling
- Whole body DXA




## RESULTS

- **To date, 60 pts were enrolled (Table 1). Follow-up ranged from 1 to 33 months.**

**Table 1: Patient Demographics and Baseline Characteristics**

| | On adjuvant ICIs (n=51) | On active surveillance (n=9) |
|---|---|---|
| **Age at diagnosis (median, range)** | 57 (28-77) | 59 (42-67) |
| **Sex (%)** | Female (27%) | Female (67%) |
| **Race (%)** | Caucasian (85%) | Caucasian (100%) |
| **Ethnicity (%)** | None-Hispanic (90%) | None-Hispanic (100%) |
| **Type of Therapy** | Adjuvant Nivolumab (68%)<br>Adjuvant Pembrolizumab (32%) | - |
| **Status per the last Follow-up (%)** | Alive (93%) | Alive (100%) |

**Table 2: Clinical Outcomes of enrolled patients on adjuvant ICIs**

| | On adjuvant ICIs (n=51) |
|---|---|
| **Any grade 2 irAEs** | 14 (30%) |
| **Hold/Discontinuation due to irAEs** | 10 (21%) |
| **Recurrence** | 15 (33%) |

- **PROs assessment showed:**
  - Significant decline in EORTC QLQ-C30 physical function scale from 3 to 6 months post ICIs (P=0.007), and cognitive functioning scale between 3 and 12 months (P=0.025),
  - Significantly worse FACIT fatigue scale between baseline and 1 month (P=0.013) and 3 months (P=0.024),
  - No significant differences in depression, anxiety, or stress scales between all timepoints in DASS-21,
  - Trend towards higher levels of sleep impairment in PROMIS score at 1 and 3 months and less impairment at 6 months (P=0.066).
- **DXA scan assessment showed:**
  - Of 11 pts who underwent baseline DXA, 6 completed follow-ups at 12 months and none had osteoporosis.

## Conclusions:

- Preliminary findings show **30% experiencing irAEs**, leading to treatment modifications but **no treatment-related deaths**.
- **Fluctuations** in physical function, cognitive functioning, fatigue, and sleep are observed, along with **preserved bone health**. The immune analysis will provide further insights.

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# Next Steps

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- Database review of response rates and IrAEs in cancer patients receiving PD-1/PD-L1 therapies to establish a benchmark
- Identify graduate students interested in this topic
- Design a database to input response rate/IrAEs and key CHB patient characteristics
- Collect public data from recent EASL & AASLD presentations
- Contact companies directly to fill data gaps

# Working Group Members

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| Academia/Clinical Research | Industry | Regulatory | Patient Representatives & Advocacy |
|---|---|---|---|
| Adam Gehring<br>Ed Gane<br>Marion Peters<br>Kosh Agarwal | Sue Currie, Virion Therapeutics<br>Farouk Chuglay, Roche<br>Audrey Lau, Gilead<br>Oliver Lenz, Janssen<br>Ruth Tarzi, GSK<br>Jinzi Jason Wu, Ascletis | Virginia Sheikh, FDA<br>Rupali Doshi, FDA<br>Stephanie Buchholz, EMA | Need input! |

# Open Discussion