THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

# Immune Checkpoint Inhibitor Working Group Update

**HBV Forum,** *Forum for Collaborative Research*

Berkeley Public Health

# Agenda

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

- Introduction and Background (Adam Gehring & Sue Currie)
- Data presentation (Mitchell Leus & Agustina Crespi)
  - Part 1: IrAEs in cancer patients → accepted as AASLD poster
  - Part 2: Risk-benefit outcomes in HBV patients
- Conclusions from these data (Sue Currie, Adam Gehring)
- Discussion and Clinical insights of CPIs and IrAEs (Ed Gane)
  - Clinical Insights (Ed Gane)
  - Q & A with Forum Participants (Ed Gane, Sue Currie, Adam Gehring)

# Introduction

**Sue Currie,** *Virion Therapeutics*

**Adam Gehring,** *Toronto Centre for Liver Disease*

# Background

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

- Anti-PD-1/anti-PD-L1 immune checkpoint inhibitors (ICIs) may benefit patients with CHB by restoring HBV-specific T & B cell magnitude and function, but the risk of immune-related adverse events (IrAEs) is a potential barrier to use
- Early oncology studies of anti-PD-1/anti-PD-L1 drugs suggested high rates of IrAEs, but these studies included patients with advanced cancers, multiple lines of treatments, and combination therapies that may have contributed to IrAEs

*Ramos-Casals M, et al. Immune-related adverse events of checkpoint inhibitors. Nat Rev Dis Primers. 2020;6(1):38*

# Aim

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

- Assess the incidence, type, and severity of IrAEs in cancer patients treated with anti-PD1/anti-PD-L1 drugs as first-line therapy
- Assess the potential risks of IrAEs in less advanced oncology patients to better understand the risk-benefit profile of anti-PD-1/anti-PD-L1 treatments in patients with CHB

# Data Presentation: Oncology Studies

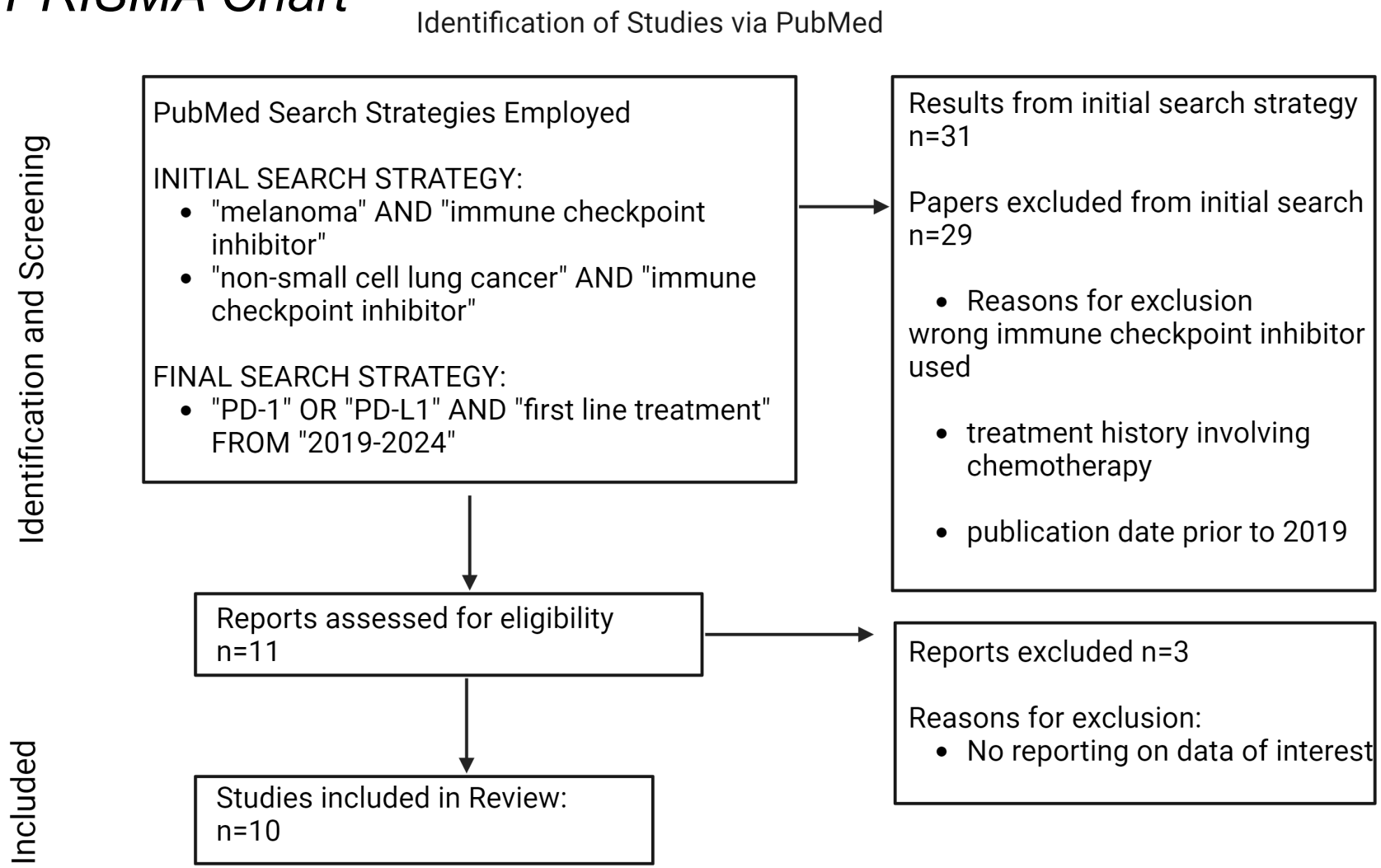
**Agustina Crespi,** *Toronto Centre for Liver Disease*

**Mitchell Leus,** *Forum for Collaborative Research*

# Methods – Paper Selection

## *PRISMA Chart*

THE FORUM For Collaborative Research℠
Berkeley's Hub for Regulatory Science




**Other considerations:**

- Patient population – 1st line – healthier, and few confounders for IrAEs
- Healthy volunteer studies of early CPIs limited
- ASCO, SITC, FDA / EMA registries limited or possible secondary focus (deprioritized due to resourcing and time)
- Studies with combination CPIs, drugs (i.e. CTLA-4 excluded)

Image created on BioRender

# Results

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

- Ten studies were included with a total of 5540 patients, of which 2378 patients were treated with anti-PD-1/anti-PDL1 therapy
- IrAEs of any grade were reported in 765 patients (32.2%), with 191 patients (8.0%) discontinuing treatment due to experiencing an IrAE
- Among those treated with PD-1/PDL1 therapy, Grade 1-2 IrAEs were reported in 622 patients (26.2%) and Grade ≥ 3 IrAEs were reported in 143 patients (6.0%)
- Most frequent IrAE was Thyroidism*: 340 cases Any Grade (14.3%), 336 cases Grade 1-2 (14.1%), and 4 cases Grade ≥ 3 (0.2%)

** Thyroidism is a composite category which includes hyperthyroidism, hypothyroidism, or increased blood TSH*

# Results

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

- Ten studies were included with a total of 5540 patients, of which 2378 patients were treated with anti-PD-1/anti-PDL1 therapy
- IrAEs of any grade were reported in 765 patients (32.2%), with 191 patients (8.0%) discontinuing treatment due to experiencing an IrAE
- Among those treated with PD-1/PDL1 therapy, Grade 1-2 IrAEs were reported in 622 patients (26.2%) and Grade ≥ 3 IrAEs were reported in 143 patients (6.0%)
- Most frequent IrAE was Thyroidism*: 340 cases Any Grade (14.3%), 336 cases Grade 1-2 (14.1%), and 4 cases Grade ≥ 3 (0.2%)

** Thyroidism is a composite category which includes hyperthyroidism, hypothyroidism, or increased blood TSH*

# Results

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

- Ten studies were included with a total of 5540 patients, of which 2378 patients were treated with anti-PD-1/anti-PDL1 therapy
- IrAEs of any grade were reported in 765 patients (32.2%), with 191 patients (8.0%) discontinuing treatment due to experiencing an IrAE
- Among those treated with PD-1/PDL1 therapy, Grade 1-2 IrAEs were reported in 622 patients (26.2%) and Grade ≥ 3 IrAEs were reported in 143 patients (6.0%)
- Most frequent IrAE was Thyroidism*: 340 cases Any Grade (14.3%), 336 cases Grade 1-2 (14.1%), and 4 cases Grade ≥ 3 (0.2%)

** Thyroidism is a composite category which includes hyperthyroidism, hypothyroidism, or increased blood TSH*

# Results

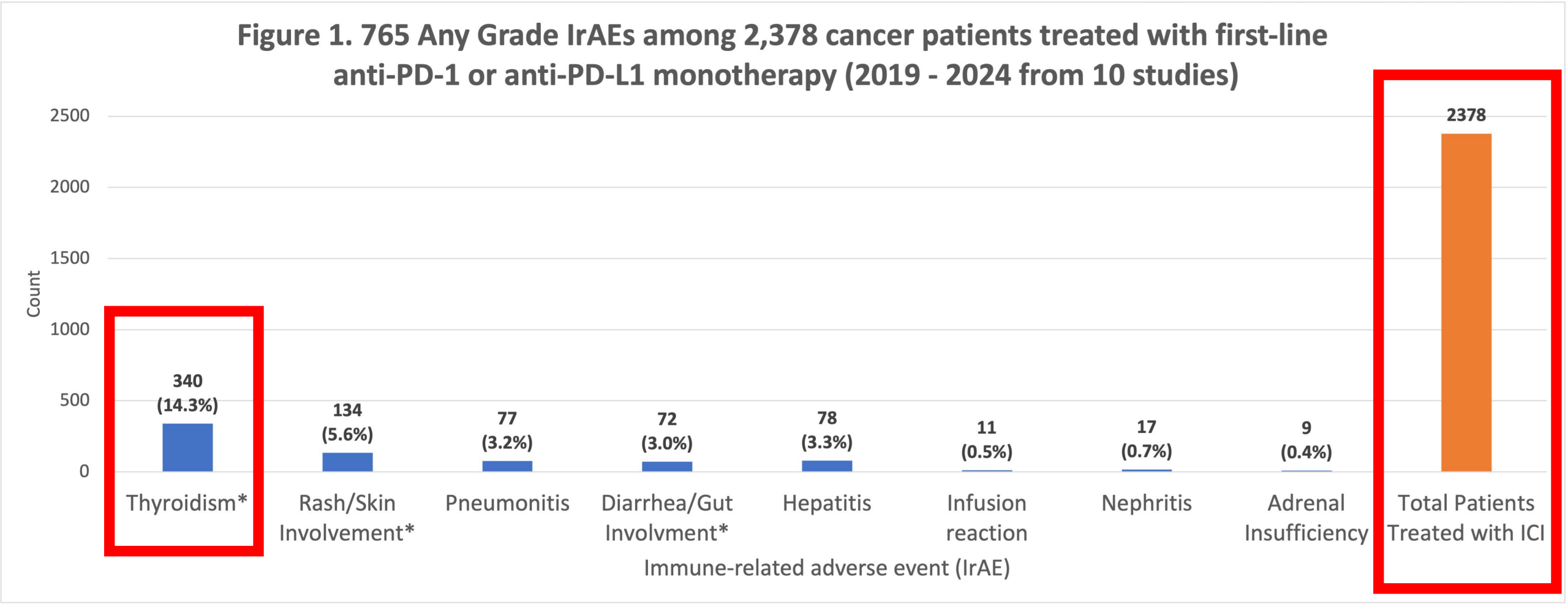
THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

- Ten studies were included with a total of 5540 patients, of which 2378 patients were treated with anti-PD-1/anti-PDL1 therapy
- IrAEs of any grade were reported in 765 patients (32.2%), with 191 patients (8.0%) discontinuing treatment due to experiencing an IrAE
- Among those treated with PD-1/PDL1 therapy, Grade 1-2 IrAEs were reported in 622 patients (26.2%) and Grade ≥ 3 IrAEs were reported in 143 patients (6.0%)
- Most frequent IrAE was Thyroidism*: 340 cases Any Grade (14.3%), 336 cases Grade 1-2 (14.1%), and 4 cases Grade ≥ 3 (0.2%)

** Thyroidism is a composite category which includes hyperthyroidism, hypothyroidism, or increased blood TSH*

# Figure 1. IrAEs of Any Grade

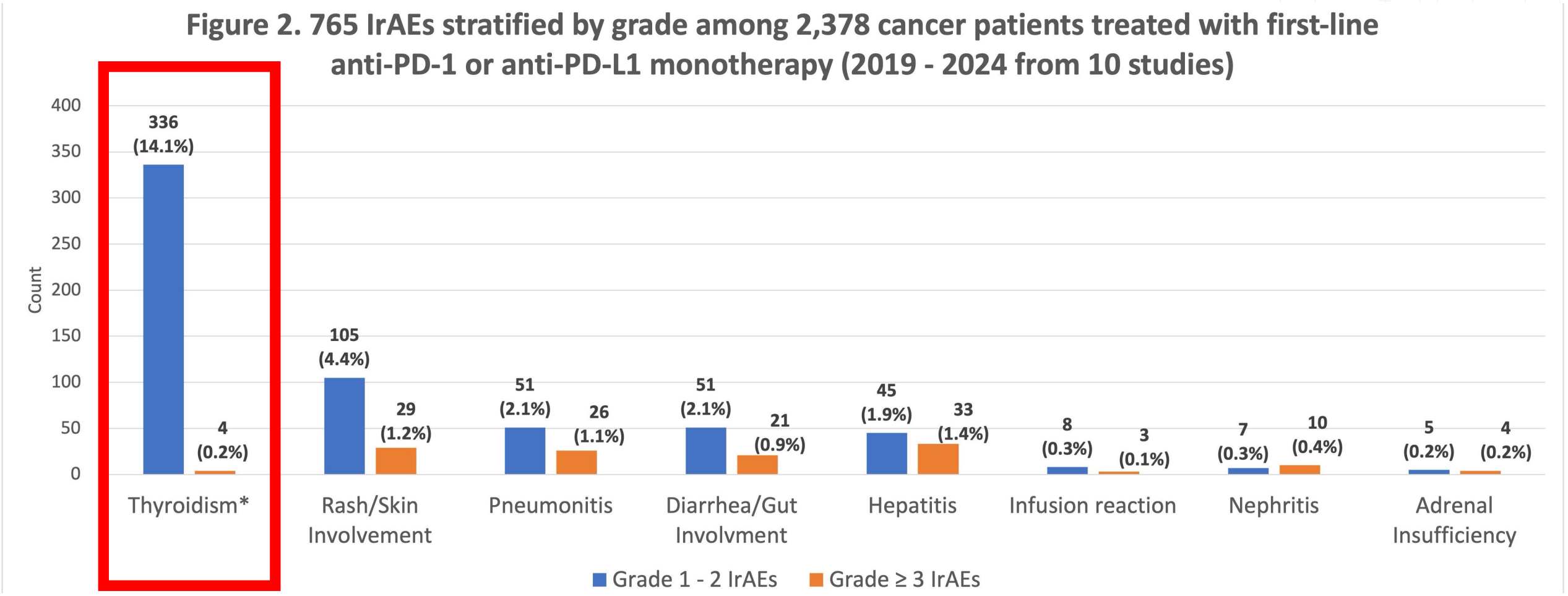
THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*




**IrAEs not visualized due to n ≤ 5 are: Anaphylactic reaction; Pancreatitis; Hypophysitis; Myositis; Uveitis; Myocarditis; Encephalitis; Peripheral neuropathy; Myasthenia gravis; Autoimmune arthritis; Guillan-Barre Syndrome; Stevens-Johnson Syndrome*

# Figure 2. IrAEs Stratified by Grade

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*




**IrAEs not visualized due to n ≤ 5 are: Anaphylactic reaction; Pancreatitis; Hypophysitis; Myositis; Uveitis; Myocarditis; Encephalitis; Peripheral neuropathy; Myasthenia gravis; Autoimmune arthritis; Guillan-Barre Syndrome; Stevens-Johnson Syndrome*

# Conclusions

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

- Among 2378 cancer patients receiving anti-PD-1/anti-PD-L1 therapy as first-line therapy, the majority (67.8%, n = 1613), did not experience an IrAE
  - Fundamental differences between oncology and CHB patients as well as the uses of ICI as therapies
  - Oncology uses higher dosage of ICI compared to low-dose ICI for CHB
  - Oncology population is potentially sicker than the CHB patients
- More granular data are needed on IrAEs of interest to a CHB patient population, including data on hepatic and thyroid toxicities

# Conclusions

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

- Among 2378 cancer patients receiving anti-PD-1/anti-PD-L1 therapy as first-line therapy, the majority (67.8%, n = 1613), did not experience an IrAE
  - Fundamental differences between oncology and CHB patients as well as the uses of ICI as therapies
  - Oncology uses higher dosage of ICI compared to low-dose ICI for CHB
  - Oncology population is potentially sicker than the CHB patients
- More granular data are needed on IrAEs of interest to a CHB patient population, including data on hepatic and thyroid toxicities

# Conclusions

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

- Among 2378 cancer patients receiving anti-PD-1/anti-PD-L1 therapy as first-line therapy, the majority (67.8%, n = 1613), did not experience an IrAE
  - Fundamental differences between oncology and CHB patients as well as the uses of ICI as therapies
  - Oncology uses higher dosage of ICI compared to low-dose ICI for CHB
  - Oncology population is potentially sicker than the CHB patients
- More granular data are needed on IrAEs of interest to a CHB patient population, including data on hepatic and thyroid toxicities

# Data Presentation: HBV Studies

**Agustina Crespi,** *Toronto Centre for Liver Disease*

**Mitchell Leus,** *Forum for Collaborative Research*

# Current ICI Studies for HBV

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

- We have looked at public data involving current aPD1/aPDL1 when possible
- Our experience with these studies has shaped our key findings and future needs for this phase of the project

| Study | Sponsor | ICI agent | Mono or Combination Therapy? |
|---|---|---|---|
| HBV003 | Barinthus Biotherapeautics | Nivolumab | Combination |
| OCTOPUS | Janssen | Nivolumab | Combination |
| Ocean Cure | Chia Tai Tiaqing Pharmaceutical Group Co | In house aPDL1 "TQB2450" | Combination |
| ASC22 | Ascletis | Envafolimab | Mono |

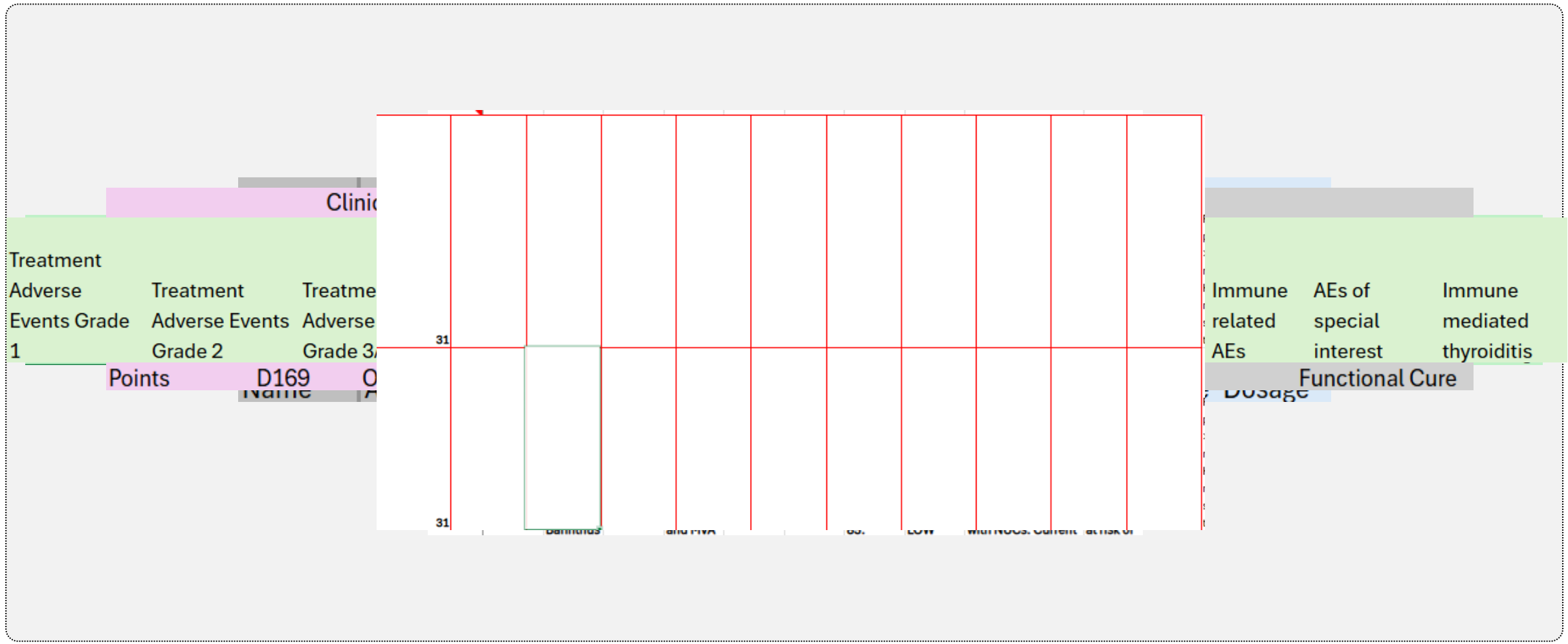
# Methodology

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

- We extracted as much information possible from publicly accessible sources
- We separated data into treatment type, clinical data, outcomes, safety

# Excel Walkthrough

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*



# Issues During Extraction Process

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

- Lack of consistency in reporting overall
  - Hard to make conclusions regarding safety or outcomes
- Data sub-setting
  - The data presented may only be representative of a fraction of the sample population
  - Hard to generalize if treatment is beneficial for HBV patients- regardless of viral load

# Conclusions

**Sue Currie,** *Virion Therapeutics*

**Adam Gehring,** *Toronto Centre for Liver Disease*

# Conclusions

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

- Highlighted a need for standardization and harmonization in IrAE reporting for CHB patients, similar to what is in place for oncology data
- There is a continued need to:
  - Assess the risk-benefit of anti-PD-1/anti-PD-L1 for patients with CHB
  - Expand IrAE reporting from oncology to ensure IrAEs of interest to patients with CHB, such as ICI-mediated hepatitis and thyroidism, are included.

# Discussion & Clinical Insights

**Sue Currie,** *Virion Therapeutics*

**Ed Gane,** *University of Auckland*

**Adam Gehring,** *Toronto Centre for Liver Disease*

# Key Questions: Benefits

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

- Functional cure = easy endpoint
- What is a partial response?
  - If we see a partial response, how do we know it is attributable to the ICI?
  - If we define a partial response here, can we expand to other immunotherapy?
- Are there other definitions, metrics, or measures that are identified with benefit?

# Key Questions: Risks

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

- How do we standardize reporting to compare the risk to the benefit?
- What are the IrAEs of interest that should be reported in CHB patients treated with ICIs?
  - Durability? Is it the same 6 month window for DAA?

Where will anti-PD-1/anti-PD-L1 therapies fit into the future treatment paradigm?
Do we foresee checkpoint inhibition delivered as concurrent or sequential therapy?

# If CPI meets benefit /risk:

THE FORUM
For Collaborative Research℠
*Berkeley's Hub for Regulatory Science*

1. Where will anti-PD-1/anti-PD-L1 therapies fit into the future treatment paradigm?
2. Do we foresee checkpoint inhibition delivered as concurrent or sequential therapy?

# Thank you