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Immune Checkpoint Inhibitor (ICI) Treatment and Immune-related Adverse Events (IrAEs): Lessons Learned from Oncology for its Potential Use for Chronic Hepatitis B (CHB) Patients

Tuesday, June 4, 2024

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Berkeley Public Health

Background

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- The potential of ICIs targeting PD-1/PD-L1 to restore HBV-specific immune function in CHB patients makes them attractive agents

- Early studies (pre-2019) of anti-PD-1/PD-L1 drugs suggested high rates of IrAEs on advanced cancer patients

- Objective: to understand the potential risks of IrAEs in less advanced patients, improving the understanding of potential risk-benefits associated with anti-PD-1/PD-L1 treatments in CHB patients

Working Group Activities

AASLD 2023 to present

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- Core working group convened 6 times (Adam, Sue, Veronica, Agustina*, Mitchell)
  - Agustina*, fellow with Adam's group joined the working group and co-leads
  - Refined the literature search and received additional input from IrAEs experts
- Convened input from working group members (via email & TC)
- Collated results and submitted an abstract to AASLD

Methods – Paper Selection

PRISMA Chart

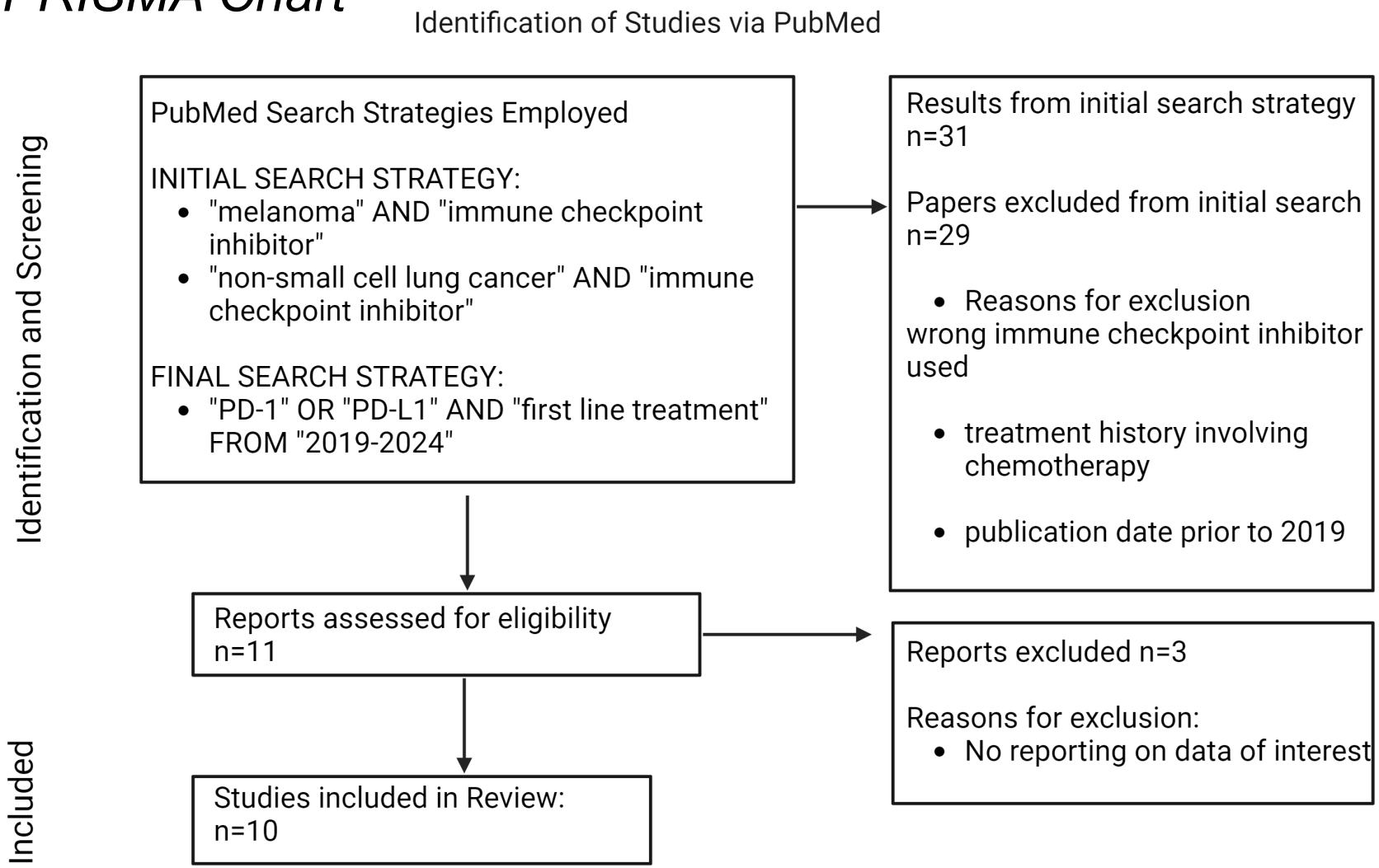

Image created on BioRender

Other considerations:

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

CTCAE Grading Scale

Adverse events of interest

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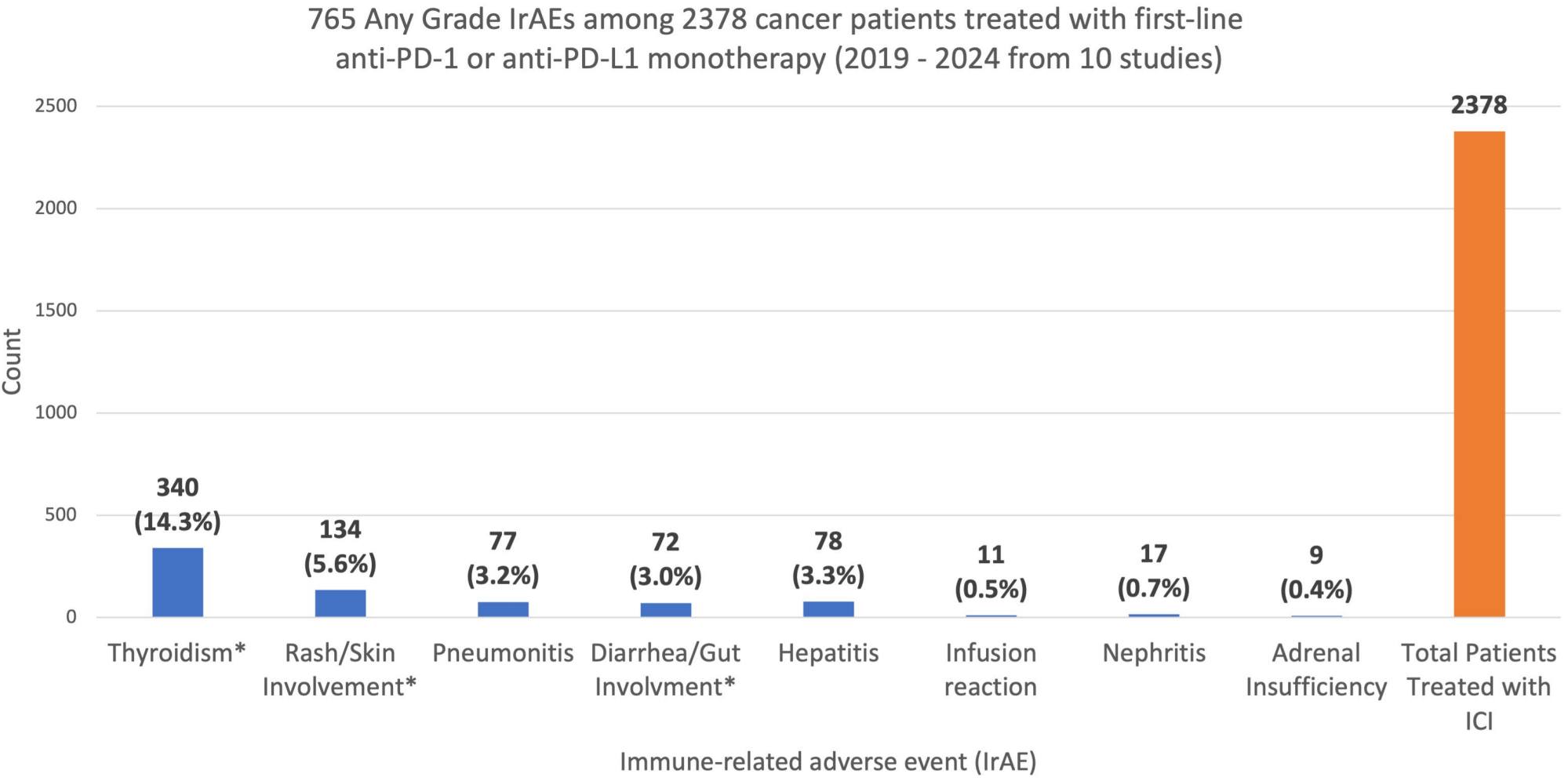
CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; lim iting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Increase in AST	>ULN –3 x ULN if baseline was normal; 1.5-3 baseline if baseline was abnormal	>3-5 x ULN if baseline was normal, >3-5 x baseline if baseline was abnormal	>5-20 x ULN if baseline was normal; > 5-20 x baseline if baseline was abnormal	>20 x ULN if baseline was normal; >20 x baseline if baseline was abnormal	-
Increase in ALT	>ULN –3 x ULN if baseline was normal; 1.5-3 baseline if baseline was abnormal	>3-5 x ULN if baseline was normal, >3-5 x baseline if baseline was abnormal	>5-20 x ULN if baseline was normal; > 5-20 x baseline if baseline was abnormal	>20 x ULN if baseline was normal; >20 x baseline if baseline was abnormal	-

Project’s Excel Database Review

Most prominent Grade 1-2 IrAEs among ICI Treated Patients												
Hepatitis	Rash/Skin Involvement	Pneumonitis	Thyroidism	Infusion Reaction	Nephritis	Pancreatitis	Adrenal Insufficiency	Encephalitis	Hypophysitis	Uveitis	Peripheral Neuropathy	Myositis	Hypersensitivity/Anaphylactic reactions
34, 11.8%	41, 14.4%	9, 3.14%	40, 13.9%	0	0	0	0	0	0	0	0	0	0
1, <1%	2, <1%	14, 4.6%	62, 20.6%	2, <1%	1, <1%	2, <1%	1, <1%	0%	0%	1, <1%	0%	0%	0%

Interim Results / Data

IrAEs of Any Grade



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

** Rash/Skin involvement is a composite category including rash and pruritus unrelated to an infusion reaction*

** Diarrhea/Gut involvement is a composite category including diarrhea, colitis, nausea, vomiting, and constipation*

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

IrAEs Stratified by Grade

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765 total IrAEs stratified by grade among 2,378 cancer patients treated with first-line anti-PD-1 or anti-PD-L1 monotherapy (2019 - 2024 from 10 studies)

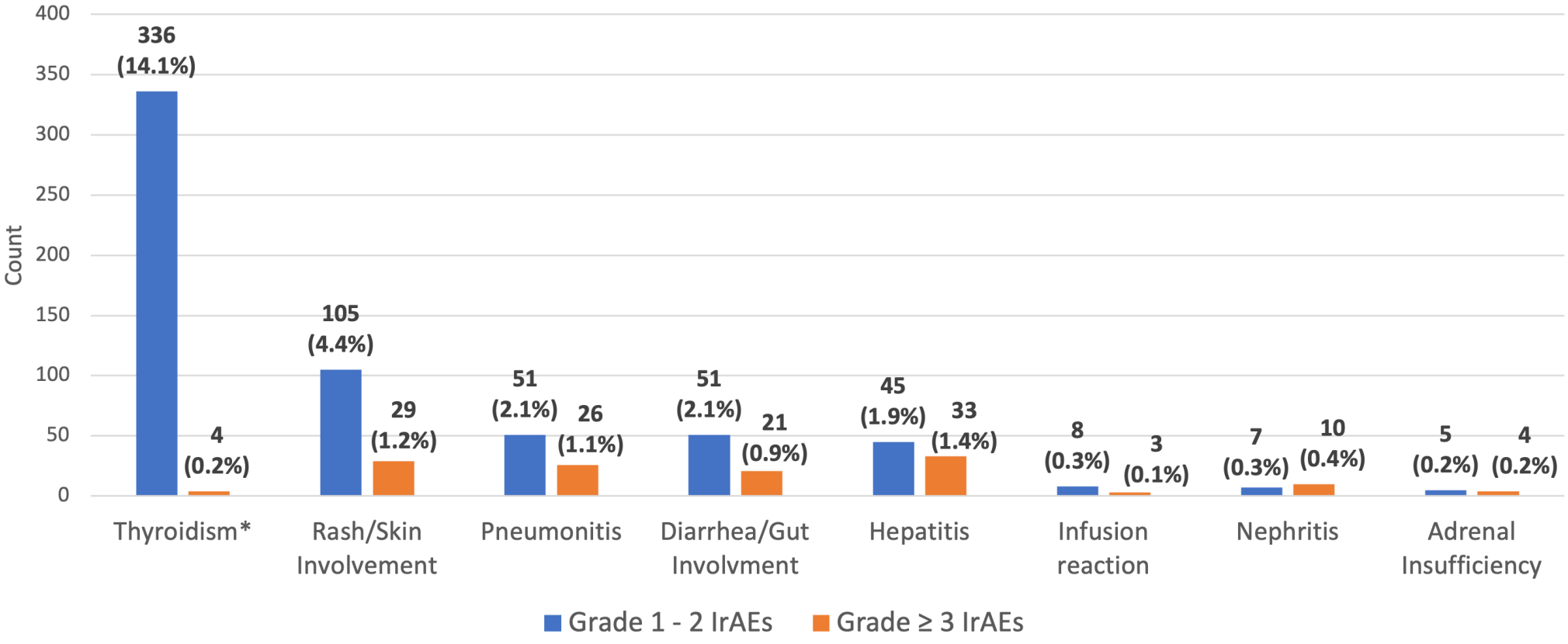

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TABLE 1. Immune-related adverse events (irAEs) among first-line cancer patients treated with anti-PD-1 or anti-PD-L1 monotherapy, n = 2,378 (2019 - 2024 from 10 studies)

Immune-related adverse event (irAE), No. (%)	Grade 1 - 2	Grade ≥ 3	Any Grade
Any irAE	622 (26.2)	143 (6.0)	765 (32.2)
irAE leading to discontinuation*	NA	NA	191 (8.0)
irAE by category			
Thyroidism[a]	336 (14.1)	4 (0.2)	340 (14.3)
Rash/Skin involvement[b]	105 (4.4)	29 (1.2)	134 (5.6)
Pneumonitis	51 (2.1)	26 (1.1)	77 (3.2)
Diarrhea/Gut involvment[c]	51 (2.1)	21 (0.9)	72 (3.0)
Hepatitis	45 (1.9)	33 (1.4)	78 (3.3)
Infusion reaction	8 (0.3)	3 (0.1)	11 (0.5)
Nephritis	7 (0.3)	10 (0.4)	17 (0.7)
Adrenal insufficiency	5 (0.2)	4 (0.2)	9 (0.4)
Anaphylactic reaction	5 (0.2)	0	5 (0.2)
Pancreatitis	3 (0.1)	2 (0.1)	5 (0.2)
Hypophysitis	3 (0.1)	2 (0.1)	5 (0.2)
Myositis	2 (0.1)	1 (0.04)	3 (0.1)
Uveitis	1 (0.04)	0	1 (0.04)
Encephalitis	0	1 (0.04)	1 (0.04)
Peripheral neuropathy	0	1 (0.04)	1 (0.04)
Myocarditis	0	2 (0.1)	2 (0.1)
Mysathenia gravis	0	1 (0.04)	1 (0.04)
Autoimmune arthritis	0	1 (0.04)	1 (0.04)
Guillan-Barre Syndrome	0	1 (0.04)	1 (0.04)
Stevens-Johnson Syndrome	0	1 (0.04)	1 (0.04)

* NA values are given because irAEs leading to discontinuation were not stratified by grade across all studies

[a] Thyroidism is a composite category including hypothyroidism, hyperthyroidism, or increased blood TSH

[b] Rash/Skin involvement is a composite category including rash and pruritus unrelated to an infusion reaction

[c] Diarrhea/Gut involvement is a composite category including diarrhea, colitis, nausea, vomiting, and constipation

ICIs in Clinical Development

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Code	Phase	Drug	Sponsor	Status
NCT05275023	II	aPD1	Janssen	Active- Not Recruiting
NCT05343481	II	Nivolumab in comb.	Barinthus Biotherapeutics	Recruiting
NCT04778904	I & II	Nivolumab in comb.	Barinthus Biotherapeutics	Active-Not Recruiting
NCT04638439	I	aPD-1	PharmaEssentia	Unknown
NCT04891770	II	Nivolumab	Gilead Sciences	Active- Not Recruiting
NCT04180072	NA	Atezolizumab	National Health Research Institutes, Taiwan	Recruiting
NCT04225715	II	aPD-L1 in comb.	Roche	Active-Not Recruiting
NCT04465890	II	aPD-L1 ASC22	Ascletis Pharmaceuticals	Active-Not Recruiting
NCT06245291	II	aPD-L1 in comb.	Arbutus Biopharma Corporation	Recruiting
NCT05769816	IV	aPD-L1	The Second Affiliated Hospital of Chongqing Medical University	Not Yet Recruiting
NCT06357806	NA	Sintilimab	Beijing 302 Hospital	Recruiting
NCT04133259	II	aPD-1 HLX10	Henlix, Inc	Unknown

Clinicaltrials.gov

Acknowledgements

- Frida Abramov, Gilead
- Farouk Chughlay, Roche
- Agustina Crespi, UHN
- Sue Currie, Virion
- Rupali Doshi, FDA
- Ed Gane, University of Auckland
- Adam Gehring, UHN
- Mitchell Leus, Forum
- Veronica Miller, Forum
- Virginia Sheikh, FDA
- Ruth Tarzi, GSK
- Lucy Walker, GSK
- Jinzi Wu, Ascletis

Next Steps & Action Items

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- Continue current activities and further refine
- AASLD abstract (if accepted) presentation
- Potential manuscript and resource checklist
- (If possible) potential collection of current studies with CPIs in CHB
- Other?

Questions to the Group

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- Was there anything that we may have missed in our literature search (i.e. inclusion criteria)? Other relevant sources that should have been considered?
- Based upon these collated data related to IrAEs:
  - Is there anything that was a surprise to you?
  - Do you think that there are specific IrAEs of greater interest for CHB? Why?
- Would a tool for collating IrAEs from current studies in our field be beneficial?
- Do you think a repository for IrAEs from current clinical trials would be beneficial?

Thank you