



Provincial Health Services Authority

Acetaminophen Interactions with Immune Checkpoint Inhibitors (ICI) Guilt by Association?

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Background & Objective

Background

- Acetaminophen is widely used and essential in cancer care
- Some observational studies showed ↓ OS/PFS associated with acetaminophen + ICI

6/8/26, 4:36 PM Interactions - UpToDate® Lexidrug™

Interaction Checking Interaction Analysis **Interaction Monograph**

Title Immune Checkpoint Inhibitors (Anti-PD-1, -PD-L1, and -CTLA4 Therapies) / Acetaminophen

Risk Rating C: Monitor

Summary Acetaminophen may decrease therapeutic effects of Immune Checkpoint Inhibitors (Anti-PD-1, -PD-L1, and -CTLA4 Therapies). **Severity** Major **Reliability Rating** Intermediate-Low

Flagged by some drug interaction databases (eg, Lexicomp) but not others (eg, Micromedex)

Problem Is the association sufficient to support causation?

Objective Assess plausibility of this interaction using:

- WHO-UMC Causality Assessment Framework
- Drug Interaction Probability Score (DIPS)*

What We Found – 1

Parameters	Four Observational Studies Identified from Medline & Embase (up to June 2025)
Temporal Relationship	<ul style="list-style-type: none"> • Did not verify if patients took acetaminophen during ICI therapy: serum levels at initiation or unknown timepoints, no verification of prescription filled, no consideration of OTC acetaminophen¹⁻⁴
Alternative Explanations	<ul style="list-style-type: none"> • Acetaminophen may reflect severity of underlying illness¹⁻⁴ • OTC acetaminophen not accounted for¹⁻⁴ • Multivariate analyses limited by poorly measured confounders (eg, acetaminophen duration & dose), important confounders not measured (eg, reasons for acetaminophen use likely independently correlate with poor prognosis, other meds, levels of pain)^{1,3} • Propensity score matching did not reliably mitigate impact of uncontrolled confounding – potential imbalance of all relevant variables not assessed <i>after</i> matching (only used imbalanced variables before matching)²
Consistency	<ul style="list-style-type: none"> • Dose-response relationship not established (average acetaminophen dose & duration not reported)¹⁻⁴ • No reports of dechallenge (stopping acetaminophen)¹⁻⁴ • No impact on survival in animal studies¹ or in patients in 1 study⁴
Biological Plausibility	<ul style="list-style-type: none"> • No pharmacokinetics studies showing acetaminophen ↓ systemic exposure of ICI • No evidence that acetaminophen suppresses effector cytotoxic T cells¹ • No impact on survival of mice implanted with tumour¹ • ↑ negative regulation of immune system process did not translate into ↓ PFS or ORR³ • ↓ OS / PFS highly significant (>50% ↓ in OS / PFS, HR 0.34-0.67), inconsistent with acetaminophen not known to be potent immunosuppressant^{1,2}

What We Found – 2

- WHO-UMC Causality Assessment = Unlikely

Assessment Criteria	Findings
<i>Event abnormality with time to drug intake makes relationship improbable (but not impossible)</i>	<ul style="list-style-type: none"> Time relationship between events (death, disease progression, tumour response) to acetaminophen intake not established because studies did not verify if patients actually took acetaminophen during ICI therapy.
<i>Disease or other drugs provide plausible explanations</i>	<ul style="list-style-type: none"> Confounders not well controlled for by Bessedé et al. Limited confounders controlled for by Nelli et al.
<i>Response to withdrawal</i>	<ul style="list-style-type: none"> Not investigated
<i>Event definitive pharmacologically or phenomenologically</i>	<ul style="list-style-type: none"> Animal studies – no difference in survival in mice with implanted tumour treated with ICI +/- acetaminophen. No direct link between main mechanism of actions of acetaminophen and immune suppression. Changes in systemic exposure of ICI not investigated.
<i>Response to rechallenge</i>	<ul style="list-style-type: none"> Not investigated
<i>More data for proper assessment needed</i>	<ul style="list-style-type: none"> More detailed information on acetaminophen intake required, including verifying if patients took acetaminophen during ICI therapy, average dose and duration of intake, any intake to acetaminophen not accounted for (e.g., OTC)

- Drug Interaction Probability Scale = Doubtful (total score <2)

Questions	Answers	Scores
1. Previous credible reports of this interaction in humans?	No	-1
2. Observed interaction consistent with known interactive properties of Acetaminophen?	No	-1
3. Observed interaction consistent with known interactive properties of ICI?	Yes	+1
4. Event consistent with known / reasonable time course of interaction (onset and/or offset)?	Unknown	0
5. Interaction remitted upon dechallenge of Acetaminophen with no change in ICI?	Unknown	0
6. Interaction reappeared when Acetaminophen readministered with continued ICI use?	Unknown	0
7. Reasonable alternative causes for the event?	Yes	-1
8. ICI detected in blood or other fluids in concentrations consistent with proposed interaction?	Unknown	0
9. Drug interaction confirmed by objective evidence consistent with effects on Acetaminophen (other than drug concentrations from question 8)	No	0
10. Interaction greater when Acetaminophen dose increased or less when ICI dose decreased?	Unknown	0

Discussion

- Significant interaction between acetaminophen and ICI seems unlikely or doubtful.
- Acetaminophen should not be restricted until more robust evidence is available.
- Association with a distant outcome is insufficient to support plausibility of drug interaction
 - Complex sequence of events between ICI administration via activated T cells to tumour cell death
 - Long temporal relationship between ICI administration and outcome susceptible to confounders
- **A well-designed study is feasible:**
 - Follow patients longitudinally until next line of treatment or disease progression
 - Outcomes analyzed using propensity score matching with baseline prognostic factors and prospectively collected information of acetaminophen intake.

References

1. Bessede A, Marabelle A, Guégan JP, et al. Impact of acetaminophen on the efficacy of immunotherapy in cancer patients. *Ann Oncol* 2022;33(9):909-915.
2. Nelli F, Virtuoso A, Giannarelli D, et al. Effects of acetaminophen exposure on outcomes of patients receiving immune checkpoint inhibitors for advanced non-small-cell lung cancer: a propensity score-matched analysis. *Curr Oncol* 2023;30(9):8117-8133.
3. Li C, Wu J, Zhang L, et al. Brief report: acetaminophen reduces neoadjuvant chemoimmunotherapy efficacy in patients with NSCLC by promoting neutrophil extracellular trap formation: analysis from a phase 2 clinical trial. *JTO Clin Res Rep* 2023;4(9):100556. doi: 10.1016/j.jtocrr.2023.100556.
4. Yamada J, Fukui T, Yatani A, et al. Impact of concurrent medications on the outcome of immunotherapy in non-small cell lung carcinoma. *Thorac Cancer* 2024;15(15):1228-1236.

Not Reviewed:

- a. Lin Y, Liao Y, Shen J. Acetaminophen use and prognosis in cancer patients treated with immune checkpoint inhibitors: evidence from a meta-analysis. *Front Immunol*. 2025 Nov 21;16:1682686. doi: 10.3389/fimmu.2025.1682686.
- b. Ye ZH, Wang S, Zhang J, et al. 2098P The impact of concomitant use of non-opioid analgesics and immune checkpoint inhibitors on survival in lung cancer patients: A Hong Kong population-based cohort study. *Ann Oncol* 2023;34:S1101.
- c. Gobbini E, Langlais A, Missy P, et al. Morphine and metformin impact immunotherapy benefit in patients with NSCLC: Results of the real-world study IFCT-1502 CLINIVO-SNDS. *Eur J Cancer* 2025;225:115560.

Association of Zodiac Signs and Nobel Prize in Medicine & Physiology

- Odds increased with Gemini
 - OR 1.90 (95% CI 1.12–3.24, p = 0.017)
- Odds decreased with Leo
 - OR 0.35 (95% CI 0.16–0.82, p = 0.011)

Table 1: Distribution of zodiac signs among winners of the Nobel Prize in Medicine and Physiology and control subjects

Zodiac sign	Group; % of subjects		Odds ratio (and 95% CI)
	Nobel laureates n = 171	Control subjects n = 375	
Aquarius ♒	6.43	9.33	0.67 (0.33–1.35)
Pisces ♓	8.77	8.53	1.03 (0.54–1.96)
Aries ♈	9.36	7.20	1.33 (0.70–2.54)
Taurus ♉	4.68	8.80	0.51 (0.23–1.13)
😊 Gemini ♊	16.37	9.33	1.90 (1.12–3.24) ←
Cancer ♋	6.43	8.00	0.79 (0.39–1.62)
🙌 Leo ♌	4.09	10.67	0.35 (0.16–0.82) ←
Virgo ♍	11.07	10.67	1.11 (0.63–1.96)
Libra ♎	8.19	8.00	1.03 (0.53–1.99)
Scorpio ♏	8.77	5.87	1.54 (0.78–3.05)
Sagittarius ♐	10.53	8.00	1.35 (0.73–2.50)
Capricorn ♑	4.68	5.60	0.83 (0.36–1.91)

Note: CI = confidence interval.