CO198

Breaking Barriers in Cancer Immunotherapy: Mechanistic Insights into Resistance and Implications for Health Economics and Outcomes Research (HEOR) and Value Assessment

Divya Pushkarna, Gaurang Nazar, Mir-Masoud Pourrahmat, Michael del Aguila, Jean-Paul Collet
Evidinno Outcomes Research Inc., Vancouver, BC, Canada.

Background

- Immune checkpoint inhibitors (ICIs) have transformed cancer care, producing durable responses in subsets of patients across multiple malignancies.[1,2]
- However, both primary and acquired resistance substantially reduce real-world durability relative to clinical trials, reflecting heterogeneous tumor-intrinsic and tumor-extrinsic escape mechanisms.[3-5] Tumor immune escape, T-cell exhaustion, compensatory checkpoint signaling, and immunosuppressive microenvironments shorten response duration, accelerate treatment sequencing, and inflate downstream costs, with negative consequences for patients.[3,4]
- Empirical analyses consistently demonstrate that real-world progression and survival outcomes are inferior to trial-based benchmarks, particularly beyond the first year of therapy, when resistance dynamics become increasingly prominent.[2,5]
- Traditional health economics and outcomes research (HEOR) models have often relied on simplified assumptions of sustained benefit or constant hazards, which insufficiently capture resistance biology and contribute to systematic overestimation of value and underestimation of uncertainty in reimbursement decisions.[1,4]
- Integrating ICI mechanistic resistance evidence with real-world outcomes is therefore essential for accurate value assessment and policy-relevant decision-making.

Objective

- To integrate mechanistic evidence on ICI resistance with HEOR data and quantify its impact on effectiveness decay, treatment sequencing, cost-effectiveness, and value uncertainty, illustrated using resistance-associated declines in real-world effectiveness.

Methods

- A targeted literature review (TLR) was conducted to identify and synthesize evidence linking ICI resistance mechanisms with real-world effectiveness, health economic outcomes, and value assessment considerations.
- The review prioritized mechanistically informative and HEOR-relevant evidence, consistent with best practices for TLRs supporting economic modeling and health technology assessment (HTA) decision-making rather than exhaustive systematic enumeration.
- The search spanned January 1, 2015, to December 31, 2025, and was conducted using PubMed as the primary database, supplemented by targeted searches of HTA agency reports, peer-reviewed economic evaluations, and HEOR-focused journals.
- Search strategies combined controlled vocabulary and free-text terms related to “immunotherapy resistance” (e.g., primary resistance, acquired resistance, immune escape), real-world outcomes (e.g., real-world evidence, observational cohorts, progression-free survival [PFS], overall survival [OS]), and value assessment (e.g., cost-effectiveness, incremental cost-effectiveness ratio [ICER], reimbursement, HTA).
- Reference lists of key mechanistic reviews, real-world outcome studies, and economic evaluations were hand-searched to ensure coverage of influential and policy-relevant publications.
- Screening proceeded in two stages. Titles and abstracts were first assessed for relevance to ICI resistance and downstream clinical or economic outcomes.

Methods (continued)

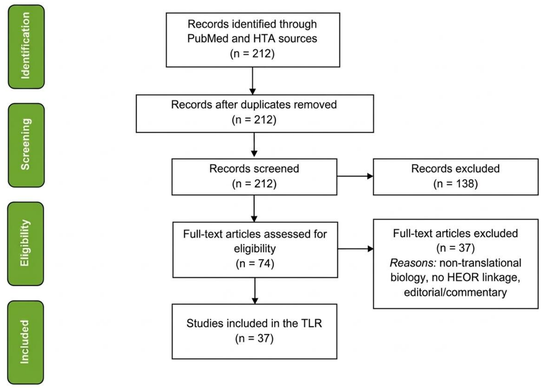
- Full-text review was then conducted for publications meeting inclusion criteria: studies reporting empirical real-world data, structured secondary analyses, or economic models explicitly linking resistance biology or resistance-associated clinical phenomena (e.g., loss of durability, early progression) with effectiveness, treatment sequencing, healthcare costs, or value assessment assumptions.
- Editorials, purely preclinical studies without translational relevance, and studies lacking clear HEOR implications were excluded.
- Extracted evidence was qualitatively synthesized across four prespecified domains: (1) resistance-associated effectiveness decay relative to trials, with consequent earlier progression and worse patient outcomes, (2) downstream impacts on treatment sequencing and costs, (3) implications for uncertainty and structural assumptions in economic models, and (4) considerations for adaptive, resistance-informed value frameworks.

Results

Evidence Base and Study Characteristics

- Across the search period, 212 unique records were identified and screened, of which 37 publications met inclusion criteria (**Figure 1**). Included evidence spanned multiple tumor types, most prominently non-small cell lung cancer (NSCLC) (=10 studies), melanoma (=8 studies), renal cell carcinoma (RCC) (=4 studies), and tumor-agnostic or multi-tumor indications (=15 studies). The evidence base comprised real-world observational cohorts and registry analyses (n=11), extended follow-up analyses of pivotal trials (n=3), systematic reviews and meta-analyses informing durability and resistance assumptions (n=11), and HEOR-focused economic evaluations or modeling guidance incorporating real-world progression data (n=8). In addition, one survivorship-focused scoping review contributed context on longer-term outcomes beyond trial follow-up windows. Most economic evaluations focused on PD-1 inhibitors, particularly pembrolizumab and nivolumab, reflecting their broad clinical use and central role in reimbursement decision-making.

Figure 1: PRISMA Diagram



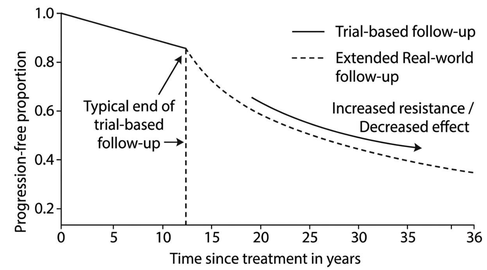
Resistance-Associated Loss of Durability in Real-World Effectiveness

- Across tumor types, resistance manifested as lower real-world effectiveness than trial-reported efficacy, driven primarily by reduced durability of response over extended follow-up periods (**Figure 2**).[6,7]
- Real-world PFS was shorter than reported in pivotal randomized trials across RCC (25-40% shorter), NSCLC (30-60% shorter), and tumor-agnostic populations (30-60% shorter), with pronounced gaps emerging beyond 10–14 months of follow-up (**Table 1**).[7,8,9]
- Real-world median PFS was consistently shorter (≈4–7 months, observed over longer and more heterogeneous follow-up) than trial-reported PFS (≈8–12 months) across tumor types (**Table 1**).[6,8]

Results (continued)

- Several real-world cohorts further demonstrated that even trial-eligible subpopulations (e.g., ECOG 0–1, biomarker-selected) experienced earlier loss of disease control than expected, translating into earlier progression and worse patient outcomes in routine clinical practice compared with controlled trial settings.[6,7]
- While a minority of patients achieved long-term benefit consistent with durable immune control such as the plateau effects observed in long-term melanoma follow-up, these patients represented a numerically small subgroup whose long-term survival did not offset population-level effectiveness decay observed in routine practice.[8,10,11]

Figure 2: Conceptual Kaplan–Meier schematic illustrating how longer real-world follow-up reveals loss of durability beyond typical trial observation horizons



Downstream Impacts on Treatment Sequencing and Costs

- Earlier progression attributable to resistance translated into accelerated treatment sequencing, with patients transitioning more rapidly to subsequent lines of therapy or intensified combination regimens.[12,13]
- Across multiple indications, resistance-associated escalation increased cumulative treatment costs by approximately 38–72% relative to models assuming sustained benefit with first-line monotherapy (**Table 1**).[12-14]
- Post-resistance strategies frequently included dual checkpoint blockade, sequential immunotherapy, or addition of cytotoxic or targeted agents, all of which substantially increased drug acquisition costs, monitoring requirements, and toxicity management costs.[12,13,15]
- These observed real-world sequencing patterns diverged materially from assumptions used in legacy HEOR frameworks, which often relied on fixed post-progression pathways and underestimated both the frequency and downstream consequences of resistance-driven treatment intensification.

Table 1: Real-World Consequences of ICI Resistance Across Tumor Types

Tumor Type	Trial-Reported Effectiveness	Real-World Effectiveness	Economic Impact
NSCLC	Median PFS ~8–12 months[2]	Median PFS ~4–7 months; ~30–60% shorter vs trials.[6,7]	↑ Costs (~38–72%) and ICER inflation.[12,13]
RCC	Median PFS ~11–15 months[2]	Median PFS ~7–10 months; ~25–40% shorter vs trials.[6,8]	Sensitive to durability assumptions; ↑ downstream costs[12]
Melanoma	Median PFS ~6–12 months; ~20–40% ≥5 yr survivors.[10]	Median PFS ~4-7 months; ~20–30% durable responders at long-term.[8,11]	Long tail responders inflate average ICERs.[12]
Tumor-agnostic	Basket trial efficacy, subtype dependent[2]	~30–60% shorter vs trials; 2–3× variability.[6,8]	High ICER uncertainty; averages mask heterogeneity.[12,13]

Ranges reflect typical median estimates reported over comparable follow-up horizons and illustrate durability loss observed with longer real-world exposure rather than fixed assessment timepoints.
Abbreviations: ICER: Incremental Cost-Effectiveness Ratio, ICI: Immune Checkpoint Inhibitor, PFS: Progression-Free Survival, NSCLC: Non-Small Cell Lung Cancer, RCC: Renal Cell Carcinoma.

Effects on Cost-Effectiveness and Value Estimates

- Resistance-associated loss of durability over longer follow-up substantially worsened cost-effectiveness outcomes. Across included HEOR and HTA-informing studies, incorporation of real-world progression patterns increased ICERs by up to 70%, frequently shifting estimates above commonly cited willingness-to-pay thresholds.[12-14]

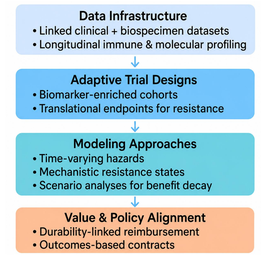
Results (continued)

- In some analyses, broader, unselected real-world populations failed to achieve acceptable cost-utility due to limited quality-adjusted life year (QALY) gains when durability was assessed over longer follow-up horizons, whereas ICIs were cost-effective only in biomarker-enriched subgroups (e.g., PD-L1–high tumors).[12,13,16] Deterministic and probabilistic sensitivity analyses consistently identified assumptions related to durability of benefit, time-to-resistance, and post-resistance treatment transitions as the dominant drivers of uncertainty.[12,13] These effects were particularly pronounced for pembrolizumab and nivolumab, where small changes in durability over time produced disproportionately large swings in ICERs, underscoring resistance-associated durability loss as a key structural determinant of value uncertainty.[12,14]

Translational Interpretation and Conceptual Framework

- Collectively, the evidence indicates that ICI resistance is not a peripheral clinical phenomenon but a structural determinant of real-world value. Resistance reshapes survival trajectories, health-related quality of life, treatment sequencing, and healthcare utilization, necessitating economic models that incorporate time-varying hazards, resistance-specific health states, and adaptive pathways reflecting real-world clinical practice. To translate these observations into actionable guidance, we outline a conceptual framework that integrates resistance dynamics into real-world effectiveness and value assessment (**Figure 3**).

Figure 3: Mechanism-Informed HEOR Roadmap



- Illustration of a mechanism-informed roadmap for integrating immunotherapy resistance into HEOR.
- Resistance biology informs upstream data infrastructure and adaptive trial designs, which in turn support economic models incorporating time-varying durability and resistance-specific health states.
- Alignment of these elements enables value and policy frameworks that better reflect real-world effectiveness.

Conclusions

- Immunotherapy resistance represents a time-dependent biological and economic inflection point shaping real-world value. Economic models that exclude resistance dynamics systematically overestimate long-term benefit and misalign reimbursement with clinical effectiveness.
- Embedding mechanistic resistance insights within HEOR frameworks, supported by real-world evidence, can improve accuracy, transparency, and adaptability in value-based pricing. Future research should link molecular correlates of resistance with economic outcomes to guide evidence generation, adaptive trials, and reimbursement strategies for evolving combination regimens.

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Acknowledgments

All authors report employment with Evidinno Outcomes Research Inc.

Email: mdelaguila@evidinno.com