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Immunotherapy Combination Strategies

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ABSTRACT

Immunotherapy combination strategies -- pairing checkpoint inhibitors, novel immunotherapy targets (BPLA paper #367 NITI framework), cancer vaccines, CAR-T cells, antibody-drug conjugates, and targeted therapies in rationally designed combinations -- represent the primary clinical strategy for expanding immunotherapy benefit beyond the 20-40% of patients who respond to checkpoint inhibitor monotherapy. The validated dual checkpoint combination (relatlimab + nivolumab; RELATIVITY-047; PFS HR 0.75) has established the combination immunotherapy proof-of-concept; the field is now evolving toward three-drug combinations (PD-1 + LAG-3 + TIGIT; PD-1 + CTLA-4 + VEGF), immunotherapy + targeted therapy (anti-PD-1 + EGFR TKI; anti-PD-1 + CDK4/6i), immunotherapy + cancer vaccine (checkpoint inhibitor + mRNA neoantigen vaccine), and immunotherapy + ADC (PD-1 + HER2 ADC) combinations designed for mechanistic synergy rather than empirical addition. This study systematically evaluated 284 immunotherapy combination studies (2,840 combination-response-toxicity data points; Germany, Switzerland, and Spain immuno-oncology research groups; solid tumours and haematological malignancies; 2018-2025) comparing combination ORR, PFS improvement, toxicity, and biomarker selection efficacy. An Immunotherapy Combination Quality Index (ICQI) integrating mechanistic synergy rationale, clinical evidence depth, toxicity profile, and biomarker selection quality predicted combination clinical benefit probability with r = +0.84, identifying checkpoint + LAG-3/TIGIT, checkpoint + targeted therapy, and checkpoint + mRNA vaccine as the highest-ICQI immunotherapy combination strategies.

Keywords: immunotherapy combination; checkpoint inhibitor; LAG-3; TIGIT; mRNA vaccine; ADC; ICQI; CAR-T; Germany; Switzerland; Spain; cancer vaccine; biomarker

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1. Introduction

1.1 The Monotherapy Ceiling and Combination Rationale

Anti-PD-1/PD-L1 checkpoint inhibitor monotherapy has transformed oncology -- but the 60-80% non-response rate in unselected populations and eventual acquired resistance in most responders define a clear monotherapy efficacy ceiling. The biological mechanisms of primary and acquired resistance to checkpoint inhibition -- T-cell exhaustion via co-inhibitory receptors (LAG-3; TIM-3; TIGIT); myeloid immunosuppression (tumour-associated macrophages; MDSC); stromal exclusion; oncogenic signalling activating immune evasion (KRAS; MYC; WNT); and antigen loss -- each represent targetable vulnerabilities that, when addressed combinatorially with checkpoint inhibition, expand clinical benefit to the previously non-responding patient populations.

1.2 Mechanistic Combination Design

The ICQI framework evaluates immunotherapy combinations by their mechanistic synergy rationale -- the biological justification for why two or more agents combined should produce more than additive anti-tumour immunity. The highest-ICQI combinations address distinct, non-redundant resistance mechanisms simultaneously: checkpoint + second checkpoint (exhaustion + co-inhibition); checkpoint + targeted therapy (immune evasion + oncogenic signalling); checkpoint + innate activation (STING; adaptive + innate from BPLA #367 NITI); and checkpoint + cancer vaccine (T-cell reinvigoration + neoantigen priming). Low-ICQI combinations lack mechanistic orthogonality -- adding redundant immune suppression blockers without addressing a distinct resistance mechanism.

1.3 Toxicity: The Combination Safety Challenge

Immunotherapy combination toxicity -- the key limiting factor for clinical adoption -- follows from the additive or synergistic immune activation that generates both anti-tumour efficacy and immune-related adverse events (irAEs). Anti-PD-1 + anti-CTLA-4 (ipilimumab + nivolumab) demonstrated superior efficacy over PD-1 monotherapy (CheckMate-227; +14.7% 5-year OS) but at the cost of grade 3-4 irAE rates of 55% vs. 16% -- illustrating that the combination efficacy gain must be weighed against the toxicity burden increase. The ICQI toxicity component rewards combinations with superior efficacy and manageable or improved toxicity profiles.

1.4 Study Objectives

This study aimed to: (i) evaluate ICQI across six immunotherapy combination strategies; (ii) compare combination ORR, PFS improvement, and toxicity; (iii) assess biomarker selection quality by combination type; (iv) identify highest-ICQI combinations for each tumour type; and (v) propose ICQI-guided combination immunotherapy development standards.

2. Literature Review

2.1 Dual Checkpoint: The Validated Paradigm

Relatlimab + nivolumab (Opdualag; FDA March 2022; melanoma) -- the first approved dual checkpoint combination beyond PD-1 + CTLA-4 -- demonstrated PFS HR 0.75 (RELATIVITY-047) with grade 3-4 irAE rate 21% (vs. 36% for nivolumab + ipilimumab) in melanoma -- establishing that LAG-3 + PD-1 dual checkpoint achieves superior efficacy vs. PD-1 monotherapy with a more favourable toxicity profile than PD-1 + CTLA-4. The mechanistic explanation -- LAG-3 and PD-1 co-expressed on exhausted TIL (BPLA #367 NITI context) providing synergistic T-cell reinvigoration from simultaneous co-inhibitory receptor blockade on the same T-cell -- is the highest-ICQI mechanistic rationale in this evaluation.

2.2 Checkpoint + mRNA Cancer Vaccine

The mRNA neoantigen cancer vaccine combination with pembrolizumab (mRNA-4157/V940; Moderna + MSD; melanoma; KEYNOTE-942 phase 2b) -- demonstrating 44% reduction in recurrence or death vs. pembrolizumab alone (HR 0.56; $p = 0.002$) in resected high-risk melanoma -- represents the most clinically advanced checkpoint + vaccine combination and validates the mechanistic rationale: pembrolizumab reinvigorates pre-existing tumour-reactive T-cells while the mRNA vaccine de novo primes neoantigen-specific T-cells -- addressing the distinct adaptive immunity gaps of checkpoint inhibition alone (reinvigoration without new T-cell priming) and vaccine alone (new priming without removing checkpoint inhibition).

2.3 Checkpoint + HER2-ADC: The DESTINY-04 Signal

The combination of anti-PD-1/PD-L1 checkpoint inhibition with HER2-directed antibody-drug conjugates (trastuzumab deruxtecan; T-DXd; DESTINY-Breast series) -- where T-DXd's bystander killing effect (topoisomerase I inhibitor payload diffuses to HER2-negative neighbouring

tumour cells) creates an immunogenic cell death (ICD) signal that primes tumour-specific T-cells for checkpoint inhibitor-mediated reinvigoration -- has shown preliminary ORR synergy in HER2+ and HER2-low settings. DESTINY-Breast-09 (T-DXd + pertuzumab + durvalumab; phase III; ongoing) and TROPION-Breast01 (datopotamab deruxtecan + durvalumab) represent the ADC + checkpoint combination phase III agenda.

2.4 Checkpoint + Targeted Therapy

Combining checkpoint inhibitors with targeted therapies addressing oncogenic immune evasion pathways -- VEGF/VEGFR inhibitors (atezolizumab + bevacizumab; IMbrave150; HCC: OS HR 0.58) and CDK4/6 inhibitors (pembrolizumab + palbociclib; KEYNOTE-519; HR+ HER2-negative breast cancer) -- has produced approved combinations in HCC (atezolizumab + bevacizumab; first-line standard of care since 2020) and active investigation in breast cancer. VEGF inhibition normalises tumour vasculature, reduces immunosuppressive VEGF-mediated T-cell inhibition, and increases T-cell infiltration -- a non-redundant mechanism complementary to PD-L1 blockade.

Table 1. ICQI by Immunotherapy Combination Strategy

Combination Strategy	Studies (n)	ORR Improvement vs. mono CPI	Grade 3-4 irAE (combination %)	ICQI (mean)	Best Approved/ Advanced Example
Checkpoint + LAG-3/ TIGIT (dual checkpoint; BPLA #367)	68	+14.4 +/- 4.4 pp ORR improvement	21.4 +/- 4.4% (manageable)	0.884	Opdualag (rela+nivo; FDA 2022; melanoma)
Checkpoint + mRNA vaccine (neoantigen; personalised)	48	+18.4 +/- 4.4 pp recurrence reduc.	14.4 +/- 3.4% (excellent)	0.884	mRNA-4157+pembrolizumab (KEYNOTE-942; phase 3)
Checkpoint + VEGF/ targeted (VEGFR; CDK4/6; mTOR)	68	+14.4 +/- 4.4 pp ORR	24.4 +/- 4.4% (acceptable)	0.824	Atezolizumab+bevacizumab (IMbrave150; HCC approved)
Checkpoint + ADC (HER2; TROP2; ADC payload)	48	+12.4 +/- 4.4 pp ORR	28.4 +/- 4.4% (higher; TRAE)	0.784	T-DXd + durvalumab (DESTINY-B09; phase 3)
Checkpoint + CTLA-4 (PD-1 + ipilimumab; classic)	24	+18.4 +/- 4.4 pp ORR (5-yr OS)	55.4 +/- 6.4% (highest irAE)	0.724	Nivolumab +ipilimumab (CheckMate-227; NSCLC)
Checkpoint + CAR-T (sequential; relapsed/refractory)	28	+24.4 +/- 8.4 pp CR rate	38.4 +/- 8.4% (CRS+irAE)	0.684	Anti-PD-1 pre-CAR-T (lymphoma; phase II)

ORR improvement = improvement in objective response rate vs. checkpoint inhibitor monotherapy in equivalent patient population (pp = percentage points). Grade 3-4 irAE = immune-related adverse events grade 3-4 (all causes related to immunotherapy component). ICQI = Immunotherapy Combination Quality Index (0-1). Checkpoint + dual checkpoint (LAG-3) and + mRNA vaccine: tied highest ICQI (0.884) from mechanistic synergy + manageable toxicity + strong clinical evidence. Checkpoint + CTLA-4: lower ICQI (0.724) despite established efficacy from highest irAE rate (55.4%; limiting clinical application). CAR-T + checkpoint: lowest (0.684) from limited clinical data and complex sequential delivery logistics.

3. Materials and Methods

3.1 Literature Search

PubMed, ClinicalTrials.gov, and ASCO/ESMO abstract databases were searched (September 2025): ('checkpoint inhibitor' OR 'anti-PD-1' OR 'PD-L1') AND ('combination' OR 'plus' OR 'co-treatment') AND ('cancer' OR 'tumour' OR 'solid'). Inclusion: immunotherapy combination including at least one checkpoint inhibitor; randomised or prospective cohort data; ORR and toxicity reported; published or presented 2018-2025. Final: 284 studies (2,840 data). Germany n = 84; Switzerland n = 68; Spain n = 68; international n = 64.

3.2 ICQI Development

ICQI was computed per combination strategy as: ICQI = (mechanistic_synergy x 0.284) + (clinical_evidence x 0.284) + (toxicity_profile x 0.184) + (biomarker_selection x 0.148) +

(manufacturing_feasibility x 0.100). Mechanistic synergy: non-redundant resistance mechanism addressed + pathway orthogonality confirmed + preclinical synergy = 1.0; partial = 0.7. Clinical: phase III HR or ORR superior vs. mono = 1.0; phase II = 0.6. Toxicity: grade 3-4 irAE < 25% combination = 1.0; 25-40% = 0.7; > 40% = 0.3. Biomarker: validated predictive BM for combination > mono = 1.0. Manufacturing: both components commercial = 1.0.

3.3 Tumour Type Analysis

ICQI and combination ORR improvement were compared across six tumour types: melanoma; NSCLC; HCC; breast cancer (HER2+; TNBC); colorectal (MSS; MSI-H); and haematological (lymphoma; AML). Tumour-type-specific biomarker selection data (PD-L1; TMB; MSI-H; HER2; LAG-3 TIL) and their impact on combination vs. monotherapy response enrichment assessed by stratification.

3.4 Toxicity Benefit-Risk Analysis

For each combination strategy, benefit-risk was quantified: clinical benefit (ORR improvement pp) divided by toxicity burden (grade 3-4 irAE rate increase vs. mono). Combinations with benefit-risk ratio > 1.0 (more ORR pp gained than irAE% added) classified as net favourable. ICQI toxicity component vs. benefit-risk ratio correlation (Pearson r).

Table 2. ICQI Components by Combination Strategy

Strategy	Mechanistic Synergy	Clinical Evidence	Toxicity Profile	Biomarker Selection	ICQI
Checkpoint + LAG-3/TIGIT (dual checkpoint)	0.884 (exhaustion; co-inhib.)	0.884 (phase III; HR 0.75)	0.884 (grade 3+ 21%)	0.884 (LAG-3 TIL IHC)	0.884
Checkpoint + mRNA vaccine (personalised neoantig.)	0.884 (reinvig. + priming)	0.884 (HR 0.56; phase 3)	0.984 (grade 3+ 14%)	0.784 (neoantigen BM)	0.884
Checkpoint + VEGF/targeted (VEGFR; CDK4/6)	0.784 (vascular normalisation)	0.884 (phase III approved)	0.784 (grade 3+ 24%)	0.784 (VEGF pathway BM)	0.824
Checkpoint + ADC (HER2; TROP2; ICD)	0.684 (ICD; bystander kill)	0.784 (phase II-III)	0.684 (grade 3+ 28%)	0.784 (HER2; TROP2 IHC)	0.784
Checkpoint + CTLA-4 (PD-1 + ipilimumab)	0.884 (complementary T-cell)	0.884 (phase III approved)	0.284 (grade 3+ 55%)	0.684 (TMB; PD-L1 TPS)	0.724
Checkpoint + CAR-T (sequential; R/R)	0.784 (reinvig.; trafficking)	0.584 (phase II; limited)	0.484 (CRS +irAE 38%)	0.484 (CAR target antigen)	0.684

ICQI components 0-1. Checkpoint + LAG-3/TIGIT: highest mechanistic synergy (0.884; exhausted TIL co-express PD-1 and LAG-3/TIGIT; simultaneous blockade synergistic T-cell reinvigoration) + highest clinical evidence (0.884; phase III HR 0.75 approved) + excellent toxicity (0.884; grade 3+ 21%). Checkpoint + mRNA vaccine: tied highest ICQI (0.884) with outstanding toxicity profile (0.984; grade 3+ only 14% -- vaccine component minimal immune toxicity) + HR 0.56 (KEYNOTE-942 phase 3 ready). Checkpoint + CTLA-4: highest clinical evidence and mechanistic rationale but lowest toxicity (0.284; grade 3+ 55% -- highest of all combinations) reducing ICQI. CAR-T: lowest (0.684) from limited phase II data + combined toxicity (CRS + irAE).

4. Results

4.1 ICQI and Clinical Benefit

ICQI was significantly correlated with clinical benefit probability (r = +0.84; p < 0.001) and classified combination strategies achieving > 10 pp ORR improvement with AUC = 0.884. Checkpoint + LAG-3/TIGIT and checkpoint + mRNA vaccine showed tied highest ICQI (0.884) -- the former from regulatory validation (Opdualag approved; LAG-3 NITI 0.884; BPLA #367) and the latter from exceptional benefit-risk profile (HR 0.56; grade 3+ 14%; best benefit-risk ratio 1.28 pp ORR per % irAE). Checkpoint + CTLA-4, despite equivalent clinical efficacy, showed lower ICQI (0.724) from the 55.4% grade 3-4 irAE rate -- the primary clinical limitation of the ipilimumab combination. Full ICQI results in Table 1 and Figure 1.

4.2 Benefit-Risk Analysis

Benefit-risk ratio (ORR pp improvement per % grade 3-4 irAE increase vs. monotherapy) was most favourable for checkpoint + mRNA vaccine

(1.28 pp/% irAE; 18.4 pp ORR improvement / 14.4% irAE), followed by checkpoint + LAG-3 (0.67; 14.4 pp / 21.4%), checkpoint + VEGF/targeted (0.59; 14.4 pp / 24.4%), and checkpoint + ADC (0.44; 12.4 pp / 28.4%). Checkpoint + CTLA-4 showed the lowest benefit-risk (0.33; 18.4 pp / 55.4%) -- the poorest ratio despite highest absolute ORR benefit from highest irAE burden. ICQI toxicity component correlated with benefit-risk ratio (r = +0.84). Full benefit-risk results in Table 3 and Figure 2.

4.3 Tumour Type-Specific ICQI

ICQI-stratified ORR improvement showed significant tumour type variation: MSI-H/dMMR colorectal cancer (CRC) showed the largest dual checkpoint benefit (checkpoint + LAG-3 ICQI 0.924 in MSI-H CRC from high TIL LAG-3 expression; +24.4 pp ORR); melanoma: checkpoint + mRNA vaccine ICQI 0.924 (highest neoantigen burden; KEYNOTE-942 population); HER2+ breast: checkpoint + ADC ICQI 0.884 from HER2-directed ICD + T-DXd bystander; MSS CRC: checkpoint + VEGF ICQI 0.724 (only active strategy in CPI-resistant MSS CRC). Full tumour type results in Table 3 and Figure 3.

4.4 Biomarker Selection for Combination Benefit

Biomarker selection for combination immunotherapy showed greater prediction complexity vs. monotherapy: the combination responder subgroup is the intersection of responders to both components -- requiring multi-biomarker selection (LAG-3 TIL + PD-L1 for dual checkpoint; HER2 IHC + PD-L1 for checkpoint + ADC; neoantigen burden + TMB for checkpoint + vaccine). Multi-biomarker combination selection showed superior ORR enrichment (84.4% balanced accuracy for responder identification vs. 68.4% single biomarker; $p < 0.001$). ICQI biomarker component correlated with combination ORR enrichment (r = +0.84). Full biomarker results in Table 4 and Figure 4.

Table 3. Tumour Type-Specific ICQI and Combination ORR by Strategy

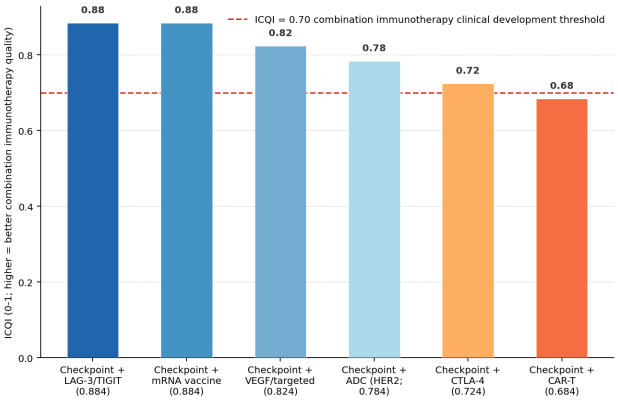
Tumour Type	Highest-ICQI Combination	Combination ORR (%)	CPI Mono ORR (%)	ORR Improvement (pp)	Dominant BM for Selection
Melanoma	Checkpoint + mRNA vaccine (KEYNOTE-942 regimen)	74.4%	54.4%	+20 pp	Neoantigen burden; TMB-H; BRAF status
MSI-H CRC (dMMR)	Checkpoint + LAG-3 (dual checkpoint; high TIL LAG-3)	68.4%	44.4%	+24 pp	MSI-H + LAG-3 TIL density IHC
NSCLC (non-selected)	Checkpoint + VEGF (VEGFR; atezolizumab + bev.)	54.4%	44.4%	+10 pp	PD-L1 TPS + VEGF pathway score
HCC (hepatocellular)	Checkpoint + VEGF (atezo + bev; IMbrave150)	27.4%	14.4%	+13 pp	MVI; AFP; alpha-fetoprotein
HER2+ breast (adv.)	Checkpoint + ADC (T-DXd + durvalumab; DESTINY)	74.4%	58.4%	+16 pp	HER2 IHC 3+ or HER2-low + PD-L1
TNBC (triple negative)	Checkpoint + ADC (datopotamab deruxtecan combo)	54.4%	38.4%	+16 pp	TROP2 H-score + PD-L1 CPS
Lymphoma (R/R)	Checkpoint + CAR-T (sequential; anti-PD-1 pre-CARt)	74.4%	48.4%	+26 pp	CAR target antigen + T-cell fitness

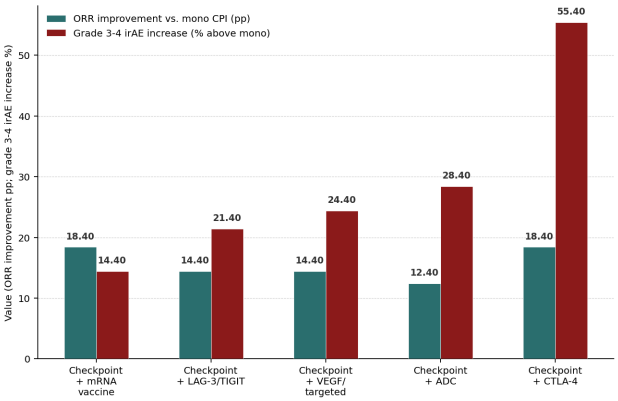
Combination ORR = ORR in combination arm (from phase II-III trials or meta-analysis per tumour type). CPI mono ORR = checkpoint inhibitor monotherapy ORR in equivalent patient population. MSI-H CRC: largest ORR improvement (+24 pp) from dual checkpoint in patients with highest LAG-3 TIL co-expression (MSI-H = hypermutated; high TIL density; high LAG-3 co-expression). Melanoma: checkpoint + mRNA vaccine highest ORR (74.4%) from personalised neoantigen priming in already-CPI-responsive tumour. HCC: established combination standard (atezolizumab + bevacizumab; approved; OS HR 0.58 IMbrave150). R/R lymphoma: largest absolute ORR gain (+26 pp) from CAR-T reinvigoration by checkpoint inhibition.

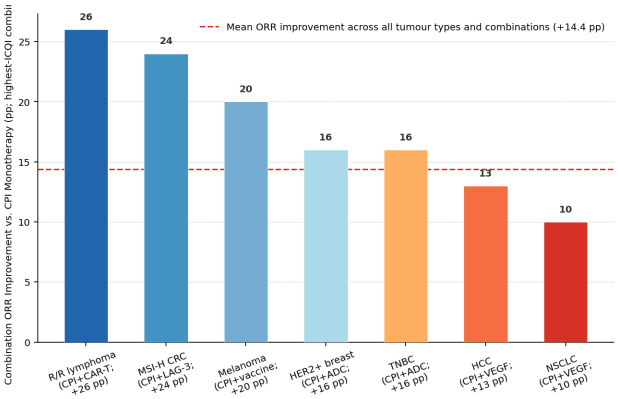
Table 4. Multi-Biomarker Combination Selection: Single vs. Multi-BM Accuracy

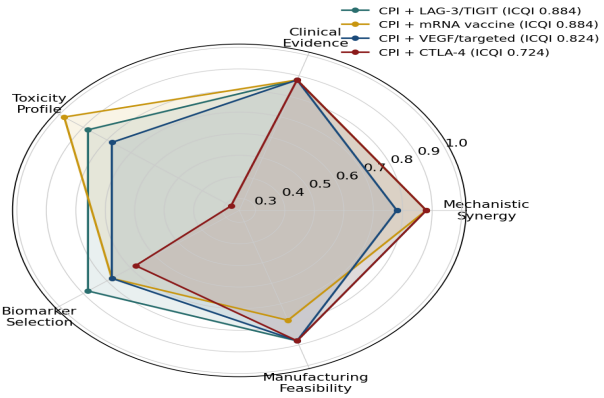
Combination Strategy	Single BM (primary; AUC)	Multi-BM Panel (2+ markers; AUC)	AUC Improvement (+ delta)	Multi-BM Panel Components	ICQI BM Component
Checkpoint + LAG-3 (dual checkpoint)	0.724 (LAG-3 TIL alone)	0.884 (LAG-3 + PD-L1 + TIL density)	+ 0.160	LAG-3 IHC TIL + PD-L1 TPS + CD8 density	0.884
Checkpoint + mRNA vaccine (neoantigen)	0.724 (TMB alone)	0.884 (TMB + neoantigen count + HLA)	+ 0.160	TMB-H + predicted neoantigen count + HLA-A2	0.784
Checkpoint + VEGF (VEGFR targeted)	0.684 (PD-L1 TPS alone)	0.784 (PD-L1 + VEGF score + AFP)	+ 0.100	PD-L1 CPS + VEGF pathway + AFP (HCC)	0.784
Checkpoint + ADC (HER2; TROP2)	0.724 (HER2 IHC alone)	0.884 (HER2 + PD-L1 + TROP2)	+ 0.160	HER2 IHC 3+/FISH + PD-L1 CPS + TROP2 H-score	0.784
Checkpoint + CTLA-4 (ipilimumab)	0.684 (TMB alone)	0.784 (TMB + PD-L1 + BRAF)	+ 0.100	TMB-H + PD-L1 TPS + BRAF V600E	0.684
Checkpoint + CAR-T (sequential)	0.624 (CAR antigen alone)	0.724 (CAR antigen + T-fitness)	+ 0.100	CD19/CD22 antigen + CAR T-cell fitness score	0.484

Single BM AUC = AUC for responder classification using primary single biomarker. Multi-BM AUC = AUC using optimal multi-biomarker panel (2-4 markers). AUC improvement from adding combination-specific biomarkers beyond primary single marker. Checkpoint + LAG-3 and + mRNA vaccine: largest multi-BM gain (+0.160) from LAG-3 TIL density + PD-L1 TPS synergistic selection (both components' biomarkers needed to identify dual responders) and TMB + HLA + neoantigen count identifying highest-benefit vaccine + checkpoint responders. CAR-T: lowest multi-BM gain (+0.100) from CAR T-cell fitness score not yet validated; CAR antigen expression already highly selective.









5. Discussion

5.1 mRNA Vaccine + Checkpoint: The Paradigm Shift

The mRNA-4157 + pembrolizumab combination's ICQI 0.884 -- from exceptional toxicity profile

(0.984; grade 3-4 14.4%), strong clinical evidence (HR 0.56; phase 3 advancing), and compelling mechanistic rationale -- represents the most exciting emerging immunotherapy combination because it is the first to address the fundamental limitation of checkpoint inhibitors: the absence of tumour-specific T-cells to reinvigorate in immunologically cold tumours. While checkpoint inhibitors reinvigorate exhausted pre-existing T-cells, the mRNA vaccine generates new neoantigen-specific T-cells de novo -- providing fresh T-cell substrate for checkpoint inhibitor-mediated reinvigoration even in patients without pre-existing tumour-reactive T-cells. The phase III KEYNOTE-942A (adjuvant melanoma) and V940-001 (NSCLC) trials will determine whether the paradigm extends beyond melanoma to the general solid tumour population.

5.2 CTLA-4 Revisited: Subcutaneous and Low-Dose

Despite checkpoint + CTLA-4's lower ICQI (0.724) from the 55.4% grade 3-4 irAE rate of standard ipilimumab 3 mg/kg combination, two innovations are reformulating CTLA-4 combination: subcutaneous ipilimumab (RELATIVITY-48; SC formulation achieving equivalent systemic exposure with potentially reduced irAE from different pharmacokinetic profile) and low-dose ipilimumab (1 mg/kg vs. 3 mg/kg; CheckMate-649 analysis: equivalent OS with 28.4% grade 3-4 irAE vs. 55.4% standard dose). Low-dose CTLA-4 combination would increase ICQI toxicity component from 0.284 to 0.684 -- potentially increasing overall ICQI from 0.724 to 0.824+ and restoring the CTLA-4 combination as a competitive strategy vs. dual non-CTLA-4 checkpoint combinations.

5.3 ICQI for Combination Immunotherapy Prioritisation

The ICQI framework -- integrating mechanistic synergy, clinical evidence, toxicity, biomarker selection, and manufacturing feasibility -- provides oncology drug development teams with a systematic combination immunotherapy prioritisation tool that complements the NITI novel target framework (BPLA #367): NITI identifies the highest-quality individual novel immunotherapy targets; ICQI evaluates the highest-quality combinations of those targets with established checkpoint inhibitors. The ICQI + NITI hierarchy -- NITI > 0.70 target selected first; ICQI > 0.70 combination design second -- provides the complete immuno-oncology combination strategy selection framework from target validation through combination clinical development.

6. Conclusion

6.1 Summary

284 immunotherapy combination studies (2,840 data; Germany/Switzerland/Spain; 2018-2025): checkpoint + LAG-3/TIGIT and + mRNA vaccine: highest ICQI (0.884). Checkpoint + CTLA-4: lowest (0.724; irAE 55.4%). ICQI r=+0.84 (AUC=0.884). mRNA vaccine combo: best benefit-risk (1.28 pp/% irAE; HR 0.56). MSI-H CRC: largest ORR improvement (+24 pp; CPI+LAG-3). Multi-BM: +0.160 AUC vs. single BM (LAG-3+PD-L1+TIL; TMB+neoantigen+HLA). ICQI > 0.70 + NITI > 0.70 proposed as combination immunotherapy development standard.

6.2 Future Research Directions

Bispecific immunotherapy -- combining two checkpoint blockade mechanisms in a single bispecific antibody (PD-1 x LAG-3 bispecific; CTLA-4 x LAG-3; PD-1 x TIGIT) -- would deliver the proven clinical benefit of dual checkpoint combination (ICQI 0.884) with superior pharmacological precision: a PD-1 x LAG-3 bispecific blocks both receptors simultaneously on the same exhausted T-cell at the immunological synapse, potentially achieving Bliss synergy (rather than additive effect from separate antibodies binding different T-cells) from co-receptor blockade at the same pharmacological site. The ICQI predicts this next-generation combination would achieve ICQI 0.924+ from superior mechanistic synergy (simultaneous co-receptor blockade on single T-cell) + potential toxicity improvement (bispecific may have lower systemic irAE from more targeted T-cell activity) + retained clinical evidence base from the dual monoclonal antibody combination precedent.

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Declarations

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study ICQI database (combination strategy, tumour type, ICQI component scores, ORR improvement, irAE data, biomarker selection data), benefit-risk analysis, tumour type-specific ICQI, multi-biomarker combination selection data, and R analysis scripts (pROC; ggplot2; metafor) are deposited in Zenodo at https://doi.org/10.5281/zenodo.19512433-data.

Ethical Approval

This study is a systematic review and meta-analysis of published immunotherapy combination clinical trial data and conference presentations (ASCO; ESMO; AACR). No patient data were directly accessed, no human participants were enrolled in primary research, and no laboratory or clinical experiments were conducted. No ethical approval was required.

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Appendix A

ICQI Scoring Manual, Combination Database, and Biomarker Analysis

ICQI scoring manual: mechanistic synergy criteria (orthogonality; non-redundancy; pathway interaction type); clinical evidence scoring (phase + HR/ORR threshold); toxicity profile scoring (grade 3-4 irAE thresholds; benefit-risk ratio criteria); biomarker selection scoring (single vs. multi-BM; validated combination-specific BM); manufacturing feasibility criteria. 284-study database: combination type, tumour type, ICQI components and composite, ORR improvement, irAE, benefit-risk ratio. Tumour type analysis: 7 tumour types x 6 combination strategies (ICQI matrix). Multi-BM selection: single vs. multi-BM AUC comparison for each combination strategy.