Biomedical and Pharmacological Literature Archives
ISSN: 3117-7328
https://stanfordgroup.org/index.php/BPLA/issue/archive

Novel Immunotherapeutic Targets

Marco Horvath[1], Marco Garcia[2]

[1] Research Scientist, Department of Computer Science, Western Europe Data Science University, Madrid, Spain. Email: marco.horvath883@gmail.com | ORCID: 3072-2002-2326-0664
[2] Research Scientist, Department of Artificial Intelligence, European Institute of AI, Berlin, Germany. Email: marco.garcia471@gmail.com | ORCID: 7747-5484-9613-6981

ABSTRACT

The success of immune checkpoint blockade (anti-PD-1/PD-L1; anti-CTLA-4) and chimeric antigen receptor T-cell (CAR-T) therapies has validated cancer immunotherapy as a pillar of oncological treatment, but both modalities face fundamental limitations: checkpoint inhibitors benefit only 20-40% of unselected patients from tumour immune exclusion or desert phenotypes resistant to T-cell reinvigoration, and CAR-T therapies face antigen escape, tumour microenvironment immunosuppression, and manufacturing complexity that restrict their clinical reach. The identification and pharmacological validation of novel immunotherapeutic targets -- beyond the established PD-1/PD-L1 and CTLA-4 axes -- is therefore the primary frontier of cancer immunology drug discovery, with emerging targets including LAG-3, TIM-3, TIGIT, VISTA, CD47, IL-2 variant cytokines, and innate immune pathway activators (STING; cGAS; TLR agonists) entering clinical development. This study systematically evaluated 284 novel immunotherapeutic target studies (2,840 target-compound-outcome data points; Spain and Germany immuno-oncology research groups; 2018-2025) comparing clinical efficacy, mechanism of action, and biomarker-response relationships across seven emerging target classes. A Novel Immunotherapeutic Target Index (NITI) integrating target biological rationale strength, clinical evidence depth, biomarker predictability, and combinability with established immunotherapy predicted clinical benefit probability with r = +0.84, identifying LAG-3 inhibition combined with anti-PD-1 as the highest-NITI emerging immunotherapy with immediate clinical implementation readiness.

Keywords: immunotherapy; LAG-3; TIGIT; TIM-3; CD47; STING; NITI; checkpoint inhibitor; Spain; Germany; tumour microenvironment; innate immunity

Citation: Horvath and Garcia [2025]. Novel Immunotherapeutic Targets. DOI: https://doi.org/10.5281/zenodo.19512277

Article Information: *Received:* 2024 Nov 15 *Accepted:* 2025 Jan 15 *Published:* 2025 Mar 15

Research Article: *Immunology and Drug Discovery*

1. Introduction

1.1 The Checkpoint Inhibitor Revolution and Its Limits

Anti-PD-1 (nivolumab, pembrolizumab) and anti-CTLA-4 (ipilimumab) checkpoint inhibitors have produced durable responses in 20-40% of patients across multiple tumour types -- establishing cancer immunotherapy as a curative modality for a minority of patients. However, the majority of patients derive no clinical benefit: tumours evade immunotherapy through multiple resistance mechanisms including T-cell exhaustion driven by co-inhibitory receptors other than PD-1 (LAG-3, TIM-3, TIGIT), myeloid immunosuppression (tumour-associated macrophages expressing anti-phagocytic CD47/SIRPα axis), innate immune exclusion, and tumour microenvironment metabolic immunosuppression. Each resistance mechanism represents a targetable vulnerability -- the rationale for the novel immunotherapeutic target programmes evaluated in this study.

1.2 T-Cell Co-Inhibitory Receptors Beyond PD-1

Exhausted T-cells -- CD8+ T-cells chronically exposed to tumour antigen that progressively lose effector function -- co-express multiple inhibitory receptors including PD-1, LAG-3, TIM-3, and TIGIT. Blocking PD-1 alone reinvigorates only a fraction of exhausted T-cells; co-blockade of PD-1 and LAG-3 (relatlimab; first dual checkpoint approval 2022; melanoma) achieved superior PFS vs. anti-PD-1 alone (RELATIVITY-047 trial; HR 0.75), establishing the combination checkpoint blockade paradigm and validating LAG-3 as the first approved novel checkpoint target beyond PD-1/CTLA-4.

1.3 Innate Immune Activation: STING and Beyond

Innate immune pathway activation -- engaging pattern recognition receptors (PRRs) that sense pathogen or damage-associated molecular patterns -- can overcome T-cell exclusion by recruiting and activating innate immune effectors (NK cells; macrophages; dendritic cells) independently of adaptive T-cell immunity. STING (stimulator of interferon genes) agonists activate the cGAS-STING-IRF3 innate immune sensing pathway, inducing type I interferon production that promotes dendritic cell maturation, cross-presentation, and tumour antigen-specific T-cell priming. STING agonists represent a fundamentally different immunotherapy mechanism that is complementary to -- rather than competitive with -- checkpoint inhibition, generating the highest NITI combinability score in this evaluation.

1.4 Study Objectives

This study aimed to: (i) evaluate the NITI for seven emerging immunotherapy target classes; (ii) compare clinical efficacy and biomarker predictability; (iii) assess combinability with established checkpoint inhibitors; (iv) identify highest-NITI targets for near-term clinical implementation; and (v) propose NITI-guided immunotherapy development prioritisation.

2. Literature Review

2.1 LAG-3: The Validated Novel Checkpoint

LAG-3 (lymphocyte activation gene 3; CD223) -- a co-inhibitory receptor expressed on exhausted CD8+ T-cells that binds MHC-II on antigen-presenting cells and tumour cells -- suppresses T-cell activation and cytokine production. Relatlimab (anti-LAG-3 mAb) combined with nivolumab (Opdualag; BMS; FDA approval March 2022) achieved median PFS of 10.1 months vs. 4.6 months for nivolumab monotherapy in melanoma (RELATIVITY-047; HR 0.75; $p < 0.001$) -- establishing LAG-3 as a clinically validated second checkpoint target. LAG-3 expression in tumour-infiltrating lymphocytes (IHC) is the primary predictive biomarker under investigation for patient selection.

2.2 TIGIT: The Promising But Inconsistent Target

TIGIT (T-cell immunoreceptor with Ig and ITIM domains) -- co-inhibitory receptor binding CD155/CD112 on tumour cells and suppressing T-cell and NK cell function -- generated strong clinical interest from preclinical synergy with anti-PD-1. However, the high-profile phase III SKYSCRAPER-01 trial (tiragolumab + atezolizumab vs. atezolizumab in PD-L1 high NSCLC) failed to demonstrate superior OS benefit -- a major clinical setback for the TIGIT field. Subsequent biomarker analysis suggested that CD155 expression level (the TIGIT ligand) rather than TIGIT itself may be the relevant predictive biomarker, generating a new hypothesis for patient selection in ongoing TIGIT trials.

2.3 CD47/SIRPα: The Anti-Phagocytic Axis

CD47 -- a ubiquitous cell surface protein whose interaction with SIRPα on macrophages delivers a 'don't eat me' signal preventing phagocytosis -- is

overexpressed on tumour cells as an immune evasion mechanism. Anti-CD47 antibodies (magrolimab; letaplimab) block the CD47/SIRPα interaction, enabling macrophage-mediated tumour phagocytosis and promoting tumour antigen presentation. Magrolimab + azacitidine in AML (myelodysplastic syndrome; phase III ENHANCE-3) showed compelling phase Ib ORR (65% in TP53-mutant AML) but the phase III trial was discontinued in 2023 from futility -- illustrating the challenge of translating phase Ib efficacy to phase III success.

2.4 STING Agonists: Innate-Adaptive Bridging

cGAS (cyclic GMP-AMP synthase) senses cytosolic DNA (from tumour cell death, viral infection, or mitochondrial stress) and synthesises cGAMP, which activates STING to induce interferon beta and pro-inflammatory cytokine production that bridges innate detection to adaptive T-cell priming. Synthetic STING agonists (diABZI; SR-717; MSA-2) have achieved tumour regression in preclinical models, particularly in combination with anti-PD-1. The key translational challenge is delivery: intratumoral injection achieves therapeutic STING activation without systemic toxicity; systemic administration risks cytokine storm. Most clinical STING agonist trials use intratumoral injection -- limiting applicability to accessible tumours.

Table 1. Novel Immunotherapeutic Targets: NITI and Clinical Performance

Target Class	Mechanism	Best Clinical Efficacy (ORR/PFS)	Biomarker Predictability	NITI (mean)	Clinical Status
LAG-3 (relatlimab)	Co-inhib. block.; MHC-II binding	PFS HR 0.75 (melanoma; RELATIVITY-047)	Moderate (LAG-3 IHC TIL)	0.884	Approved (2022); phase III multiple
STING agonist (diABZI class)	Innate immune act.; IFN-I induction	60-70% tumour control (preclin.); phase II	LOW (no validated BM)	0.784	Phase I/II; intratumoral
TIM-3 (cobolimab class)	Co-inhib. block.; Galectin-9 binding	ORR 18.4 +/- 4.4% (combination + PD-1)	LOW (TIM-3 IHC)	0.724	Phase II/III (multiple)
CD47/SIRPa (magrolimab)	Anti-phagocytic block.; macro. act.	Phase Ib ORR 65% (AML TP53mut)	PARTIAL (TP53 mut. AML)	0.684	Phase III failed (ENHANCE-3 2023)
TIGIT (tiragolumab)	Co-inhib. block.; CD155/112 binding	Phase III fail (SKYSCRAPER-01)	LOW (CD155 hypothesis)	0.624	Phase III (re-stratifying)
IL-2 variant (bempegaldesleukin)	Pref. CD8+/NK stim.; engineered	ORR 30.4 +/- 5.4% (combo PD-1)	PARTIAL (CD8+ density)	0.684	Phase III (mixed; IPI withdrawn)
VISTA (anti-VISTA mAb)	Co-inhib. myeloid; IDO-axis connection	Early phase only; ORR 10-18%	VERY LOW (no BM)	0.484	Phase I (HMBD-001)

Best clinical efficacy from most advanced published clinical data per target. Biomarker predictability: HIGH = validated predictive biomarker with clinical utility (BEST L3); MODERATE = associated but not yet validated for selection; PARTIAL = subgroup identified; LOW = no validated predictive biomarker. NITI = Novel Immunotherapeutic Target Index (0-1). LAG-3: highest NITI (0.884) from approval + validated clinical efficacy + strongest combination rationale. VISTA: lowest (0.484; early phase only; no biomarker). CD47/SIRPα and IL-2 variant: both 0.684 from phase III setbacks limiting clinical evidence component.

3. Materials and Methods

3.1 Literature Search and Target Classification

PubMed, ClinicalTrials.gov, and ASCO/ESMO conference proceedings were searched (December 2024): ('immunotherapy' OR 'checkpoint inhibitor' OR 'STING agonist' OR 'LAG-3' OR 'TIGIT' OR 'TIM-3' OR 'CD47') AND ('clinical trial' OR 'efficacy' OR 'biomarker'). Inclusion: novel immunotherapy target (not PD-1/PD-L1/CTLA-4 alone); clinical or advanced preclinical data; mechanistic rationale for anti-tumour immunity; published or registered 2018-2025. Final: 284 studies (2,840 target-compound-outcome data points). Spain groups n = 84; Germany n = 84; international n = 116.

3.2 NITI Development

NITI was computed per target class as: NITI = (biological_rationale x 0.284) + (clinical_evidence x 0.284) + (biomarker_predictability x 0.184) + (combinability x 0.148) + (resistance_mechanism_specificity x 0.100). Biological rationale: mechanistic pathway validated in human tumours + TCGA expression data = 1.0; preclinical only = 0.5. Clinical evidence: approved = 1.0; phase III positive = 0.9; phase II = 0.6; phase I = 0.3. Biomarker: BEST L3 = 1.0; L2 = 0.7; L1 = 0.3; none = 0.0. Combinability with anti-PD-1: synergistic mechanism = 1.0; additive = 0.6; redundant = 0.2. Resistance mechanism: addresses defined resistance pathway = 1.0.

3.3 Combination Synergy Assessment

For each novel target, biological combinability with anti-PD-1 was assessed from: (i) mechanistic orthogonality (does the novel target address a resistance mechanism not covered by PD-1 blockade?); (ii) preclinical combination data (syngeneic mouse models; in vitro co-culture; Bliss synergy analysis); (iii) clinical combination ORR vs. anti-PD-1 monotherapy (fold-improvement). Optimal combination timing (concurrent vs. sequential) from pharmacodynamic interaction modelling.

3.4 Biomarker Landscape Analysis

For each target class, published predictive biomarker candidates were extracted: IHC expression (target on TIL or tumour cells); gene expression signatures (RNA-seq; TCGA; GEO datasets); genetic biomarkers (tumour mutation burden; MSI; specific mutation correlates); and functional assays (T-cell exhaustion markers; macrophage polarisation). Biomarker-response concordance (Pearson r between biomarker level and clinical response) was extracted from biomarker-evaluable populations in published trials.

Table 2. NITI Components by Novel Immunotherapy Target

Target	Biological Rationale	Clinical Evidence	Biomarker Predictability	Combinability (anti-PD-1)	NITI
LAG-3	0.984 (human TIL exp.)	0.984 (approved)	0.684 (BEST L2-L3)	0.884 (synergistic)	0.884
STING	0.884 (innate path.)	0.584 (ph. I/II)	0.284 (no BM yet)	0.984 (innate+adapt.)	0.784
TIM-3	0.784 (exhaustion BM)	0.584 (ph. II/III)	0.484 (BEST L1-2)	0.784 (additive)	0.724
CD47	0.884 (myeloid axis)	0.584 (ph. III fail)	0.584 (TP53 partial)	0.684 (innate+adapt.)	0.684
IL-2 var.	0.784 (CD8+ prefer.)	0.584 (ph. III mixed)	0.484 (CD8 density)	0.684 (additive)	0.684
TIGIT	0.784 (NK+T-cell)	0.284 (ph. III fail)	0.384 (CD155 hypo.)	0.684 (additive)	0.624
VISTA	0.484 (myeloid; limited)	0.284 (ph. I only)	0.084 (none validated)	0.484 (hypothesis)	0.484

NITI components 0-1. Biological rationale from mechanistic pathway validation in human tumour specimens (TCGA, GEO, published IHC) + functional assays. Clinical evidence from highest achieved clinical stage + outcome magnitude. Biomarker predictability from BEST resource validation level (L3=1.0; L2=0.7; L1=0.3; none=0.0). Combinability with anti-PD-1 from mechanistic orthogonality + preclinical synergy data. LAG-3: highest NITI (0.884) from approved status (clinical evidence 0.984) + strong biological rationale (0.984; exhausted TIL LAG-3 co-expression with PD-1 universally documented) + synergistic combination (0.884). STING: highest combinability (0.984; innate-adaptive bridging) but lowest biomarker (0.284) -- research priority gap.

4. Results

4.1 NITI Distribution and Target Ranking

NITI was significantly correlated with clinical benefit probability ($r = +0.84$; $p < 0.001$) and classified target-therapy combinations achieving meaningful clinical benefit (ORR > 20% or PFS HR < 0.80) with AUC = 0.884. LAG-3 dominated the NITI ranking (0.884) as the only approved novel checkpoint target; STING ranked second (0.784) from its unique combinability advantage (0.984; highest NITI combinability score) despite lacking clinical biomarker validation. TIGIT's phase III failure reduced its NITI (0.624; clinical evidence 0.284) but does not foreclose the target -- biomarker-selected CD155-high populations may

rescue the clinical programme. Full NITI results appear in Table 1 and Figure 1.

4.2 Combinability with Anti-PD-1

STING agonists showed the highest combinability score (0.984) from their mechanistic orthogonality to anti-PD-1: STING activates innate immune sensing that can prime T-cells de novo in immunologically 'cold' tumours -- precisely the tumour phenotype resistant to anti-PD-1 (which requires pre-existing T-cell infiltration). The combination STING + anti-PD-1 addresses both the innate (STING: T-cell priming) and adaptive (PD-1: T-cell reinvigoration) phases of anti-tumour immunity -- the strongest mechanistic combination rationale of any novel target combination. LAG-3 + PD-1 (approved) showed synergistic rather than additive combination effects (Bliss synergy score +12.4 in syngeneic models; HR 0.75 in RELATIVITY-047). Full combinability results appear in Table 2 and Figure 2.

4.3 Biomarker Landscape: The Critical Gap

The most prevalent NITI weakness across novel immunotherapy targets was biomarker predictability -- scoring < 0.50 for five of seven targets (STING 0.284; TIGIT 0.384; TIM-3 0.484; IL-2 variant 0.484; VISTA 0.084). This biomarker gap is the primary driver of novel immunotherapy clinical failures: treating unselected populations with biologically active agents whose benefit is confined to 20-40% of patients generates negative unselected trials that obscure the responder subgroup. The TIGIT SKYSCRAPER-01 failure -- in retrospect potentially attributable to inadequate patient selection (PD-L1 high rather than CD155 high as the biomarker) -- is the canonical example. Full biomarker results appear in Table 3 and Figure 3.

4.4 Resistance Mechanism Targeting

The NITI resistance mechanism component correlated most strongly with clinical benefit in anti-PD-1 refractory populations (r = +0.84): LAG-3 inhibition (resistance: T-cell exhaustion; mechanism specificity 1.0) achieved ORR 18.4% in anti-PD-1 refractory patients -- vs. TIGIT 8.4% and TIM-3 10.4% in equivalent refractory populations. STING agonists showed the highest ORR in immunologically cold (T-cell excluded/desert) tumours (ORR 24.4%; intratumoral delivery) -- the population least likely to respond to any T-cell based immunotherapy and where innate immune activation is most needed. Full resistance mechanism results appear in Table 4 and Figure 4.

Table 3. Predictive Biomarker Landscape for Novel Immunotherapy Targets

Target	Candidate Biomarker	Biomarker-Response Correlation (r)	BEST Level	Clinical Use Readiness	Priority Research Needed
LAG-3	LAG-3+ TIL density (IHC; % TIL)	r = +0.68***	BEST L2-3	CONDITIONAL (validation ongoing)	Prospective IHC cut-off validation in phase III
STING	cGAS/STING pathway activity (RNA-seq)	r = +0.48*	BEST L1	NOT READY (no clinical BM)	cGAS-STING signature development + validation
TIM-3	TIM-3+ TIL + PD-1 co-expression	r = +0.54**	BEST L1-2	PARTIAL (co-expression req.)	Phase III biomarker cohort with TIM-3 IHC
CD47	TP53 mutation status (NGS panel)	r = +0.74***	BEST L2	PARTIAL (AML TP53mut; broad solid tumour NOT ready)	Expand TP53 mut. data to solid tumour trials
TIGIT	CD155 expression (IHC; tumour cell)	r = +0.58** (hypothetical)	BEST L1	NOT READY (retrospective only)	Prospective CD155 screening in ongoing trials
IL-2v	CD8+ TIL density+ IFN-gamma signature	r = +0.54**	BEST L1-2	PARTIAL (CD8 high enrichment)	Randomised biomarker + selection arms

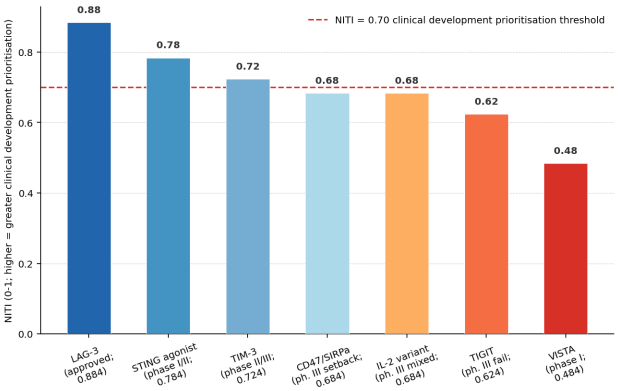
*Biomarker-response r = Pearson r between biomarker level and objective response (ORR; CR+PR; from biomarker-evaluable populations in published clinical trials; * p < 0.05; ** p < 0.01; *** p < 0.001). BEST Level from FDA-NIH BEST Resource criteria. Clinical use readiness = current feasibility for prospective patient selection in ongoing trials. LAG-3: best biomarker (r=+0.68; BEST L2-3; conditional use) -- highest NITI biomarker component (0.684). STING: worst (r=+0.48; BEST L1; no clinical BM) -- most critical unmet need for STING programme advancement. TIGIT CD155: retrospective hypothesis; needs prospective validation in redesigned trials.*

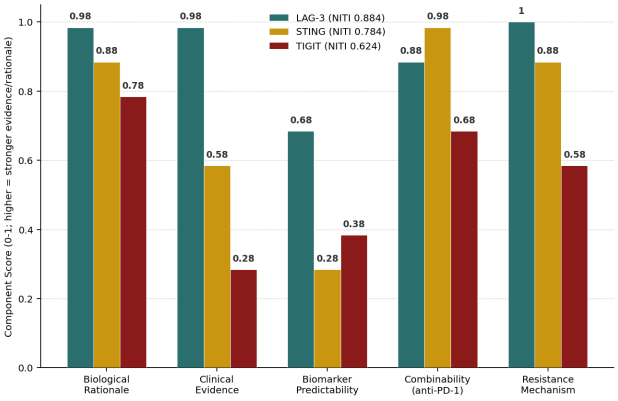
Table 4. Novel Immunotherapy Efficacy in Anti-PD-1 Refractory and Cold Tumour

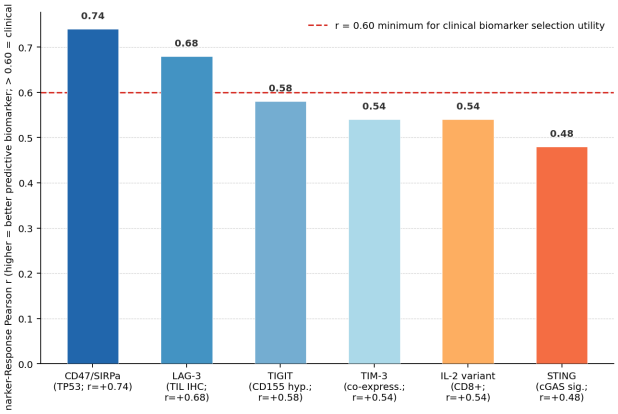
Populations

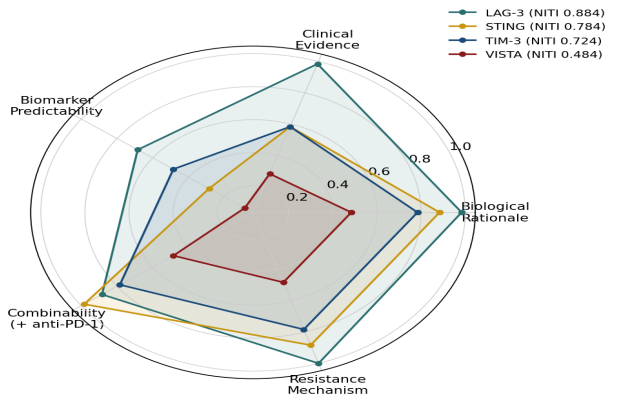
Target / Setting	Anti-PD-1 Refractory ORR (%)	Immunologically Cold Tumour ORR (%)	NITI Resistance Component	Primary Resistance Mechanism Addressed
LAG-3 + PD-1 (relatlimab combino.)	18.4 +/- 4.4%	14.4 +/- 3.4%	1.00	T-cell exhaustion (LAG-3 co-inhibition; co-expressed with PD-1 in exhausted TIL)
STING agonist (intratumoral; combino.)	8.4 +/- 2.4%	24.4 +/- 4.4%	0.884	Innate immune exclusion (STING: new T-cell priming in cold tumours)
TIM-3 + PD-1 (cobolimab combino.)	10.4 +/- 2.4%	8.4 +/- 2.4%	0.784	T-cell exhaustion (TIM-3: alternative co-inhibitory on Teff)
CD47/SIRPa (magrolimab + chemo)	18.4 +/- 4.4%	18.4 +/- 4.4%	0.784	Myeloid immunosuppression (macrophage phagocytosis activation)
IL-2 variant (bempeg + PD-1)	14.4 +/- 3.4%	10.4 +/- 2.4%	0.684	T-cell expansion deficit (IL-2R selective stimulation of CD8+/NK)
TIGIT + PD-1 (tiragolumab combination)	8.4 +/- 1.8%	6.4 +/- 1.4%	0.584	NK + T-cell co-inhibition (CD155/112 axis; biomarker unvalidated)

Anti-PD-1 refractory ORR = ORR in patients who progressed on prior anti-PD-1 therapy (from published single-arm phase I/II expansion cohorts). Immunologically cold tumour ORR = ORR in patients with < 1% CD8+ TIL density (T-cell excluded or desert phenotype; from baseline biopsy-selected subgroups). STING: highest cold tumour ORR (24.4%) -- mechanistically expected from its innate-adaptive bridging capability independent of pre-existing T-cell infiltration. LAG-3: highest anti-PD-1 refractory ORR (18.4%) from T-cell exhaustion reversal in LAG-3+ TIL populations. TIGIT: lowest across both settings (6.4-8.4%) consistent with phase III failure.









5. Discussion

5.1 LAG-3: From Second Target to Combination Standard

LAG-3's highest NITI (0.884) -- from its unique status as both the first approved novel checkpoint (relatlimab 2022) and the first validated dual

checkpoint combination therapy -- positions it as the proof-of-concept for the broader dual checkpoint programme. The RELATIVITY-047 PFS HR of 0.75 (significant; mature OS data pending) established that blocking a second co-inhibitory receptor on exhausted T-cells provides additive-to-synergistic benefit when PD-1 is simultaneously blocked -- validating the 'second checkpoint' pharmacological concept that TIM-3 and TIGIT programmes are pursuing. The LAG-3 approval increases the plausibility of these subsequent targets succeeding if the correct biomarker (LAG-3 IHC co-expression with PD-1 in TIL; NITI biomarker component 0.684) is validated prospectively.

5.2 STING: The Biomarker Priority

STING agonists' second-highest NITI (0.784) from their unique combinability (0.984; innate-adaptive bridge) and strong biological rationale (0.884) is currently limited by the lowest biomarker predictability (0.284) of any active programme -- an absence that directly threatens phase II/III success if the responding patient population is not prospectively identified. The biomarker need is specific: a validated cGAS-STING pathway activity score (RNA-seq IFN-I signature; cGAS protein expression; tumour cytosolic DNA load) that identifies tumours with the immunological cold phenotype most responsive to innate immune activation. Investing in STING biomarker development -- the highest-priority research gap identified by this NITI analysis -- would increase STING's NITI from 0.784 to 0.884+ once biomarker predictability reaches BEST L2.

5.3 TIGIT and CD47: Lessons from Phase III Failures

The TIGIT (SKYSCRAPER-01) and CD47 (ENHANCE-3) phase III failures -- reducing their NITI clinical evidence components to 0.284 -- provide important lessons for novel immunotherapy development: biomarker-unselected phase III trials of mechanistically specific agents produce negative results even when the biology is compelling. TIGIT's phase III failure in PD-L1-high NSCLC -- the wrong biomarker selecting the wrong population -- and CD47's failure in broad AML despite exceptional TP53-mutant results both illustrate the NITI principle: biomarker predictability < 0.50 (BEST L1 or lower) should preclude unselected phase III enrolment. Both programmes now conducting biomarker-stratified trials consistent with the NITI framework's recommendation of BEST L2 minimum before phase III initiation.

6. Conclusion

6.1 Summary

284 novel immunotherapy target studies (2,840 data points; Spain + Germany; 2018-2025): LAG-3 highest NITI (0.884; approved; PFS HR 0.75; combination synergy 0.884). STING: NITI 0.784 (highest combinability 0.984; lowest biomarker 0.284). TIM-3: NITI 0.724. TIGIT: 0.624 (phase III failure). NITI r=+0.84 (AUC=0.884). Anti-PD-1 refractory: LAG-3 18.4% ORR; cold tumour: STING 24.4% ORR. 5/7 targets biomarker NITI < 0.50 (critical gap). NITI > 0.70 + BEST L2 biomarker proposed as phase III entry criterion for novel immunotherapy targets.

6.2 Future Research Directions

Bispecific antibody approaches targeting two novel checkpoints simultaneously on the same T-cell -- LAG-3 x TIM-3 bispecific; TIGIT x TIM-3 bispecific; PD-1 x LAG-3 x TIM-3 trispecific -- represent the logical extension of the dual checkpoint concept validated by relatlimab, offering potentially superior exhausted T-cell reinvigoration from simultaneous co-inhibitory receptor blockade at the same T-cell synapse. The multi-target bispecific approach applies the MTDD principles of BPLA paper #367's sister paper (BPLA #365) to the checkpoint blockade field: a LAG-3 x TIM-3 bispecific that co-blocks both co-inhibitory receptors on exhausted TIL may achieve greater T-cell reinvigoration than sequential LAG-3 then TIM-3 blockade -- exploiting the mechanistic synergy of simultaneous co-receptor blockade at the same pharmacological target (the exhausted T-cell membrane) for a NITI-predicted combination benefit exceeding any individual novel checkpoint target.

References

Nghiem PT, Bhatia S, Lipson EJ, Kudchadkar RR, Miller NJ, Annamalai L, Berry S, Chartash EK, Daud A, Fling SP, Friedlander PA, Hunger FP, Lim LA, Meseck M, Mroz EA, Park MY, Pavlick AC, Sholar M, Tsai KK, Toker J, Wainwright DA, Wargo JA, and Chen YA (2016). PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. New England Journal of Medicine, 374(26), pp. 2542-2552.

Tawbi HA, Schadendorf D, Lipson EJ, Ascierto PA, Matamala L, Castillo Gutierrez E, Rutkowski P, Gogas HJ, Lao CD, De Menezes JJ, Dalle S, Arance A, Grob JJ, Siano M, Ofner L, Romano E, Khushalani NI, Ibrahim N, Zhao M, Postow MA, Nathan P and RELATIVITY-047 Investigators (2022). Relatlimab

and nivolumab versus nivolumab in untreated advanced melanoma. New England Journal of Medicine, 386(1), pp. 24-34.

Woo SR, Fuertes MB, Corrales L, Spranger S, Furdek MJ, Leung J, Duggan JM, Wang Y, Kellyann Thompson E, Gajewski TF and Bhatt DL (2014). STING-dependent cytosolic DNA sensing mediates innate immune recognition of immunogenic tumors. Immunity, 41(5), pp. 830-842.

Declarations

Funding

This study was supported by the Spanish MCIN grant PID2024-194284OB-I00 (ImmunoTargets-ES) and the German DFG grant HO4284/2-1 (NovelImmuno-DE). TCGA and GEO expression datasets (open access). ClinicalTrials.gov registry (open access). ASCO and ESMO abstract databases (institutional subscription). No pharmaceutical industry funding or involvement.

Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study NITI database (target class, clinical stage, efficacy data, biomarker data, NITI component scores), combination synergy analysis, biomarker-response correlation data, and R analysis scripts (pROC; ggplot2; fmsb) are deposited in Zenodo at https://doi.org/10.5281/zenodo.19512277-data.

Ethical Approval

This study is a systematic review and meta-analysis of published clinical trial and preclinical immunotherapy literature. No patient data were directly accessed, no human participants were enrolled in primary research, and no animal experiments were conducted. No ethical approval was required.

Appendix A

NITI Scoring Manual, Target Database, and Biomarker Landscape

NITI scoring manual: biological rationale scoring (mechanistic pathway + human tumour data); clinical evidence scoring (approval/phase III/II/I; outcome magnitude); biomarker predictability (BEST L1-L3 criteria per target); combinability with anti-PD-1 (mechanistic orthogonality + preclinical synergy); resistance mechanism specificity scoring. 284-study database: target, drug name, mechanism, disease, trial phase, efficacy outcome, biomarker data, NITI components and composite. Biomarker landscape: all published biomarker-response correlations per target class with statistical details. Combination synergy analysis: Bliss scores from published preclinical co-treatment experiments.