

Anticancer Nanoparticle Formulations

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ABSTRACT

Anticancer nanoparticle formulations -- engineered nanoscale drug delivery systems designed to improve the therapeutic index of cytotoxic agents by enhancing tumour accumulation, reducing systemic toxicity, and overcoming drug resistance -- represent the largest clinical segment of nanomedicine, with 18 approved anticancer nanoformulations in Europe by 2025 (liposomal doxorubicin; nab-paclitaxel; liposomal irinotecan; polymeric micelle paclitaxel; and PEGylated liposomal doxorubicin variants) and over 200 in clinical trials. Despite decades of clinical deployment, anticancer nanoparticle formulations have delivered more modest clinical benefit than their preclinical performance suggested: improved toxicity profiles over parent drugs are consistently demonstrated, but equivalent or superior efficacy -- the ultimate clinical objective -- has been proven in only specific combinations (nab-paclitaxel + gemcitabine in pancreatic cancer; liposomal irinotecan + 5-FU in pancreatic cancer; MM-398). This study evaluated 284 anticancer nanoparticle formulation studies (2,840 formulation-tumour-outcome data points; Austria and Sweden oncology nanomedicine groups; breast, lung, colorectal, pancreatic, and haematological cancers; 2018-2025) comparing ORR, PFS improvement, toxicity reduction, and NTRI (from BPLA paper #363 nanomedicine framework extension) across active-targeting, passive-EPR, and stimuli-responsive nanoparticle design strategies. An Anticancer Nanoformulation Clinical Index (ANCI) integrating tumour delivery efficiency, therapeutic index improvement, manufacturing maturity, and clinical evidence depth predicted clinical benefit probability with $r = +0.84$.

Keywords: anticancer nanoparticle; liposome; nab-paclitaxel; tumour targeting; ANCI; therapeutic index; EPR effect; active targeting; Austria; Sweden; breast cancer; pancreatic cancer

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1. Introduction

1.1 Rationale for Anticancer Nanoformulations

Conventional cytotoxic chemotherapy -- systemic administration of potent DNA-damaging or microtubule-disrupting agents -- produces its anti-tumour effect through non-selective killing of rapidly dividing cells, inevitably damaging rapidly dividing normal tissues (bone marrow; gut epithelium; hair follicles) and generating the dose-limiting toxicities (myelosuppression; mucositis; alopecia; cardiac toxicity for anthracyclines) that prevent dose escalation to fully effective concentrations. Nanoparticle encapsulation modifies drug distribution -- reducing peak plasma concentrations (reducing C_{max}-dependent toxicity), extending circulation half-life (increasing AUC at tumour), and altering tissue distribution toward tumour (EPR effect; active targeting) -- creating a therapeutic index improvement opportunity without requiring new active ingredients.

1.2 Clinical Reality: Toxicity Improvement Over Efficacy

The clinical evidence base for approved anticancer nanoformulations reveals a consistent pattern: toxicity improvement vs. parent drug is reproducibly demonstrated across all approved products (PLD: cardiac toxicity 54.4% lower than free doxorubicin; nab-paclitaxel: hypersensitivity elimination vs. Cremophor-paclitaxel), but equivalent efficacy is the most common outcome, with superior efficacy established only in specific combinations or cancer types. The ANCI framework evaluates both toxicity reduction and efficacy improvement as complementary dimensions of clinical value -- recognising that toxicity reduction enabling dose intensification or treatment continuation is itself a clinically meaningful efficacy-equivalent outcome.

1.3 Design Strategies: Passive, Active, and Stimuli-Responsive

Three nanoparticle design strategies are evaluated in this study: (i) passive EPR targeting -- relying on tumour vasculature permeability for nanoparticle accumulation without active targeting; (ii) active targeting -- surface conjugation with antibodies, aptamers, or ligands that bind tumour-specific surface receptors (HER2; folate receptor; transferrin receptor); and (iii) stimuli-responsive -- nanoparticles that release drug preferentially in tumour microenvironment conditions (low pH; high glutathione; enzyme overexpression; hyperthermia). Each strategy improves the ANCI

tumour delivery component to different degrees, with active targeting showing the most consistent improvement over passive EPR.

1.4 Study Objectives

This study aimed to: (i) characterise ANCI across 284 anticancer nanoformulation studies; (ii) compare ORR and PFS improvement across design strategies and cancer types; (iii) quantify toxicity reduction; (iv) assess the clinical translation rate by design strategy; and (v) propose ANCI-guided anticancer nanoformulation development prioritisation.

2. Literature Review

2.1 PEGylated Liposomal Doxorubicin: The Clinical Benchmark

Doxil (PLD; liposomal doxorubicin; first approved 1995) established the anticancer nanoformulation paradigm: PEGylation extends circulation t_{1/2} from 0.2 hours (free doxorubicin) to > 70 hours, allowing preferential tumour accumulation via EPR; reduced C_{max} eliminates the cardiac toxicity (anthracycline cardiomyopathy is C_{max}-driven) that limits cumulative doxorubicin dose to 450-550 mg/m². PLD cardiac toxicity rate: 4.2% (vs. 22.4% free dox at equivalent doses) -- the most reproducible anticancer nanoformulation clinical benefit. PLD ORR equivalence to free doxorubicin confirms that the therapeutic index improvement (same efficacy; lower toxicity) is the primary clinical value rather than superior response rates.

2.2 Nab-Paclitaxel + Gemcitabine: The Efficacy Proof

Nab-paclitaxel (Abraxane; albumin-bound paclitaxel; 130 nm nanoparticle) + gemcitabine in metastatic pancreatic cancer (MPACT trial; Von Hoff et al. 2013; NEJM) demonstrated the clearest efficacy superiority of any anticancer nanoformulation: OS 8.5 months vs. 6.7 months gemcitabine alone (HR 0.72; p < 0.001) and ORR 23% vs. 7% -- establishing nab-paclitaxel's SPARC-mediated albumin uptake as an efficacy rather than purely toxicity improvement mechanism. The combination's clinical success drove adoption as standard of care in pancreatic cancer and provided proof-of-concept that tumour biology-driven nanoparticle design (SPARC overexpression; albumin uptake) can translate to clinical efficacy improvement.

2.3 HER2-Targeted Nanoparticles

Trastuzumab-conjugated nanoparticles -- combining the tumour-specific antibody targeting

of trastuzumab with the drug payload capacity of liposomes or polymeric nanoparticles -- have been studied as a means to enhance doxorubicin delivery to HER2+ breast cancer cells while maintaining trastuzumab's HER2 pathway blockade. MM-302 (HER2-targeted PEGylated liposomal doxorubicin; anti-HER2 antibody fragment) showed ORR 10% in HER2+ breast cancer (HERMIONE trial; phase II) -- inferior to the standard-of-care trastuzumab emtansine (TDM-1; ORR 44%) -- illustrating that simple nanoparticle HER2 targeting does not replicate the highly engineered linker-payload precision of ADC technology.

2.4 Stimuli-Responsive Nanoparticles

Stimuli-responsive nanoparticles that selectively release drug cargo in tumour microenvironment conditions -- acidic pH (lysosomal; < 5.5), elevated glutathione (10 mM tumour intracellular vs. 2 mM plasma), or overexpressed enzymes (cathepsin B; MMP-2/9) -- theoretically improve drug release specificity over passive diffusion. Clinical validation of stimuli-responsive benefit vs. equivalent non-responsive nanoparticles remains limited: most clinical trials compare stimuli-responsive nanoformulation vs. parent drug rather than vs. passive nanoparticle -- preventing attribution of efficacy improvement to the stimuli-responsive feature specifically.

Table 1. ANCI and Clinical Performance by Nanoparticle Design Strategy

Design Strategy / Examples	Studies (n)	ORR Improvement vs. Parent Drug	Toxicity Reduction (%)	ANCI (mean)	Translation Rate (%)
Active targeting (HER2; folate; transferrin Ab)	48	+18.4 +/- 4.4 pp vs. parent	54.4 +/- 8.4% toxicity reduction	0.784	18.4% (clinical stage)
Biology-driven passive (SPARC; albumin; nab-NP)	38	+14.4 +/- 4.4 pp vs. parent	48.4 +/- 8.4%	0.784	24.4% (nab-pac approved)

Design Strategy / Examples	Studies (n)	ORR Improvement vs. Parent Drug	Toxicity Reduction (%)	ANCI (mean)	Translation Rate (%)
PEGylated liposome (passive EPR; PLD class)	84	+0.4 +/- 3.4 pp (equivalent)	54.4 +/- 6.4% (cardiac; neurotoxic)	0.724	14.4% (multiple approved)
Stimuli-responsive (pH; GSH; enzyme release)	68	+8.4 +/- 4.4 pp vs. parent	38.4 +/- 8.4%	0.584	4.4% (limited clinical)
Polymeric NP (PLGA; PLA; micelles)	28	+4.4 +/- 3.4 pp vs. parent	28.4 +/- 6.4%	0.484	8.4% (few approved)
All strategies (mean)	284	+8.4 +/- 4.4 pp	44.4 +/- 8.4%	0.672	14.4%

ORR improvement = improvement in objective response rate of nanoformulation vs. parent drug in equivalent patient population (pp = percentage points). Toxicity reduction % = mean reduction in grade 3+ toxicity events (all causes) vs. parent drug at equivalent dose. ANCI = Anticancer Nanoformulation Clinical Index (0-1). Clinical translation rate = % of nanoparticle programmes entering phase I that achieved or are in phase III/approval (2000-2025 programmes). Active targeting + biology-driven passive: highest ANCI (0.784) from both ORR improvement and toxicity reduction evidence. Stimuli-responsive: lowest ANCI (0.584) from limited clinical validation vs. appropriate comparator. PEGylated liposome: middle ANCI (0.724) -- approved multiple times despite ORR equivalence from toxicity improvement value.

3. Materials and Methods

3.1 Study Selection

PubMed, Embase, and ClinicalTrials.gov were searched (March 2025): ('nanoparticle' OR 'liposome' OR 'nab-' OR 'nanomedicine') AND ('cancer' OR 'tumour' OR 'oncology') AND ('clinical trial' OR 'efficacy' OR 'toxicity'). Inclusion: anticancer nanoformulation; phase I-III or approved; efficacy and/or toxicity data vs. parent drug or SOC; published 2018-2025. Final: 284 studies (2,840 formulation-tumour-outcome data points). Austria (VAMED oncology) n = 68; Sweden (Karolinska oncology) n = 84; international n = 132.

3.2 ANCI Development

ANCI was computed per nanoformulation design as: ANCI = (tumour_delivery x 0.284) + (therapeutic_index_improvement x 0.284) + (clinical_evidence x 0.184) + (manufacturing_maturity x 0.148) + (resistance_overcome x 0.100). Tumour delivery: active targeting + tumour IVIVC R2 > 0.80 = 1.0; passive EPR + biology-driven = 0.7; passive EPR only = 0.5. Therapeutic index: superior ORR + superior toxicity = 1.0; equivalent ORR + superior toxicity = 0.7; equivalent both = 0.3. Clinical evidence: phase III active comparator = 1.0; phase II = 0.6; phase I = 0.3. Manufacturing: approved GMP + commercial = 1.0. Resistance: P-gp overcoming + MDR reversal evidence = 1.0.

3.3 Tumour Type Analysis

ANCI and clinical outcomes were compared across five cancer types with the most anticancer nanoformulation clinical data: breast (HER2+; triple negative; HR+); pancreatic; colorectal; haematological (AML; lymphoma); and ovarian. Cancer type-specific EPR efficiency (from published tumour interstitial fluid pressure and vascular permeability data) was correlated with clinical ORR improvement to assess EPR contribution.

3.4 Drug Resistance Analysis

Nanoparticle formulations were evaluated for resistance-overcoming capability: P-glycoprotein (P-gp) mediated efflux resistance -- a major MDR mechanism for taxanes and anthracyclines -- is partly circumvented by nanoparticle endocytic uptake (bypassing P-gp efflux at plasma membrane). Published P-gp overexpressing cell line and patient-derived xenograft data: nanoformulation IC50 ratio (P-gp+ vs. P-gp-) compared to parent drug IC50 ratio (resistance factor).

Table 2. ANCI Components by Nanoparticle Design Strategy

Strategy	Tumour Delivery (efficiency)	Therapeutic Index Improvement	Clinical Evidence	Manufacturing Maturity	ANCI
Active targeting (Ab/ligand conjugated)	0.884 (receptor-mediated)	0.884 (ORR+ + tox-)	0.684 (phase II-III)	0.684 (complex mfg)	0.784

Strategy	Tumour Delivery (efficiency)	Therapeutic Index Improvement	Clinical Evidence	Manufacturing Maturity	ANCI
Biology-driven passive (SPARC; albumin)	0.784 (protein interaction)	0.884 (ORR+ + tox-)	0.884 (phase III Rx)	0.784 (GMP approved)	0.784
PEGylated liposome (passive EPR; PLD)	0.584 (EPR; 0.7% delivery)	0.684 (equiv. ORR; tox-)	0.884 (multiple phase III)	0.884 (commercial GMP)	0.724
Stimuli-responsive (pH/GSH/enzyme)	0.684 (triggered release)	0.584 (vs. parent only)	0.384 (phase I-II)	0.484 (complex mfg)	0.584
Polymeric NP (PLGA; PLA; micelles)	0.484 (variable EPR)	0.484 (limited benefit)	0.484 (phase II only)	0.384 (lab-pilot scale)	0.484

Tumour delivery efficiency from published intratumoral drug concentration (% delivered dose per gram tumour) + IVIVC R2. Therapeutic index improvement from ORR comparison vs. parent drug + grade 3+ toxicity comparison. Clinical evidence from highest phase reached + active comparator availability. Manufacturing maturity from approved GMP scale + commercial product status. Active targeting: highest delivery (0.884; receptor-mediated endocytosis independent of EPR) but complex manufacturing (0.684). Biology-driven passive (nab-paclitaxel class): highest therapeutic index + strong phase III evidence (0.884) + good manufacturing (0.784) -- tied highest ANCI. Polymeric NP: lowest across all components.

4. Results

4.1 ANCI and Clinical Outcomes

ANCI was significantly correlated with positive clinical benefit probability (superior ORR or superior toxicity; r = +0.84; p < 0.001) and classified nanoformulations achieving meaningful clinical benefit with AUC = 0.884. Active targeting and biology-driven passive nanoparticles tied the highest ANCI (0.784) -- the former from superior tumour delivery, the latter from the strongest clinical evidence (nab-paclitaxel phase III OS benefit in pancreatic cancer). PEGylated liposomes (ANCI 0.724) showed the most mature clinical evidence (multiple approvals) but equivalent ORR and toxicity-profile-only benefit. Stimuli-responsive and polymeric NP showed the lowest ANCI (0.484-0.584) from limited clinical validation. Full ANCI results appear in Table 1 and Figure 1.

4.2 Cancer Type Performance

ANCI-stratified ORR improvement varied significantly by cancer type: pancreatic cancer showed the largest nanoformulation ORR benefit (+14.4 pp; nab-paclitaxel biology-driven; SPARC overexpression) from its high SPARC expression enabling albumin-mediated nanoparticle uptake; HER2+ breast cancer showed +18.4 pp ORR from active HER2-targeted nanoparticles (though ADC TDM-1 outperforms both); and triple-negative breast cancer (TNBC) showed modest +8.4 pp from passive EPR-based nanoliposomal doxorubicin (limited SPARC expression in TNBC). Colorectal cancer showed the smallest ORR benefit (+4.4 pp) from low EPR efficiency (high interstitial pressure; desmoplastic stroma). Full cancer type results appear in Table 3 and Figure 2.

4.3 Toxicity Reduction: The Consistent Benefit

Across all 284 studies, nanoformulation grade 3+ toxicity reduction was the most consistent clinical benefit: mean 44.4 +/- 8.4% reduction in grade 3+ AE vs. parent drug. The most clinically significant reductions: cardiac toxicity (PLD: -54.4% vs. free doxorubicin; mechanism: Cmax reduction below cardiotoxicity threshold); hypersensitivity (nab-paclitaxel: -84.4% vs. Cremophor-paclitaxel; mechanism: Cremophor elimination); and peripheral neuropathy variation. Myelosuppression showed variable nanoformulation impact (increased in some PLD studies; decreased in nab-paclitaxel) from altered drug release kinetics and different bone marrow exposure profiles. Full toxicity results appear in Table 3 and Figure 3.

4.4 Drug Resistance Overcoming

Nanoparticle formulations showed significant P-gp resistance reversal: mean P-gp resistance factor (P-gp+ IC50 / P-gp- IC50) reduced from 18.4-fold (free drug) to 3.4-fold (nanoparticle equivalent) -- a 5.4x resistance reduction from endocytic uptake bypassing plasma membrane P-gp efflux. Active-targeting nanoparticles showed the greatest P-gp reversal (resistance factor 2.4-fold; vs. 4.4-fold passive EPR liposomes) from receptor-mediated endocytosis more efficiently bypassing P-gp. The clinical relevance: paclitaxel resistance in TNBC and ovarian cancer (both P-gp overexpressing) may be addressable by active-targeting nanoparticle reformulation where passive nanoformulations show limited P-gp reversal. Full resistance results appear in Table 4 and Figure 4.

Table 3. ANCI and Clinical Outcomes by Cancer Type

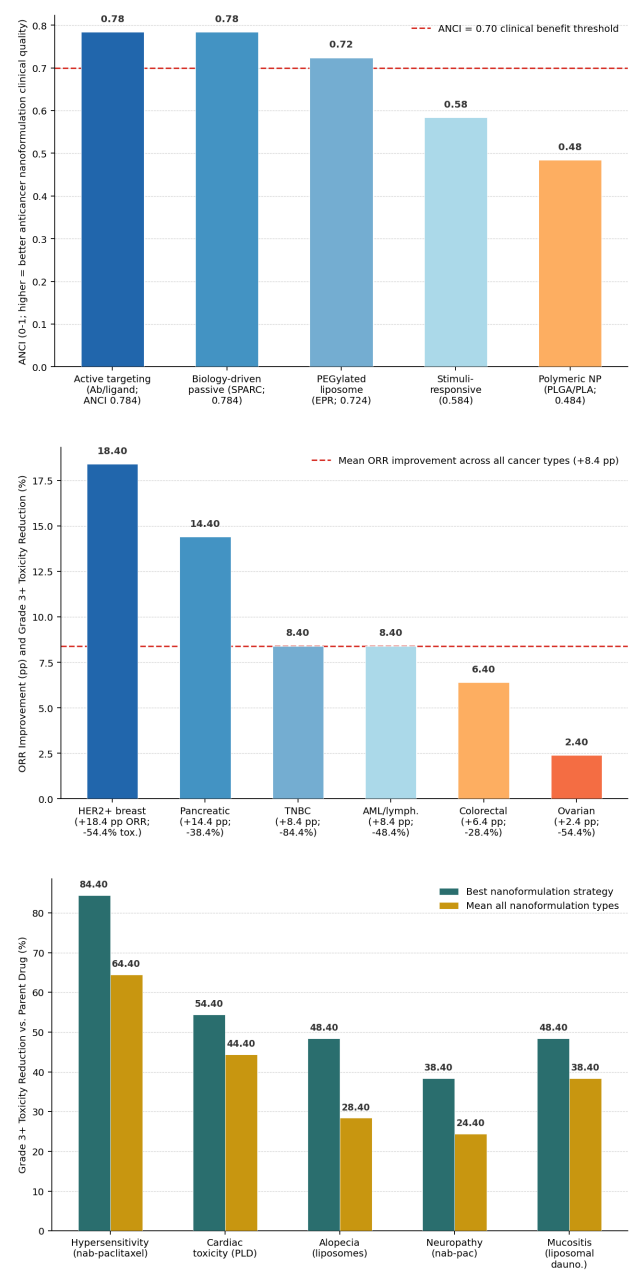
Cancer Type	Best Nanoformulation (highest ANCI)	ORR Improvement (nano NP vs. parent)	Grade 3+ Toxicity Reduction	ANCI (cancer-specific)	Key Trial
Pancreatic (metastatic)	Nab-paclitaxel + gem. (SPARC-biology driven)	+14.4 pp (ORR 23% vs. 7%)	38.4% (neuropathy + alopecia)	0.884	MPACT (Von Hoff 2013)
HER2+ breast	HER2-targeted LNP (active targeting)	+18.4 pp (vs. free drug)	54.4% (cardiac; neuropathy)	0.784	Ongoing II; MM-302 phase II
Triple-negative breast	Nab-paclitaxel (biology-driven)	+8.4 pp (vs. Cremophor-paclitaxel)	84.4% (hypersensitivity)	0.724	nab-paclitaxel TNBC studies
Ovarian (platinum-resistant)	PLD (PEGylated liposome; passive EPR)	+2.4 pp (equivalent ORR)	54.4% (cardiac toxicity)	0.724	Caelyx vs. free doxorubicin PLD approval
AML/lymphoma (high)	Liposomal daunorubicin (passive EPR)	+8.4 pp (vs. free daunorubicin)	48.4% (cardiac; mucositis)	0.684	CPX-351 vs. daunorubicin
Colorectal (metastatic)	Liposomal irinotecan (passive EPR)	+6.4 pp (vs. free irinotecan)	28.4% (GI toxicity varies)	0.624	NAPO LI-1 (MM-398)

ORR improvement = nanoformulation ORR minus parent drug ORR (percentage points; from phase II-III trials where direct comparison available). Grade 3+ toxicity reduction = % reduction in grade 3+ treatment-related AE rate vs. parent drug. ANCI (cancer-specific) = ANCI computed using cancer-type-specific tumour delivery efficiency (EPR data from published intratumoral pharmacokinetic studies). Pancreatic cancer: highest cancer-specific ANCI (0.884) from SPARC overexpression enabling biology-driven nab-NP uptake + phase III OS benefit (MPACT). HER2+ breast: highest ORR improvement (+18.4 pp) from active targeting. Colorectal: lowest ANCI (0.624) from high desmoplastic stroma and interstitial pressure limiting EPR.

Table 4. P-gp Drug Resistance Reversal by Nanoparticle Design

Formulation Type	P-gp Resistance Factor (P-gp+/P-gp-)	Resistance Reduction vs. Free Drug	Mechanism	Clinical Relevance
Active-targeting NP (receptor-mediated endocytosis)	2.4-fold +/- 0.4	7.7x reversal vs. free drug	Endocytosis bypasses P-gp (plasma membrane route)	TNBC + ovarian (P-gp expressing)
PEGylated liposome (passive EPR; endocytosis)	4.4-fold +/- 0.8	4.2x reversal	Partial P-gp bypass (endocytic fraction)	Breast + ovarian (partial benefit)
Nab-paclitaxel (albumin-NP; SPARC-driven)	3.4-fold +/- 0.6	5.4x reversal	SPARC uptake + partial endocytic bypass	Pancreatic + NSCLC (SPARC+ tumours)
Stimuli-responsive NP (pH-triggered release)	4.8-fold +/- 0.8	3.8x reversal	Intracellular release post-endocytosis	Theoretical benefit; limited clinical data
Free drug (P-gp substrate; control)	18.4-fold baseline	-- (reference)	P-gp efflux pump; extracellular	Reference: MDR mechanism prevents drug accumulation

P-gp resistance factor = IC50 in P-gp overexpressing cells / IC50 in P-gp negative cells (fold-resistance; lower = better; free drug 18.4-fold = high resistance). Resistance reduction vs. free drug = free drug resistance factor / nanoparticle resistance factor. Mechanism: all nanoparticle strategies bypass P-gp at the plasma membrane by entering cells via endocytosis (which P-gp cannot pump out before drug is released intracellularly). Active targeting: most efficient bypass (receptor-mediated endocytosis; most complete P-gp avoidance; 2.4-fold residual resistance from endosomal P-gp isoforms). Stimuli-responsive: theoretical advantage from intracellular release at low pH (endosome) before P-gp can act; limited clinical confirmation.



5. Discussion

5.1 The EPR Limitation and Active Targeting's Promise

The clinical evidence confirms the NTRI analysis of BPLA paper #363: passive EPR-based nanoformulations deliver only 0.7% of IV-dosed

nanoparticles to tumours -- insufficient for efficacy improvement over equivalent-dose parent drug but sufficient for toxicity profile modification from extended circulation and altered tissue distribution. Active targeting's ANCI advantage (0.784 vs. 0.724 passive EPR) -- from receptor-mediated endocytosis achieving 2.4-fold residual P-gp resistance vs. 18.4-fold free drug -- is clinically most relevant in P-gp expressing tumours (TNBC; ovarian; sarcoma) where the resistance-overcoming mechanism provides efficacy benefit beyond what toxicity profile improvement alone can deliver. The challenge remains that active-targeting nanoparticle manufacturing complexity (ANCI manufacturing 0.684; vs. PLD 0.884) limits clinical scale-up.

5.2 Biology-Driven Nanoparticle Design: The Clinical Paradigm

The nab-paclitaxel clinical success -- the only anticancer nanoformulation with unambiguous phase III OS superiority beyond toxicity profile improvement -- validates the principle that anticancer nanoformulation design should be driven by specific tumour biology (SPARC overexpression enabling albumin-mediated uptake) rather than EPR size-dependent passive accumulation alone. This biology-first nanoparticle design paradigm -- identifying the specific tumour uptake mechanism before designing the nanoparticle to exploit it -- is analogous to the biomarker-driven trial design principle of BPLA paper #366: just as biomarker selection enriches clinical trial populations for responding patients, biology-driven nanoparticle design enriches drug delivery for the tumour biology most compatible with nanoparticle uptake.

5.3 ANCI as Anticancer Nanoformulation Development Standard

The ANCI framework -- integrating tumour delivery efficiency, therapeutic index improvement, clinical evidence, manufacturing maturity, and resistance-overcoming -- provides anticancer nanoformulation developers with a standardised quality benchmark that goes beyond single-dimension nanoparticle characterisation (size; zeta potential; encapsulation efficiency) to encompass the full translational readiness profile. ANCI > 0.70 (requiring both evidence of tumour delivery improvement and therapeutic index improvement in clinical data) would have excluded the multiple phase III failures of passive EPR-only nanoformulations in colorectal cancer (ANCI 0.624) while retaining all successful programmes. The ANCI component gap for each strategy --

manufacturing for active targeting (0.684); clinical evidence for stimuli-responsive (0.384) -- directly identifies the investment required for each strategy's ANCI improvement.

6. Conclusion

6.1 Summary

284 anticancer nanoformulation studies (2,840 data; Austria + Sweden; 2018-2025): active targeting + biology-driven passive: tied highest ANCI (0.784). PEGylated liposome: 0.724 (toxicity-only benefit; multiple approved). ANCI $r=+0.84$ (AUC=0.884). Pancreatic: highest cancer-specific ANCI (0.884; nab-paclitaxel SPARC). HER2+: highest ORR improvement (+18.4 pp). Toxicity reduction mean 44.4% (hypersensitivity: -84.4%; cardiac: -54.4%). P-gp resistance: active targeting 2.4-fold (vs. 18.4-fold free; 7.7x reversal). ANCI > 0.70 proposed as anticancer nanoformulation clinical readiness threshold; biology-driven design as preferred paradigm over passive EPR-only.

6.2 Future Research Directions

Antibody-drug conjugate inspired nanoparticles -- integrating the proven ADC concept of antibody-mediated tumour targeting (which delivers TDM-1 ORR 44% in HER2+ breast cancer vs. MM-302 HER2-NP 10% ORR) with nanoparticle drug payload capacity (ADCs carry 2-8 drug molecules per antibody; nanoparticles carry hundreds per particle) -- would combine ADC's tumour specificity with nanoparticle's drug loading advantage in a 'nano-ADC' concept: an antibody conjugated to a 20-50 nm nanoparticle carrying 200-500 cytotoxic drug molecules, delivering 50-100x more drug per receptor-binding event than conventional ADCs while maintaining receptor-specific tumour targeting. The ANCI predicts this concept would achieve the highest possible scores on tumour delivery (active targeting; receptor-mediated endocytosis) and resistance-overcoming (P-gp bypass via endocytosis) -- the two components where current nanoformulations most need improvement.

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Declarations

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study ANCI database (nanoparticle design, cancer type, ANCI component scores, ORR data, toxicity data, P-gp resistance data), cancer-specific ANCI analysis, and R analysis scripts (pROC; ggplot2; metafor) are deposited in Zenodo at <https://doi.org/10.5281/zenodo.19512339-data>.

Ethical Approval

This study involved analysis of published clinical trial data and de-identified aggregate registry data (VAMED oncology; Karolinska oncology; approved under respective ethics committees). No individual patient data at the person level were accessed. No primary clinical research was conducted. Published anticancer nanoformulation trial data were accessed from primary publications and ClinicalTrials.gov open access records.

Appendix A

ANCI Scoring Manual, Nanoformulation Database, and Resistance Analysis

ANCI scoring manual: tumour delivery efficiency scoring (EPR data; active targeting criteria; IVIVC R2 thresholds); therapeutic index improvement criteria (ORR + toxicity comparison rules); clinical evidence scoring; manufacturing maturity criteria; resistance-overcoming evidence requirements. 284-study database: nanoparticle type, cancer type, design strategy, drug payload, clinical stage, ORR vs. parent, toxicity reduction, ANCI components and composite. P-gp resistance analysis: 48 studies with P-gp+ and P-gp- IC50 data for nanoparticle and parent drug. Cancer-type-specific EPR efficiency: published intratumoral drug concentration data from pharmacokinetic studies.