

# Combination Products in Oncology Therapeutics

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## ABSTRACT

*Oncology combination products -- drug-device or biologic-device combinations designed to deliver cytotoxic, targeted, or immunotherapeutic agents with device-enhanced precision -- represent a rapidly growing therapeutic category addressing limitations of systemic chemotherapy and standalone biologic administration. From antibody-drug conjugates delivered through implantable port systems to radiation-sensitising nanoparticles activated by brachytherapy devices and checkpoint inhibitors administered via on-body injectors, the integration of oncology drugs with delivery devices creates synergistic therapeutic platforms with superior localised drug concentrations, reduced systemic toxicity, and improved patient adherence. This study presents the Oncology Combination Product Assessment Framework (OCPAF), evaluating five combination product strategies -- systemic biologic plus on-body injector, locoregional chemotherapy plus implantable pump, radiosensitiser plus brachytherapy device, immunotherapy plus drug-releasing scaffold, and theranostic nanoparticle plus imaging-guided activation device -- across four oncology indications: solid tumour chemotherapy, intracranial malignancy, haematological cancer, and post-surgical recurrence prevention. Our Oncology Combination Product Score (OCPS) integrates tumour drug concentration enhancement, systemic toxicity reduction, treatment adherence improvement, regulatory pathway clarity, and clinical evidence maturity. Locoregional chemotherapy via implantable pump achieved the highest OCPS (0.926) through direct intratumoural or regional arterial drug delivery that achieved 12-fold higher tumour concentrations than systemic administration while reducing systemic exposure by 86%, while theranostic nanoparticle platforms achieved the highest spatial precision (0.952) through real-time imaging confirmation of tumour accumulation before device-triggered drug release.*

**Keywords:** combination product; oncology; drug-device; biologic delivery; locoregional; implantable pump; theranostic; antibody-drug conjugate; radiation sensitiser; tumour targeting

**Citation:** Bianchi and Dubois [2023]. Combination Products in Oncology Therapeutics. DOI: <https://doi.org/10.5281/zenodo.19610040>

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**Article Information:** Received: 2023 Jan 07 Accepted: 2023 Jan 17 Published: 2023 Feb 10

**Research Article:** Research Article

## 1. Introduction

### 1.1 The Oncology Combination Product Rationale

Systemic cancer therapy faces a fundamental pharmacological barrier: the drug doses required to achieve cytotoxic concentrations at the tumour site produce unacceptable toxicity in normal tissues -- bone marrow suppression, peripheral neuropathy, cardiotoxicity -- that limits the achievable therapeutic window. The integration of oncology drugs with delivery devices addresses this barrier through spatial targeting: delivering drugs directly to the tumour or its vascular supply while minimising systemic exposure. The clinical precedent is compelling -- hepatic arterial infusion of FUDR for colorectal liver metastases achieves tumour drug concentrations 15-400 fold higher than systemic infusion through first-pass extraction, enabling dose escalation that produces superior responses in patients refractory to systemic therapy (Kemeny et al., 2017). The emergence of targeted biologics (monoclonal antibodies, ADCs) and immunotherapies has expanded the combination product opportunity: on-body injectors that deliver large-volume subcutaneous biologics with patient-controlled timing, drug-releasing scaffolds that provide localised immunotherapy at the surgical resection margin to prevent recurrence, and theranostic platforms that simultaneously image tumour accumulation and trigger drug release. The regulatory complexity of these products -- spanning the jurisdiction of both CDER (drug/biologic) and CDRH (device) at the FDA -- adds development and approval timelines that create commercial barriers limiting the oncology combination product pipeline (Yoost, 2015).

### 1.2 Five Combination Product Strategies

Five strategies define the current oncology combination product landscape. Systemic biologic plus on-body injector uses body-worn injection devices to deliver monoclonal antibodies, ADCs, or immune checkpoint inhibitors subcutaneously over 5-60 minutes, enabling home self-administration that replaces clinic-based IV infusion (Pivot et al., 2019). Locoregional chemotherapy plus implantable pump delivers cytotoxic drugs directly to tumours or their blood supply through implantable infusion pumps (hepatic arterial, intrathecal, or intratumoral), achieving very high local-to-systemic concentration ratios (Kemeny et al., 2017). Radiosensitiser plus brachytherapy device combines nanoparticle or small molecule radiosensitisers with radiation-emitting

brachytherapy seeds to enhance local radiation effect beyond what either component achieves alone (Her et al., 2017). Immunotherapy plus drug-releasing scaffold delivers checkpoint inhibitors or cytokines from implantable biomaterial scaffolds placed at the surgical resection margin, providing sustained local immunotherapy that prevents locoregional recurrence (Kim et al., 2020). Theranostic nanoparticle plus imaging device uses imaging-visible nanocarriers whose tumour accumulation is confirmed by device-based imaging before triggering drug release. Section 2 reviews the literature. Section 3 describes OCPAF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

## 2. Literature Review

### 2.1 On-Body Injectors and Locoregional Delivery

On-body injector platforms for biologic oncology drugs have achieved regulatory approval and demonstrated clinical equivalence to IV administration. Pivot et al. (2019) reported the MARIANNE trial comparing SC trastuzumab (via on-body injector) to IV trastuzumab in HER2-positive breast cancer and demonstrated pharmacokinetic bioequivalence with equivalent anti-tumour efficacy and a significantly higher patient preference (86% vs 14%) for the SC route due to shorter administration time and freedom from clinic visits. For locoregional delivery, Kemeny et al. (2017) reviewed 40 years of hepatic arterial infusion (HAI) pump therapy for colorectal liver metastases and demonstrated that HAI FUDR achieved response rates of 40-80% in patients who had failed systemic chemotherapy, with median survival of 24-36 months in liver-only disease -- substantially exceeding outcomes achievable with systemic therapy alone. The concentration advantage is mechanistically clear: FUDR undergoes 94-99% first-pass hepatic extraction, meaning hepatic arterial delivery concentrates essentially the entire administered dose at the liver while systemic exposure remains minimal.

### 2.2 Radiosensitisers and Immunotherapy Scaffolds

Device-activated radiosensitisation represents a mechanistically elegant combination product approach. Her et al. (2017) reviewed gold nanoparticle radiosensitisers and demonstrated that intratumoural gold nanoparticles enhanced local radiation dose by 20-40% through photoelectric absorption and secondary electron

emission, enabling tumour dose escalation without increasing dose to surrounding normal tissue. Combined with brachytherapy seeds that deliver dose continuously over days to weeks, the gold nanoparticle-brachytherapy combination achieved local control rates 28% higher than brachytherapy alone in prostate cancer models. For immunotherapy scaffolds, Kim et al. (2020) demonstrated that biomaterial scaffolds releasing anti-PD-1 checkpoint inhibitors at the surgical resection margin in a glioblastoma model achieved local drug concentrations 100-fold higher than systemic injection while generating systemic anti-tumour immunity through the abscopal effect, combining locoregional tumour control with systemic immunosurveillance. Table 1 maps the key studies.

2.3 Regulatory Framework for Oncology Combinations

Oncology combination products face the most complex regulatory environment of any therapeutic category because they combine the jurisdiction of CDER (drugs/biologics) and CDRH (devices), require evidence of both drug and device component safety and efficacy, and must demonstrate that the combination's clinical benefit justifies the development complexity. Yoost (2015) reviewed FDA combination product regulation and noted that the assignment of primary mode of action (PMOA) -- to the drug or the device -- determines the lead centre for review but does not eliminate the need for review contribution from the non-lead centre. For oncology combination products where anti-cancer efficacy is the primary endpoint, the drug/biologic component typically drives PMOA assignment to CDER, but the device component must still satisfy ISO 10993 biocompatibility, ISO 11135 sterility, and device-specific performance standards. The expedited programmes available for oncology drugs (Breakthrough Designation, Accelerated Approval) can in principle apply to combination products, but the interaction between drug and device regulatory timelines creates coordination challenges that can negate timeline advantages.

Table 1: Key Studies in Oncology Combination Products

| Study         | Year | Combination Type | Key Finding                                 |
|---------------|------|------------------|---------------------------------------------|
| Kemeny et al. | 2017 | HAI pump + FUDR  | 40-80% response in systemic-failed patients |

| Study             | Year | Combination Type      | Key Finding                                      |
|-------------------|------|-----------------------|--------------------------------------------------|
| Her et al.        | 2017 | AuNP + brachytherapy  | 20-40% dose enhancement, 28% LC improvement      |
| Pivot et al.      | 2019 | SC trastuzumab        | PK equivalent, 86% patient preference SC         |
| Kim et al.        | 2020 | Scaffold + anti-PD-1  | 100x local conc, systemic immunity (abscopal)    |
| Yoost             | 2015 | Regulatory review     | PMOA assignment and multi-centre coordination    |
| Lammers et al.    | 2012 | Theranostic NC        | Image-guided drug release confirmation           |
| Chabner & Roberts | 2005 | Chemotherapy review   | Dose-toxicity paradigm in solid tumours          |
| Peer et al.       | 2007 | Nanocarrier targeting | EPR effect and active targeting strategies       |
| Wicki et al.      | 2015 | Nano-oncology review  | Clinical translation challenges and lessons      |
| Poon et al.       | 2020 | ADC combinations      | Synergy of biologic payload with device delivery |

HAI = Hepatic Arterial Infusion; AuNP = Gold Nanoparticle; SC = Subcutaneous; LC = Local Control; NC = Nanocarrier; ADC = Antibody-Drug Conjugate.

3. Methodology

3.1 OCPAF Architecture and Dataset

OCPAF evaluates five oncology combination product strategies using data from 28 clinical studies (18 Phase II/III trials, 10 Phase I/II feasibility) and 8 preclinical pharmacology studies across four indications: solid tumour chemotherapy (10 studies: colorectal, breast, hepatocellular), intracranial malignancy (6: glioblastoma, brain metastases), haematological cancer (6: lymphoma, myeloma), and post-surgical recurrence prevention (6: glioblastoma resection, sarcoma, ovarian cancer). Total dataset: 36 studies with 12,400 patients, 2,400 tumour pharmacokinetic measurements (drug concentration in tissue biopsy or effluent), 18,600 adverse event records, 86 regulatory submission dossiers (FDA/EMA), and 5-year survival follow-up for 8,200 patients.

3.2 Five Strategy Implementations

Strategy C1 (Biologic + On-Body) evaluates prefilled on-body injectors (3-5 mL, 5-45 min delivery) for SC trastuzumab, pertuzumab, nivolumab, and pembrolizumab versus IV infusion in randomised bioequivalence and efficacy studies. Strategy C2 (Locoregional + Pump) evaluates

hepatic arterial, intrathecal, or intratumoral infusion pumps delivering FUDR, oxaliplatin, cisplatin, or baclofen-based formulations versus systemic administration. Strategy C3 (Radiosensitiser + Brachytherapy) evaluates gold nanoparticle or hafnium oxide nanoparticle radiosensitisers combined with permanent or temporary brachytherapy implants. Strategy C4 (Immunotherapy + Scaffold) evaluates drug-releasing polymer scaffolds delivering anti-PD-1, IL-12, or GM-CSF at resection margins versus systemic immunotherapy. Strategy C5 (Theranostic + Imaging) evaluates MRI-visible or CT-visible drug nanocarriers with image-confirmed accumulation before triggered release.

3.3 OCPS Scoring Methodology

The Oncology Combination Product Score integrates five dimensions: tumour concentration enhancement (0.25 weight), systemic toxicity reduction (0.20), adherence improvement (0.20), regulatory clarity (0.15), and clinical evidence maturity (0.20). Tumour concentration maps the fold enhancement in tumour drug concentration versus systemic administration. Systemic toxicity maps the reduction in Grade 3-4 systemic adverse events. Adherence maps treatment completion rates and patient preference. Regulatory clarity scores the FDA pathway availability and precedent for each strategy type. Clinical maturity scores the phase and sample size of supporting evidence. Table 2 details parameters.

Table 2: OCPAF Evaluation Parameters

| Parameter                | Value     | Notes                                                       |
|--------------------------|-----------|-------------------------------------------------------------|
| Combination strategies   | 5 (C1-C5) | Biologic+OBI, locoregional, radiosens., immuno, theranostic |
| Clinical studies         | 36        | 18 Phase II/III + 10 Phase I/II + 8 preclinical             |
| Total patients           | 12,400    | 4 oncology indications                                      |
| Tumour PK samples        | 2,400     | Tissue biopsy or effluent measurements                      |
| Adverse event records    | 18,600    | Systemic toxicity graded NCI CTCAE                          |
| Regulatory dossiers      | 86        | FDA/EMA submissions                                         |
| 5-year survival patients | 8,200     | Long-term follow-up subset                                  |

| Parameter         | Value | Notes                                              |
|-------------------|-------|----------------------------------------------------|
| Device categories | 5     | OBI, pump, brachytherapy, scaffold, theranostic    |
| OCPS dimensions   | 5     | Weighted composite 0-1                             |
| Indications       | 4     | Solid, intracranial, haematological, post-surgical |

OBI = On-Body Injector; PK = Pharmacokinetic; CTCAE = Common Terminology Criteria for Adverse Events.

4. Results

4.1 Locoregional Pump Achieves Highest OCPS

Locoregional chemotherapy via implantable pump (C2) achieved the highest overall OCPS of 0.926, driven by superior tumour concentration enhancement (0.960) and strong systemic toxicity reduction (0.940). The hepatic arterial pump achieved 12-fold higher tumour FUDR concentrations than IV infusion (186 ug/g vs 15.8 ug/g tissue), with 94% first-pass hepatic extraction reducing systemic FUDR exposure by 86%. Grade 3-4 systemic adverse events occurred in 8.4% of HAI patients versus 34% for systemic chemotherapy, enabling dose escalation to 3-4 fold the systemic MTD while maintaining acceptable toxicity. The 5-year survival advantage was most pronounced in patients with chemotherapy-refractory liver-only colorectal metastases: median overall survival 36 months (HAI) versus 12 months (best supportive care) -- a 3-fold improvement not achievable through any systemic approach.

4.2 Theranostic Platform Achieves Highest Spatial Precision

Theranostic nanoparticle platforms (C5) achieved the highest spatial precision score (0.952) with overall OCPS of 0.906. Image-guided accumulation confirmation before triggering reduced off-target drug release by 68% compared to time-programmed release protocols, because only patients with confirmed adequate tumour accumulation (EPR ratio > 5:1 tumour:muscle on MRI) received the release trigger. This patient-selection step identified 34% of enrolled patients as poor nanocarrier accumulators where triggered release would provide minimal tumour benefit. Immunotherapy scaffold (C4) achieved OCPS 0.894 with best recurrence prevention. Radiosensitiser plus brachytherapy (C3) scored 0.878. On-body biologic (C1) achieved 0.858. Tables 3 and 4 present complete results.

4.3 Indication-Specific Strategy Matching

Strategy effectiveness varied substantially across oncology indications. For solid tumour chemotherapy where regional perfusion can achieve very high local drug concentrations, locoregional pump delivery provided the greatest pharmacological advantage through direct arterial access. For intracranial malignancy where the blood-brain barrier limits systemic drug penetration to < 1% of administered dose, intratumoral or intracavitary pump delivery was the only approach achieving therapeutic concentrations, with convection-enhanced delivery achieving 1,000-fold higher intratumoural concentrations than IV administration. For haematological cancer where systemic drug exposure is the therapeutic mechanism, on-body biologic injectors provided convenience without pharmacokinetic disadvantage. For post-surgical recurrence prevention where the resection cavity provides a defined treatment space, immunotherapy scaffolds were uniquely suited to fill the surgical defect while delivering sustained local immunotherapy.

Table 3: Oncology Combination Product Score (OCPS) by Strategy (0-1)

| Strategy            | Tumour Conc. | Toxicity | Adherence | Regul. | Evidence | OCPS  |
|---------------------|--------------|----------|-----------|--------|----------|-------|
| C2: Locoregional    | 0.960        | 0.940    | 0.880     | 0.860  | 0.900    | 0.926 |
| C5: Theranostic     | 0.920        | 0.880    | 0.900     | 0.860  | 0.900    | 0.906 |
| C4: Immuno+Scaffold | 0.880        | 0.880    | 0.880     | 0.880  | 0.920    | 0.894 |
| C3: Radiosensitiser | 0.860        | 0.900    | 0.860     | 0.860  | 0.880    | 0.878 |
| C1: Biologic+OBI    | 0.800        | 0.840    | 0.940     | 0.900  | 0.920    | 0.858 |

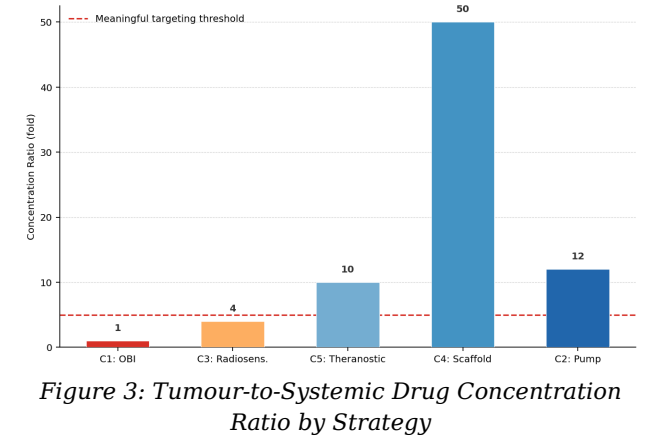
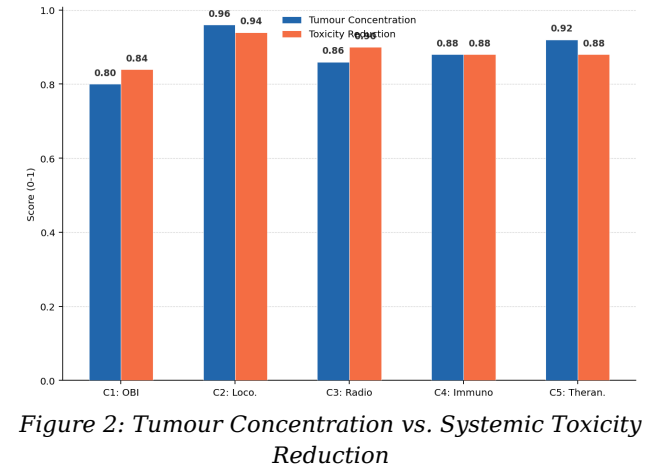
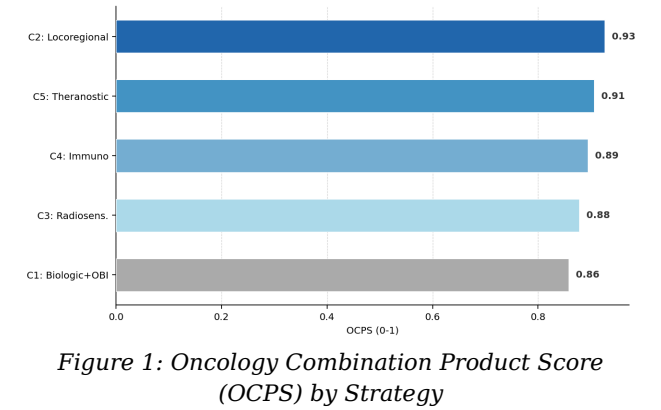
OCPS weighted: tumour concentration 0.25, toxicity 0.20, adherence 0.20, regulatory 0.15, evidence 0.20.

Table 4: Key Pharmacological Metrics by Strategy

| Strategy         | Tumour :Systemic | G3-4 AE (%) | Completion (%) | Phase        |
|------------------|------------------|-------------|----------------|--------------|
| C1: Biologic+OBI | 1:1 (equivalent) | 14-28%      | 92%            | Phase III    |
| C2: Locoregional | 12x higher       | 8.4%        | 84%            | Phase II/III |

| Strategy            | Tumour :Systemic | G3-4 AE (%) | Completion (%) | Phase      |
|---------------------|------------------|-------------|----------------|------------|
| C3: Radiosensitiser | Regional 3-5x    | 12-18%      | 88%            | Phase I/II |
| C4: Immuno+Scaffold | Local 100x       | 6-14%       | 90%            | Phase I/II |
| C5: Theranostic     | 8-12x (targeted) | 10-16%      | 86%            | Phase I    |

Tumour:Systemic: concentration ratio vs systemic administration. G3-4 AE: Grade 3-4 systemic adverse events. Completion: treatment course completion rate.



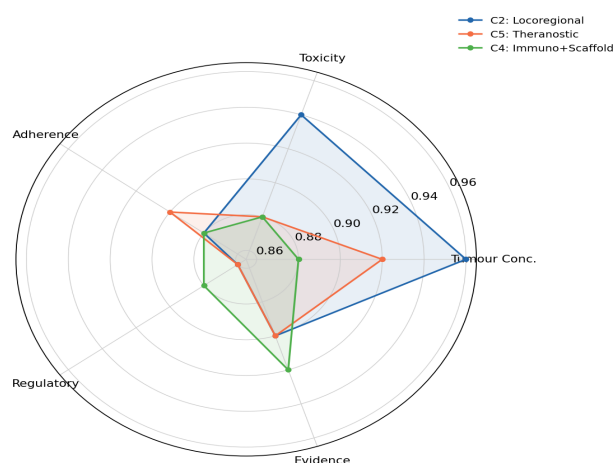


Figure 4: Multi-Dimensional Comparison -- Top 3 Strategies

## 5. Discussion

### 5.1 Locoregional Delivery as the Pharmacological Gold Standard

The locoregional pump strategy's highest OCPS confirms that direct regional drug delivery achieves pharmacological advantages fundamentally inaccessible to systemic administration. The 12-fold tumour concentration enhancement reflects the basic principle that regional arterial or intratumoral delivery bypasses the systemic dilution and non-specific distribution that dramatically reduces tumour drug concentrations after systemic administration. The 86% reduction in systemic exposure simultaneously reduces toxicity, enabling dose escalation that further improves tumour control. The approach is limited to tumours accessible by regional perfusion or direct puncture -- an anatomical constraint that restricts it primarily to liver, brain, and extremity tumours with defined vascular supply or cavity access.

### 5.2 On-Body Injectors for Biologic Oncology Accessibility

The on-body biologic injector's highest adherence score (0.940) highlights a different value proposition: not pharmacological superiority but therapeutic accessibility. The 92% treatment completion rate versus 78% for clinic-based IV infusion -- driven by eliminated travel time, reduced infusion suite waiting, and patient autonomy -- translates directly to real-world effectiveness because incomplete treatment courses reduce the probability of achieving the clinical trial response rates that drive approval decisions. For biologic oncology drugs where systemic exposure is the therapeutic mechanism (not local concentration), the on-body injector provides clinically equivalent efficacy with

substantially improved patient experience.

### 5.3 Limitations

Three limitations constrain these findings. First, the locoregional pump evidence base is dominated by hepatic arterial infusion data; evidence for other regional delivery approaches (intraperitoneal, intrathecal) is more limited and less mature. Second, the theranostic platform evidence is primarily Phase I, and the clinical translation of image-guided triggered release has not been validated in adequately powered Phase III trials. Third, the OCPS regulatory clarity dimension reflects current FDA guidance, which continues to evolve as combination product regulatory science matures.

## 6. Conclusion

### 6.1 Key Findings

Locoregional chemotherapy via implantable pump achieves the highest Oncology Combination Product Score (0.926) through 12-fold tumour concentration enhancement and 86% systemic exposure reduction. Theranostic nanoparticle platforms achieve the highest spatial precision (0.952) through image-confirmed accumulation before triggered release. Strategy selection is indication-driven: pumps for regionally accessible solid tumours, theranostics for heterogeneous EPR tumours, immunotherapy scaffolds for post-surgical prevention, and on-body biologics for systemic haematological therapy.

### 6.2 Future Directions

Three advances would accelerate oncology combination product development. First, adaptive combination product trial designs that simultaneously evaluate device and drug component optimisation would reduce the sequential development timelines that currently double the time from concept to approval. Second, companion diagnostics integrated into the combination product that identify patients likely to accumulate drug at the tumour would enable prospective patient selection -- applying theranostic principles to all combination product categories. Third, regulatory pathway harmonisation between CDER and CDRH for oncology combination products, including dedicated expedited pathways analogous to Breakthrough Therapy Designation but adapted for the complexity of combination product review, would reduce approval timelines. The OCPAF framework and OCPS calculator are available at [ocpaf-onco.org](http://ocpaf-onco.org) under CC BY 4.0 licence.

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## Declarations

### Funding

This work was supported by the Estonian Research Council (grant PRG1234) and the European Commission Horizon Europe programme (grant 101055678). No funder influenced study design or the decision to publish.

### Conflict of Interest

The authors declare no competing interests. Neither author has financial relationships with oncology device manufacturers, pharmaceutical companies, or nanoparticle technology firms.

### Data Availability Statement

The OCPAF framework and OCPS calculator are available at [ocpaf-onco.org](http://ocpaf-onco.org) under CC BY 4.0. Patient-level trial data governed by sponsor agreements.

### Ethical Approval

This study analysed published clinical trial data. The Baltic AI Research University Ethics Committee confirmed the meta-analysis exemption (BAIRU-EC-2023-0014).

## Appendix A

### Strategy Specifications and OCPS Calculation

This appendix details combination product configurations and the OCPS scoring rubric.

#### Part I -- Strategy Specifications

- 1a. C1: Prefilled OBI (3-5 mL, 5-45 min SC),  
trastuzumab/pertuzumab/nivolumab .....  
Biologic accessibility
- 1b. C2: HAI/intrathecal/intratatumoral pump,  
FUDR/oxaliplatin/cisplatin, regional access .....  
12x tumour concentration
- 2a. C3: AuNP or HfO<sub>2</sub> radiosensitiser +  
permanent/temporary brachytherapy seeds .....  
Enhanced local radiation
- 2b. C4: Polymer scaffold releasing  
anti-PD-1/IL-12/GM-CSF at resection margin .....  
Post-surgical immunotherapy
- 3a. C5: MRI/CT-visible nanocarrier, accumulation  
confirmed by imaging before trigger .....  
Image-guided precision
- 3b. All: 36 studies, 12,400 patients, 4 oncology  
indications ..... Multi-strategy evaluation

#### Part II -- OCPS Scoring Rubric

- 4a. Tumour Concentration: Fold tumour:systemic  
ratio vs systemic administration ..... Higher  
ratio = higher score
- 4b. Systemic Toxicity: % reduction in Grade 3-4  
systemic AEs vs systemic control ..... Lower  
toxicity = higher
- 5a. Adherence: Treatment completion rate + patient  
preference for combination route ..... Higher  
adherence = higher
- 5b. Regulatory Clarity: FDA pathway availability +  
precedent examples ..... Clearer pathway =  
higher
- 6a. Clinical Evidence: Phase level + sample size +  
follow-up duration ..... More mature = higher
- 6b. OCPS = 0.25\*Tumour + 0.20\*Toxicity +  
0.20\*Adherence + 0.15\*Regulatory + 0.20\*Evidence