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A Clinical Evidence-Guided Bioinformatics Framework for Expanding Cisplatin-Based Combination Therapies in Cervical Cancer

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2. Abstract

Background: Cisplatin-based combination therapy remains the foundation of systemic treatment for advanced cervical cancer; however, identifying effective therapeutic partners is challenging because of tumour heterogeneity and the large number of possible drug combinations. Existing computational platforms primarily evaluate experimentally generated drug combinations and provide limited support for systematically expanding clinically established treatment regimens while integrating mechanistic evidence to explain candidate prioritisation.

Methods: We developed a clinical evidence-guided computational decision-support and hypothesis-generation platform for systematic expansion of cisplatin-containing cervical cancer therapies. Clinically investigated cisplatin combination regimens were identified from ClinicalTrials.gov and used as pharmacological reference backbones. Model-specific dose–response profiles were reconstructed from Genomics of Drug Sensitivity in Cancer (GDSC2) data and evaluated using Bliss independence, Highest Single Agent, Loewe additivity, and Zero Interaction Potency interaction models. Candidate third-drug additions were systematically prioritised relative to the pharmacological performance of each reference regimen. Pharmacological findings were subsequently integrated with Cancer Dependency Map CRISPR gene dependency, transcriptomic expression, and somatic mutation data, followed by graph-learning analyses and patient-level molecular contextualisation using the independent GSE299125 cervical cancer transcriptomic cohort.

Results: The framework demonstrated substantial model-specific heterogeneity in the pharmacological performance of clinically established cisplatin regimens and identified distinct candidate third-drug partners across cervical cancer models. Integrating functional genomic dependency, transcriptomic expression, and genomic context provided mechanistic interpretation beyond pharmacological interaction scores alone, while graph-learning analyses captured systems-level relationships among prioritised therapeutic candidates. Patient-level projection further demonstrated that prioritised molecular targets were represented across independent cervical cancer transcriptomic profiles, providing biological contextualisation of experimentally derived therapeutic hypotheses.

Conclusions: This study presents a clinically grounded, explainable computational framework that extends conventional drug-combination analysis from retrospective synergy assessment toward evidence-guided therapeutic optimisation. By integrating clinical trial evidence, reconstructed pharmacology, functional genomics, graph learning, and patient-level molecular contextualisation within a unified workflow, the platform provides a reproducible foundation for therapeutic hypothesis generation, systems pharmacology, and precision oncology research in cervical cancer.

Implementation and Availability: The platform is implemented as an interactive R Shiny application. A publicly accessible prototype is available through Posit Connect Cloud, and the complete source code and supporting datasets are available through the accompanying GitHub repository.

Keywords: Cervical cancer; chemotherapy; cisplatin regimens; clinical trials, drug synergy analysis; precision oncology; computational drug discovery; functional genomics; neural network graph learning

3. Introduction

Cervical cancer remains one of the leading causes of cancer-related mortality among women worldwide despite substantial advances in surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy. Cisplatin remains the backbone of systemic therapy for locally advanced, recurrent, and metastatic cervical cancer, with recent clinical development increasingly focusing on combination strategies designed to improve response rates and overcome therapeutic resistance. Historically, cisplatin has been combined with conventional cytotoxic agents including paclitaxel^{1,2}, topotecan^{3,4}, gemcitabine^{5–7}, fluorouracil, vinorelbine, pemetrexed^{8–10}, and ifosfamide, several of which have demonstrated improved clinical activity and have become established treatment options for advanced disease. Among these, the cisplatin–paclitaxel doublet remains a cornerstone of first-line therapy, while the addition of bevacizumab has further improved survival and established the cisplatin–paclitaxel–bevacizumab regimen as a standard treatment for recurrent or metastatic cervical cancer^{8–11}. More recently, clinical development has shifted toward integrating immunotherapy with platinum-based chemotherapy. Multiple immune checkpoint inhibitors, including pembrolizumab, nivolumab¹², atezolizumab^{10,13,14}, camrelizumab^{15–17}, cadonilimab^{18–20}, toripalimab^{21,22}, tislelizumab^{23,24}, socazolimab^{25–27}, adebrelimab, and several investigational PD-1/PD-L1 antibodies, are currently being evaluated in combination with cisplatin-containing regimens. Notably, the KEYNOTE-826 study established pembrolizumab combined with platinum-based chemotherapy with or without bevacizumab as a new standard of care for persistent, recurrent, or metastatic cervical cancer, highlighting the growing importance of immunochemotherapy in disease management^{28–31}. Beyond immunotherapy, numerous targeted therapeutic strategies are also under active investigation. These include combinations with anti-angiogenic agents²², EGFR inhibitors³², DNA damage response inhibitors, PARP inhibitors³³, hypoxia-targeting agents^{34,35}, radiosensitisers^{5,32,36–38}, and monoclonal antibodies^{39,40}, reflecting continued efforts to exploit complementary biological pathways that enhance cisplatin efficacy while delaying resistance (**Table 1**).

Table 1. Recent clinical evaluation of cisplatin-based combination therapies for cervical cancer

Therapeutic category	Representative cisplatin combination(s)	Current clinical status
Standard chemotherapy	Paclitaxel, Topotecan, Gemcitabine, Fluorouracil	Established/standard therapy
Anti-angiogenic therapy	Bevacizumab + Paclitaxel + Cisplatin	Standard of care for advanced disease
Immune checkpoint inhibitors	Pembrolizumab, Nivolumab, Atezolizumab, Camrelizumab, Cadonilimab, Toripalimab, Tislelizumab, Socazolimab, Adebrelimab, AK104, SHR-1701, Rulonilimab, QL1706, GLS-010, HLX10, SG001	Phase I–III clinical trials; pembrolizumab regimen FDA-approved
Targeted therapies	Cetuximab, Panitumumab, Erlotinib, Nimotuzumab	Clinical evaluation
DNA damage response/PARP inhibitors	Veliparib	Completed clinical trials
Hypoxia/radiosensitisation	Triapine, Tirapazamine, Nelfinavir, Methazolamide	Clinical evaluation/completed
Other cytotoxic	Vinorelbine, Pemetrexed,	Completed clinical trials or

combinations	Ifosfamide, Methotrexate, Bleomycin, Mitomycin C, Vinblastine, Vindesine, Vincristine, S-1	historical regimens
Supportive/protective approaches	Amifostine	Multiple clinical studies

Collectively, these clinical studies demonstrate that cisplatin remains the central therapeutic backbone upon which increasingly diverse cytotoxic, targeted, and immune-based combination strategies are being developed. This expanding clinical landscape provides an important translational framework for evaluating computationally predicted drug combinations and identifying novel candidates with the potential to improve cervical cancer treatment. Cisplatin-based therapeutic response is constrained by substantial tumour heterogeneity and the development of intrinsic or acquired drug resistance. Cancer cells can maintain survival through different molecular architectures. In some tumour states, survival is distributed across interconnected receptor tyrosine kinase and mTOR signalling, anti-apoptotic buffering, metabolic adaptation, and stress-response mechanisms. In others, survival may be more strongly centred on dominant DNA damage, replication, or transcription-associated programmes^{41–46}. Consequently, pharmacological inhibition of a single pathway may produce incomplete responses because alternative survival mechanisms can compensate for the targeted process. Combination therapy provides an opportunity to disrupt these compensatory networks. Existing drug-prioritisation and combination-analysis approaches commonly evaluate pharmacological interactions or rank candidate compounds according to response metrics. However, there remains a need for computational frameworks that begin with clinically evaluated treatment backbones and systematically ask whether additional agents can improve their model-specific pharmacological activity while providing a mechanistic explanation for the prioritised combination. This is particularly relevant to cervical cancer, where cisplatin is combined with multiple cytotoxic, targeted, and emerging therapeutic agents, yet response to these regimens can vary substantially between tumour models. Against this clinical background, we conceptualised cisplatin-based cervical cancer treatment as an expanding therapeutic landscape encompassing established chemotherapy, anti-angiogenic therapy, immune checkpoint inhibition, targeted therapy, DNA damage response and PARP inhibition, hypoxia-directed or radiosensitising strategies, other cytotoxic combinations, and supportive or protective approaches (**Figure 1**). These therapeutic categories span different levels of clinical maturity, ranging from established standards of care and regulatory-approved regimens to agents undergoing clinical evaluation and combinations examined in completed or historical studies. The diversity of cervical cancer cell models and histological contexts represented in the pharmacological evidence base further highlights the need for model-specific assessment, because therapeutic activity observed in one biological context may not translate uniformly across others. This clinical and biological heterogeneity provided the rationale for developing a clinical evidence-guided pharmacological prioritisation platform that uses clinically investigated cisplatin combinations as reference treatment backbones, reconstructs model-specific drug responses, quantitatively evaluates candidate combination partners, and integrates functional dependency and molecular evidence to support mechanistic interpretation. Rather than prioritising combinations solely according to a numerical synergy score, the framework was designed to identify therapeutic additions that exceed the pharmacological activity of an established clinical reference regimen within the same cervical cancer model while targeting biologically supported vulnerabilities.

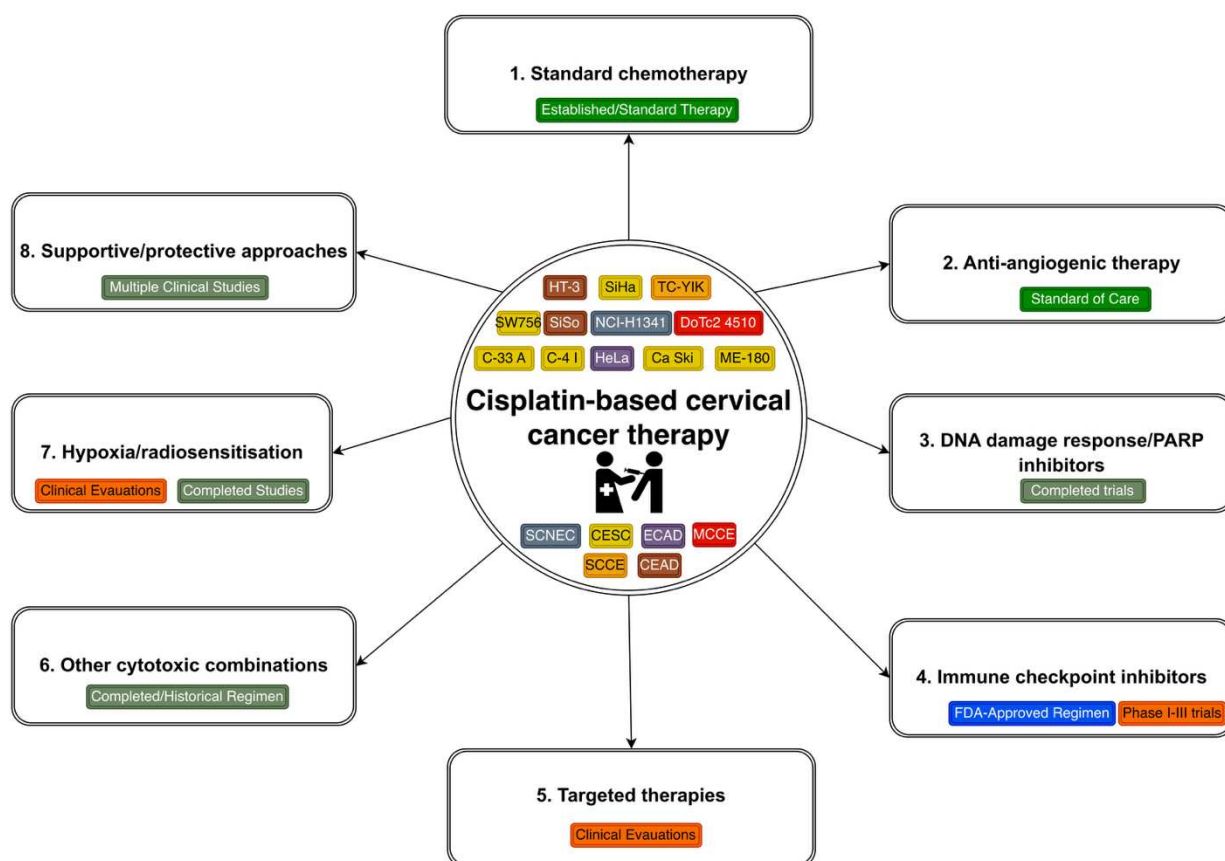


Figure 1. Clinical landscape of cisplatin-based combination therapies evaluated in cervical cancer. The schematic positions cisplatin-based therapy as the central treatment backbone and summarises the major therapeutic categories investigated in combination with cisplatin, including standard chemotherapy, anti-angiogenic therapy, DNA damage response and PARP inhibitors, immune checkpoint inhibitors, targeted therapies, other cytotoxic combinations, hypoxia-directed or radiosensitising agents, and supportive or protective approaches. The cervical cancer cell-line models and histological classifications displayed within the central node illustrate the biological diversity across which cisplatin-containing regimens may be evaluated. Clinical-status labels distinguish established or standard therapies (green), FDA-approved regimens (blue), agents or combinations undergoing clinical evaluation or Phase I–III trials (orange), and completed, historical, or supportive clinical studies (grey). The connecting arrows organise the therapeutic categories around the common cisplatin backbone and do not indicate mechanistic, causal, or temporal relationships. This clinical landscape provided the evidence base for selecting reference cisplatin-containing regimens for subsequent model-specific pharmacological reconstruction and candidate-drug prioritisation. **Abbreviations:** CEAD, cervical adenocarcinoma; CESC, cervical squamous cell carcinoma; ECAD, endocervical adenocarcinoma; FDA, United States Food and Drug Administration; MCCE, mixed cervical carcinoma; PARP, poly(adenosine diphosphate-ribose) polymerase; SCCE, small cell carcinoma of the cervix; SCNEC, small cell neuroendocrine carcinoma. HT-3, SiHa, TC-YIK, SW756, SiSo, NCI-H1341, DoTc2 4510, C-33 A, C-4 I, HeLa, Ca Ski, and ME-180 are cell-line designations rather than abbreviations.

Cancer drug discovery has increasingly shifted from empirical compound screening towards **integrative bioinformatics approaches** that combine pharmacological, molecular, and clinical evidence to support the rational selection of personalised therapeutic strategies. Advances in pharmacogenomics, functional genomics, systems biology, structural bioinformatics, and network biology have enabled computational frameworks to identify molecular vulnerabilities, characterise tumour-specific therapeutic dependencies, and prioritise candidate drugs for experimental validation⁴⁷. Rather than relying solely on high-throughput screening, these approaches integrate diverse biomedical data—including drug-response profiles, molecular target annotations, gene dependency screens, transcriptomic and genomic datasets, and curated biological knowledge—to provide mechanistic insight into therapeutic response and improve the efficiency of drug discovery. Combination therapy represents one of the most important applications of computational pharmacology because effective cancer treatment frequently requires simultaneous perturbation of multiple biological processes to overcome intrinsic or acquired therapeutic resistance. However, the number of possible drug combinations increases exponentially with the number of available compounds, making comprehensive experimental evaluation impractical. Consequently, computational approaches have become essential for prioritising biologically plausible therapeutic

combinations by integrating pharmacological response data with molecular evidence, pathway information, and systems-level biological knowledge. These strategies substantially reduce the experimental search space while providing a rational basis for selecting combinations for subsequent laboratory investigation. Several computational resources have been developed to facilitate this process. Platforms such as DrugComb provide comprehensive repositories for analysing experimentally generated drug-combination datasets using pharmacological interaction models including Bliss Independence, Loewe Additivity, Highest Single Agent (HSA), Zero Interaction Potency (ZIP), and the Combination Sensitivity Score (CSS)^{48–53}. Complementary bioinformatics approaches integrate functional genomic dependency datasets, molecular target annotations, transcriptomic and genomic profiles, pathway databases, and biological interaction networks to identify candidate biomarkers and mechanistically interpret pharmacological responses. More recently, network-based and graph-learning approaches have been introduced to exploit relationships between drugs, molecular targets, pathways, and biological processes, enabling therapeutic prioritisation within a systems biology framework rather than through isolated pharmacological metrics alone⁵⁴. Despite these advances, existing computational platforms remain largely focused on retrospective analysis of experimentally generated drug-combination datasets or prediction of pharmacological interactions between arbitrary drug pairs. Relatively few frameworks begin with **clinically established treatment regimens** and systematically evaluate whether additional therapeutic agents improve their pharmacological performance. Furthermore, although many platforms provide pharmacological interaction scores, fewer integrate complementary mechanistic evidence—including functional genomic dependency, transcriptomic target expression, somatic mutation context, and patient-derived molecular data—into a unified framework for interpreting why specific therapeutic combinations should be prioritised. Consequently, pharmacological interaction scores often remain difficult to interpret biologically, limiting their utility for hypothesis generation and translational decision-making. In this study, we present a **clinical evidence-guided bioinformatics framework** for systematic expansion of established cisplatin-based cervical cancer therapies. Rather than beginning with arbitrary user-defined drug pairs, the workflow starts with clinically investigated cisplatin-containing regimens identified from ClinicalTrials.gov, which serve as reference treatment backbones for model-specific pharmacological benchmarking. Dose–response profiles are reconstructed from GDSC2 pharmacological data, and candidate third-drug additions are evaluated according to whether they improve the pharmacological performance of the corresponding clinical reference regimen. Pharmacological prioritisation is subsequently interpreted through sequential integration of DepMap CRISPR functional dependency, transcriptomic target expression, somatic mutation profiling, reconstructed monotherapy activity, patient-level transcriptomic contextualisation, and graph-learning analyses. By combining clinical evidence, pharmacological modelling, functional genomics, and systems-level biological interpretation within a reproducible analytical workflow, the platform provides a bioinformatics framework for the rational prioritisation of personalised cisplatin-based combination therapies and the generation of biologically interpretable therapeutic hypotheses.

4. Materials

Clinical trial evidence resource

Clinical trial evidence was obtained from the ClinicalTrials.gov registry. The downloaded ctg-studies.csv dataset contains study identifiers, intervention information, disease conditions, recruitment status, sponsors, collaborators, and additional study metadata for registered clinical trials. This resource served as the source of clinically investigated cisplatin-containing cervical cancer treatment regimens⁵⁵.

Pharmacological response resource

Drug-response data were obtained from the Genomics of Drug Sensitivity in Cancer (GDSC2) resource. The `GDSC2ResponseCurves.csv` dataset contains fitted dose–response parameters, including EC50, Hill slope, upper and lower asymptotes, tested concentration ranges, compound identifiers, and model identifiers for experimentally screened anticancer compounds ^{56–58}.

Compound annotation resource

Compound annotations were obtained from **PortalCompounds.csv**, including Drug Perturbation Catalogue identifiers, compound names, synonyms, annotated molecular targets, mechanisms of action, ChEMBL identifiers, PubChem identifiers, and chemical descriptors ⁵⁹.

Cancer model metadata

Cancer model metadata were obtained from **Model.csv**, including model identifiers, cell-line names, tissue annotations, disease classifications, and DepMap identifiers used for cross-resource integration ⁵⁹.

Functional genomics resource

Genome-scale CRISPR dependency data were obtained from the *CRISPRGene-Dependency.csv* dataset provided through the Cancer Dependency Map. The dataset contained model-specific gene dependency estimates derived from genome-scale CRISPR knockout screening across cancer cell lines ⁵⁹.

Transcriptomic resource

Model transcriptomic profiles were obtained from **OmicsExpressionTPMLogp1Human-ProteinCodingGenesStranded.csv**, containing stranded RNA sequencing expression values reported as $\log_2(\text{TPM} + 1)$ ⁵⁹.

Somatic mutation resource

Somatic mutation annotations were obtained from `OmicsSomaticMutationsMAF.maf`, including genomic coordinates, variant classifications, protein changes, and gene annotations for molecularly characterised cancer models ⁵⁹.

Independent cervical patient transcriptomic cohort

Independent patient transcriptomic analyses were performed using GSE299125, a publicly available RNA sequencing dataset comprising cervical samples from HIV-positive and HIV-negative Kenyan women across normal cervix, precancerous lesions, and invasive cervical carcinoma ⁶⁰.

Software and computational environment

Interactive functionality was implemented using the Shiny framework, while data manipulation and preprocessing were performed using the tidyverse suite of packages ⁶¹. Graph-based analyses were implemented using `igraph` ⁶², and predictive performance was evaluated using pROC for receiver operating characteristic analysis and `caret` for classification performance assessment ⁶³. Heatmaps and hierarchical clustering visualisations were generated using `pheatmap`, with additional publication-quality graphics produced using `ggplot2` ⁶⁴. Interactive tables and user-interface components were implemented using `DT`, `shinyWidgets`, `bslib`, and related Shiny packages ^{65–68}. The interactive application was deployed through Posit Connect Cloud, enabling browser-based execution of the complete analytical workflow without requiring local installation of R or additional software dependencies ⁶⁹. The source code was managed using Git and is publicly available through the accompanying GitHub repository to facilitate reproducibility, independent evaluation, and future development. All analyses were

conducted within the R statistical computing environment on Linux-based computational infrastructure. The analytical workflow was designed to ensure reproducible integration of clinical trial evidence, pharmacological response modelling, functional genomic annotation, graph-learning analyses, and patient-level transcriptomic contextualisation within a single computational framework.

5. Method

Clinical evidence-guided definition of reference cisplatin regimens

Clinical evidence formed the first analytical layer of the decision-support platform. Registered cervical cancer clinical studies were retrieved from the ClinicalTrials.gov registry using the publicly available **ctg-studies.csv** dataset. Studies were systematically filtered to identify cervical cancer trials containing cisplatin as part of the reported therapeutic intervention. Intervention descriptions were manually curated to extract clinically evaluated cisplatin-containing treatment regimens and classify partner agents according to therapeutic mechanism, including conventional chemotherapy, anti-angiogenic therapy, epidermal growth factor receptor (EGFR)-targeted therapy, immune checkpoint inhibition, DNA damage response inhibition, and other investigational strategies. To ensure compatibility with downstream pharmacological analyses, all intervention names were reconciled against the Genomics of Drug Sensitivity in Cancer version 2 (GDSC2) PortalCompounds resource using compound identifiers, synonyms, and annotated compound names. Only clinically investigated combinations with corresponding GDSC2 pharmacological profiles were retained as computational reference regimens. These clinically grounded combinations established the pharmacological backbones from which systematic third-drug expansion was performed. Consequently, all subsequent analyses originated from therapies with existing clinical evidence rather than arbitrary computationally generated drug pairs (**Table 2**).

Table 2. Clinical trials evaluating cisplatin-based combination therapies for cervical cancer identified from ClinicalTrials.gov

Combination partner(s)	Example cervical cancer trials	Clinical development	GDSC2
Paclitaxel + Cisplatin	Multiple Phase II/III trials; standard first-line backbone ^{1,3}	Very well established	YES
Topotecan + Cisplatin	Multiple recurrent/metastatic cervical cancer trials ^{8,10}	Well established	YES
Gemcitabine + Cisplatin	Concurrent chemoradiation and metastatic disease ^{9,12,54}	Established	YES
Bevacizumab + Paclitaxel + Cisplatin	Several first-line trials ^{2,5–7}	Standard of care in advanced disease	Partially
Pembrolizumab + Paclitaxel + Cisplatin ± Bevacizumab	KEYNOTE-826 and related studies ^{14–18}	FDA-approved regimen	Partially
Nivolumab + Cisplatin	Chemoradiotherapy combinations ¹⁹	Clinical trials	NO
Atezolizumab + Cisplatin	Concurrent chemoradiotherapy ^{4,20,21}	Clinical trials	NO
Camrelizumab + Cisplatin	Neoadjuvant and concurrent therapy ^{22–24}	Clinical trials	NO
Cadonilimab + Cisplatin	Neoadjuvant immunochemotherapy ^{25,26,35}	Clinical trials	NO
Toripalimab + Cisplatin	First-line metastatic disease ^{27,28}	Clinical trials	NO

Tislelizumab + Cisplatin	Recurrent/metastatic disease ^{29,30}	Clinical trials	NO
Socazolimab + Cisplatin	Phase III ^{31–33}	Clinical trials	NO
AK104 + Cisplatin	First-line advanced disease ³⁴	Clinical trials	NO
SHR-1701 + Cisplatin	First-line metastatic disease ³⁶	Clinical trials	NO
QL1706 + Cisplatin	Advanced disease ³⁷	Clinical trials	NO
GLS-010 + Cisplatin	First-line treatment ³⁸	Clinical trials	NO
HLX10 + Cisplatin	Advanced cervical cancer ³⁹	Clinical trials	NO
SG001 + Cisplatin	PD-L1-positive cervical cancer ⁴⁰	Clinical trials	NO
Sacituzumab tirumotecan + Pembrolizumab + Cisplatin	Maintenance therapy ⁴²	Clinical trials	NO
Nimotuzumab + Cisplatin	Multiple chemoradiotherapy trials ⁴⁴	Clinical trials	NO
Cetuximab + Cisplatin	Recurrent/persistent disease ^{45–47}	Completed	NO
Erlotinib + Cisplatin	EGFR-targeted therapy ⁴⁸	Clinical trials	NO
Triapine + Cisplatin	Radiosensitization ^{49,50}	Multiple trials	NO
Veliparib + Paclitaxel + Cisplatin	PARP inhibitor combination ⁵¹	Completed	YES
Pemetrexed + Cisplatin	Advanced disease ⁵³	Completed	NO
Vinorelbine + Cisplatin	Recurrent disease/Radiosensitization ^{36,95}	Completed	YES
Tirapazamine + Cisplatin	Hypoxia-targeted therapy ^{34,35}	Completed	NO
Celecoxib + Fluorouracil + Cisplatin	Chemoradiotherapy ^{96–99}	Completed	NO
Fluorouracil + Cisplatin	Concurrent chemoradiotherapy ^{100–102}	Multiple trials	YES
Ifosfamide + Cisplatin	Multi-agent chemotherapy ^{103–105}	Completed	NO
Methotrexate + Cisplatin	Combination chemotherapy ^{106–108}	Completed	YES
Bleomycin + Cisplatin	Historical multi-agent regimen ^{103,109–113}	Completed	YES
Mitomycin C + Cisplatin	Historical combination ^{113,114}	Completed	NO
Vinblastine + Cisplatin	Historical combination ^{107,108,115}	Completed	YES
Vindesine + Cisplatin	Historical combination ^{113,116}	Completed	NO
Vincristine + Cisplatin	Adjuvant chemotherapy ^{112,117,118}	Completed	NO
S-1 + Cisplatin	Phase III ^{119,120}	Completed	NO
Nelfinavir + Cisplatin	Radiosensitization ¹²¹	Completed	NO
Amifostine + Cisplatin	Radioprotection ¹²²	Multiple studies	NO

Footnote:

This dataset is derived from the supplementary file ctg-studies.csv downloaded from Clinicaltrials.gov

Pharmacological resources and dose–response reconstruction

The *GDSC2ResponseCurves.csv* dataset from the Genomics of Drug Sensitivity in Cancer was used as the primary pharmacological response resource. The dataset contains fitted parameters describing experimentally derived compound–cell line dose–response relationships, including the half-maximal effective concentration (EC_{50}), lower asymptote, upper asymptote, Hill slope, and minimum and maximum tested concentrations. These parameters provide a compact mathematical representation of experimentally observed drug responses and enable reconstruction of continuous dose–response profiles without direct reanalysis of raw viability measurements. Cervical cancer-associated experimental models were identified using *Model.csv*, with DepMap model identifiers used to link cell-line annotations to the GDSC2 response data. Compound identities, synonyms, annotated gene targets, and mechanisms of action were obtained from *PortalCompounds.csv*. For each compound–model pair, concentration-dependent viability was reconstructed from the fitted response parameters as:

$$V(d) = L + \frac{U}{1 + \left(\frac{d}{EC_{50}}\right)^s}$$

where $v(d)$ represents predicted viability at dose d , L and U represent the lower and upper asymptotes respectively, and s represents the fitted slope parameter. predicted inhibition was subsequently calculated as $100 \times (1 - V[d])$ and constrained to the interval 0-100%^{70,71}.

Model-specific simulation of clinical reference regimens

Reference cisplatin-containing combinations were simulated independently within each eligible cervical cancer model using reconstructed single-agent dose-response profiles. Eligibility required complete pharmacological response information for every constituent drug within the reference regimen. Expected combination activity was estimated using four complementary drug-interaction models implemented within the platform.

Bliss independence

The Bliss model assumes probabilistic independence between drugs acting through distinct biological mechanisms. Expected inhibition was calculated as:

$$E_{Bliss} = 100 \left[1 - \prod_{i=1}^n \left(1 - \frac{E_i}{100} \right) \right]$$

where E_i represents the predicted inhibition produced by each constituent drug^{72–74}.

Highest Single Agent (HSA)

The Highest Single Agent model defines the expected combination effect as the maximum inhibition produced by any constituent monotherapy

$$E_{HSA} = \max(E_1, E_2, \dots, E_3)$$

providing a conservative estimate of combination benefit relative to the best-performing individual agent^{73,74}.

Loewe additivity

Loewe additivity assumes that compounds with similar mechanisms of action behave as dose equivalents. Expected responses were estimated by comparing observed combination activity with the theoretical additive response required to achieve equivalent inhibition under dose equivalence assumptions ^{73,74}.

Zero Interaction Potency (ZIP)

The ZIP model integrates principles from Bliss independence and Loewe additivity by simultaneously considering potency shifts and expected independence. ZIP scores quantify deviations from non-interaction while accounting for changes in the underlying dose-response surface ^{73,74}. For every simulated dose combination, observed responses were generated by perturbing expected inhibition using model-specific stochastic variation to approximate biological variability. Synergy scores were calculated as the difference between observed and expected inhibition under the selected interaction model. Positive scores indicated synergistic interactions, values near zero represented additive behaviour, and negative values indicated antagonism. The platform permits users to dynamically select the preferred interaction model during analysis, enabling direct comparison of candidate prioritisation across alternative pharmacological assumptions.

Monotherapy evaluation

To distinguish intrinsic drug activity from combination-specific pharmacological effects, monotherapy responses were reconstructed for every pharmacologically eligible compound across all cervical cancer models using the same fitted dose–response parameters applied during combination modelling. Predicted inhibition was calculated across the common concentration grid for each compound independently, and summary statistics including mean, maximum, minimum, and concentration-specific inhibition were generated ^{70,71}. Following systematic third-drug screening, intrinsic monotherapy activity was compared with the observed inhibition of the corresponding compound following incorporation into the selected cisplatin reference regimen. Combination gain was quantified by comparing inhibition achieved in the multidrug setting with inhibition predicted from the candidate drug alone. Candidate drugs demonstrating substantially greater inhibition after incorporation into the clinical backbone were interpreted as exhibiting pharmacological benefit beyond intrinsic cytotoxicity, whereas compounds with high monotherapy activity but limited additional combination improvement were considered primarily effective as standalone agents. This monotherapy evaluation provides an independent interpretive layer within the platform, enabling investigators to distinguish compounds selected because of inherent potency from those prioritised because they enhance the activity of an established cisplatin-containing regimen.

Systematic third-drug prioritisation

Clinically defined cisplatin-containing reference regimens were computationally expanded through systematic evaluation of additional therapeutic partners. For each eligible cervical cancer model, every pharmacologically characterised compound present in the GDSC2 resource was considered as a potential third drug, excluding agents already contained within the selected reference backbone. Candidate-expanded regimens were reconstructed using the same dose–response framework and interaction models applied during simulation of the reference combinations. For every candidate–model pair, summary interaction statistics were calculated and directly compared with the model-specific interaction profile of the corresponding clinical reference regimen. Rather than applying a universal synergy threshold, candidate performance was benchmarked relative to the experimentally reconstructed reference regimen within the same biological model. Candidate drugs producing interaction scores exceeding the reference combination were classified as stronger than reference, whereas compounds producing equivalent or lower interaction scores were classified as weaker or additive or antagonistic, depending on the selected interaction model. The platform

supports two complementary screening strategies. The unrestricted screening mode evaluates all pharmacologically eligible compounds within GDSC2, allowing systematic discovery of novel therapeutic hypotheses. Alternatively, the hypothesis-driven screening mode enables investigators to evaluate predefined candidate drug sets derived from previous computational analyses, biological studies, or experimental observations. Candidate rankings, interaction summaries, reconstructed dose–response profiles, and model-specific pharmacological statistics were generated for both screening modes.

Mechanistic evidence integration

Pharmacological prioritisation was subsequently complemented by integration of functional genomic and molecular evidence to determine whether prioritised candidate drugs targeted biologically relevant vulnerabilities within the same cervical cancer model. Three complementary evidence layers were incorporated: CRISPR gene dependency, transcriptomic expression, and somatic mutation. Each layer was evaluated independently and subsequently integrated with the pharmacological results, allowing mechanistic evidence to support—but not replace—pharmacological prioritisation.

CRISPR gene dependency

Functional dependency information was obtained from the Cancer Dependency Map (DepMap) CRISPR gene dependency resource. Candidate drug targets were extracted from compound annotations contained within the PortalCompounds dataset and mapped to corresponding CRISPR dependency scores using shared gene symbols and DepMap model identifiers. Compounds associated with multiple annotated targets generated independent drug–target–model associations for each target gene. CRISPR dependency scores were categorised into four evidence levels: strong dependency, moderate dependency, weak dependency, and non-dependent according to predefined dependency thresholds. Candidate compounds lacking annotated molecular targets were retained separately as unannotated, while genes absent from the dependency dataset were classified as unavailable. Rather than serving as an independent ranking criterion, CRISPR dependency provided functional evidence indicating whether the molecular target underlying a pharmacologically prioritised candidate represented an experimentally supported survival requirement within the corresponding cervical cancer model.

Gene expression

Transcriptomic evidence was incorporated by integrating candidate drug targets with matched DepMap gene-expression profiles. Expression values corresponding to each target gene were extracted for the relevant cervical cancer model and classified into high, moderate, or low expression according to gene-specific expression distributions across the available model population. Expression analysis was interpreted as evidence of target availability rather than therapeutic vulnerability. Consequently, transcript abundance was evaluated alongside pharmacological response and CRISPR dependency without being used independently to prioritise candidate compounds. Agreement between functional dependency and transcriptional abundance strengthened biological support for a candidate target, whereas discordance highlighted context-specific differences between target expression and functional importance.

Somatic mutation

Somatic mutation profiles for cervical cancer models were incorporated as an additional genomic evidence layer using matched mutation annotation data. Candidate drug targets were evaluated for the presence or absence of coding alterations within the corresponding experimental model, including missense mutations, nonsense mutations, insertions, deletions, and other annotated sequence variants. Mutation information was interpreted as contextual

molecular evidence rather than a primary prioritisation criterion. Candidate drugs targeting mutated genes were therefore considered alongside pharmacological performance, functional dependency, and transcriptomic representation. This integrated approach enabled identification of model-specific therapeutic hypotheses supported by multiple complementary biological evidence layers while avoiding reliance on mutation status alone.

Patient-level projection of prioritised therapeutic targets

To investigate whether therapeutic vulnerabilities identified during model-specific pharmacological prioritisation were represented within independent patient cohorts, prioritised candidate targets were projected into external cervical cancer transcriptomic datasets. Gene-expression data from the independent GSE299125 cohort were used as a patient-level molecular evidence layer. This cohort comprises normal cervical tissue, precancerous cervical lesions, and invasive cervical carcinomas from both HIV-positive and HIV-negative individuals. For unrestricted pharmacological screening, the strongest available CRISPR-supported target associated with each prioritised model–candidate combination was retained for patient-level projection. For hypothesis-driven analyses, all measurable molecular targets associated with the user-selected candidate drugs were evaluated independently. Gene-expression matrices were normalised and row-scaled to facilitate comparison of relative expression patterns across patients while preserving gene-specific variation. Hierarchical clustering was performed using Euclidean distance and complete-linkage clustering to identify groups of patients sharing similar target-expression profiles. Patient annotations, including disease category and HIV status, were incorporated to provide clinical context for the observed molecular heterogeneity. The resulting heatmaps were interpreted as evidence of transcriptional representation of therapeutically relevant target programmes rather than predictors of treatment response. Importantly, patient projection was performed only after pharmacological prioritisation and mechanistic annotation had been completed. Consequently, patient-level analyses preserved the complete analytical chain linking the clinically defined reference regimen, pharmacologically prioritised third drug, experimentally supported molecular target, and patient-specific transcriptional context. This design enables identification of molecularly compatible patient subgroups while avoiding inference of therapeutic benefit from transcriptomic expression alone.

Graph-learning framework

To complement conventional pharmacological ranking, a graph-learning framework was developed to capture systems-level relationships among candidate therapeutic agents. Candidate drugs were represented as nodes within weighted similarity graphs constructed independently for each cervical cancer model⁷⁵. Edges between nodes quantified pairwise similarity derived from multiple complementary evidence layers, including reconstructed pharmacological responses, molecular target annotations, mechanisms of action, functional genomic evidence, transcriptomic context, somatic mutation profiles, and interaction-model-derived similarity. Separate graph representations were generated for each pharmacological interaction model (Bliss independence, Highest Single Agent (HSA), Loewe additivity, and Zero Interaction Potency (ZIP)), allowing evaluation of how alternative assumptions regarding drug interaction influenced network topology and candidate prioritisation. This multi-graph strategy enabled comparison of candidate behaviour across complementary pharmacological frameworks while maintaining identical biological evidence layers. For each interaction model, pairwise similarity between candidate drugs was quantified by integrating pharmacological and biological evidence into a weighted edge score,

$$w_{ij} = \alpha S_{\text{pharm}} + \beta S_{\text{target}} + \gamma S_{\text{MOA}} + \delta S_{\text{CRISPR}} + \epsilon S_{\text{expr}} + \zeta S_{\text{mut}},$$

where

- S_{pharm} denotes similarity in reconstructed pharmacological responses (including the selected interaction model),
- S_{target} represents molecular target similarity,
- S_{MOA} represents mechanism-of-action similarity,
- S_{CRISPR} denotes similarity in CRISPR dependency profiles,
- S_{expr} represents transcriptomic similarity,
- S_{mut} represents similarity in somatic mutation profiles, and
- $\alpha, \beta, \gamma, \delta, \varepsilon, \zeta$ are weighting coefficients controlling the contribution of each evidence layer.

The resulting weighted adjacency matrix $A = [w_{ij}]$ was subsequently used to construct a graph $G = (V, E)$, where candidate drugs formed the graph nodes and weighted similarities defined the graph edges.

Graph convolutional learning was then performed according to:

$$H^{(l+1)} = \sigma(\tilde{D}^{-1/2} \tilde{A} \tilde{D}^{-1/2} H^{(l)} W^{(l)}),$$

where

- $\tilde{A} = A + I$ is the adjacency matrix with self-loops,
- $\tilde{D}$ is the corresponding degree matrix,
- $H^{(l)}$ represents the node embeddings at layer l ,
- $W^{(l)}$ denotes the trainable weight matrix, and
- $\sigma(\cdot)$ represents a nonlinear activation function.

The initial node representation was defined as:

$$H^{(0)} = X$$

Following graph convolution, the learned node embeddings were passed to a sigmoid output layer to estimate the probability that each candidate drug would outperform the corresponding clinically established cisplatin reference regimen within the same cervical cancer model,

$$P(y = 1 | x) = \frac{1}{1 + \exp(-z)},$$

where z denotes the graph-derived prediction score for each candidate drug. Rather than evaluating candidate drugs independently, graph convolution propagates information across neighbouring nodes according to the learned network topology, allowing biologically related compounds to contribute to one another's representation. Consequently, candidate rankings incorporated both intrinsic pharmacological performance and systems-level relationships among therapeutically related compounds. This graph-learning framework therefore provides an additional prioritisation layer capable of identifying broadly applicable therapeutic strategies while simultaneously preserving model-specific biological differences. Unless otherwise specified, all graph-learning analyses were conducted using a fixed parameter configuration. All available candidate drugs were retained, and the graph incorporated CRISPR dependency, target-expression and somatic-mutation evidence. Candidate drugs were represented as nodes, with edges constructed from shared targets, shared mechanism or pathway annotations, pharmacological similarity, CRISPR-dependency similarity, expression similarity and mutation context. Edges with a composite weight below 0.20 were excluded. Because the R torch framework was available, graph prioritisation was performed using the two-layer graph convolutional network. The model was trained for 250 epochs with 16 hidden units. The Validation Agent used five-fold stratified node-level cross-validation within each cervical cancer model, with a probability threshold of 0.50 for binary classification. The graph model was benchmarked against a pharmacology-only logistic-regression model and a prevalence base-

line. These parameters were held constant across the analyses to ensure comparability among cervical cancer models, candidate compounds and clinical reference combinations.

Internal validation framework

To evaluate the robustness of graph-based candidate prioritisation, an internal validation framework was implemented using complementary statistical and machine-learning performance metrics. Candidate predictions generated by the graph convolutional network were evaluated using cross-validation, with held-out candidate–model combinations used to estimate predictive performance independently of the training data. Predictive discrimination was assessed using receiver operating characteristic (ROC) analysis and the corresponding area under the ROC curve (ROC-AUC) ⁶³. Classification performance was further summarised using confusion matrices, from which accuracy, sensitivity, specificity, precision, F1-score, and Matthews correlation coefficient were calculated ⁵⁴. These metrics quantified the ability of the graph-learning framework to distinguish candidates predicted to outperform clinically established reference regimens from those predicted to provide limited additional benefit ⁷⁶. To determine whether graph learning provided additional value beyond conventional pharmacological modelling, graph-based predictions were compared with a pharmacology-only logistic regression model and a prevalence-based baseline classifier. Comparative evaluation enabled assessment of the contribution of network-derived biological relationships beyond pharmacological response features alone ^{75,77}. Decision Curve Analysis (DCA) was subsequently performed across a range of probability thresholds to estimate the potential utility of graph-derived prioritisation under alternative decision strategies. Net benefit curves were calculated for individual cervical cancer models and compared with both the pharmacology-only model and treat-all approaches. Because different tumour models exhibited distinct pharmacological landscapes, decision-curve analysis was used to identify model-specific operating thresholds rather than assuming a universal probability cutoff ⁷⁸. Finally, graph topology was evaluated using unsupervised graph-clustering analysis. Communities identified within the candidate similarity networks were compared with pharmacological interaction classes using the Rand Index, Adjusted Rand Index, and silhouette coefficient ^{79,80}. These complementary analyses assessed whether the learned graph structure reflected biologically meaningful pharmacological organisation and provided an additional systems-level assessment of model performance beyond conventional classification metrics. Collectively, this validation framework provides complementary evaluation of predictive discrimination, classification accuracy, clinical decision utility, and network organisation, thereby supporting robust assessment of graph-based therapeutic prioritisation while identifying model-specific limitations requiring future external validation.

Interactive decision-support platform

The analytical framework was implemented as an interactive web-based decision-support and hypothesis-generation platform using the R Shiny framework. Rather than serving as a repository of precomputed results, the platform dynamically reconstructs pharmacological responses and executes the complete analytical workflow in response to user-defined inputs. The platform was designed to guide investigators through successive evidence layers, beginning with clinically established cisplatin-containing treatment backbones and progressing through pharmacological prioritisation, mechanistic interpretation, network-based learning, and patient-level contextualisation. The analytical workflow is organised into sequential modules that mirror the computational framework described in this study. Users first select a clinically established cisplatin-containing reference regimen derived from ClinicalTrials.gov evidence. Eligible cervical cancer models are then identified according to the availability of complete pharmacological response profiles for all constituent drugs. Reference interaction profiles are reconstructed using the selected pharmacological interaction model, after which candidate third drugs are evaluated either through unrestricted screening of all pharmacologically eligible compounds or through user-defined hypothesis-driven candidate selection. Following

pharmacological prioritisation, the platform automatically integrates complementary mechanistic evidence, including CRISPR gene dependency, transcriptomic expression, and somatic mutation data, thereby providing biological context for candidate therapeutic hypotheses. Patient-level projection subsequently maps prioritised molecular targets into independent transcriptomic cohorts to identify patient-specific expression states consistent with the model-derived therapeutic vulnerabilities. Finally, graph-learning modules provide systems-level prioritisation by evaluating candidate drugs within weighted similarity networks, while the validation module summarises predictive performance using receiver operating characteristic analysis, confusion matrices, decision curve analysis, and graph-clustering metrics. All analytical outputs are generated dynamically from the underlying computational workflow and can be exported as publication-ready tables and figures (Figure 2). This modular architecture enables reproducible exploration of clinically established cisplatin regimens while maintaining complete traceability from clinical evidence through pharmacological simulation, biological interpretation, graph-based learning, and patient-level hypothesis generation.

Cloud deployment and software availability

The interactive platform was deployed using Posit Connect Cloud to provide browser-based access without requiring local installation of R or associated software dependencies. The application was developed as a single-file R Shiny application with supporting analytical modules and was deployed directly from the project source repository. Application dependencies were managed using the standard **rsconnect** deployment framework to ensure reproducibility of the computational environment⁸¹. The cloud deployment incorporates the clinical trial evidence, pharmacological response data, compound annotation resources, and cervical cancer model metadata required to execute the interactive analytical workflow. Large-scale molecular datasets, including complete CRISPR dependency, transcriptomic expression, and somatic mutation resources, are maintained within the full analytical framework and source repository to support comprehensive offline analyses while reducing the computational requirements of the publicly accessible deployment. The platform is intended as a research tool for computational therapeutic prioritisation, hypothesis generation, and methodological reproducibility. It is not designed for clinical diagnosis, treatment recommendation, or patient management. The publicly accessible prototype, source code, and supporting analytical resources are available through the Code Availability statement, enabling independent evaluation, reproduction, and extension of the computational framework presented in this study.

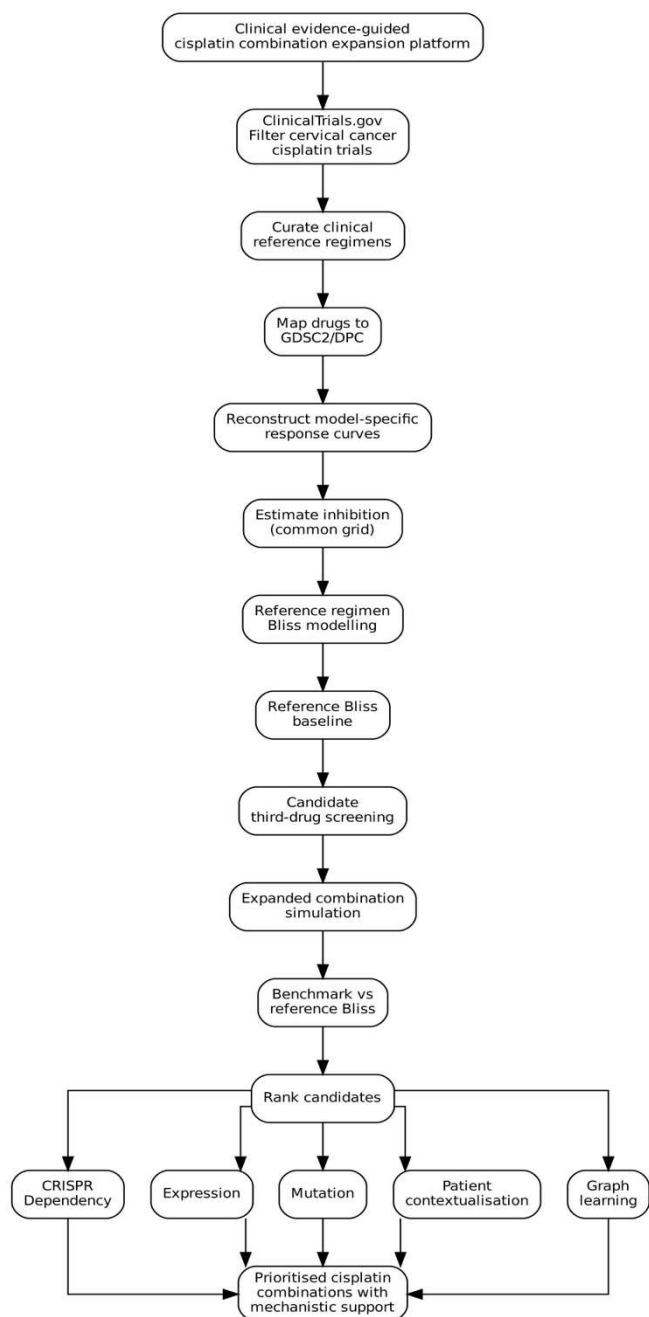


Figure 2. Clinical evidence-guided computational workflow for systematic expansion of cisplatin-based combination therapies in cervical cancer. Clinical evidence from ClinicalTrials.gov is used to identify and curate clinically investigated cisplatin-containing regimens, which are mapped to GDSC2 compounds to establish model-specific reference treatment backbones. Dose–response parameters from GDSC2 are reconstructed for cervical cancer models and used to estimate pharmacological responses across a common concentration grid. Reference regimens are modelled using the Bliss independence framework, and their model-specific mean Bliss scores are retained as pharmacological baselines. Each eligible GDSC2 compound is subsequently evaluated as a candidate third drug, and expanded multidrug combinations are simulated and benchmarked against the corresponding reference regimen. Candidate combinations demonstrating improved pharmacological performance are prioritised and integrated with complementary biological evidence, including DepMap CRISPR gene dependency, transcriptomic expression, somatic mutation profiling, patient-level transcriptomic contextualisation, and graph-learning analyses, to generate biologically interpretable therapeutic hypotheses. The workflow provides a transparent, clinically grounded framework for explainable therapeutic prioritisation and hypothesis generation in precision oncology. Implementation and Availability: The platform is implemented as an interactive R Shiny application Cisplatin Clinical Reference Combination Explorer prototype

6. Results

Baseline synergy of the reference regimens

Baseline pharmacological interactions were first characterised for the clinically evaluated cisplatin-based reference regimens across eligible cervical cancer models. In total, 101 model–regimen combinations were evaluated across eight reference backbones, including cisplatin combined with paclitaxel, topotecan, fluorouracil, methotrexate, bleomycin, vinorelbine, vinblastine, or paclitaxel plus veliparib. Reference mean Bliss scores varied substantially across cell lines, demonstrating pronounced model-specific heterogeneity in the interaction profiles of clinically established cisplatin combinations. Across all model–regimen pairs, 41 exhibited positive mean Bliss scores, whereas 60 exhibited negative mean Bliss scores, indicating that the same therapeutic backbone could produce synergistic or antagonistic interactions depending on the cervical cancer model. At the regimen level, mean reference Bliss scores averaged across eligible models were generally close to zero, ranging from -0.249 for cisplatin–topotecan to -0.055 for cisplatin–fluorouracil. Cisplatin–paclitaxel, cisplatin–methotrexate, cisplatin–bleomycin, cisplatin–vinorelbine, and cisplatin–vinblastine produced mean scores of -0.179 , -0.170 , -0.248 , -0.195 , and -0.098 , respectively. The cisplatin–paclitaxel–veliparib combination similarly showed a near-additive overall profile, with a mean reference Bliss score of -0.087 . Despite these modest regimen-level averages, individual models exhibited markedly stronger positive interactions. The highest reference mean Bliss score was observed for cisplatin–topotecan in DoTc2 4510 cells (1.612), while several regimens reached scores of approximately 1.576 , particularly in Ca Ski or DoTc2 4510 models. Conversely, the strongest negative interaction was observed for cisplatin–paclitaxel in TC-YIK cells (-2.024). These findings demonstrate that averaging pharmacological interactions across cervical cancer models can obscure substantial cell-line-specific variation. Accordingly, the model-specific reference mean Bliss score was retained as the baseline threshold for subsequent third-drug prioritisation, rather than applying a single global synergy cut-off across all models and regimens. This design enabled candidate compounds to be evaluated according to whether they improved the pharmacological interaction of an established cisplatin backbone within the same biological model. The complete model-specific baseline interaction profiles are provided in **Supplementary File S1**.

Systematic third-drug screening against the cisplatin–paclitaxel reference backbone

To demonstrate unrestricted application of the developed platform, the clinically established cisplatin–paclitaxel combination was selected as the reference backbone and screened against all pharmacologically eligible cervical cancer compounds available in the GDSC2 response resource. The screening space comprised 286 candidate third drugs across 13 eligible cervical cancer-associated models, generating 3,368 evaluable third-drug–model combinations. For each model, the Mean Bliss score of the cisplatin–paclitaxel reference was retained as a model-specific pharmacological threshold, and candidate additions were ranked according to their change relative to this baseline. The ten highest-ranked candidates per model were retained for visualisation, yielding 130 prioritised candidate–model combinations representing 102 unique third drugs; the complete model-specific rankings are provided in **Supplementary File S2**. The pharmacological screen demonstrated pronounced model dependence in the capacity of third-drug additions to improve upon cisplatin–paclitaxel. Of the 130 top-ranked candidate–model combinations, 109 were stronger than the corresponding model-specific reference, 16 were weaker or additive, and five were antagonistic. All ten top-ranked candidates exceeded the reference threshold in C-33 A, Ca Ski, DoTc2 4510, HeLa, ME-180, MS751, NCI-H1341, SiHa, SISO, and SW756. In contrast, only three of ten candidates exceeded the reference in C-4 I and one of ten in HT-3. TC-YIK showed the most restrictive pharmacological profile, with five stronger-than-reference and five antagonistic

candidate additions (**Figure 3**). The leading candidate differed substantially between models. Glutathione was the highest-ranked addition in C-33 A (Mean Bliss = 1.607; Δ versus reference = 3.678), alpha-lipoic acid in C-4 I (1.577; Δ = 0.251), compound 615590 in Ca Ski (1.865; Δ = 2.465), BDILV000379A in DoTc2 4510 (1.791; Δ = 0.948), navitoclax in HeLa (1.877; Δ = 2.820), vistusertib in ME-180 (1.834; Δ = 1.966), AT13148 in NCI-H1341 (1.847; Δ = 1.629), docetaxel in SiHa (1.791; Δ = 2.533), niraparib in SISO (2.112; Δ = 2.907), and teniposide in SW756 (2.112; Δ = 3.412). Although GSK-LSD1-2HCL ranked first in HT-3, its improvement above the already positive reference was minimal (Δ = 0.002), demonstrating that high absolute Bliss scores do not necessarily represent substantial improvement over an established pharmacological backbone. These findings emphasise the importance of model-specific reference benchmarking rather than ranking candidates by absolute interaction scores alone.

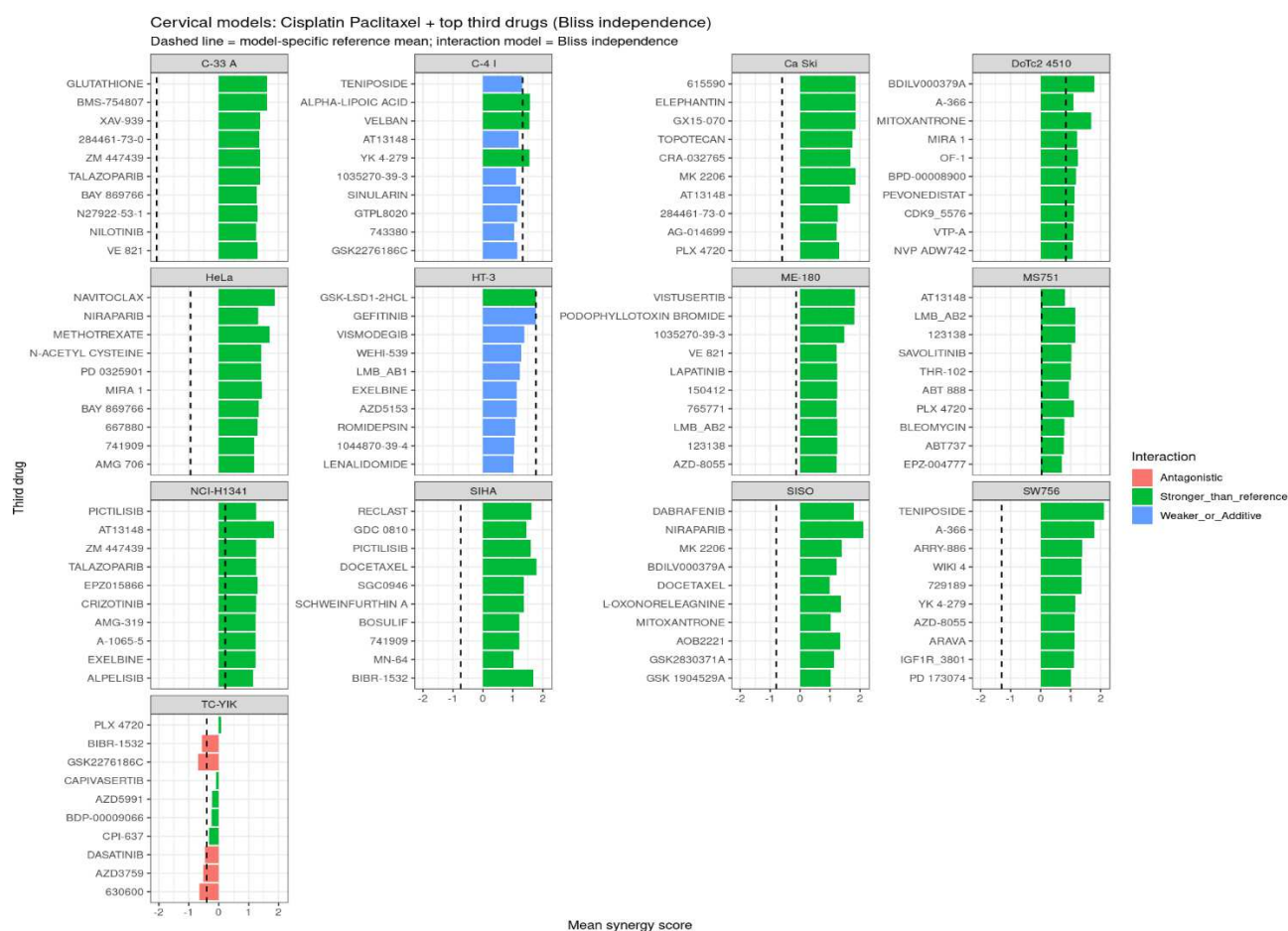


Figure 3. Model-specific pharmacological prioritisation of third-drug candidates added to the cisplatin–paclitaxel reference regimen. Mean Bliss scores for the ten highest-ranked third-drug candidates in each of 13 eligible cervical cancer-associated models. The dashed vertical line represents the model-specific Mean Bliss score of the cisplatin–paclitaxel reference combination. Candidate additions are classified as stronger than reference, weaker or additive, or antagonistic according to their interaction relative to the corresponding model-specific pharmacological baseline. The figure demonstrates substantial heterogeneity in candidate prioritisation and the magnitude of improvement achievable above the clinical reference backbone.

Monotherapy Evaluations

The unrestricted pharmacological screen revealed that intrinsic monotherapy activity varied markedly across cervical cancer models. Among the highest-ranked monotherapy candidates retained for each model, nearly all compounds demonstrated high predicted intrinsic inhibition, reflecting the selection of the strongest pharmacological responders from the complete screening space (**Supplementary File S3**). However, the identity of the highest-performing compounds differed substantially between models, highlighting pronounced tumour-specific pharmacological heterogeneity. C-33 A was characterised by highly active compounds including GTPL8020, entinostat, APR-246, AOB5560, MIRIN, and AZD2171, whereas C-4 I

prioritised AZD5991, ICL-SIRT078, NVP ADW742, MK-0683, MIRIN, and crizotinib. Ca Ski demonstrated particularly strong responses to BMS-345541, HKMTI-1-005, GSK2276186C, entinostat, navitoclax, and AMG-319, while DoTc2 4510 prioritised LGK-974, ZM447439, vismodegib, EXEL-2880, and ICI-46474. Distinct pharmacological profiles were similarly observed in the remaining models, including PLX4720 and lapatinib in HeLa, gefitinib and ruxolitinib in HT-3, AZD5991 and pinometostat in ME-180, gefitinib and BMS536924 in NCI-H1341, EXEL-2880 and ABT737 in SiHa, THR-103 and NVP ADW742 in SISO, ELOXATIN and crizotinib in SW756, and GSK-2141795 together with BMS-345541 in TC-YIK. Collectively, these findings demonstrate that although strong intrinsic cytotoxicity was observed across all cervical cancer models, the optimal monotherapy candidates differed considerably according to the underlying biological context (**Figure 4**).



Figure 4. Top predicted monotherapy responses across cervical cancer models. Mean monotherapy inhibition was reconstructed from fitted GDSC2 dose–response parameters for every pharmacologically eligible compound. For each cervical cancer model, the ten compounds with the highest predicted intrinsic inhibition were retained and classified according to intrinsic response. Distinct monotherapy profiles were observed across the thirteen models, demonstrating substantial tumour-specific heterogeneity in intrinsic drug sensitivity.

Comparison of intrinsic monotherapy activity with observed inhibition following incorporation into the cisplatin–paclitaxel reference regimen further demonstrated that monotherapy potency alone did not predict combination benefit (**Figure 5**). Candidate drugs positioned above the identity line produced greater observed inhibition following addition to the clinical backbone than was predicted from monotherapy alone, indicating pharmacological

improvement beyond intrinsic activity. This pattern was particularly evident for compounds such as 284461-73-0 in C-33 A, TOPOTECAN and AT13148 in Ca Ski, NVP ADW742 and CDK9_5576 in DoTc2 4510, vistusertib and lapatinib in ME-180, crizotinib in NCI-H1341, docetaxel and pictilisib in SiHa, mitoxantrone in SISO, PD173074 and teniposide in SW756, and BDP-00009066 together with CPI-637 in TC-YIK, all of which produced markedly greater inhibition following addition to the cisplatin–paclitaxel regimen than as predicted single agents. Conversely, several compounds exhibiting strong intrinsic monotherapy activity showed only limited improvement following combination or remained pharmacologically antagonistic relative to the model-specific reference. These observations indicate that intrinsic cytotoxicity and combination efficacy represent complementary but biologically distinct pharmacological characteristics. Consequently, the monotherapy evaluation provides an important interpretive layer that enables investigators to distinguish compounds functioning primarily as potent standalone therapeutics from those whose principal benefit arises through enhancement of an established clinical treatment backbone.

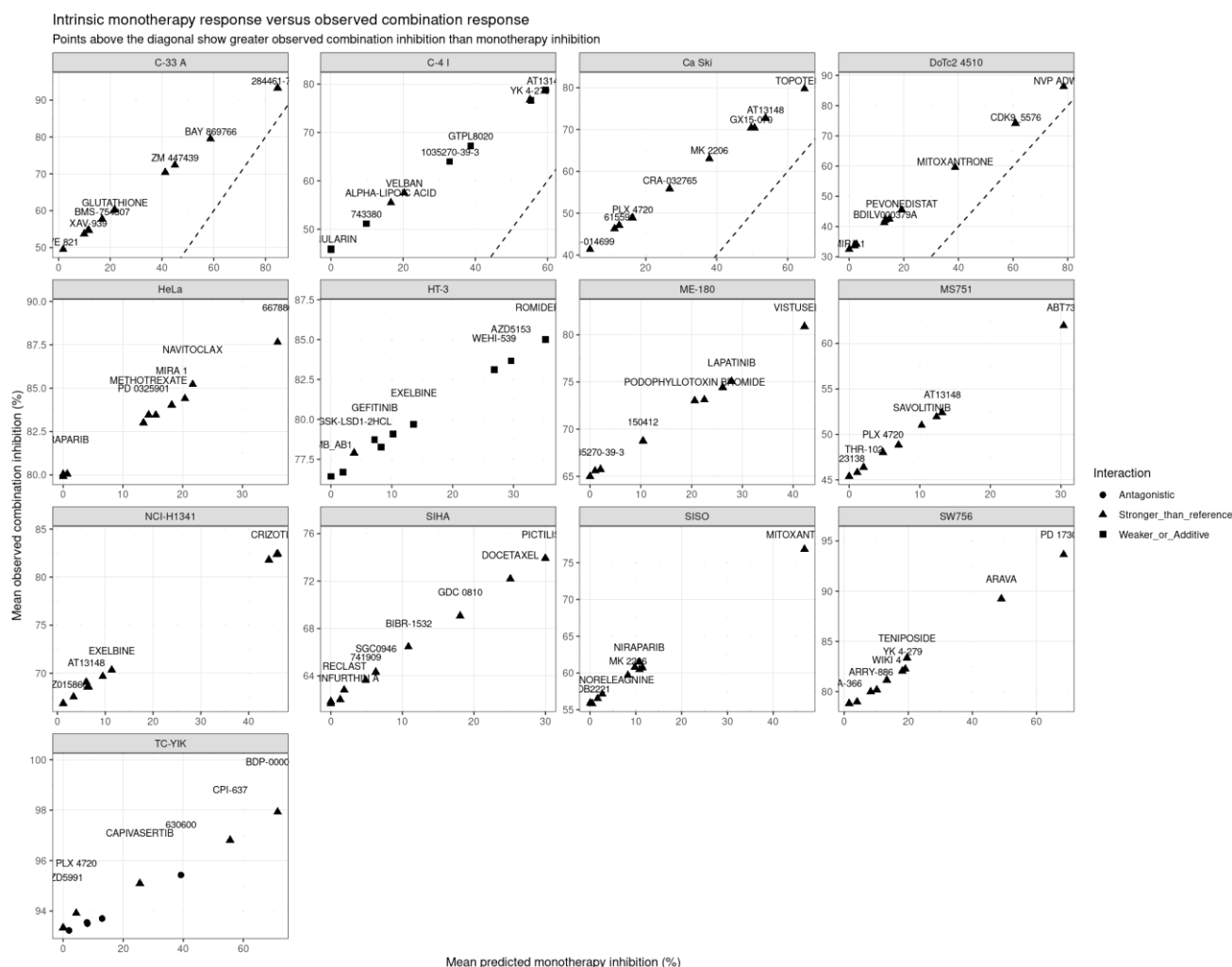


Figure 5. Comparison of intrinsic monotherapy activity and observed inhibition following addition to the cisplatin–paclitaxel reference regimen. Each point represents a prioritised candidate–model combination. The dashed diagonal denotes equal monotherapy and combination inhibition. Points above the diagonal indicate greater observed inhibition following incorporation into the cisplatin–paclitaxel backbone than predicted from monotherapy alone, whereas points below the diagonal indicate limited additional benefit despite intrinsic pharmacological activity. Together, the analysis demonstrates that strong intrinsic cytotoxicity does not necessarily translate into improved combination performance, highlighting the importance of evaluating both pharmacological layers during candidate prioritization.

Functional dependency reveals model-specific target vulnerabilities among prioritised candidates

The 117 anti-angiogenic candidate–model combinations were mapped to compound target annotations and integrated with matched DepMap CRISPR gene-dependency profiles. Target expansion generated 793 drug–target–model associations across the functional, molecular-

expression and mutation-evidence layers (**Supplementary File S4**). The CRISPR results revealed a heterogeneous and strongly model-specific dependency landscape rather than a single anti-angiogenic vulnerability shared across all cervical cancer models (**Figure 6**). PLK4 and CDK2 represented the most recurrent functional dependencies. Strong PLK4 dependency was observed in C-33 A, C-4 I, Ca Ski, DoTc2 4510, MS751, SiHa, SISO and SW756, whereas HT-3 showed moderate PLK4 dependency. CDK2 was strongly dependent in C-4 I, Ca Ski, DoTc2 4510, HT-3, SiHa and SW756, but showed moderate dependency in C-33 A, MS751 and SISO. These recurrent signals indicate that the prioritised anti-angiogenic compounds may capture broader cell-cycle-associated vulnerabilities in addition to their annotated vascular targets. Several dependencies were restricted to individual models. C-33 A displayed strong ERBB2 dependency and pronounced moderate PDGFRA dependency. DoTc2 4510 showed strong ERBB2 dependency, while SISO demonstrated a particularly strong IGF1R dependency. SiHa displayed the most prominent model-specific signal, with strong FGFR1 dependency substantially exceeding the corresponding values in the other models. SW756 additionally exhibited strong MAPK1 dependency. By contrast, many canonical angiogenesis-associated targets—including KDR, FLT1, FLT3, FLT4, PDGFRB, FGFR2, FGFR3, CSF1R and RET—were predominantly classified as weak dependencies, although their dependency scores varied across models. Overall, functional support for the anti-angiogenic candidates was less uniformly clustered around the canonical VEGF–VEGFR axis than expected. Instead, the analysis identified a dispersed dependency architecture involving PLK4, CDK2, ERBB2, IGF1R, FGFR1, MAPK1 and PDGFRA. These findings demonstrate that pharmacological prioritisation above the cisplatin–paclitaxel reference did not necessarily correspond to dependency on the candidate’s canonical anti-angiogenic target. The CRISPR layer therefore provides an important mechanistic filter, distinguishing candidates supported by model-specific target essentiality from those whose predicted benefit may arise through alternative targets, pathway-level effects or target-independent pharmacological mechanisms.

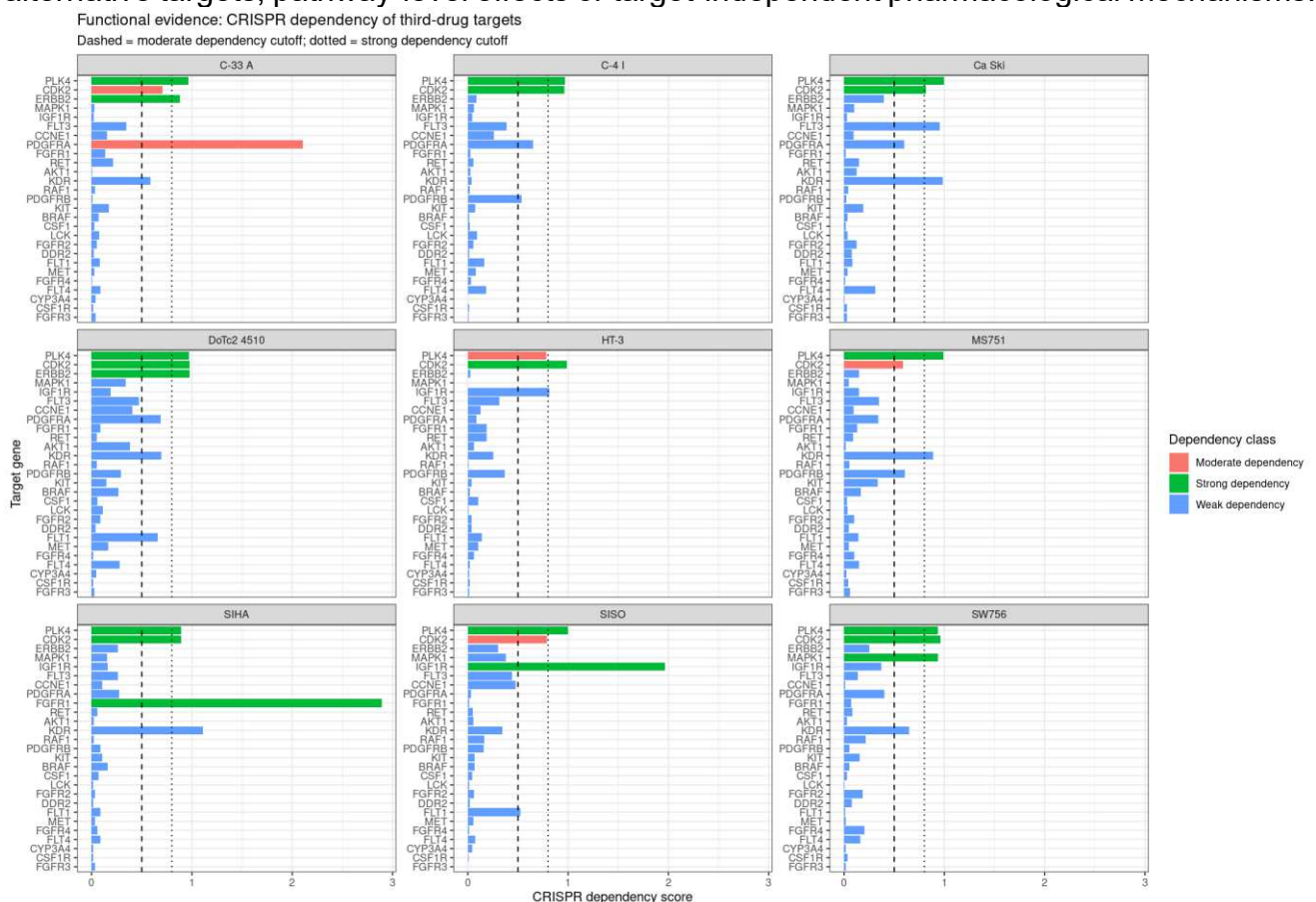


Figure 6. Model-specific CRISPR dependencies associated with prioritised anti-angiogenic third-drug candidates. DepMap CRISPR dependency scores are shown for target genes associated with the anti-angiogenic compounds prioritised through Bliss-independence screening against the cisplatin–paclitaxel reference combination. Facets represent individual cervical cancer models. Colours indicate weak,

moderate and strong dependency classifications; Dashed and dotted vertical lines indicate the moderate (≥ 0.5) and strong (≥ 0.8) dependency thresholds, respectively. The results reveal recurrent PLK4 and CDK2 dependencies alongside more restricted vulnerabilities involving ERBB2, IGF1R, FGFR1, MAPK1 and PDGFRA.

Molecular target expression contextualises functional dependencies in matched models

To determine whether the targets associated with the prioritised anti-angiogenic candidates were transcriptionally represented in the corresponding experimental models, the 117 candidate–model combinations were expanded using compound target annotations and integrated with matched DepMap expression profiles. This generated 793 drug–target–model associations across the molecular-expression evidence layer. Target expression was evaluated as $\log_2(\text{TPM} + 1)$ and classified as low, moderate or high using target-specific expression percentiles (**Supplementary File S5**). The resulting profiles demonstrated substantial heterogeneity between cervical cancer models (**Figure 7**). Several dependencies identified by CRISPR analysis were supported by transcriptional availability in the same models. In C-33 A, the strong PLK4 and ERBB2 dependencies were accompanied by high expression of both targets, while CDK2 was moderately expressed. C-4 I similarly exhibited high CDK2 and PLK4 expression, supporting the strong dependencies observed for these targets. In SiHa, the pronounced FGFR1 dependency coincided with exceptionally high FGFR1 expression, whereas the strongly dependent PLK4 and CDK2 targets were expressed at moderate levels. SW756 also showed concordant functional and molecular evidence: CDK2 and MAPK1 were highly expressed, and PLK4 was moderately expressed, consistent with the strong dependencies detected for these genes. Other models demonstrated partial or limited concordance between expression and functional dependency. SISO showed transcriptional availability of its functionally supported targets, although PLK4 and IGF1R were classified as moderately expressed rather than highly expressed. In DoTc2 4510, the strongly dependent ERBB2 target showed moderate expression, whereas PLK4 was classified as low and CDK2 as moderate. Ca Ski also exhibited strong PLK4 and CDK2 dependencies despite both genes falling within the low-expression class according to their target-specific percentiles. These observations indicate that comparatively low transcriptional abundance does not necessarily preclude functional target essentiality. Expression of receptor-tyrosine-kinase and angiogenesis-associated targets was particularly heterogeneous. FGFR1 showed very high expression in C-33 A and SiHa and was also highly expressed in SW756, while FGFR2 and FGFR3 were highly expressed in selected models such as Ca Ski, HT-3, MS751 and DoTc2 4510. IGF1R expression was high in HT-3 and MS751 but moderate in several other models. MET was highly expressed in C-4 I, DoTc2 4510 and SW756 and moderately expressed in HeLa, HT-3, MS751, SiHa and SISO. By contrast, several canonical vascular targets—including KDR, FLT1, FLT3 and FLT4—showed comparatively low absolute expression in most models, even when classified as high relative to their target-specific expression distributions. Overall, the molecular layer confirmed that many prioritised targets were transcriptionally available but also revealed substantial discordance between expression level and CRISPR dependency. High expression did not consistently indicate target essentiality, and strong dependency could occur at moderate or comparatively low expression. Target expression was therefore interpreted as evidence of molecular availability rather than as an independent measure of therapeutic vulnerability. Its integration with pharmacological prioritisation and CRISPR dependency provides a more complete model-specific basis for evaluating anti-angiogenic third-drug candidates.

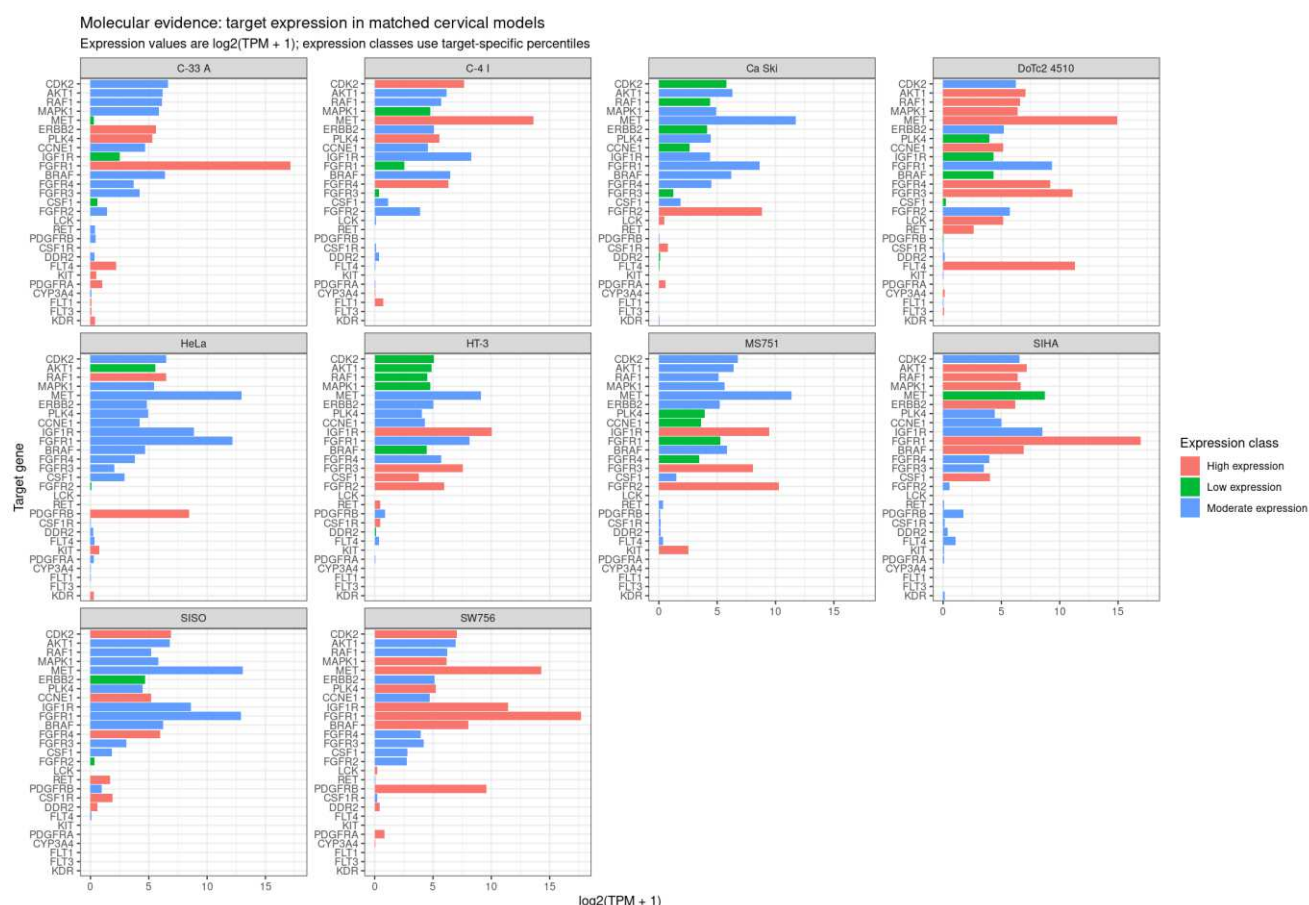


Figure 7. Molecular expression of targets associated with prioritised anti-angiogenic third-drug candidates. Model-specific expression of annotated targets linked to anti-angiogenic candidates prioritised through Bliss-independence screening against the cisplatin–paclitaxel reference combination. Expression is reported as $\log_2(\text{TPM} + 1)$, with low, moderate and high classes assigned using target-specific expression percentiles. Facets represent the cervical cancer models with matched expression data. The profiles demonstrate heterogeneous transcriptional availability of cell-cycle, receptor-tyrosine-kinase and angiogenesis-associated targets and enable direct comparison with the corresponding CRISPR dependencies.

Somatic mutation context provides an additional but limited biomarker layer

Somatic mutation profiles were integrated as an optional genomic biomarker layer for the 793 anti-angiogenic drug–target–model associations. Most associations involved targets classified as wild-type or without a recorded mutation (763/793; 96.2%), whereas only 30 associations (3.8%) involved a target-specific somatic alteration. Because the same altered target could be linked to multiple candidate compounds, these 30 associations represented nine unique altered model–target pairs across 19 candidate–model contexts (**Supplementary File S6**). Mutated associations were confined to C-33 A, HT-3, SiHa and SW756; the remaining nine models contained no recorded mutations among the evaluated targets (**Figure 8**). C-33 A accounted for 16 mutated associations involving five distinct targets: BRAF p.A115V, CSF1 p.D225A, DDR2 p.R709Ter, FLT1 p.K1153NfsTer2 and FLT4 p.R589C/p.V175A. These alterations were distributed across seven anti-angiogenic candidates—284461-73-0, AG-13736, PD 173074, AMG 706, EXEL-2880, PLX 4720 and AZD 2171—all of which produced Bliss scores above the model-specific cisplatin–paclitaxel reference. The multikinase candidate 284461-73-0 was associated with altered BRAF, DDR2, FLT1 and FLT4 and demonstrated the greatest improvement among these candidates, with a mean Bliss score of 1.37 compared with a reference score of -2.07 . In SiHa, a PLK4 p.E417Q alteration was identified in the context of AG-13736. This candidate was classified as stronger than the reference, although its improvement was modest (Δ versus reference = 0.21). The PLK4 alteration coincided with strong CRISPR dependency and moderate PLK4 expression, providing convergent pharmacological, functional and molecular evidence for this model–candidate context. SW756 contained 11 mutated associations involving KDR p.G220V and

MET p.D741N. The KDR alteration was shared across nine candidate contexts because KDR was included in the target annotations of multiple anti-angiogenic compounds. Eight of these candidates exceeded the cisplatin–paclitaxel reference, whereas AZD 2171 was antagonistic. MET p.D741N was associated with BMS 536924 and EXEL-2880, both of which were stronger than the reference. However, KDR showed weak CRISPR dependency and negligible expression in SW756, whereas MET was highly expressed but weakly dependent. These findings illustrate that mutation, expression and functional dependency can provide non-equivalent forms of mechanistic evidence. In HT-3, the IGF1R p.K339N alteration occurred in the contexts of 1035270-39-3 and BMS 536924. Despite high IGF1R expression, its CRISPR dependency was weak, and neither candidate improved upon the reference: 1035270-39-3 was classified as weaker or additive, while BMS 536924 was antagonistic. This provides direct evidence that the presence of a target-specific alteration, even in a highly expressed gene, is insufficient to infer pharmacological benefit.

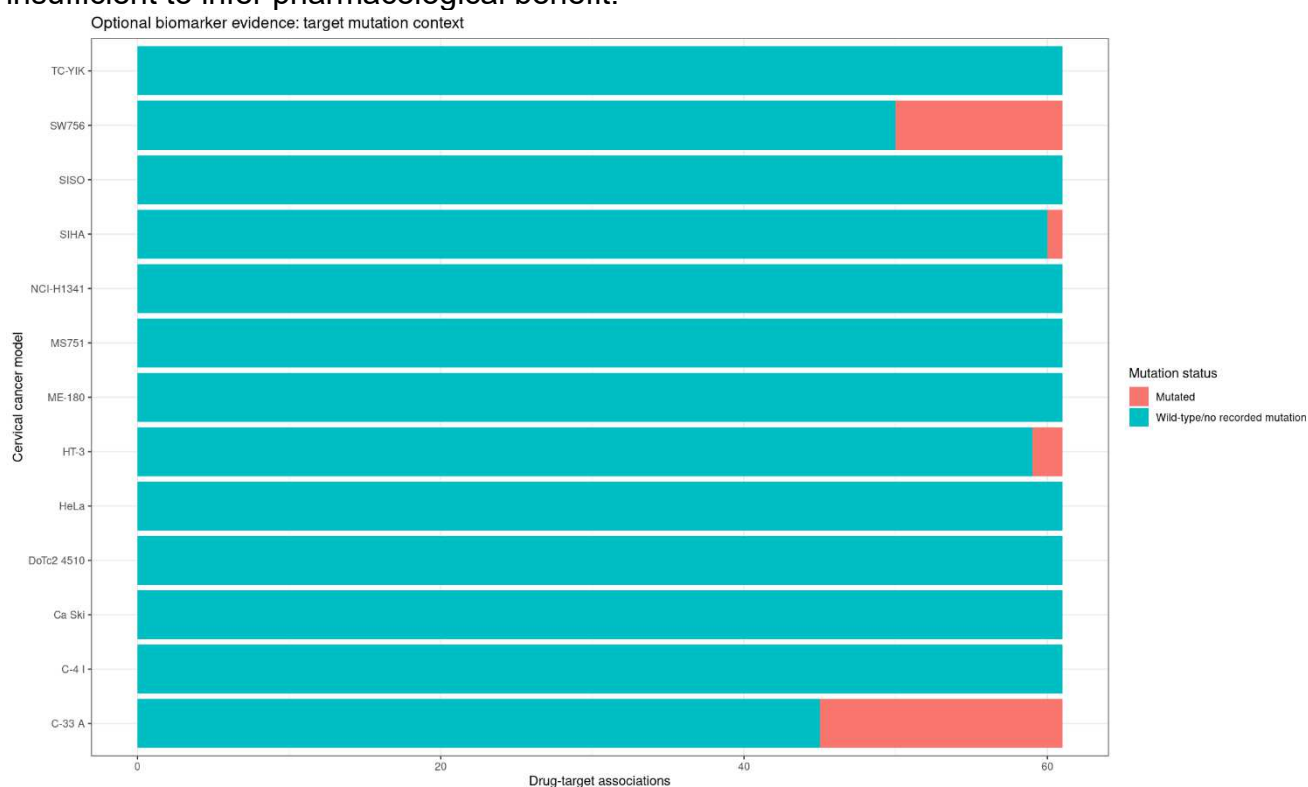


Figure 8. Somatic mutation context of targets associated with prioritised anti-angiogenic third-drug candidates. Distribution of mutation status across 793 anti-angiogenic drug–target–model associations generated through Bliss-independence screening against the cisplatin–paclitaxel reference combination. Associations are classified as mutated or wild-type/no recorded mutation. Mutated associations were restricted to C-33 A, HT-3, SiHa and SW756 and represented only 3.8% of the evaluated associations. Their occurrence in both stronger-than-reference and antagonistic candidate contexts demonstrates that target mutation status alone did not consistently predict pharmacological improvement.

Application of the platform User-selected cervical cancer drug candidates

To demonstrate the practical application of the developed platform, seven candidate drugs previously identified as potential therapeutic agents for cervical cancer in our preceding analyses were evaluated against the clinically established cisplatin–paclitaxel reference backbone. The candidates comprised ABT737, BMS-754807, dactinomycin, docetaxel, fulvestrant, SN38, and XAV-939. Rather than performing an unrestricted compound screen, the user-selected third-drug mode was applied to demonstrate how investigators can interrogate a predefined hypothesis-driven candidate set. The analytical outputs are presented below in the order in which they are generated and displayed within the user interface. Following selection of the cisplatin–paclitaxel reference regimen, the Eligible models panel identified cervical cancer models for which fitted GDSC2 response curves were available for both cisplatin and paclitaxel. Thirteen models fulfilled these requirements: NCI-H1341, SiHa, HeLa, C-33 A, C-4 I, Ca Ski, DoTc2 4510, ME-180, MS751, SW756, HT-3, SISO, and TC-YIK

(Table 3). The models represented multiple DepMap histological classifications, including CESC, CEAD, SCNEC, ECAD, MCCE, and SCCE. This initial panel therefore defines the experimental space before candidate testing. Models lacking pharmacological response information for any component of the selected clinical backbone are excluded, ensuring that subsequent candidate comparisons are made only where a model-specific reference interaction can first be established. The Reference summary panel next reconstructed the cisplatin–paclitaxel response in each eligible model and calculated a model-specific reference Mean Bliss score. Reference Mean Bliss values differed substantially between cell lines, ranging from –2.071 in C-33 A to 1.326 in C-4 I. SiHa showed a reference Mean Bliss score of –0.742, Ca Ski –0.600, SISO –0.795, and SW756 –1.299, whereas positive reference scores were observed in models including NCI-H1341 and C-4 I. These differences demonstrate why a universal Bliss cutoff is inappropriate for this application. The platform instead retains the experimentally informed cisplatin–paclitaxel interaction of each model as its internal pharmacological baseline. A candidate is consequently prioritised when its Mean Bliss score exceeds the corresponding model-specific reference Mean Bliss, rather than simply when its Bliss score is greater than zero. The complete model-specific cisplatin–paclitaxel reference statistics, including mean, maximum, minimum, and standard deviation of Bliss scores and the corresponding expected and observed inhibition values, are provided in **Supplementary File S7**. Marked heterogeneity in intrinsic drug sensitivity was observed across the thirteen cervical cancer models (**Figure 9**).

Table 3. Cervical cancer models eligible for evaluation of the cisplatin paclitaxel reference combination

Model ID	Cell line	DepMap model type
ACH-000129	NCI-H1341	SCNEC
ACH-000556	SiHa	CECSC
ACH-001086	HeLa	ECAD
ACH-001333	C-33 A	CECSC
ACH-001334	C-4 I	CECSC
ACH-001336	Ca Ski	CECSC
ACH-001341	DoTc2 4510	MCCE
ACH-001359	ME-180	CECSC
ACH-001360	MS751	CECSC
ACH-001402	SW756	CECSC
ACH-001525	HT-3	CEAD
ACH-001650	SISO	CEAD
ACH-002201	TC-YIK	SCCE



Figure 9. Predicted monotherapy activity of user-selected candidate drugs across cervical cancer models. Mean predicted inhibition was reconstructed from fitted GDSC2 dose–response parameters for each candidate drug and classified as high, moderate, low, or no intrinsic response. Considerable inter-model heterogeneity was observed, with ABT737 demonstrating consistently high intrinsic activity in several models, whereas BMS-754807, dactinomycin, SN38, docetaxel, fulvestrant, and XAV-939 exhibited varying degrees of model-specific sensitivity.

Several compounds demonstrated consistently high monotherapy activity within specific cellular contexts. ABT737 showed almost complete predicted inhibition in SiHa, DoTc2 4510, NCI-H1341, Ca Ski, and TC-YIK, indicating strong intrinsic cytotoxicity independent of cisplatin–paclitaxel. Fulvestrant similarly produced exceptionally high predicted inhibition in C-33 A, whereas BMS-754807 exhibited high intrinsic activity in NCI-H1341 and moderate activity in ME-180, MS751, TC-YIK, C-4 I, and SISO. Dactinomycin displayed intermediate activity across multiple models, while SN38 and docetaxel generally produced low-to-moderate intrinsic inhibition despite subsequently demonstrating strong combination performance in selected cellular contexts. XAV-939 consistently exhibited relatively weak intrinsic activity, suggesting that its potential therapeutic contribution is more likely to arise through modulation of combination responses rather than direct cytotoxicity. Overall, the monotherapy summary demonstrates that the user-selected candidates encompass drugs with markedly different intrinsic pharmacological properties rather than representing a uniformly cytotoxic candidate set. Evaluation of reconstructed monotherapy dose–response profiles further demonstrated substantial differences in concentration-dependent drug behaviour between both compounds and models. Highly active compounds such as ABT737 frequently maintained near-complete inhibition across the evaluated dose range, indicating broad concentration-independent activity within sensitive models including SiHa, DoTc2 4510, Ca Ski, NCI-H1341, and TC-YIK. In contrast, compounds such as BMS-754807, SN38, docetaxel, and dactinomycin generally displayed progressive reductions in predicted inhibition with decreasing concentration, reflecting more typical sigmoidal pharmacological response

curves. XAV-939 and fulvestrant exhibited pronounced model-specific behaviour, with strong responses confined to only selected cell lines. These reconstructed dose–response profiles therefore provide important pharmacodynamic context for interpreting subsequent combination analyses, demonstrating that several candidates possess substantial intrinsic efficacy before evaluation within multi-drug regimens (**Figure 10**).

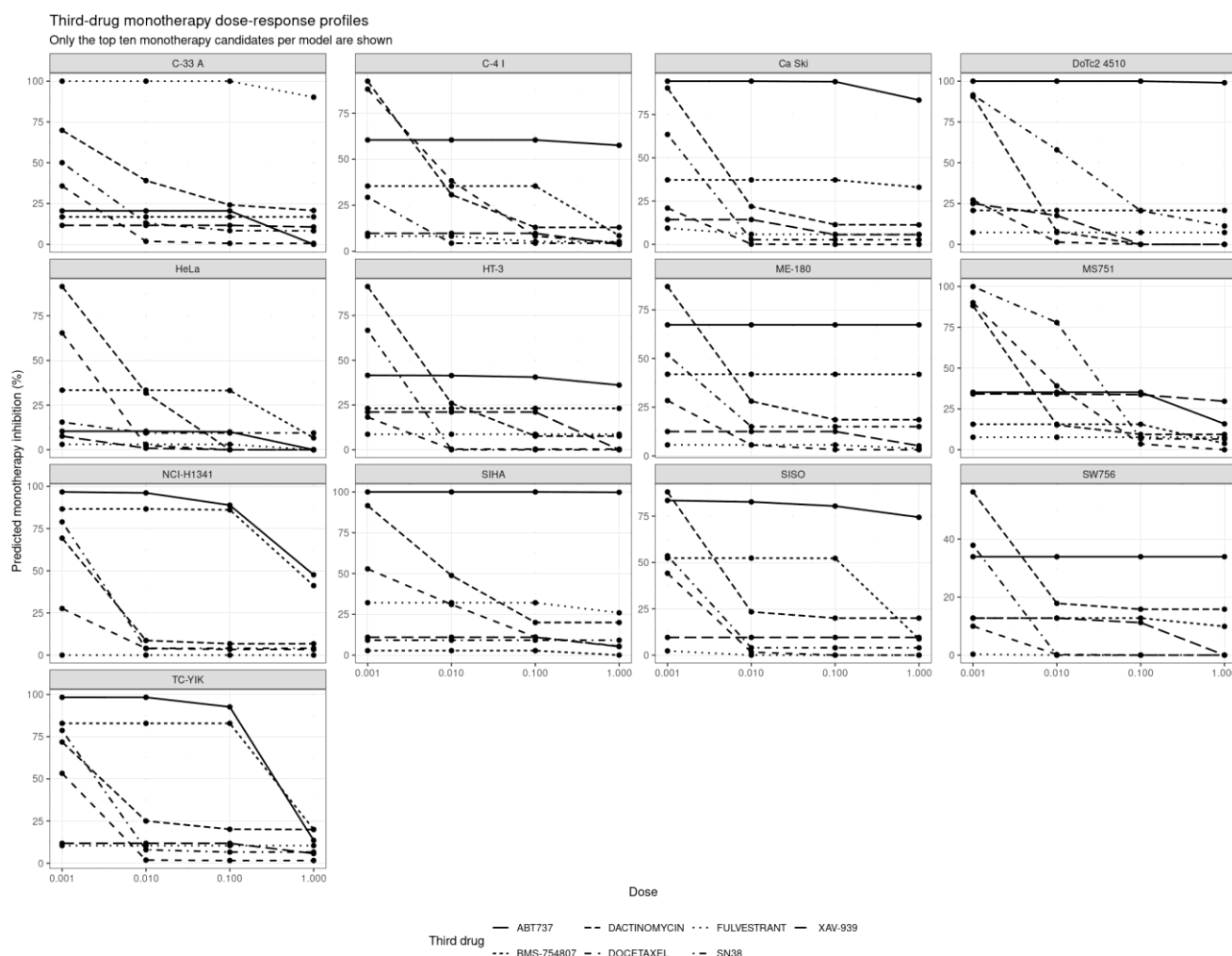


Figure 10. Reconstructed monotherapy dose–response profiles of the user-selected candidate drugs. Predicted inhibition was calculated across the evaluated concentration range using fitted GDSC2 pharmacological response curves. Highly active compounds maintained strong inhibition across multiple dose levels in sensitive models, whereas other candidates displayed progressive concentration-dependent reductions in activity. These dose–response profiles provide pharmacodynamic context for subsequent combination analyses.

The Selected third drugs panel documented the seven user-selected compounds and linked each candidate to its GDSC2 compound identifier, synonyms, molecular targets, and annotated mechanism of action (**Table 4**). The selected candidates represented distinct therapeutic mechanisms, including apoptosis modulation, IGF1R/INSR inhibition, transcriptional inhibition, microtubule stabilisation, estrogen receptor inhibition, topoisomerase I inhibition, and tankyrase inhibition. The panel illustrates the candidate-selection function of the platform. Users can therefore move from unrestricted pharmacological discovery to focused validation of compounds derived from previous computational analyses, molecular studies, or investigator-defined therapeutic hypotheses. The Third-drug ranking panel evaluated each selected candidate independently as an additional drug to the cisplatin–paclitaxel backbone. Ninety evaluable candidate–model combinations were generated across the 13 eligible cervical cancer models. Each combination was summarised using its Mean Bliss score and compared directly with the reference Mean Bliss of the corresponding model. Of the 90 candidate–model combinations, 45 were classified as stronger than reference, 38 as antagonistic, and 7 as weaker or additive. The response pattern was strongly model dependent. All seven selected candidates exceeded the cisplatin–paclitaxel reference in C-33

A, HeLa, and SW756, whereas TC-YIK showed antagonistic responses to all evaluated candidates. Intermediate patterns were observed across the remaining models. The strongest improvement relative to the clinical reference was observed for docetaxel in SiHa, with a Mean Bliss score of 1.791 compared with a reference Mean Bliss of -0.742, corresponding to a Δ Bliss of 2.533. BMS-754807 in C-33 A produced a Mean Bliss score of 1.607 compared with -2.071 for the reference, while XAV-939 in the same model achieved a Mean Bliss score of 1.378. These results demonstrate that candidate ranking is determined by improvement relative to the pharmacological state of the selected model rather than by the absolute Bliss score alone. The complete 90 candidate-model interaction profiles are provided in **Supplementary File S8**. The Top 10 per model panel retains the highest-ranking candidate combinations within each cervical model. Because only seven candidate drugs were selected in this application, all evaluable selected candidates were retained where available, producing 90 ranked entries. The corresponding Bliss plot visualised the candidate Mean Bliss scores together with the model-specific cisplatin-paclitaxel reference threshold (**Figure 11**).

Table 4. User-selected cervical cancer candidate drugs evaluated against the cisplatin-paclitaxel reference backbone

Compound ID	Candidate drug	Molecular target(s)	Annotated mechanism
DPC-000247	ABT737	Not annotated	Not annotated
DPC-001165	BMS-754807	IGF1R; INSR	IGF1R and INSR inhibitor
DPC-000258	Dactinomycin	Not annotated	Natural product and inhibitor of transcription
DPC-002313	Docetaxel	TUBB; TUBB1; TUBB2A; TUBB2B; TUBB3; TUBB4A; TUBB4B; TUBB6; TUBB8	Microtubule stabilising agent
DPC-002900	Fulvestrant	ESR1	ESR1 inhibitor
DPC-006002	SN38	TOP1	TOP1 inhibitor
DPC-004707	XAV-939	TNKS; TNKS2	TNKS and TNKS2 inhibitor

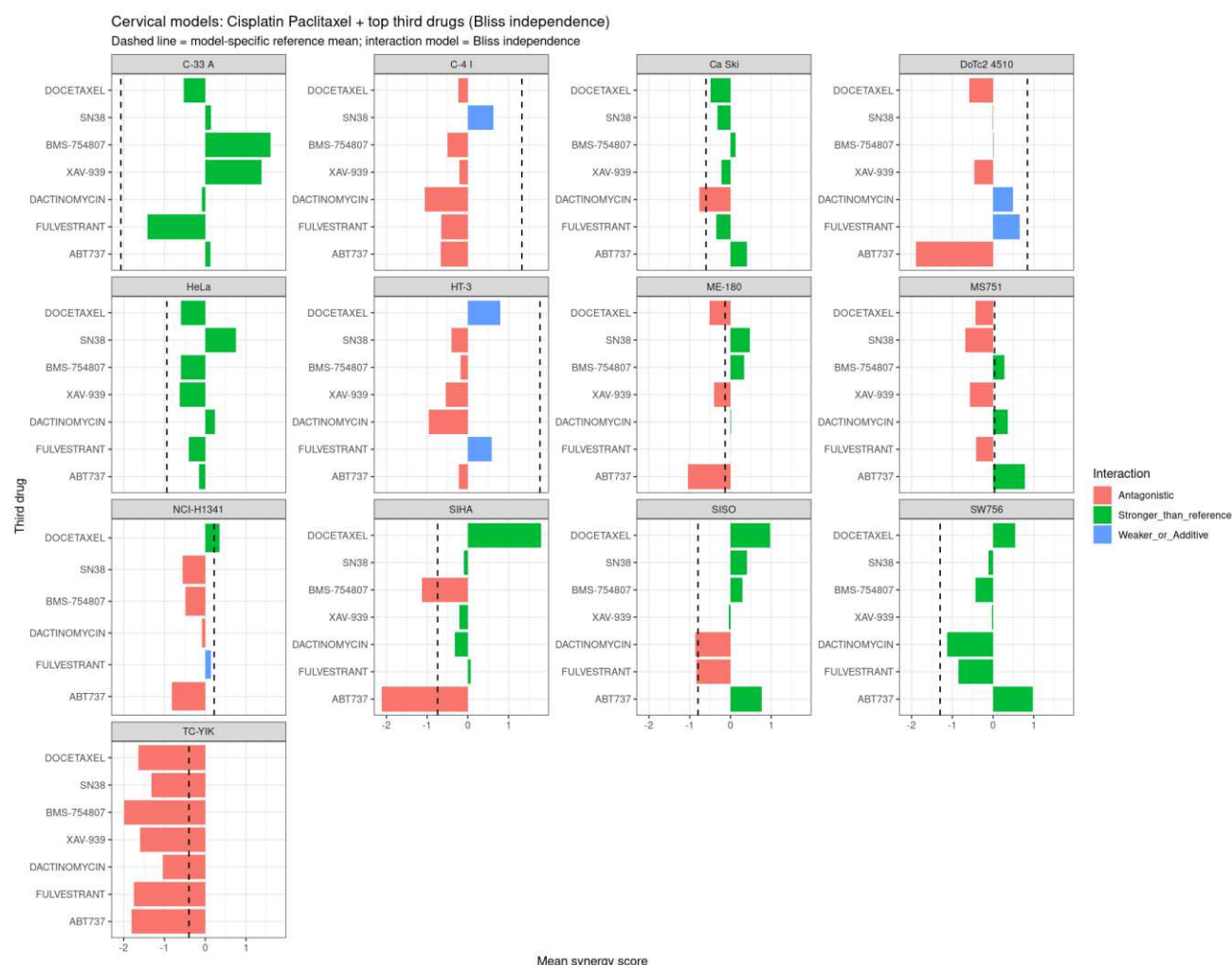


Figure 11. Model-specific prioritisation of user-selected third-drug candidates relative to the cisplatin–paclitaxel clinical reference backbone. Mean Bliss scores are shown for seven previously identified cervical cancer candidate drugs evaluated as additional agents to cisplatin–paclitaxel across eligible GDSC2 cervical cancer models. The dashed line in each facet represents the model-specific cisplatin–paclitaxel reference Mean Bliss score. Green bars denote candidate combinations stronger than the corresponding clinical reference, blue bars indicate weaker or additive interactions, and red bars indicate antagonistic interactions. The model-specific reference threshold enables candidate improvement to be interpreted relative to the pharmacological behaviour of the established clinical backbone within each experimental model.

The dashed line within each facet represents the reference Mean Bliss for that specific cell line and therefore changes between models. The plot revealed marked heterogeneity in candidate performance. In C-33 A, all seven candidates exceeded the strongly negative cisplatin–paclitaxel reference, with BMS-754807 and XAV-939 producing the largest Mean Bliss scores. SiHa showed a pronounced response to docetaxel, whereas SISO demonstrated stronger-than-reference interactions with several candidates, including docetaxel, SN38, BMS-754807, and ABT737. SW756 similarly showed broad improvement relative to its negative reference baseline. Conversely, candidate addition was predominantly unfavourable in TC-YIK, where all selected compounds remained antagonistic. Thus, the visual output allows the user to identify both candidate-specific activity and model-specific therapeutic context. A positive candidate score does not automatically indicate prioritisation, and a negative candidate Mean Bliss may still represent improvement when the reference regimen is more strongly antagonistic. Comparison of intrinsic monotherapy activity with observed inhibition following addition of each candidate to the cisplatin–paclitaxel backbone revealed that intrinsic potency alone did not determine combination performance (**Figure 12**). Drugs positioned above the identity line produced greater observed inhibition in combination than predicted from monotherapy alone, indicating additional benefit following incorporation into the clinical reference regimen. Several compounds with relatively modest intrinsic activity, including docetaxel and SN38, achieved substantial combination inhibition in selected models

such as SiHa, SISO, Ca Ski, SW756, and C-33 A, demonstrating that clinically meaningful combination benefit can occur even when single-agent activity is limited. Conversely, highly active monotherapy agents including ABT737 and BMS-754807 did not consistently exhibit proportional improvements following combination and, in several models, remained pharmacologically antagonistic relative to the model-specific cisplatin–paclitaxel reference. These findings demonstrate that intrinsic cytotoxicity and combination benefit represent complementary but distinct pharmacological properties.

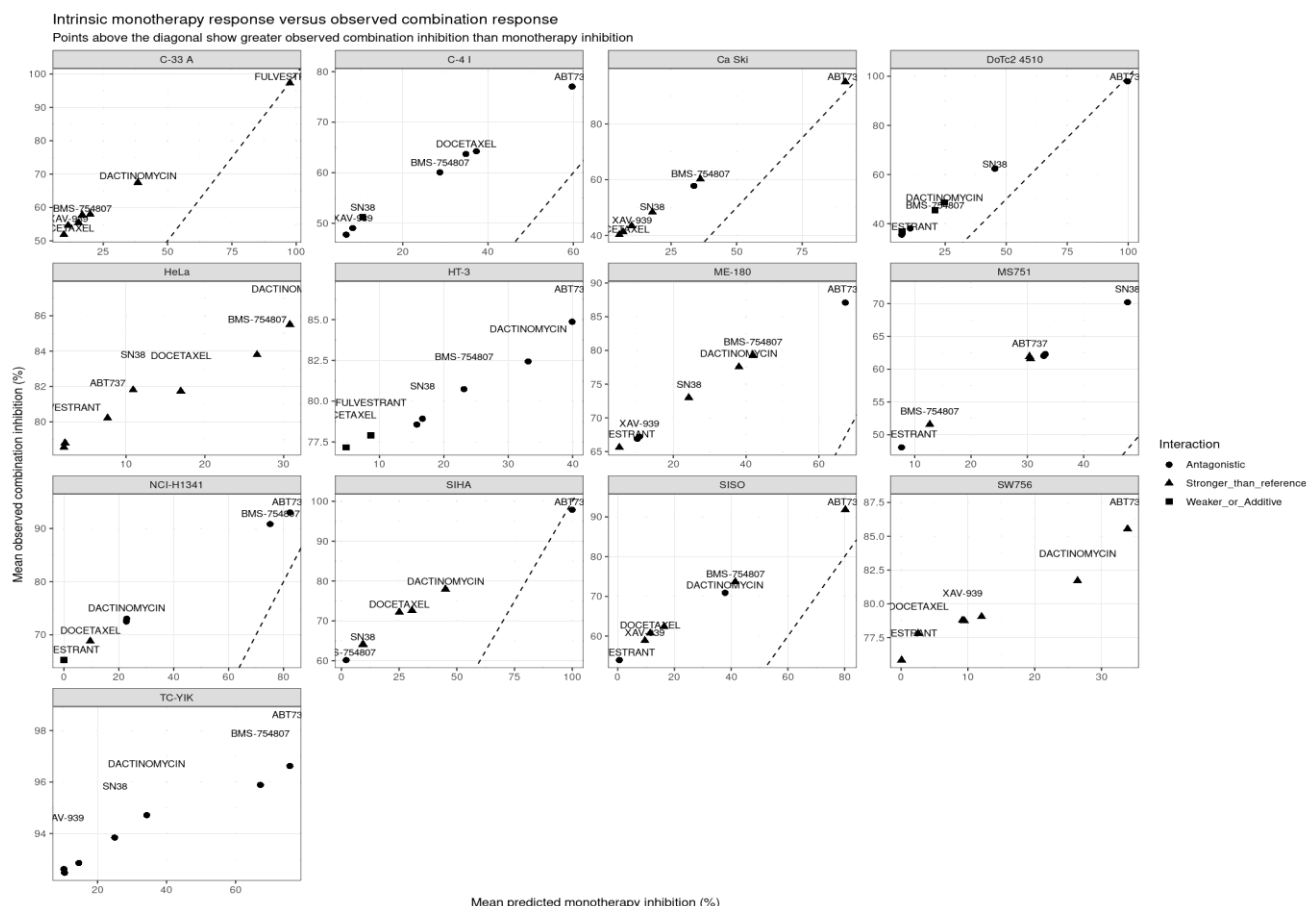


Figure 12. Comparison of intrinsic monotherapy response with observed inhibition following addition to the cisplatin–paclitaxel reference regimen. Each point represents a candidate drug evaluated within an individual cervical cancer model. The dashed diagonal indicates equal monotherapy and combination inhibition. Points above the diagonal indicate greater observed inhibition following addition to the clinical reference backbone than predicted from monotherapy alone. The analysis demonstrates that strong combination responses are not solely determined by intrinsic cytotoxicity, with several compounds exhibiting enhanced activity only in the combination setting

Following pharmacological ranking, the CRISPR dependency panel mapped annotated candidate targets to DepMap CRISPR gene-dependency profiles in the corresponding cervical cancer models. The 90 candidate–model profiles generated 219 target–model associations because several drugs, particularly docetaxel, were linked to multiple molecular targets (**Supplementary Table S9**). Of these associations, 101 were classified as weak dependencies, 19 as strong dependencies, and 6 as moderate dependencies. CRISPR measurements were unavailable for 67 target–model associations, while 26 associations lacked a target annotation. The CRISPR output revealed particularly strong functional support for the microtubule and topoisomerase-targeting candidates. Docetaxel-associated TUBB dependency approached 1.0 in C-33 A and Ca Ski and remained strongly supported in several additional models. SN38-associated TOP1 dependency was similarly strong across multiple cervical cancer models, including Ca Ski, DoTc2 4510, C-4 I, HT-3, SISO, C-33 A, SiHa, and SW756. Importantly, the CRISPR panel does not independently classify a candidate as therapeutically favourable. Instead, dependency evidence is displayed alongside the pharmacological result, enabling the user to determine whether stronger-than-reference activity is accompanied by functional dependence on the candidate target. The CRISPR

summary panel condensed the complete dependency output into five evidence categories. Weak dependencies represented the largest class ($n = 101$), followed by unavailable CRISPR measurements ($n = 67$) and target-unannotated associations ($n = 26$). Strong and moderate dependencies accounted for 19 and 6 associations, respectively. This summary provides an immediate overview of the strength and completeness of mechanistic evidence underlying the selected candidate screen. In the present application, only 25 of the 219 target–model associations reached the predefined moderate or strong dependency thresholds, demonstrating that pharmacological improvement and target dependency are not equivalent measures. The Strong/moderate CRISPR panel restricted the results to the 25 target–model associations with CRISPR dependency scores ≥ 0.5 . This filtering step highlighted candidate–model pairs with the strongest functional genomic support. Docetaxel accounted for a substantial proportion of these associations through dependency on tubulin-family genes. Strong TUBB dependencies were identified in C-33 A, Ca Ski, C-4 I, SW756, and SiHa. SN38 showed strong TOP1 dependency across several models. More context-specific signals included strong IGF1R dependency for BMS-754807 in SISO and strong TNKS2 dependency for XAV-939 in C-4 I. However, comparison with the Bliss classification demonstrated the importance of retaining both evidence layers. For example, XAV-939 targeted a strong TNKS2 dependency in C-4 I but remained pharmacologically antagonistic relative to the cisplatin–paclitaxel reference. Similarly, several docetaxel-associated dependencies occurred in models in which docetaxel did not improve the reference regimen. Functional dependency alone was therefore insufficient to infer combination benefit. The complete strong and moderate CRISPR-supported candidate–model associations are shown in **Table 5**. The Drug-level CRISPR summary panel aggregated dependency evidence across models and targets for each candidate. Docetaxel generated 117 target–model associations and contained 9 strong and 5 moderate dependencies, with a maximum dependency score of 1.000. SN38 showed the most concentrated target-specific dependency profile, with 8 strong and 1 moderate TOP1 dependencies among 13 target–model associations and a mean CRISPR dependency score of 0.928. BMS-754807 contained one strong dependency event across 26 IGF1R/INSR target–model associations, while XAV-939 contained one strong dependency event across 24 TNKS/TNKS2 associations. Fulvestrant showed predominantly weak ESR1 dependency. ABT737 and dactinomycin could not be evaluated mechanistically using this layer because their GDSC2 compound records lacked gene-level target annotations. Finally, the CRISPR plot panel visualised target dependency across the individual cervical cancer models (**Figure 13**). The moderate and strong dependency thresholds are indicated by dashed and dotted lines, respectively, allowing rapid identification of functionally supported drug targets. The plot showed that tubulin dependency was heterogeneous despite the recurrent strong TUBB signal. Individual tubulin-family genes differed substantially between models, demonstrating that a multi-target drug such as docetaxel cannot be interpreted from a single gene alone. In contrast, SN38 produced a comparatively coherent TOP1 dependency profile across multiple cervical cancer models. More restricted dependency signals were observed for IGF1R and TNKS2, consistent with the model-specific activity of BMS-754807 and XAV-939.

Table 5. Drug-level CRISPR dependency summary for user-selected candidate third drugs

Compound ID	Third drug	Mechanism	Target–model pairs	Strong	Moderate	Weak	Maximum dependency	Mean dependency
DPC-002313	Docetaxel	Microtubule stabilising agent	117	9	5	58	1.000	0.256
DPC-006002	SN38	TOP1 inhibitor	13	8	1	0	1.000	0.928
DPC-001165	BMS-754807	IGF1R/INSR inhibitor	26	1	0	17	0.983	0.127
DPC-004707	XAV-939	TNKS/TNKS2 inhibitor	24	1	0	17	0.891	0.075

DPC-002900	Fulvestrant	ESR1 inhibitor	13	0	0	9	0.057	0.023
DPC-000247	ABT737	Not annotated	13	0	0	0	NA	NA
DPC-000258	Dactinomycin	Transcription inhibitor	13	0	0	0	NA	NA

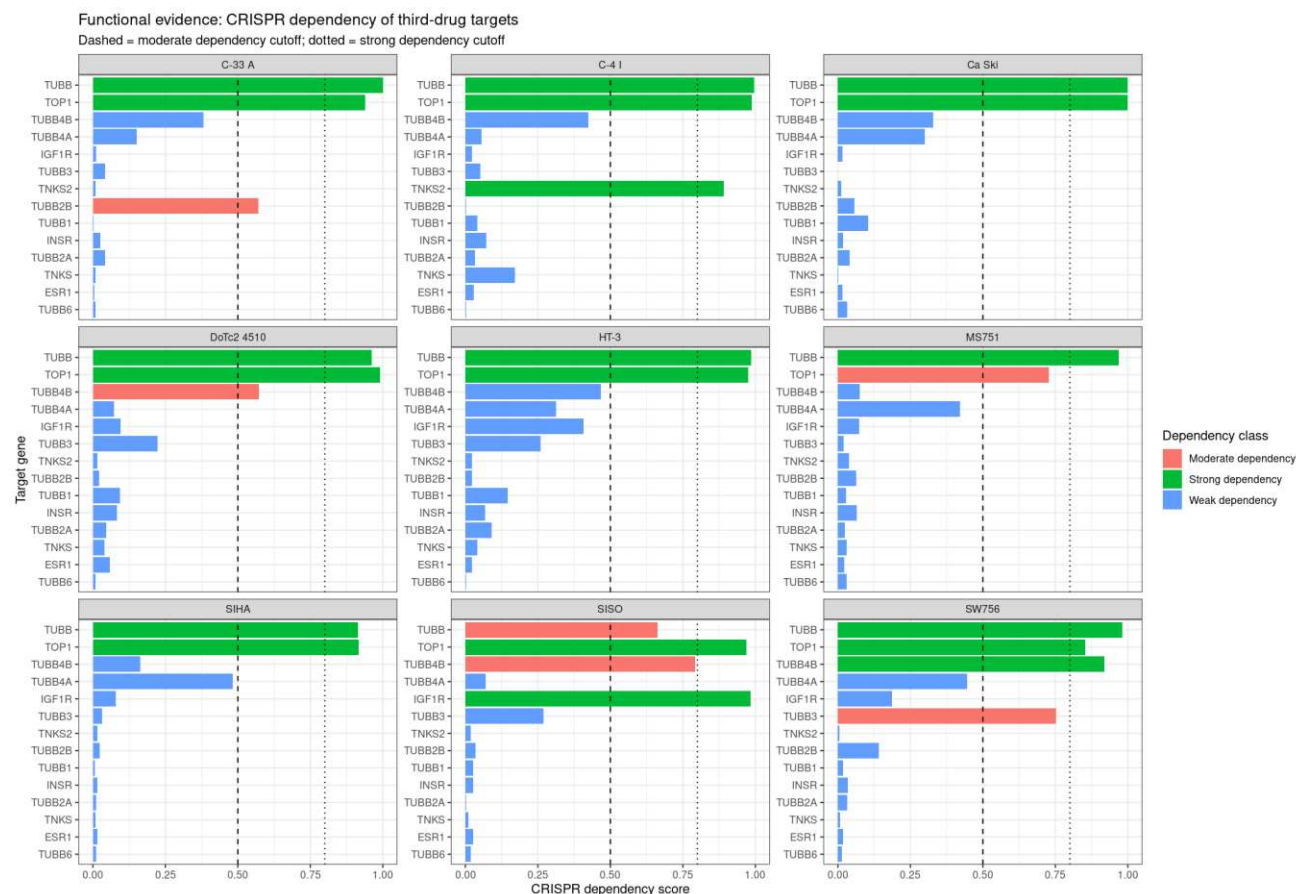


Figure 13. Model-specific CRISPR dependency landscape of user-selected third-drug targets. DepMap CRISPR dependency scores are shown for molecular targets of the seven user-selected cervical cancer candidate drugs across eligible models. The dashed line indicates the moderate dependency threshold (≥ 0.5), and the dotted line indicates the strong dependency threshold (≥ 0.8). Bars are classified according to dependency strength. The panel provides a functional genomic interpretation of pharmacologically prioritised candidates and enables comparison of target dependency across cervical cancer model contexts.

Expression evidence was available for 163 of the 219 drug–target–model associations. Of these, 37 were classified as high expression, 84 as moderate expression, and 42 as low expression based on gene-specific expression percentiles across the DepMap model population. Thirty associations lacked expression data for the corresponding model, while 26 lacked gene-level target annotation (**Supplementary Table S10**). Target expression varied substantially both between genes and across cervical cancer models (**Figure 14**). Tubulin-family genes targeted by docetaxel were among the most abundantly expressed candidate targets. TUBB, TUBB4B, and TUBB6 frequently showed moderate-to-high expression, although their relative expression differed between C-33 A, C-4 I, Ca Ski, DoTc2 4510, HeLa, HT-3, MS751, NCI-H1341, SiHa, SISO, and SW756. This model-specific variation complemented the CRISPR dependency findings by demonstrating that the tubulin dependency profile occurred within a transcriptionally active target system. TOP1 was also consistently expressed across the evaluated models, providing molecular support for the SN38-associated functional dependency observed in the CRISPR analysis. In contrast, IGF1R, TNKS, TNKS2, INSR, and ESR1 demonstrated greater inter-model variability. For example, IGF1R expression ranged from low to high across the cervical cancer models, consistent with the model-specific rather than universal CRISPR dependency observed for BMS-754807. Similarly, TNKS and TNKS2 showed heterogeneous expression, supporting

context-dependent evaluation of XAV-939 rather than uniform prioritisation across all models. Importantly, target expression and CRISPR dependency provided complementary rather than interchangeable evidence. High target expression did not necessarily indicate functional dependency, while some highly dependent targets were not among the most highly expressed genes within the corresponding model. The molecular expression panel therefore enabled confirmation of target availability while the CRISPR panel independently assessed whether the target represented a survival requirement. Together, these findings demonstrate the value of evaluating transcriptional presence and functional dependency as separate mechanistic dimensions following pharmacological prioritisation. Among the 219 drug–target–model associations, 189 showed no recorded mutation in the target gene, 26 lacked target annotation, and only four associations contained a target-gene mutation (**Supplementary File S11**). Thus, the majority of candidate target dependencies and pharmacological responses occurred in the absence of direct somatic alteration of the drug target. The four mutated target–model associations demonstrated distinct pharmacological and functional contexts. In C-4 I cells, the docetaxel-associated TUBB1 target contained an in-frame deletion, p.C201_A206del; however, this association showed weak CRISPR dependency and an antagonistic pharmacological interaction relative to the cisplatin–paclitaxel reference. INSR, a target of BMS-754807, was altered in both Ca Ski and DoTc2 4510 cells. The Ca Ski INSR alteration comprised an in-frame deletion, p.F1321_E1325del, and occurred in a combination classified as stronger than the model-specific reference, despite weak INSR dependency and low target expression. By contrast, the DoTc2 4510 INSR p.H212D missense alteration occurred in a weaker-or-additive pharmacological context, despite high INSR expression. In HT-3 cells, IGF1R carried the p.K339N missense mutation and was highly expressed with a CRISPR dependency score of 0.406; nevertheless, BMS-754807 produced an antagonistic interaction relative to the cisplatin–paclitaxel reference. These observations indicate that mutation of the direct drug target was uncommon and did not consistently predict either functional dependency or improvement over the clinical reference regimen. The mutation panel was therefore interpreted as a contextual biomarker layer rather than as a primary candidate-selection criterion. In particular, the discordant BMS-754807 examples demonstrate that the presence of an IGF1R or INSR alteration alone is insufficient to infer combination benefit. Instead, genomic alterations can be viewed alongside pharmacological interaction, target dependency, and target expression to identify model-specific biological contexts requiring further investigation.

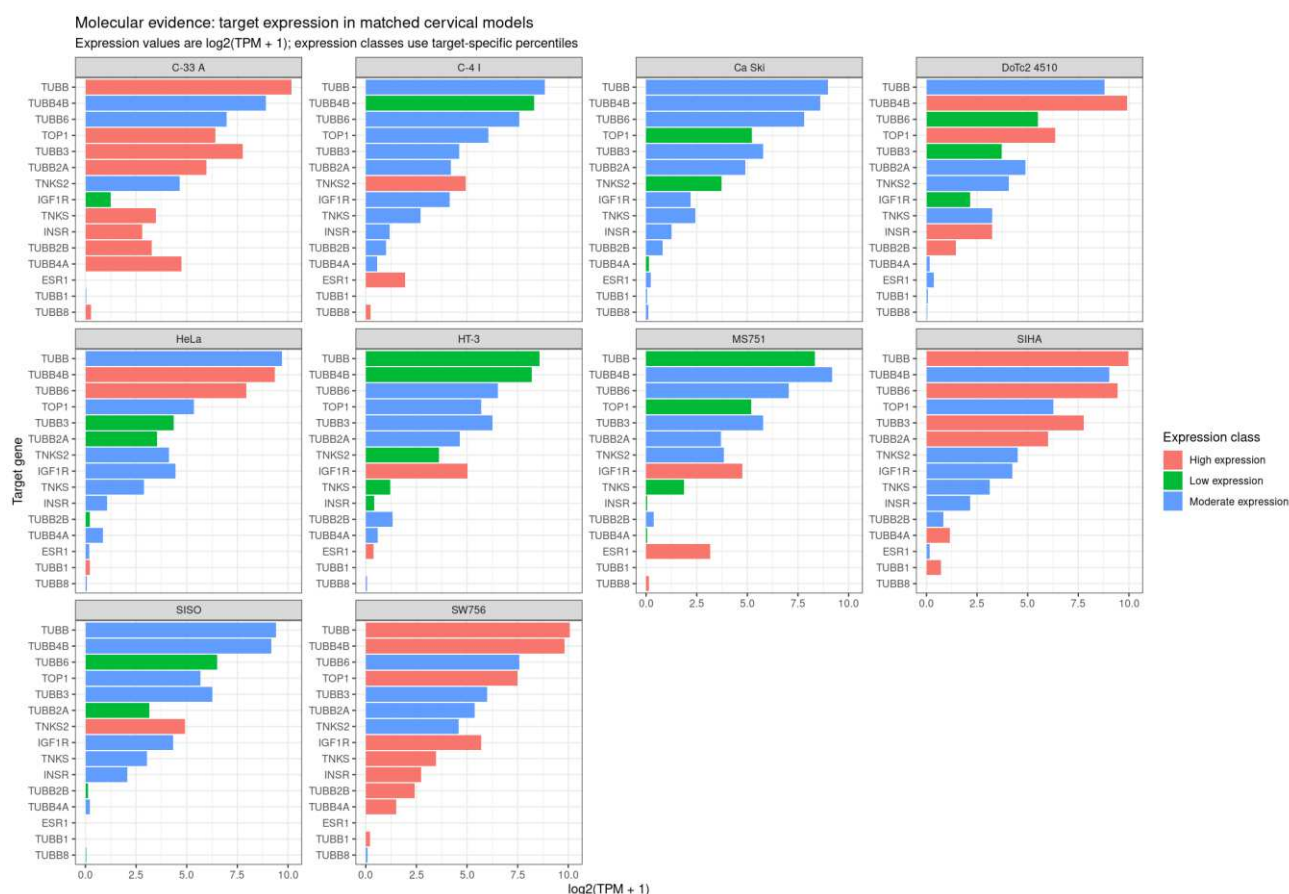


Figure 14. Molecular expression evidence for third-drug targets in matched cervical cancer models. Expression of candidate drug targets is shown as $\log_2(\text{TPM} + 1)$ in the corresponding DepMap cervical cancer models. Expression classes were assigned using gene-specific percentiles across the DepMap model population, with targets classified as low, moderate, or high expression. Faceting preserves model-specific differences in target availability.

Network-based graph learning identifies global and model-specific therapeutic communities

The unrestricted screen comprised 286 pharmacologically eligible cervical cancer compounds evaluated across 13 cervical cancer models, generating 3,368 candidate drug–model combinations. The graph-learning module was successfully applied to the complete pharmacological search space, while monotherapy evaluation generated 3,368 intrinsic response profiles and 13,472 reconstructed dose–response predictions. Functional dependency, molecular expression, and mutation layers were disabled during this analysis, allowing assessment of network-based prioritisation independently of additional biological evidence. The resulting candidate-drug networks demonstrated extensive connectivity while simultaneously revealing model-specific organisational differences between cervical cancer cell lines (**Figure 15 A-B**). Despite both networks containing the same candidate drug repertoire, the HeLa and SiHa graphs exhibited distinct local neighbourhoods and hub structures, reflecting differences in pharmacological similarity among prioritised compounds. Several highly connected hubs occupied central positions within each network, whereas numerous peripheral compounds formed smaller local communities connected through fewer shared relationships. The dense interconnectivity observed across both models indicates that many candidate drugs share overlapping biological characteristics despite belonging to different therapeutic classes. At the same time, differences in node connectivity and community organisation between HeLa and SiHa illustrate that network topology remains highly dependent on tumour context, consistent with the pronounced model-specific pharmacological heterogeneity observed throughout the screening analysis. Graph-based prioritisation further identified candidate third drugs predicted to outperform the model-specific cisplatin–paclitaxel clinical reference across all thirteen cervical cancer models (**Figure 15C**). Rather than relying solely on observed Bliss interaction scores, the graph-learning framework

estimated the probability that each candidate would exceed the corresponding model-specific reference by integrating pharmacological relationships within the candidate network. Across virtually all models, predicted probabilities were consistently high, generally exceeding 0.80 for the highest-ranked compounds, indicating strong confidence in the prioritised candidates. Several compounds emerged repeatedly across independent cervical cancer models, suggesting broad therapeutic relevance. EXEL-2880 represented the most consistently prioritised candidate, appearing among the highest-ranked predictions in C-33 A, C-4 I, Ca Ski, HeLa, HT-3, ME-180, SiHa, SISO, SW756, TC-YIK, and additional models. Other frequently prioritised compounds included topotecan, SN38, irinotecan, BMS-536924, BKM120, teniposide, AZD8931, GX15-070, and afuresertib, whereas several model-specific candidates such as osimertinib, gefitinib, ceralasertib, vismodegib, birabresib, romidepsin, and PFI-1 were preferentially identified within individual tumour contexts. Collectively, these findings demonstrate that graph-based learning successfully integrated network topology with pharmacological evidence to distinguish broadly applicable therapeutic candidates from those exhibiting model-specific activity, thereby providing an additional systems-level prioritisation layer beyond conventional drug ranking.

Candidate-drug graph: HeLa

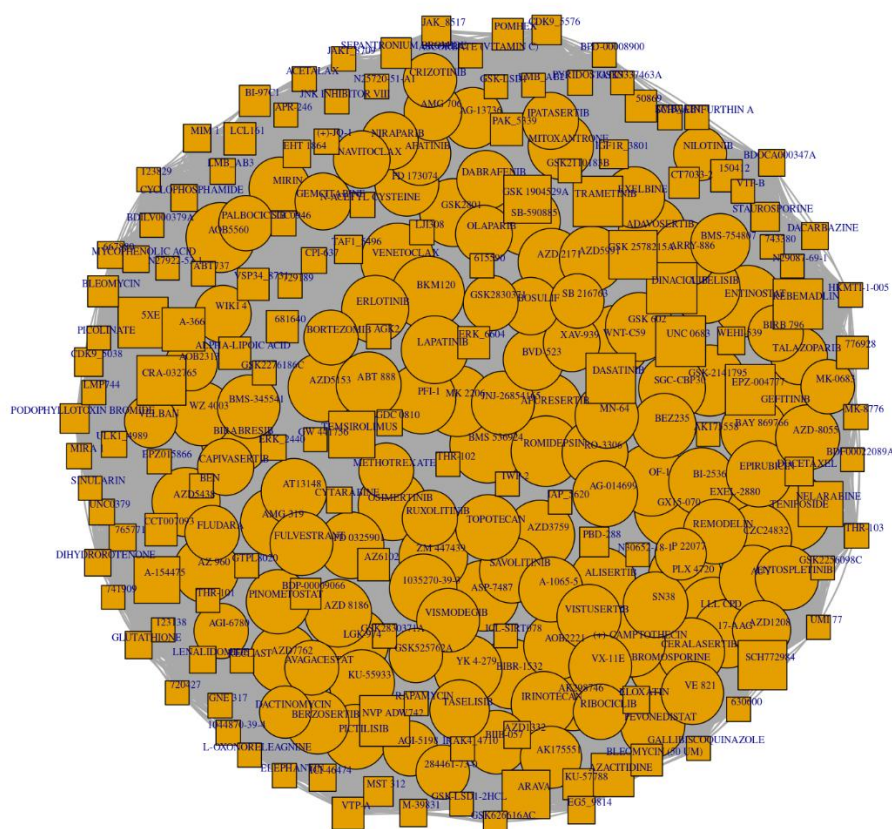


Figure 15A. HeLa candidate-drug similarity network. Graph-based similarity network of the 286 candidate third drugs evaluated in the HeLa cervical cancer model. Candidate compounds are represented as nodes connected according to shared biological and pharmacological relationships. Node size reflects graph-derived connectivity, with larger nodes indicating compounds occupying more central positions within the therapeutic network. The HeLa network demonstrates extensive interconnectivity among candidate drugs, revealing multiple highly connected hub compounds and densely linked therapeutic communities that represent shared pharmacological characteristics within the model.

[illegible]

Figure 15B. *SiHa* candidate-drug similarity network. Graph-based similarity network of the same 286 candidate third drugs evaluated in the *SiHa* cervical cancer model. Candidate compounds are represented as nodes connected according to shared biological and pharmacological relationships. Node size reflects graph-derived connectivity, with larger nodes indicating compounds occupying more central positions within the therapeutic network. Although the overall network remains highly interconnected, the organisation of major hub compounds and local therapeutic communities differs from that observed in HeLa, demonstrating model-specific restructuring of candidate-drug relationships despite evaluation of the same pharmacological search space.

biological context rather than intrinsic drug activity alone. To visualise relationships among the selected compounds, candidate drugs were further represented as model-specific similarity networks for HeLa and SiHa (**Figure 16B-C**). Despite containing the same seven candidate drugs, the two graphs displayed distinct network organisations. In the **HeLa** network, **BMS-754807** and **dactinomycin** occupied the largest and most central nodes, indicating the greatest network influence within this model. Docetaxel formed a secondary hub connected extensively to neighbouring compounds, whereas ABT737, fulvestrant, SN38, and XAV-939 occupied smaller peripheral positions. The dense connectivity between all seven compounds indicates that multiple therapeutic mechanisms shared overlapping biological characteristics within the HeLa molecular context. The **SiHa** network exhibited a markedly different topology. Here, **ABT737** emerged as the dominant network hub, while the remaining compounds formed comparatively smaller interconnected nodes. BMS-754807, docetaxel, fulvestrant, SN38, dactinomycin, and XAV-939 remained extensively connected but contributed less to the overall network centrality than observed in HeLa. The redistribution of network influence between HeLa and SiHa demonstrates that graph learning captures tumour-specific therapeutic organisation rather than simply reproducing pharmacological ranking. Collectively, these findings demonstrate that network-based learning extends conventional drug-combination analysis by evaluating candidate compounds within an integrated biological similarity framework. Rather than treating each third drug as an independent pharmacological entity, the graph-learning module identifies candidate therapies according to both their predicted pharmacological performance and their relationships with other therapeutically relevant compounds. This provides an additional systems-level evidence layer that complements Bliss interaction analysis and supports context-specific prioritisation of candidate additions to established cisplatin-based cervical cancer regimen.



Figure 16A. Graph neural network-based prioritisation of user-selected candidate third drugs across thirteen cervical cancer models. Graph-learning predictions estimating the probability that each user-selected candidate drug will outperform the corresponding model-specific cisplatin–paclitaxel clinical reference regimen. Blue bars indicate compounds predicted to provide greater pharmacological

benefit than the reference regimen, whereas red bars indicate candidates predicted not to exceed the model-specific reference. Predictions were generated independently for each cervical cancer model using graph propagation across the candidate similarity network.

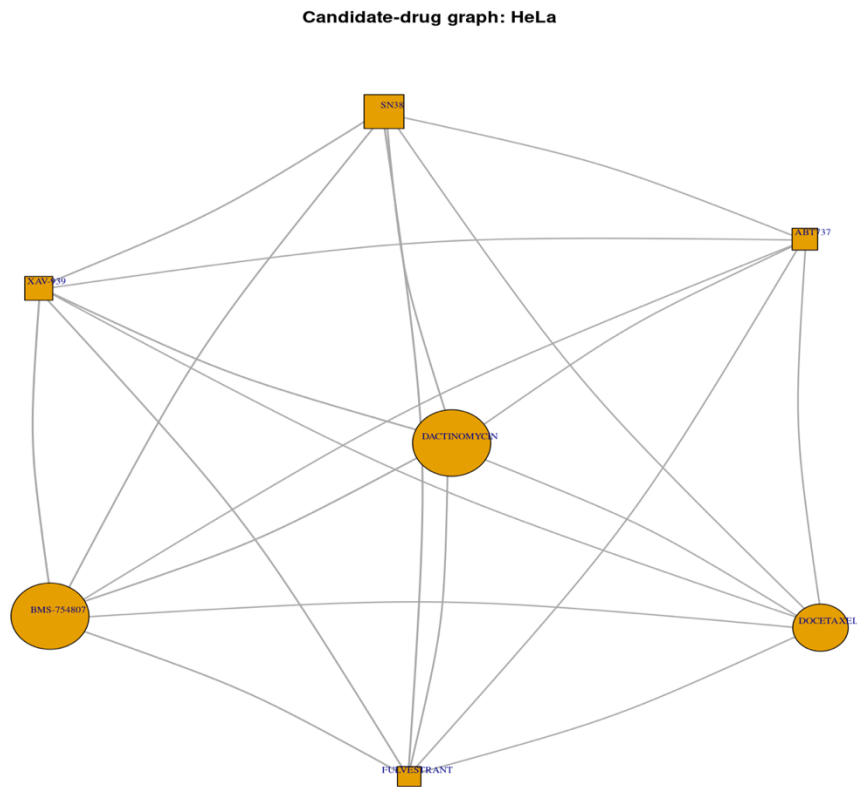


Figure 16B. HeLa candidate-drug similarity network. Graph-based similarity network of the seven user-selected candidate drugs (**ABT737**, **BMS-754807**, **dactinomycin**, **docetaxel**, **fulvestrant**, **SN38**, and **XAV-939**) evaluated in the HeLa cervical cancer model. Nodes represent candidate drugs, and edges indicate shared biological and pharmacological relationships used by the graph-learning framework. Node size is proportional to graph-derived network importance, with larger nodes indicating greater centrality within the HeLa therapeutic network. **BMS-754807** forms the dominant central hub, followed by **dactinomycin** and **docetaxel**, whereas **SN38**, **ABT737**, **XAV-939**, and **fulvestrant** occupy comparatively peripheral positions despite remaining connected within the overall therapeutic network.

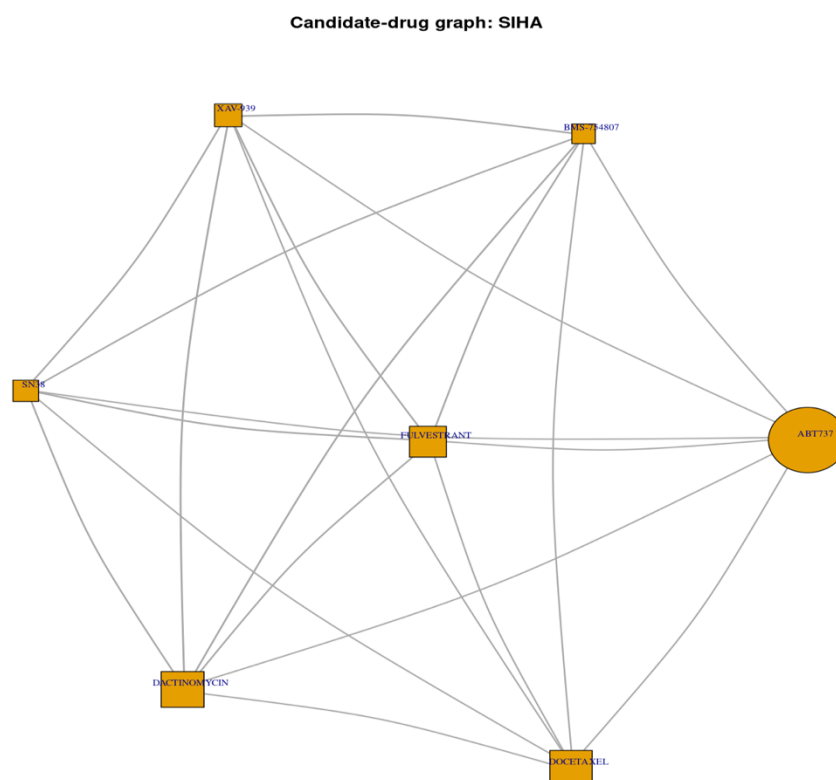


Figure 16C. SiHa candidate-drug similarity network. Graph-based similarity network of the same seven user-selected candidate drugs (**ABT737**, **BMS-754807**, **dactinomycin**, **docetaxel**, **fulvestrant**, **SN38**, and **XAV-939**) evaluated in the SiHa cervical cancer model. Nodes represent candidate drugs, and edges indicate shared biological and pharmacological relationships used by the graph-learning framework. Node size is proportional to graph-derived network importance, with larger nodes indicating greater centrality within the SiHa therapeutic network. In contrast to HeLa, **ABT737** represents the dominant network hub, while **BMS-754807**, **dactinomycin**, and **docetaxel** display intermediate centrality. **SN38**, **XAV-939**, and **fulvestrant** occupy smaller peripheral nodes, illustrating model-specific reorganisation of therapeutic relationships despite evaluation of the same candidate drug set.

Biologically contextualised graph-learning prioritisation of candidate third drugs

To investigate whether incorporation of tumour-specific molecular information influenced therapeutic prioritisation, graph-learning predictions were generated after integrating CRISPR gene dependency, target expression, and somatic mutation profiles for each cervical cancer model. The biologically contextualised model demonstrated substantial heterogeneity in candidate prioritisation across the thirteen cervical cancer cell lines (**Figure 17-19**), indicating that therapeutic selection was strongly dependent on model-specific molecular characteristics rather than pharmacological performance alone. The integrated model identified distinct candidate third drugs for different cervical cancer models. In **HeLa**, **SN38** showed the highest probability of exceeding the model-specific cisplatin–paclitaxel clinical reference, followed by **dactinomycin**, whereas **docetaxel**, **BMS-754807**, **ABT737**, and **fulvestrant** were predicted to provide comparatively limited additional benefit. In contrast, **SiHa** displayed a markedly different prioritisation profile in which **docetaxel**, **SN38**, **XAV-939**, **dactinomycin**, and **fulvestrant** were all predicted to outperform the clinical reference, while **BMS-754807** and **ABT737** were predicted to provide lower benefit. Pronounced tumour-specific variation was also observed across the remaining cervical cancer models. **DoTc2 4510**, **ME-180**, and **SISO** demonstrated broadly favourable predictions for most candidate drugs, suggesting multiple biologically supported therapeutic opportunities. Conversely, **Ca Ski** and **TC-YIK** exhibited more selective prioritisation patterns, with only a limited subset of compounds predicted to exceed the reference regimen. **MS751**, **HT-3**, **NCI-H1341**, **C-33 A**, **C-4 I**, and **SW756** displayed intermediate profiles in which only selected compounds achieved high predicted probabilities, further illustrating substantial inter-model heterogeneity. Incorporation of

CRISPR dependency, transcriptomic expression and somatic mutation information altered candidate prioritisation in a model-specific manner. In HeLa, graph learning initially prioritised BMS-754807, dactinomycin and docetaxel; however, following biological contextualisation, SN38 emerged as the highest-ranked candidate, whereas the relative priority of BMS-754807 and docetaxel decreased. In contrast, SiHa underwent a more substantial redistribution of therapeutic priorities. The original graph-learning model identified ABT737 as the dominant candidate, whereas integration of molecular evidence shifted prioritisation towards docetaxel, SN38, XAV-939, dactinomycin and fulvestrant, with ABT737 no longer representing the leading prediction. These changes demonstrate that incorporation of functional genomic dependency, target expression and mutation profiles refines graph-based pharmacological predictions by favouring compounds supported by tumour-specific molecular evidence rather than pharmacological similarity alone.



Figure 17. Biologically contextualised graph-learning prioritisation of candidate third drugs across thirteen cervical cancer models. Graph-learning predictions following integration of CRISPR gene dependency, target expression, and somatic mutation information for each cervical cancer model. Horizontal bars represent the predicted probability that each candidate third drug will outperform the corresponding model-specific cisplatin–paclitaxel clinical reference regimen after biological contextualisation. Blue bars indicate compounds predicted to provide greater therapeutic benefit than the reference regimen, whereas red bars indicate candidates predicted not to exceed the reference. Integration of multiple molecular evidence layers refines pharmacological prioritisation by incorporating tumour-specific biological context into graph-based therapeutic prediction.

Candidate-drug graph: HeLa (Bliss independence)

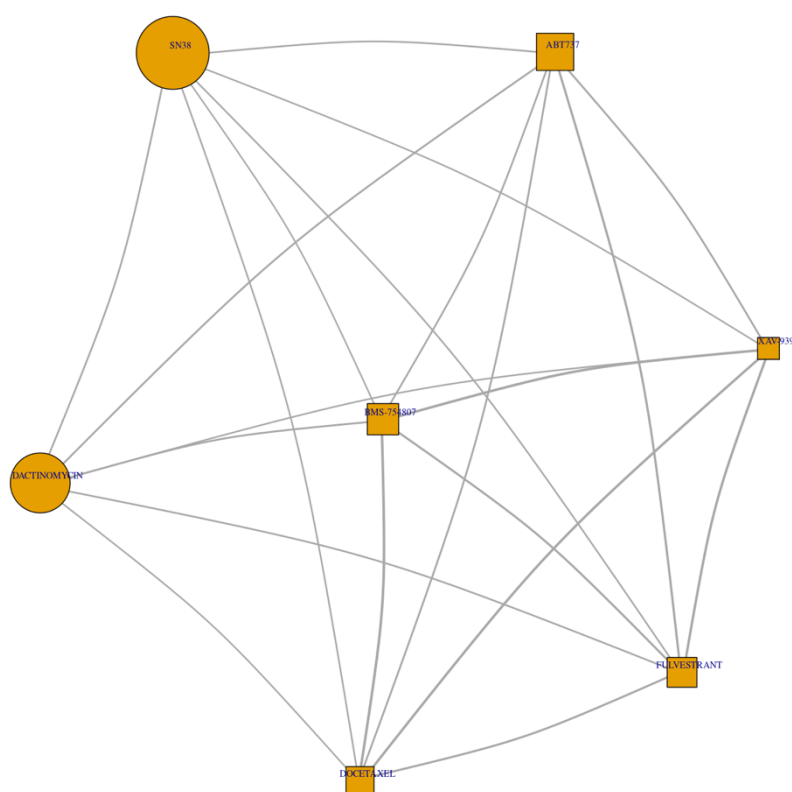


Figure 18. Biologically contextualised HeLa candidate-drug similarity network. Graph-based similarity network of the seven candidate third drugs (**ABT737**, **BMS-754807**, **dactinomycin**, **docetaxel**, **fulvestrant**, **SN38**, and **XAV-939**) following integration of **CRISPR dependency**, **target expression**, and **somatic mutation** data in the HeLa cervical cancer model. Nodes represent candidate drugs and edges represent graph-derived biological similarity after incorporation of functional genomic and molecular evidence. Node size is proportional to graph-derived network importance, with larger nodes indicating greater centrality within the biologically contextualised therapeutic network. Following molecular integration, **SN38** emerged as the dominant network hub, whereas **dactinomycin** retained high network importance and **BMS-754807** and **docetaxel** exhibited reduced relative influence compared with the pharmacology-only network, illustrating refinement of therapeutic prioritisation through biological evidence.

Candidate-drug graph: SiHa (Bliss independence)

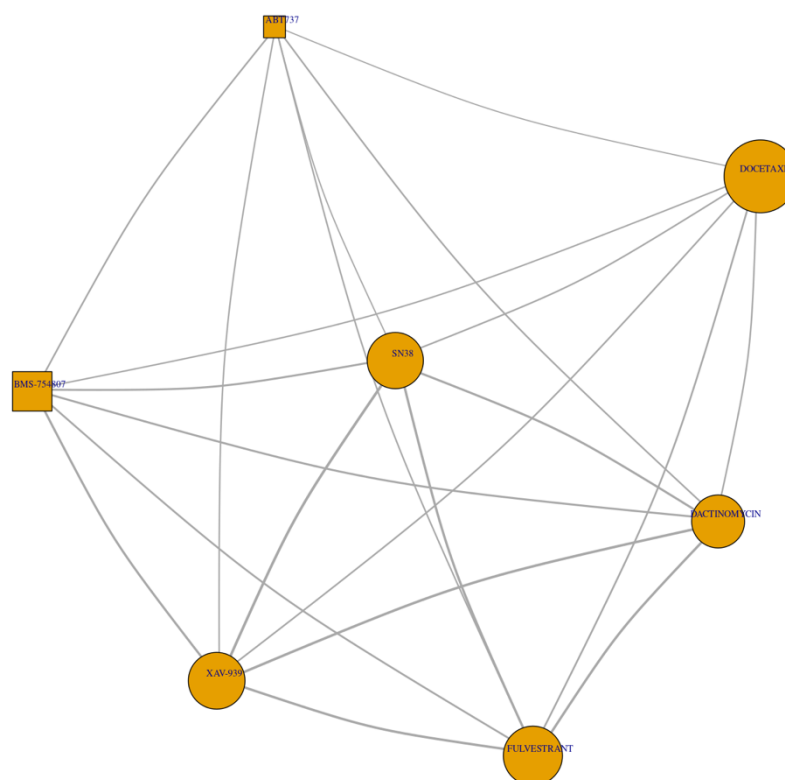


Figure 19. Biologically contextualised SiHa candidate-drug similarity network. Graph-based similarity network of the same seven candidate third drugs (ABT737, BMS-754807, dactinomycin, docetaxel, fulvestrant, SN38, and XAV-939) following integration of CRISPR dependency, target expression, and somatic mutation data in the SiHa cervical cancer model. Nodes represent candidate drugs and edges indicate graph-derived biological similarity following molecular contextualisation. Node size is proportional to graph-derived network importance within the biologically contextualised therapeutic network. In contrast to the pharmacology-only network, integration of molecular evidence redistributed network importance from ABT737 towards SN38, docetaxel, dactinomycin, XAV-939, and fulvestrant, demonstrating that incorporation of tumour-specific functional genomic and molecular information substantially reorganises therapeutic relationships and candidate prioritisation within the SiHa model.

Validation of graph-learning prioritisation using cross-validation and comparative benchmarking

prioritisation, separate candidate-drug similarity networks were constructed using Bliss independence, Highest Single Agent (HSA), Loewe additivity, and Zero Interaction Potency (ZIP) for the subset of anti-angiogenic compounds with available GDSC2 pharmacological response data in cervical cancer models (**Figure 20**). Each graph integrated pharmacological response, target similarity, mechanism of action, CRISPR dependency, gene expression, somatic mutation, and synergy-specific features into weighted graph edges before graph-learning-based prioritisation. Despite representing the same candidate drug set, the four synergy models produced distinct graph topologies and node rankings, demonstrating that the selected interaction model directly influenced graph construction. Across all four networks, compounds including EXEL-2880, PD173074, AZD2171, AMG706, AG-13736, BMS536924, PLX4720, 284461-73-0, and 1035270-39-3 remained interconnected, indicating consistent mechanistic similarity among anti-angiogenic candidates (**Table 6**). However, the relative importance of individual compounds varied between synergy models, reflecting differences in predicted interaction behaviour with the cisplatin–paclitaxel reference regimen. Under the Bliss independence model (**Figure 20A**), the network was characterised by prominent hubs centred on AMG706, PD173074, AZD2171, and 1035270-39-3, suggesting these compounds

combined favourable pharmacological interaction profiles with similar molecular characteristics. The HSA network (**Figure 20B**) redistributed node importance toward EXEL-2880 while retaining strong connectivity among VEGFR- and FGFR-associated inhibitors. In contrast, the Loewe additivity graph (**Figure 20C**) produced a more dispersed topology with increased prominence of BMS536924, consistent with altered similarity relationships when dose additivity rather than probabilistic independence was assumed. Finally, the ZIP network (**Figure 20D**) retained a densely connected graph but shifted graph centrality toward BMS536924 and EXEL-2880, indicating that the interaction model substantially affected graph-learning prioritisation even when the underlying biological evidence remained unchanged. Although several anti-angiogenic compounds were consistently identified across all four networks, variation in node size, edge weights, and graph organisation demonstrates that graph-learning predictions are sensitive to the underlying synergy framework. This finding supports the incorporation of multiple interaction models within the platform, allowing investigators to assess the robustness of candidate prioritisation across alternative pharmacological assumptions rather than relying on a single synergy metric.

Table 6. Anti-angiogenic compounds identified in the GDSC2 drug perturbation catalogue with targets corresponding to clinically relevant angiogenic pathways

Compound ID	Representative compound	Major target(s)	Primary mechanism of action	Matched anti-angiogenic annotation
DPC-000027	AZD4547	FGFR1, FGFR2, FGFR3, FGFR4, IGF1R, KDR	FGFR inhibitor	KDR
DPC-000083	Sorafenib (BAY 43-9006, Nexavar)	BRAF, DDR2, FGFR1, FLT1, FLT3, FLT4, KDR, KIT, PDGFRB, RAF1, RET	Multi-kinase inhibitor (VEGFR/RAF/KIT/FLT3/RET)	VEGF, VEGFR, FLT1, FLT4, KDR
DPC-000366	Axitinib (AG-13736, Inlyta)	CSF1, FLT1, FLT4, KDR, PLK4	VEGFR/PDGFR inhibitor	VEGF, VEGFR, FLT1, FLT4, KDR
DPC-000504	Motesanib (AMG-706)	FLT1, FLT4, KDR, KIT	VEGFR/KIT inhibitor	VEGF, VEGFR, FLT1, FLT4, KDR
DPC-000816	Cediranib (AZD2171, Receptin)	CSF1R, FLT1, FLT3, FLT4, KDR, KIT, PDGFRA, PDGFRB	VEGFR/KIT inhibitor	VEGF, VEGFR, FLT1, FLT4, KDR
DPC-001140	BMS-536924	AKT1, CCNE1, CDK2, CYP3A4, ERBB2, IGF1R, KDR, LCK, MAPK1, MET, PDGFRA, PDGFRB	IGF-1 receptor inhibitor	KDR
DPC-001409	BX-795	CDK2, CHEK1, GSK3B, KDR, PDK1, PDPK1	IKK/PDK1 inhibitor	KDR
DPC-002683	Foretinib (XL-880, GSK1363089)	FLT1, FLT4, KDR, MET	VEGFR/MET inhibitor	VEGF, VEGFR, FLT1, FLT4, KDR
DPC-004948	PD173074	FGFR1, FGFR2, FGFR3, FGFR4, FLT1, FLT4, KDR, PDGFRA, PDGFRB	FGFR/VEGFR inhibitor	VEGF, VEGFR, FLT1, FLT4, KDR
DPC-005247	PLX4720	BRAF, KDR	RAF inhibitor	KDR

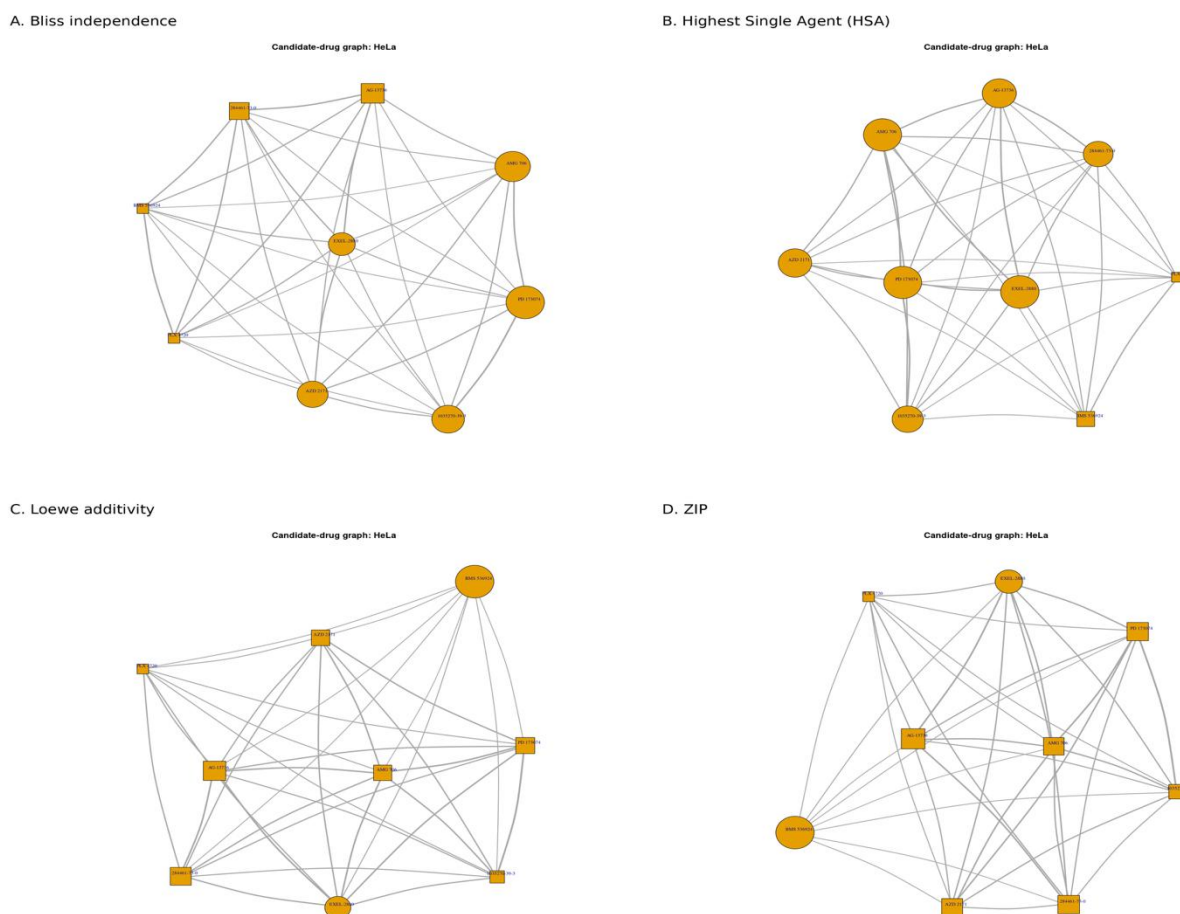


Figure 20. Graph-learning prioritisation of anti-angiogenic candidate drugs across four synergy models in the HeLa cervical cancer model. Candidate-drug similarity networks were constructed using the subset of anti-angiogenic compounds with available GDSC2 pharmacological response data in cervical cancer models. Networks were generated using four alternative combination-response models: (A) Bliss independence, (B) Highest Single Agent (HSA), (C) Loewe additivity, and (D) Zero Interaction Potency (ZIP). Nodes represent anti-angiogenic candidate third drugs evaluated for addition to the clinically derived cisplatin–paclitaxel reference regimen, with node size proportional to the graph-learning prioritisation score. Edges represent weighted similarities derived from integrated pharmacological, target, mechanistic, CRISPR dependency, gene expression, somatic mutation, and synergy-specific features. Differences in node prominence, edge weights, and overall network topology demonstrate how the choice of synergy model influences graph-based prioritisation of anti-angiogenic therapeutic candidates for cervical cancer.

The Validation Agent evaluated the Bliss-specific graph convolutional network using cross-validation and compared its performance with a pharmacology-only logistic-regression model and a prevalence-based baseline. Across the 54 held-out candidate predictions, the graph convolutional network achieved an accuracy of 0.833, sensitivity of 0.852, specificity of 0.815, F1-score of 0.836, Matthews correlation coefficient of 0.667, and pooled ROC-AUC of 0.907. The pharmacology-only model produced slightly lower accuracy (0.815), specificity (0.778), F1-score (0.821), MCC (0.631) and ROC-AUC (0.840), whereas the prevalence baseline showed substantially weaker discrimination, with an accuracy of 0.648, MCC of 0.314, and ROC-AUC of 0.671. These results indicate that integration of graph topology, pharmacological response and molecular-context features improved discrimination beyond pharmacological features alone (**Supplementary Files S12 – S14**). Cross-validated ROC analysis showed that the graph model provided strong separation between candidates classified as stronger or not stronger than the cisplatin–paclitaxel clinical reference regimen (**Figure 21, A**). Particularly strong discrimination was evident for Ca Ski, ME-180 and NCI-H1341, while HeLa, SiHa and SISO retained informative but more model-dependent prediction profiles. Although the mean fold-level ROC-AUC for the graph model was reported as 1.00, this value should be interpreted cautiously because several individual folds contained only two or three held-out candidates. The pooled cross-validated ROC-AUC of 0.907, calculated across all held-out predictions, provides the more conservative overall estimate of model discrimination. At the predefined

probability threshold of 0.50, the graph model correctly classified 23 stronger-than-reference candidates and 22 not-stronger candidates, with five false-positive and four false-negative predictions (**Figure 21, B**). The pharmacology-only comparator produced the same number of true positives but one fewer true negative, resulting in six false positives. In contrast, the prevalence baseline generated 14 false-positive and five false-negative classifications. The improved balance between sensitivity and specificity for the graph model supports its use as a candidate-prioritisation layer rather than a simple high-sensitivity screening rule. Decision Curve Analysis showed that the clinical utility of the graph model depended on both the cervical cancer model and the selected decision threshold (**Figure 21, C**). The graph model generated positive net benefit across broad threshold ranges in Ca Ski, HeLa, SiHa and SISO. In Ca Ski, its net benefit increased to approximately 0.56 at a threshold of 0.55, exceeding the pharmacology-only model and the treat-all strategy. In SiHa, the graph model outperformed the pharmacology-only comparator at intermediate thresholds around 0.40–0.60, including a net benefit of approximately 0.44 at the 0.50 threshold. In SISO, the graph model retained particularly high net benefit across low-to-intermediate thresholds and reached approximately 0.78 at a threshold of 0.60. Conversely, the pharmacology-only model provided more consistent net benefit for ME-180 and NCI-H1341, demonstrating that graph integration was not uniformly superior for every biological model. These findings support model-specific threshold selection rather than application of a single universal operating threshold. Graph-clustering analysis provided complementary evidence regarding whether the learned graph topology captured the observed pharmacological interaction classes (**Figure 21, D**). Ca Ski showed complete agreement between graph-derived clusters and stronger-than-reference labels, with Rand and adjusted Rand indices of 1.00. HeLa, SiHa and SISO also showed comparatively strong cluster–label agreement, with Rand indices of approximately 0.78 and adjusted Rand indices of approximately 0.55, accompanied by positive silhouette scores indicating moderate graph-cluster separation. ME-180 showed intermediate agreement, whereas NCI-H1341 had a positive Rand index but a negative adjusted Rand index, suggesting that its graph partitioning did not reproduce the pharmacological labels beyond chance expectation. Several models lacked sufficient anti-angiogenic candidate numbers or cluster variation for reliable calculation, and therefore no clustering scores were displayed. Taken together, these analyses show that the Validation Agent provides multiple, complementary assessments of the graph-learning framework. The graph convolutional network improved pooled predictive discrimination and confusion-matrix performance relative to the pharmacology-only and prevalence comparators, while Decision Curve Analysis identified cancer-model and threshold ranges in which this improvement translated into higher net benefit. Graph-clustering metrics further demonstrated that pharmacological interaction classes were reflected in network organisation for several, but not all, cervical cancer models. The results therefore support the graph model as an internally validated hypothesis-prioritisation component while also identifying model-specific limitations that require external validation using experimentally measured drug-combination datasets.

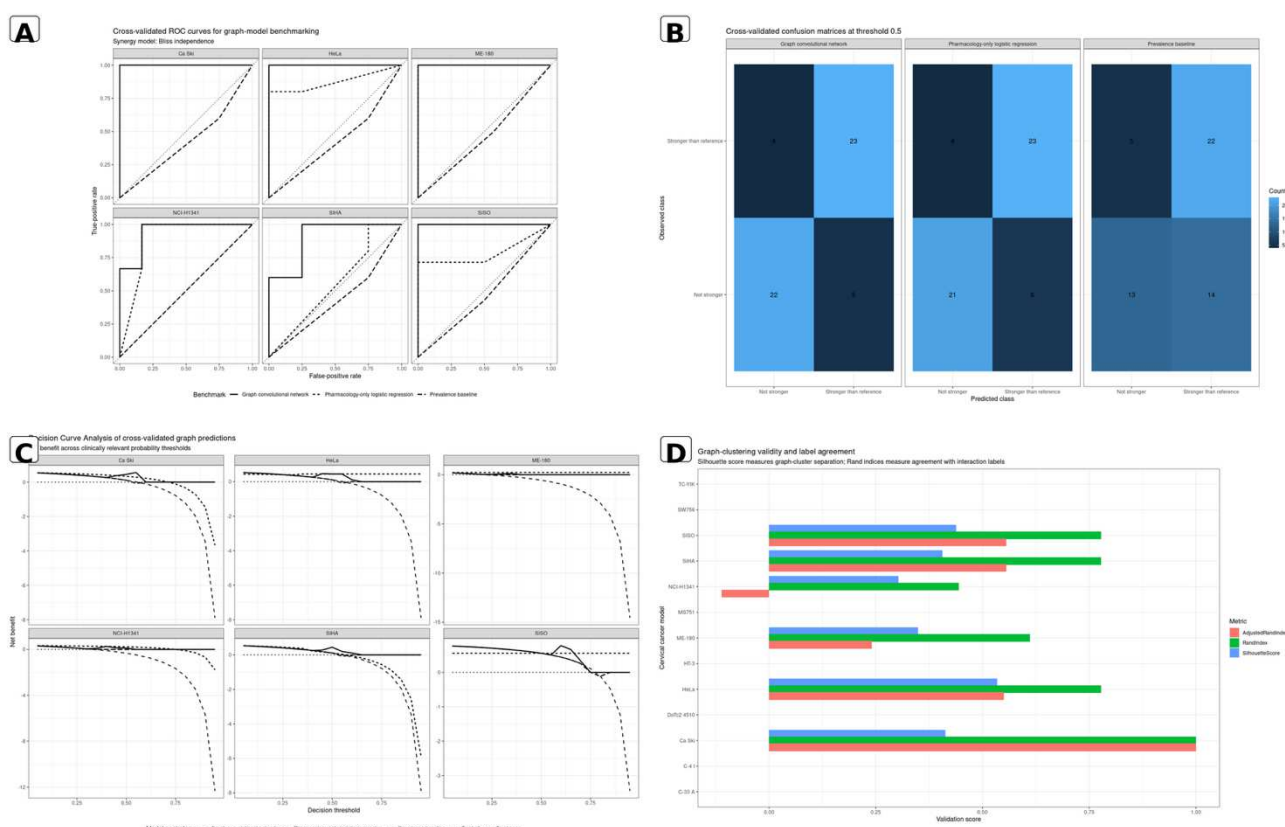


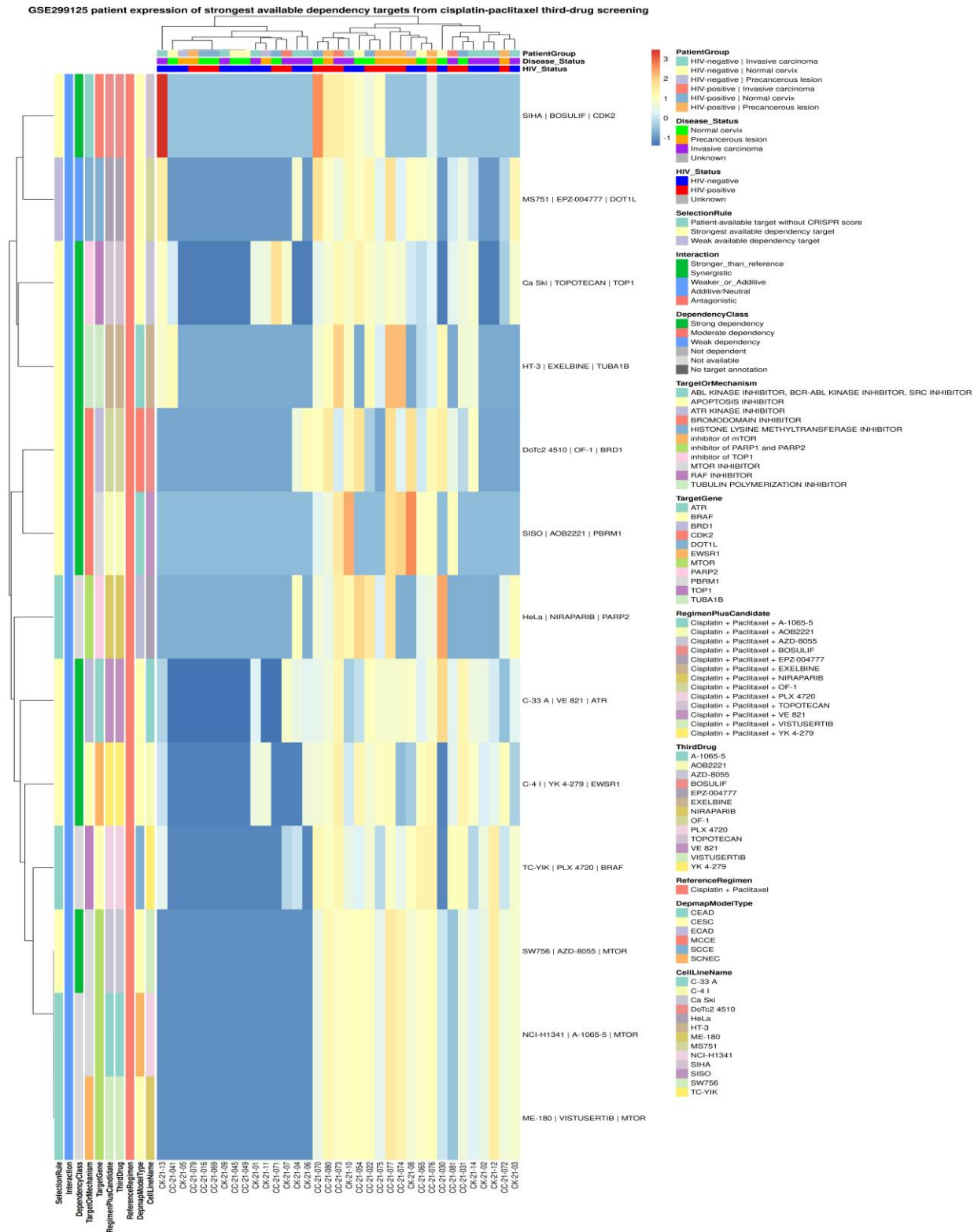
Figure 21. Internal validation and benchmarking of the Bliss-specific graph-learning model for anti-angiogenic candidate prioritisation. (A) Cross-validated receiver operating characteristic curves comparing the graph convolutional network, pharmacology-only logistic regression and prevalence baseline across cervical cancer models. (B) Aggregated cross-validated confusion matrices at a classification threshold of 0.50. (C) Decision Curve Analysis showing the net benefit of the graph model and benchmark strategies across alternative probability thresholds. Treat-all and treat-none strategies are included as clinical reference strategies. (D) Graph-clustering validity and agreement between graph-derived communities and observed stronger-than-reference interaction labels, quantified using silhouette score, Rand index and adjusted Rand index. Validation was performed on the subset of anti-angiogenic compounds with available GDSC2 pharmacological response data in cervical cancer models using Bliss independence as the selected synergy model.

CRISPR dependencies identify patient-aligned therapeutic vulnerabilities in an HIV-stratified cervical cancer cohort

Projection of the strongest available model-specific dependency targets into the 35-patient GSE299125 cohort revealed marked inter-patient heterogeneity in the expression of therapeutic vulnerabilities derived from unrestricted cisplatin–paclitaxel third-drug screening (**Figure 22**). The cohort-level analysis retained 13 model-derived target–candidate contexts: SIHA–bosulif–CDK2, MS751–EPZ-004777–DOT1L, Ca Ski–topotecan–TOP1, HT-3–exelbine–TUBA1B, DoTc2 4510–OF-1–BRD1, SISO–AOB2221–PBRM1, HeLa–niraparib–PARP2, C-33 A–VE 821–ATR, C-4 I–YK 4-279–EWSR1, TC-YIK–PLX 4720–BRAF, SW756–AZD-8055–MTOR, NCI-H1341–A-1065-5–MTOR, and ME-180–vistusertib–MTOR. Thus, the patient extension preserved the model-specific chain linking the cisplatin–paclitaxel reference backbone, prioritised third drug, strongest available dependency target, and expression of that target in individual cervical samples. The heatmap resolved the cohort into heterogeneous target-expression states rather than a uniform treatment-recommendation group. CK-21-13 showed one of the most distinct patient-specific profiles, characterised by pronounced relative expression of CDK2 and additional elevation within several model-derived target states. This pattern provides molecular support for further evaluation of the cisplatin–paclitaxel–bosulif hypothesis linked to the SIHA–CDK2 dependency context. Elevated CDK2-associated expression was also evident in a restricted subset of patients, including CC-21-070, CC-21-016, CC-21-069, CK-21-05, and CC-21-041, although the magnitude of the expression state differed between individuals. A second clinically relevant pattern involved the TOP1-directed topotecan strategy derived from the Ca Ski model. Increased relative TOP1 expression was concentrated in a subset of patients that included CC-21-101, CC-21-077, CC-21-075, CC-

21-074, and CK-21-13, with additional intermediate expression observed in neighbouring patient profiles. These patients therefore represent candidate molecular contexts for further evaluation of cisplatin–paclitaxel plus topotecan. Importantly, this recommendation is supported by the originating pharmacological and functional model context and is not inferred from TOP1 expression alone. The TUBA1B-associated exelbine hypothesis, originating from HT-3, similarly displayed patient-restricted expression. Comparatively increased TUBA1B expression was evident particularly in CC-21-101, CC-21-077, CC-21-075, and CC-21-074, with additional elevated states in selected samples including CC-21-080 and CC-21-073. These findings identify a subset of the cohort in which the microtubule-associated vulnerability supporting the exelbine-containing third-drug strategy is transcriptionally represented. DNA damage response-associated recommendations were also heterogeneous. The ATR-directed VE 821 strategy derived from C-33 A showed increased ATR expression across a broader central patient cluster, including CC-21-070, CC-21-080, CC-21-073, CK-21-10, CC-21-054, CC-21-022, CC-21-075, CC-21-077, and CC-21-074. In contrast, the PARP2-associated niraparib strategy derived from HeLa was concentrated more strongly in patients including CC-21-070, CC-21-080, CC-21-073, CK-21-10, and CC-21-054. The partially overlapping ATR and PARP2 expression states indicate that selected patients may harbour broader DNA damage response-associated molecular contexts, but the platform retains VE 821 and niraparib as separate model-derived therapeutic hypotheses rather than combining them into a single inferred treatment class. The three independently derived MTOR-associated contexts were particularly informative. MTOR was selected as the strongest available target for the SW756–AZD-8055, NCI-H1341–A-1065-5, and ME-180–vistusertib model–candidate pairs. Because these three recommendations converge on the same molecular target, their patient expression profiles were concordant. Increased relative MTOR expression was concentrated in a patient subset including CC-21-070, CC-21-080, CC-21-073, CK-21-10, CC-21-054, CC-21-022, CC-21-075, CC-21-077, and CC-21-074, with more moderate target states extending to additional patients. The recurrence of MTOR across three independent cervical model contexts strengthens the rationale for investigating mTOR-directed third-drug strategies in this molecularly defined patient subset. However, the specific choice between AZD-8055, A-1065-5, and vistusertib cannot be assigned from patient MTOR expression alone and remains dependent on the originating pharmacological evidence and subsequent experimental comparison. Chromatin and transcription-associated vulnerabilities identified additional patient subsets. DOT1L, supporting the MS751-derived EPZ-004777 hypothesis, showed increased expression predominantly in the central expression cluster, particularly CC-21-070, CC-21-080, CC-21-073, CK-21-10, CC-21-054, CC-21-022, CC-21-075, CC-21-077, and CC-21-074. The BRD1-associated OF-1 context and PBRM1-associated AOB2221 context also displayed restricted increases within this region of the cohort. In contrast, BRAF, linked to the TC-YIK–PLX 4720 model context, and EWSR1, linked to C-4 I–YK 4-279, showed broader but quantitatively variable expression states and therefore generated less sharply defined patient subsets from transcriptomic expression alone. Overall, the cohort analysis identified patient-specific rather than disease-group-wide therapeutic contexts. Patients CC-21-070, CC-21-080, CC-21-073, CK-21-10, CC-21-054, CC-21-022, CC-21-075, CC-21-077, and CC-21-074 formed a particularly notable multi-target expression group, showing recurrent elevation across ATR-, PARP2-, DOT1L-, and MTOR-associated vulnerabilities. These patients may therefore represent a molecularly enriched subgroup for prioritising DNA damage response, epigenetic, and mTOR-directed third-drug hypotheses. Conversely, CK-21-13 displayed a distinct CDK2-dominant state supporting the bosulif-associated model context, while the TOP1- and TUBA1B-enriched profiles observed in selected patients support more focused topoisomerase- and microtubule-directed strategies. Importantly, these findings do not assign treatment benefit to individual patients. Rather, the analysis identifies patients in whom a target already supported by model-specific pharmacological screening and CRISPR dependency is transcriptionally represented at a comparatively elevated level. The resulting

recommendations therefore constitute a hierarchy of patient-aligned therapeutic hypotheses. The cohort application demonstrates that the developed platform can progress from an established cisplatin–paclitaxel backbone, through unrestricted third-drug screening and functional dependency prioritisation, to identification of individual patients whose transcriptomic states are concordant with the strongest available model-derived therapeutic vulnerabilities.



class, target or mechanism of action, interaction classification, regimen-plus-candidate context, reference regimen, DepMap model type, and cell-line identity. Hierarchical clustering revealed heterogeneous and partially overlapping patient target-expression states, including a multi-target subgroup comprising CC-21-070, CC-21-080, CC-21-073, CK-21-10, CC-21-054, CC-21-022, CC-21-075, CC-21-077, and CC-21-074, with increased expression across several ATR-, PARP2-, DOT1L-, and MTOR-associated contexts. Distinct patient-specific patterns were additionally observed for CDK2-, TOP1-, and TUBA1B-associated vulnerabilities. The figure demonstrates the extension of model-specific pharmacological and functional genomic evidence into patient-level molecular hypothesis prioritisation; target expression is interpreted as supportive molecular context and not as a direct prediction of clinical response.

To determine whether therapeutic targets prioritised during the user-selected candidate-drug application were represented in patient-derived cervical samples, the candidate target space was evaluated in the independent GSE299125 transcriptomic cohort. The cohort comprised 35 cervical samples, including 12 normal cervical samples, 10 precancerous cervical lesions, and 13 invasive cervical carcinomas. HIV stratification identified 16 HIV-positive and 19 HIV-negative participants, with both HIV groups represented across the cervical disease states. Platform-derived targets associated with the selected third drugs for the cisplatin–paclitaxel reference backbone were mapped to the patient transcriptome and evaluated using row-scaled normalised expression profiles (**Figure 23**). Ten measurable targets mapped to five of the user-selected third-drug programmes: IGF1R and INSR for BMS-754807; TUBB2A, TUBB2B, TUBB3, TUBB4B, and TUBB6 for docetaxel; ESR1 for fulvestrant; TOP1 for SN38; and TNKS for XAV-939. Hierarchical clustering demonstrated substantial inter-patient heterogeneity in these target-expression states rather than uniform expression across the cohort. This heterogeneity was evident within the same disease and HIV categories, supporting the model-resolved principle underlying the developed platform and indicating that the five candidate strategies would not be equally supported across all 35 patients. The BMS-754807-associated IGF1R–INSR programme identified a restricted patient subset with comparatively increased target expression. IGF1R expression was particularly increased in CK-21-02, CK-21-11, CC-21-072, CC-21-076, and CC-21-079, whereas increased INSR expression was apparent in patients including CC-21-075, CC-21-077, CK-21-10, and CK-21-13. The non-identical distribution of IGF1R and INSR expression is important because BMS-754807 was annotated as a dual IGF1R/INSR inhibitor. Thus, the patient cohort suggests that BMS-754807-associated target context is heterogeneous even within its own target programme, with some patients showing predominantly IGF1R-associated states and others showing greater INSR representation. The docetaxel-associated tubulin programme showed the broadest and most heterogeneous patient-level target architecture. Increased TUBB3 expression was evident across a central patient cluster including CK-21-06, CC-21-070, CC-21-074, CC-21-022, CC-21-065, CC-21-081, CC-21-054, CC-21-076, CC-21-073, CC-21-075, and CC-21-077. In contrast, TUBB2A and TUBB2B showed more patient-restricted peaks. CK-21-13 demonstrated pronounced expression of multiple tubulin-associated targets, including TUBB2A, TUBB2B, and TUBB4B, whereas CK-21-07 showed a particularly marked TUBB2B state. TUBB6 was also strongly represented in CK-21-13 and CK-21-07. These patterns identify CK-21-13 as a notable multi-tubulin target context and suggest that the molecular rationale for docetaxel may differ between patients according to the specific tubulin-family programme expressed. The SN38–TOP1 programme also identified a distinct subset of patients. Comparatively increased TOP1 expression was observed in CK-21-14, CK-21-11, CK-21-02, CC-21-041, CK-21-10, CC-21-071, CC-21-101, CK-21-07, and CK-21-13. This patient-level pattern complements the functional evidence obtained during platform application, where TOP1 showed strong CRISPR dependency across multiple cervical cancer models. The convergence of model-level TOP1 dependency and patient-level TOP1 expression therefore provides a biologically traceable rationale for prioritising the SN38-associated strategy in this molecularly defined patient subset. Importantly, this interpretation identifies patients with a supportive TOP1 expression context and does not classify them as predicted SN38 responders. The fulvestrant-associated ESR1 programme was considerably more restricted. The strongest ESR1 expression states were observed in CC-21-105 and CK-21-081, with additional comparatively elevated expression in selected patients including CC-21-103, CC-21-074, CC-21-022, CC-21-065, CC-21-054, and CC-21-076. This restricted

patient distribution is consistent with the earlier model-level analysis, in which ESR1 expression was detectable but functional CRISPR dependency was limited. Consequently, the patient cohort does not provide broad support for uniform fulvestrant prioritisation; instead, it identifies a small ESR1-enriched subset in which the candidate could be investigated further. The XAV-939–TNKS programme displayed a separate patient-expression pattern. Increased TNKS expression was evident in patients including CK-21-05, CC-21-081, CK-21-04, CK-21-08, CC-21-030, CC-21-103, CC-21-074, CC-21-022, CC-21-065, CC-21-054, and CK-21-13. The distribution extended across HIV and disease-state categories and did not define a single clinically homogeneous group. This observation is consistent with the restricted and context-dependent functional dependency support observed for the tankyrase-associated candidate during the cell-line analysis. The patient data therefore identify specific TNKS-high molecular contexts rather than supporting XAV-939 as a cohort-wide third-drug strategy. Several patients were notable because they showed increased expression across multiple user-selected candidate target programmes. In particular, CK-21-13 displayed strong tubulin-family expression together with increased TOP1, TNKS, and INSR-associated states, identifying this patient as a multi-target molecular context potentially relevant to docetaxel-, SN38-, XAV-939-, and BMS-754807-associated hypotheses. CK-21-07 showed increased tubulin and TOP1 states, whereas CC-21-074, CC-21-022, CC-21-065, CC-21-054, and CC-21-076 showed overlapping ESR1-, TNKS-, and tubulin-associated expression patterns. Conversely, other patients exhibited comparatively restricted target profiles, demonstrating that candidate-drug contextualisation can distinguish both broad multi-target states and more focused molecular vulnerabilities. Disease- and HIV-associated trends remained detectable but did not supersede patient-level heterogeneity. IGF1R showed comparatively increased expression in several precancerous samples, whereas INSR was elevated in selected invasive carcinoma samples. TUBB3 was broadly represented within the precancerous-associated central expression cluster, while individual invasive carcinoma samples demonstrated marked TUBB2A, TUBB2B, or TUBB4B expression. Mean row-scaled expression of TNKS, TUBB3, TUBB2B, TOP1, IGF1R, and ESR1 was higher in HIV-positive than HIV-negative cervical samples; however, the heatmap demonstrates that these shifts were driven by heterogeneous individual expression states rather than a uniform HIV-positive molecular phenotype. Collectively, application of the user-selected candidate set to GSE299125 identified patient-specific therapeutic target contexts for each of the five measurable candidate programmes. BMS-754807 was aligned with distinct IGF1R- or INSR-enriched patient subsets; docetaxel showed the broadest support through heterogeneous tubulin-family programmes, with CK-21-13 representing a particularly prominent multi-tubulin state; SN38 was supported by increased TOP1 expression in a defined patient subset; fulvestrant was restricted to a smaller ESR1-enriched group; and XAV-939 identified a heterogeneous TNKS-associated subset. Thus, rather than recommending BMS-754807, docetaxel, fulvestrant, SN38, or XAV-939 uniformly to cervical cancer patients, the platform maps each pharmacologically and functionally evaluated candidate to the individual patients in whom its target programme is comparatively represented. These findings extend the user-selected drug workflow from model-level candidate testing to patient-aligned therapeutic hypothesis generation, while retaining the requirement for subsequent pharmacological and experimental validation.

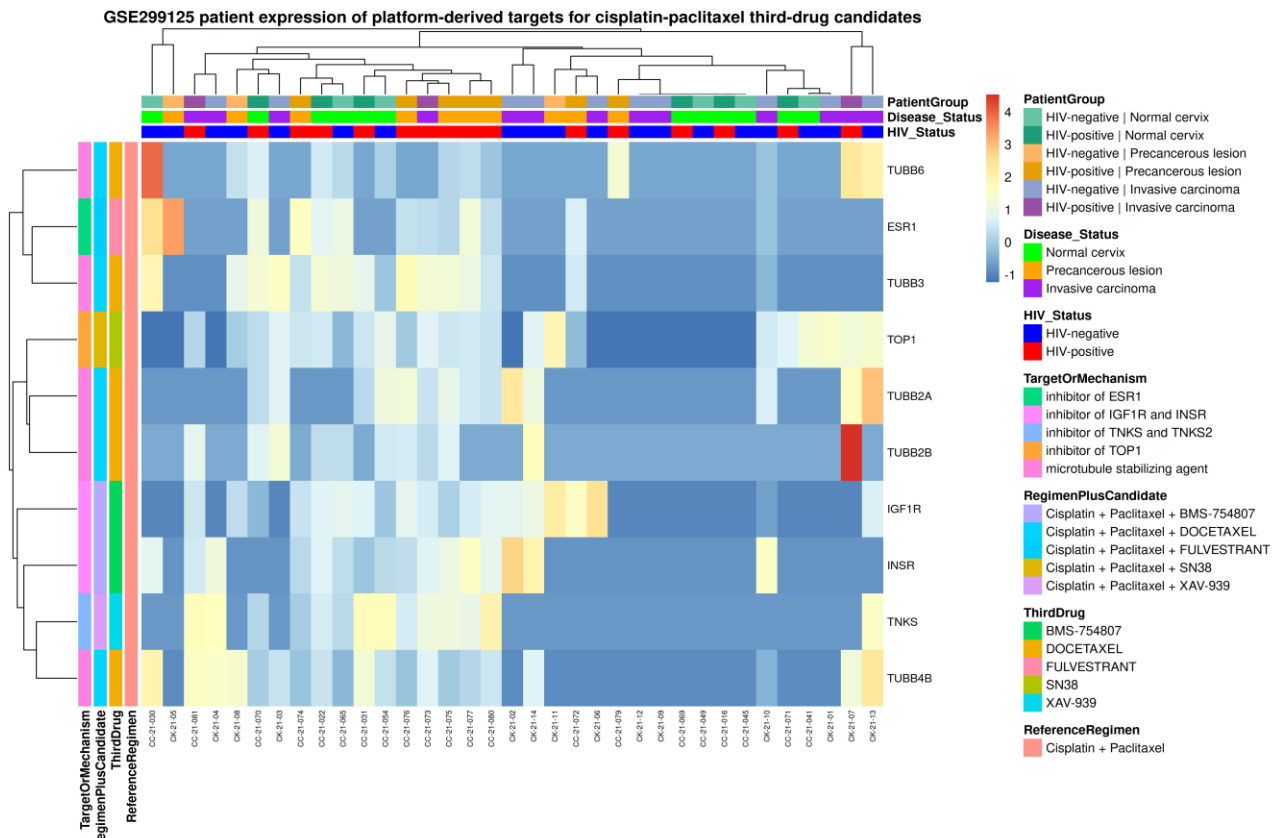


Figure 23. Patient-level expression of therapeutic targets associated with user-selected cisplatin–paclitaxel third-drug candidates in the GSE299125 cervical cohort. Row-scaled heatmap showing expression of ten measurable platform-derived targets across 35 cervical samples. Columns represent individual patient samples and are annotated by HIV status, cervical disease status, and integrated patient group. Rows represent IGF1R and INSR for BMS-754807; TUBB2A, TUBB2B, TUBB3, TUBB4B, and TUBB6 for docetaxel; ESR1 for fulvestrant; TOP1 for SN38; and TNKS for XAV-939. Row annotations retain target or mechanism of action, cisplatin–paclitaxel plus candidate regimen, third-drug identity, and reference regimen. Hierarchical clustering demonstrates substantial inter-patient heterogeneity and identifies candidate-specific target-expression subsets, including a prominent multi-tubulin state in CK-21-13, TOP1-enriched patients supporting the SN38-associated context, restricted ESR1-high patients relevant to fulvestrant, and heterogeneous IGF1R/INSR- and TNKS-associated states for BMS-754807 and XAV-939, respectively. Target-expression states provide patient-level molecular context for platform-derived therapeutic hypotheses and are not interpreted as direct predictions of clinical treatment response.

7. Discussion

Cisplatin remains the therapeutic backbone for locally advanced, recurrent, and metastatic cervical cancer despite major advances in targeted therapies and immunotherapy. Consequently, improving clinically established cisplatin-containing regimens remains a major objective in precision oncology. In this study, we developed a clinical evidence-guided computational framework that systematically expands established cisplatin-based therapies through integration of pharmacological modelling, functional genomics, molecular profiling, graph learning, and patient-level transcriptomic contextualisation. Unlike conventional drug-combination platforms that begin with arbitrary user-selected compounds or retrospectively analyse experimentally generated combination screens, our workflow begins with clinically investigated cisplatin-containing regimens identified from ClinicalTrials.gov and evaluates whether candidate therapeutic additions improve the pharmacological performance of these clinically relevant treatment backbones. By integrating complementary biological evidence into a unified analytical workflow, the platform extends conventional synergy analysis toward mechanistically interpretable therapeutic prioritisation. More broadly, this approach reflects the ongoing evolution of computational oncology from isolated pharmacological prediction toward explainable decision-support systems capable of integrating heterogeneous biomedical data into biologically informed therapeutic hypotheses. A principal finding of this study is that clinically established cisplatin-containing regimens exhibit substantial pharmacological heterogeneity across cervical cancer models. Although average interaction scores were generally close to additive, individual models demonstrated markedly different responses to the same therapeutic backbone, ranging from strongly synergistic to strongly antagonistic

interactions. These findings reinforce the concept that therapeutic response is determined not only by drug identity but also by tumour-specific biological context. Differences in genomic architecture, signalling network organisation, functional dependencies, and adaptive resistance mechanisms create distinct pharmacological landscapes in which identical therapies engage different molecular vulnerabilities. Consequently, averaging responses across heterogeneous experimental systems risks obscuring biologically meaningful variation that is directly relevant to precision medicine. These observations motivated one of the central methodological innovations of the framework: benchmarking candidate therapies against the reconstructed pharmacological performance of a clinically established reference regimen within the same biological model rather than applying universal synergy thresholds. Conventional drug-combination analyses classify interactions according to pharmacological metrics such as Bliss Independence, Highest Single Agent, Loewe Additivity, or Zero Interaction Potency. Although these metrics quantify interaction strength, they do not directly address whether a proposed therapeutic modification offers a meaningful improvement over existing standards of care. By preserving the pharmacological behaviour of clinically investigated cisplatin regimens as model-specific reference backbones, our framework reframes computational drug prioritisation from identifying theoretically synergistic drug pairs to evaluating whether candidate additions improve clinically relevant treatment strategies. This benchmarking strategy provides a more clinically interpretable basis for therapeutic prioritisation than reliance on universal interaction cut-offs alone. The unrestricted third-drug screening further demonstrated that candidate compounds differed markedly in their ability to enhance cisplatin–paclitaxel across cervical cancer models. While some compounds substantially improved the pharmacological performance of the reference regimen, others produced little additional benefit or antagonistic interactions despite being evaluated against the same treatment backbone. Furthermore, the highest-ranked candidate differed between models, indicating that therapeutic optimisation is fundamentally tumour-state dependent rather than universally drug-specific. These findings support the increasingly recognised view that cervical cancer represents a collection of biologically distinct disease states requiring context-specific therapeutic strategies rather than universal treatment optimisation. An additional observation was the distinction between intrinsic monotherapy activity and combination-specific therapeutic benefit. Several compounds demonstrated strong single-agent cytotoxicity but contributed relatively little additional improvement when incorporated into established cisplatin-containing regimens. Conversely, some compounds with only moderate intrinsic activity substantially enhanced combination performance. These findings indicate that intrinsic potency and combination benefit represent related but distinct pharmacological properties. Explicitly comparing reconstructed monotherapy activity with combination-specific improvement therefore enables compounds functioning primarily as effective standalone therapies to be distinguished from those that specifically augment established treatment regimens. This distinction reduces the likelihood that intrinsically cytotoxic compounds are preferentially prioritised despite providing limited additional value within multidrug therapy. Although pharmacological modelling effectively identifies candidate therapeutic combinations, interaction scores alone provide limited insight into the biological mechanisms responsible for therapeutic benefit. High pharmacological performance does not necessarily indicate that the corresponding molecular target represents a biologically meaningful vulnerability, nor does it explain why one candidate outperforms another.

To address this limitation, pharmacological prioritisation was complemented by sequential integration of functional genomic dependency, transcriptomic target expression, somatic mutation profiling, and patient-level molecular contextualisation. Rather than replacing pharmacological evidence, these complementary molecular layers provide mechanistic interpretation that allows each prioritised candidate to be evaluated within the broader biological context of the tumour model. Integration of genome-scale CRISPR dependency

profiling was particularly informative because it distinguished pharmacological activity from biological essentiality. Whereas pharmacological modelling determines whether a candidate improves a clinically established regimen, CRISPR dependency establishes whether the corresponding molecular target is required for tumour survival. Although many prioritised compounds targeted strongly dependent genes, others showed comparatively weak dependency despite favourable pharmacological performance, demonstrating that therapeutic efficacy may arise through multiple biological mechanisms, including pathway modulation, network perturbation, or polypharmacology. Accordingly, CRISPR dependency functions as an independent evidence layer that strengthens mechanistic confidence without replacing pharmacological evaluation. Transcriptomic expression provided complementary evidence by assessing target availability within individual tumour models. However, expression and functional dependency were frequently discordant, consistent with the broader understanding that transcriptional abundance alone is an incomplete predictor of therapeutic vulnerability. Protein activity, signalling architecture, pathway redundancy, and post-transcriptional regulation collectively determine cellular dependence. Consequently, transcriptomic expression is most informative when interpreted together with pharmacological performance and functional dependency rather than as an isolated biomarker of drug response. Similarly, somatic mutation analysis contributed important biological context but comparatively fewer informative therapeutic associations. Only a subset of prioritised targets contained coding alterations, and these mutations were not consistently associated with improved pharmacological performance or increased functional dependency. This observation reinforces an important principle of precision oncology: genomic alterations alone do not necessarily define therapeutic vulnerability. Instead, many effective treatment strategies exploit broader functional states such as replication stress, pathway activation, lineage-specific dependency, or synthetic lethality. Accordingly, mutation status was incorporated as contextual genomic evidence rather than a primary prioritisation criterion. Projection of prioritised molecular targets into the independent GSE299125 cohort extended the framework beyond experimental cell lines by establishing whether computationally prioritised molecular programmes were represented within patient-derived cervical cancer transcriptomes. Importantly, this analysis was intended to establish biological relevance rather than predict clinical response. Instead, it provides a translational bridge between experimentally reconstructed pharmacological vulnerabilities and patient molecular heterogeneity, strengthening confidence that prioritised targets represent biologically meaningful disease-associated programmes. Collectively, the sequential integration of pharmacological modelling, functional dependency, transcriptomic expression, genomic profiling, and patient-level contextualisation illustrates a broader shift in computational oncology toward explainable therapeutic prioritisation. Recent developments in intelligent bioinformatics increasingly emphasise that clinically useful computational systems should integrate heterogeneous biomedical evidence into coherent, interpretable analytical workflows rather than relying on isolated predictive algorithms. Within this framework, computational prediction becomes the starting point for biological reasoning rather than the final analytical output, allowing each therapeutic hypothesis to be evaluated through multiple complementary evidence layers before experimental validation. An important systems-level contribution of the present study is the incorporation of graph learning following pharmacological and molecular prioritisation. Conventional drug-combination analyses evaluate candidate compounds independently according to predefined interaction metrics, whereas graph learning represents therapeutic candidates as interconnected biological networks incorporating pharmacological similarity, molecular targets, mechanisms of action, functional dependency, transcriptomic context, and genomic evidence. This enables therapeutic prioritisation to exploit relationships between biologically related compounds rather than considering each candidate in isolation. Consistent with principles of network medicine, graph-learning analyses demonstrated that therapeutically related compounds organised into distinct model-specific communities,

indicating that pharmacological similarity is strongly influenced by tumour biology rather than representing an intrinsic property of individual compounds. The improved predictive performance of graph learning further suggests that systems-level biological relationships provide complementary information beyond conventional pharmacological scoring alone.

The present framework also differs conceptually from existing computational drug-combination resources such as DrugComb. DrugComb provides an invaluable resource for analysing experimentally generated drug-combination datasets through standardised synergy metrics, network visualisation, biomarker exploration, and machine-learning prediction of pharmacological responses. In contrast, our framework addresses a different translational objective. Rather than evaluating arbitrary drug pairs or retrospectively analysing experimental screens, the workflow begins with clinically investigated treatment regimens, reconstructs model-specific pharmacological baselines, systematically evaluates candidate therapeutic additions, integrates mechanistic evidence across multiple biological layers, contextualises prioritised targets within independent patient cohorts, and finally applies graph learning for systems-level therapeutic reasoning^{54,82–85}. Consequently, the platform functions not simply as a pharmacological analysis tool but as a clinical evidence-guided decision-support and hypothesis-generation framework designed to support rational expansion of established cervical cancer cisplatin-therapies. Several limitations should nevertheless be acknowledged. First, pharmacological interactions were reconstructed from experimentally derived GDSC2 dose–response parameters rather than measured through prospective third-drug combination experiments. Although this strategy enables systematic exploration of large therapeutic search spaces, the predicted improvements should be regarded as computational hypotheses requiring experimental validation. Second, the framework is constrained by the availability and quality of publicly accessible pharmacological and molecular datasets, limiting evaluation of compounds lacking comprehensive characterisation. Third, although multiple molecular evidence layers were integrated, they capture only part of the biological complexity underlying therapeutic response and do not account for proteomic regulation, metabolic adaptation, tumour–microenvironment interactions, pharmacokinetic effects, or spatial tumour organisation. Furthermore, while graph learning improved systems-level prioritisation, the network topology remains dependent on currently available biological knowledge and therefore requires validation using independent pharmacological datasets and prospective experimental systems. Finally, although projection into the GSE299125 cohort established biological relevance, it should not be interpreted as evidence of clinical efficacy or treatment response. Despite these limitations, the modular architecture of the framework enables straightforward incorporation of additional pharmacological resources, emerging multi-omics datasets, advanced graph-learning methodologies, and prospective validation studies^{49,86–89}. Future integration of patient-derived organoids, xenograft models, single-cell and spatial transcriptomics, proteomics, and longitudinal clinical data could further strengthen biological interpretation and therapeutic prioritisation while supporting increasingly personalised treatment strategies^{90–94}. In conclusion, this study presents a clinically grounded computational framework for systematic expansion of established cisplatin-based cervical cancer therapies through integration of pharmacological modelling, functional genomics, molecular profiling, graph learning, and patient-level transcriptomic contextualisation. More broadly, the work illustrates a transition from conventional drug-combination analysis toward intelligent therapeutic reasoning, in which clinical evidence, systems biology, and complementary molecular evidence are integrated into transparent and explainable decision-support. As public pharmacological resources, multimodal molecular datasets, and artificial intelligence methodologies continue to evolve, computational frameworks that generate biologically interpretable therapeutic hypotheses will play an increasingly important role in accelerating translational cancer research and advancing precision oncology.

8. Supplementary Files

Supplementary_File_S1_Cisplatin_Paclitaxel_BLISS_Reference_Summary.csv
Supplementary_File_S2_Cisplatin_Paclitaxel_BLISS_ThirdDrug_Ranking.csv
Supplementary_File_S3_Cisplatin_Paclitaxel_Monotherapy_Response_Summary.csv
Supplementary_File_S4_Cisplatin_Paclitaxel_Functional_CRISPR_Evidence.csv
Supplementary_File_S5_Cisplatin_Paclitaxel_Molecular_Expression_Evidence.csv
Supplementary_File_S6_Cisplatin_Paclitaxel_Optional_Mutation_Biomarker_Evidence.csv
Supplementary_File_S7_Cisplatin_Paclitaxel_BLISS_Reference_Summary.csv
Supplementary_File_S8_Cisplatin_Paclitaxel_BLISS_ThirdDrug_Ranking.csv
Supplementary_File_S9_Cisplatin_Paclitaxel_Functional_CRISPR_Evidence.csv
Supplementary_File_S10_Cisplatin_Paclitaxel_Molecular_Expression_Evidence.csv
Supplementary_File_S11_Cisplatin_Paclitaxel_Optional_Mutation_Biomarker_Evidence.csv
Supplementary_File_S12_Cisplatin_Paclitaxel_BLISS_CrossValidation_Fold_Metrics (1).csv
Supplementary_File_S13_Cisplatin_Paclitaxel_BLISS_CrossValidation_Predictions (1).csv
Supplementary_File_S14_Cisplatin_Paclitaxel_BLISS_Validation_Agent_Summary (1).csv

9. Data Availability

All datasets used in the development, evaluation, and cohort-level application of the platform are publicly available. Clinical trial information used to define clinically investigated cisplatin-containing reference regimens was obtained from ClinicalTrials.gov. The initial study-record export was downloaded in comma-separated value format as **ctg-studies.csv** and contained the NCT number, study title, study URL, study status, conditions, interventions, sponsor, collaborators, and study type. These fields correspond to the standard study-record fields available through the ClinicalTrials.gov CSV download interface. The registry and study-record download resources are publicly accessible through ClinicalTrials.gov and its Data and API portal.

Pharmacological, cancer-model, compound-annotation, functional genomic, molecular expression, and somatic mutation datasets used for platform development were obtained from the DepMap Portal. The developmental datasets comprised **GDSC2ResponseCurves.csv**, used for reconstruction of model-specific drug dose-response profiles; **PortalCompounds.csv**, used for compound identity, synonym, molecular-target, and mechanism-of-action annotation; **Model.csv**, used for DepMap model identifiers, cell-line names, and model-type annotation; **CRISPRGeneDependency.csv**, used to evaluate model-specific functional dependency of candidate drug targets; **OmicsExpressionTPMLogp1HumanProteinCodingGenesStranded.csv**, used to quantify target-gene expression in matched cancer models; and **OmicsSomaticMutationsMAF.maf**, used to evaluate target-specific somatic mutation context. The DepMap Portal provides public access to cancer dependency, genomic, molecular, and pharmacological datasets and associated downloadable releases. The GDSC2 pharmacological resource represents large-scale drug sensitivity screening across human cancer cell lines and is available within the Sanger GDSC1/GDSC2 data collection.

Independent patient-level transcriptomic application was performed using **GSE299125**, obtained from the NCBI Gene Expression Omnibus. The analysed **GSE299125_raw_counts.txt.gz** file contained RNA-sequencing count data from 35 cervical samples from HIV-positive and HIV-negative Kenyan women with normal cervix, precancerous cervical lesions, or invasive cervical carcinoma. GEO is a public repository for array- and

sequence-based functional genomics datasets and provides study metadata and downloadable processed and raw data. The GSE299125 transcriptomic dataset can be accessed through the NCBI GEO accession viewer; the associated study reports GSE299125 as the GEO Series accession for the cervical transcriptomic data.

10. Code Availability

The source code used to develop the computational workflow, perform pharmacological screening, integrate functional dependency, molecular expression, and somatic mutation evidence, and conduct the independent patient-level transcriptomic application is available from the corresponding author upon reasonable request. The complete platform source code, supporting analysis scripts, and documentation required to reproduce the analytical workflow will be made publicly available through the Bafana-saltiel CisplatinApp repository on GitHub upon publication of the manuscript. The public repository will contain the code required to deploy the platform and reproduce the principal computational analyses reported in this study. A web-accessible prototype of the interactive platform is deployed using Posit Connect Cloud and is available at:

Cisplatin Clinical Reference Combination Explorer prototype

The deployed prototype is provided for research, reproducibility, and hypothesis-generation purposes and is not intended for clinical diagnosis, treatment selection, or direct patient management.

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12. Author Contributions

Saltiel Hamese completed this research and wrote the research paper together with the contributions from all the authors as follows: Dr. Mutsa Takundwa, Prof. Earl Prinsloo. and Dr. Deepak B. Thimiri Govinda Raj. All the authors have read and approved the manuscript.

13. Competing Interest

The authors declare no competing financial or non-financial interests.

14. Consent to Participate

The authors declare that all data used in the manuscript are open-source data.

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