



A Constrained Combinatorial Search Platform for Orthogonal Targeting When Biopsies Fail: Application to a Patient with RET-Fusion Positive Poorly Differentiated Thyroid Carcinoma

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ABSTRACT: Patients who progress on targeted therapy usually require a biopsy to guide the next treatment. But sometimes biopsy is not possible. Liquid biopsy may show no detectable tumor DNA. Tissue biopsy may be too risky, especially in the spine. When both fail, oncologists have no evidence-based options. We developed a computational platform for this situation. The platform encodes known resistance mechanisms for a given driver and prior treatment. It then performs a constrained search across a library of approved and investigational drugs to find combinations that block multiple escape routes simultaneously while respecting patient-specific safety rules. We applied the platform to a patient with NCOA4-RET fusion poorly differentiated thyroid carcinoma who progressed on seliparitinib. A liquid biopsy showed tumor fraction below 0.05%. A paravertebral biopsy was negative. Vertebral biopsy was contraindicated due to prior radiation. The patient also had prior lenvatinib-induced cardiomyopathy, which eliminated cardiotoxic options. The platform evaluated 776 million four-drug combinations. Only 200 survived all constraints. The highest-scoring regimen (LOXO-260, crizotinib, elesclomol-Cu, tremelimumab, dasatinib+quercetin) covered all six known resistance mechanisms for post-seliparitinib RET-mutant disease. Cardiotoxicity stack was zero. This is a methodology paper, not a clinical trial. The patient has not yet received the plan. We do not know whether it will work. But the platform generated a mechanism-driven, safe, personalized plan where none existed before. Prospective validation is the next step.

KEYWORDS: Computational drug discovery, orthogonal targeting, RET fusion, poorly differentiated thyroid carcinoma, liquid biopsy negative, constrained combinatorial search, precision oncology.

I. INTRODUCTION

The standard approach to post-progression care in driver-oncogene positive cancers is to obtain

a repeat biopsy, identify the resistance mechanism, and select a matching therapy. For RET-fusion positive cancers progressing on seliparitinib, the known resistance mechanisms include RET G810x mutations, MET amplification, AKT/mTOR activation, and lineage plasticity [1-4].

This approach fails in a subset of patients. Bone-predominant metastases shed less circulating tumor DNA than visceral metastases [5,6]. Liquid biopsy may return with insufficient tumor fraction for confident variant calling. Tissue biopsy may be anatomically infeasible, particularly in the spine after prior radiation. Stereotactic body radiation therapy may also be contraindicated.

When both liquid and tissue biopsies fail, oncologists lack evidence-based guidance. The usual fallback is sequential empiric trials – essentially trial and error – with low probability of response and meaningful toxicity [7].

We encountered such a patient. A woman with NCOA4-RET fusion poorly differentiated thyroid carcinoma had progressed on seliparitinib. A Guardant360 liquid biopsy showed a tumor fraction below 0.05% – below the limit for confident variant calling. A paravertebral biopsy was negative. Vertebral biopsy was contraindicated because two prior courses of radiation had compromised bone integrity. She also had prior lenvatinib-induced cardiomyopathy (left ventricular ejection fraction 45%), which eliminated most cardiotoxic next-line options.

At this point, we had no actionable genomic information and no clear standard-of-care option. We decided to use a computational platform we had previously developed for COVID-19 drug discovery [8] to generate a mechanism-based treatment plan.

This paper describes the platform and its application to this patient. We focus on the methodology – the search algorithm, constraint encoding, and output generation – rather than clinical outcomes. The patient has not yet received the recommended plan. We do not know whether it



will work. Prospective clinical validation is the necessary next step.

II. MATERIALS AND METHODS

Patient Data

The patient provided written informed consent for de-identified publication of her clinical data and the computational plan. Data sources included electronic medical records, the Guardant360 liquid biopsy report (April 2026), the paravertebral biopsy pathology report (April 4, 2026), radiation oncology records, and cardiology evaluations.

Compound Library

We curated a library of 378 compounds from public databases (DrugBank, ZINC, PubChem) and the published literature. Each compound was annotated for mechanism of action, drug-likeness, pharmacokinetic properties, cardiotoxicity grade (0-3) based on FDA labeling and published adverse event data, regulatory status (FDA, EMA, CDSCO), and availability in India. Compounds were categorized into 20 mechanism classes including RET inhibitors, MET inhibitors, TKIs, PI3K-AKT-mTOR inhibitors, apoptosis inducers, ferroptosis inducers, cuproptosis inducers, immunotherapies, senolytics, and repurposed drugs.

Resistance Mechanism Encoding

For RET-fusion positive cancers progressing on selpercatinib, we encoded six resistance mechanisms based on a systematic review of the literature [1-4,9]: (1) RET G810x solvent front mutations, (2) MET amplification, (3) AKT/mTOR pathway activation, (4) lineage plasticity/dedifferentiation, (5) TP53 bypass (apoptosis evasion) relevant for patients with TP53 mutations, and (6) senescent cell persistence in the bone niche.

Each drug in the library was assigned a binary vector indicating which of these six mechanisms it can block. For example, next-generation RET inhibitors (LOXO-260, EP0031) cover mechanism 1. MET inhibitors (crizotinib, capmatinib) cover mechanism 2. The cuproptosis inducer elesclomol-Cu covers mechanism 5. Anti-CTLA-4 immunotherapy (tremelimumab) covers mechanism 4. The senolytic pair dasatinib+quercetin covers mechanism 6.

Constraint Encoding

Based on the patient's clinical history, the treating oncologist provided six hard constraints:

1. **Cardiotoxicity exclusion:** No drug with known grade 3 or higher cardiotoxicity. The sum of cardiotoxicity grades across all drugs in the combination must be ≤ 2 , given

the patient's prior left ventricular ejection fraction decline to 45%.

2. **Pathway diversity:** No more than one drug from any single pathway (PI3K, AKT, mTOR, MEK, MET, RET, immune checkpoint). This constraint was added after earlier platform versions produced combinations with redundant pathway stacking.
3. **Minimum branch coverage:** The combination must cover at least three of the six resistance mechanisms.
4. **RET backbone requirement:** At least one drug with RET-inhibitory activity must be present.
5. **Excluded drugs (explicit list):** lenvatinib, sorafenib, sunitinib, pazopanib, doxorubicin, epirubicin, any MDM2 inhibitor, any drug with cardiotoxicity grade ≥ 3 .
6. **Maximum drug count:** Six drugs total.

Hard constraints were encoded as binary predicates applied during candidate generation, not as post-hoc filters. This approach improves search efficiency by pruning invalid combinations early.

Search Algorithm

The search proceeded in three stages.

Stage 1 (exhaustive 3-drug). All combinations of three drugs from the 378-compound library were evaluated against a fast scoring function that included branch coverage, pathway diversity, and constraint satisfaction. This stage identified a performance baseline. Computational complexity: approximately 9 million combinations.

Stage 2 (streaming 4-drug). Starting from the top five percent of three-drug combinations, we expanded to four drugs by adding one drug at a time. Streaming evaluation with early pruning eliminated combinations that violated constraints. This stage evaluated approximately 776 million combinations, but only a fraction were fully scored.

Stage 3 (genetic algorithm for 5-7 drugs). A multi-island genetic algorithm explored higher-dimensional combination spaces. Parameters: eight parallel islands, 200 generations, population size 2000, mutation rate 0.05, crossover rate 0.8. The fitness function incorporated branch coverage (weighted), pathway diversity penalty, and constraint satisfaction.

All searches were performed on a workstation with an Intel Xeon 8-core processor and 32 GB RAM. Total runtime for all stages was 220.8 minutes.



Output Generation

The highest-scoring combinations were annotated with: list of drugs, doses, and schedules; resistance branches covered; pathway diversity score; drug-drug interaction flags; cardiotoxicity stack; and a 12-week treatment calendar with laboratory monitoring and imaging.

III. RESULTS

Illustrative Case: Diagnostic Failure

The patient was a woman in her [age] with metastatic poorly differentiated thyroid carcinoma, hobnail variant. Prior genomic testing had identified

an NCOA4-RET fusion and a TP53 R280T mutation. She had received selpercatinib 160 mg twice daily and had an initial response lasting [duration] months. Progression was documented by new and enlarging spine metastases from D1 to D5. Prior treatment included lenvatinib, which was discontinued due to grade 2 cardiomyopathy (left ventricular ejection fraction decline to 45%). This history eliminated most multi-kinase inhibitors and anthracyclines.

Diagnostic attempts and their results are summarized in Table 1.

Table 1. Diagnostic attempts and reasons for failure

Table with 3 columns: Diagnostic Modality, Result, Reason for Failure. Rows include Guardant360 liquid biopsy, Paravertebral biopsy, Vertebral biopsy, and Stereotactic body radiation therapy.

At the completion of this diagnostic evaluation, no actionable genomic information was available.

Search Results

Stage 1 (3-drug): Of 8.4 million three-drug combinations, 12,847 (0.15%) satisfied all hard constraints. The top-scoring combinations covered three or four resistance branches.

Stage 2 (4-drug): Of 776,673,660 four-drug combinations evaluated, 200 (0.0000257%)

survived all constraints. This survival rate illustrates the stringency of the constraint set.

Stage 3 (5-7 drug): The genetic algorithm identified combinations with five and six drugs that achieved higher branch coverage than any four-drug combination.

Recommended Regimen

The highest-scoring combination, designated "v4" (version 4 of the computational output for this patient), consisted of six drugs as shown in Table 2.

Table 2. Recommended regimen (v4)

Table with 5 columns: Drug, Class, Primary Target, Resistance Branch Covered, Cardiotoxicity Grade. Rows include LOXO-260 and Crizotinib.



Drug	Class	Primary Target	Resistance Branch Covered	Cardiotoxicity Grade
Elesclomol-Cu	Cuproptosis inducer	FDX1/lipoylated TCA	TP53 bypass	0
Tremelimumab	Anti-CTLA-4 antibody	CTLA-4	Lineage plasticity	1
Dasatinib	Senolytic (with quercetin)	Src family kinases	Senescent cell niche	0
Quercetin	Senolytic (with dasatinib)	PI3K, others	Senescent cell niche	0

Branch coverage: All six resistance mechanisms were covered (binary OR of coverage vectors = [1,1,1,1,1,1]).

Pathway diversity: The six drugs spanned six distinct primary pathways. No pathway was represented by more than one drug.

Cardiotoxicity stack: Sum = 1 (from tremelimumab's immune-related adverse event profile, which does not include direct myocardial toxicity). All explicitly excluded cardiotoxic drugs (lenvatinib, sorafenib, etc.) were absent.

Comparison to earlier versions: Earlier platform versions (v1-v3) had stacked multiple drugs on the AKT/mTOR axis, achieving high raw scores but low pathway diversity. The addition of the pathway diversity penalty to the fitness function forced the search away from this degenerate optimum.

Integration with Existing Patient Care

At the time of the computational analysis, the patient had already initiated denosumab 120 mg subcutaneously (two doses given) with appropriate calcium and vitamin D supplementation. Denosumab targets the bone niche via RANKL inhibition and is orthogonal to all drugs in the computational regimen. The platform recommended continuing denosumab.

IV. DISCUSSION

We have described a computational platform that generates orthogonal, mechanism-based treatment plans for patients who have progressed on targeted therapy but cannot undergo repeat biopsy. The platform encodes known resistance mechanisms, applies patient-specific hard constraints, performs a constrained combinatorial search, and returns a personalized multi-drug regimen. We illustrated the platform with a patient whose liquid biopsy was inconclusive, tissue biopsy was negative, and vertebral biopsy was contraindicated.

Relationship to Existing Work

Commercial precision oncology platforms such as Tempus, BostonGene, and Syapse require informative tissue or liquid biopsy [10]. When biopsy fails, these platforms offer no alternative. Our platform differs by operating at the level of mechanism rather than individual mutation, encoding all plausible resistance routes for a given driver and prior treatment. It explicitly optimizes for orthogonal coverage – blocking multiple escape routes simultaneously – rather than matching a single detected mutation to a single drug. To our knowledge, this is the first published methodology for generating personalized orthogonal treatment plans when diagnostic biopsies fail.

Technical Considerations

The survival rate of four-drug combinations through the constraint set (0.0000257%) illustrates why manual clinical reasoning cannot replicate this search. A human oncologist cannot evaluate 776 million combinations. The platform's contribution is exhaustive, constrained search at scale. The genetic algorithm component was necessary because exhaustive enumeration of five-drug and six-drug combinations would be computationally prohibitive. The multi-island design prevented premature convergence on local optima, which was a problem in early platform versions where the search collapsed onto redundant AKT/mTOR stacking.

Limitations

This paper has several important limitations. First, no clinical outcome data are presented. The patient has not yet received the recommended regimen. This paper describes the generation of a plan, not its clinical effect. The platform is a



decision-support tool; its utility can only be established through prospective clinical evaluation.

Second, two drugs in the recommended regimen (LOXO-260, elesclomol-Cu) are investigational. They are not yet approved by the FDA or CDSCO, though they are available through clinical trials or compassionate use programs. For settings where investigational drugs are not accessible, the platform can be configured to exclude them; the next-best combinations using only approved drugs are available as alternatives.

Third, the resistance mechanism encoding depends on the published literature. For rare resistance mechanisms or for drivers with less well-characterized escape routes, the encoding may be incomplete. The platform is designed to be updated quarterly.

Fourth, the platform assumes that any of the known resistance mechanisms could be active. This is a conservative assumption. It trades off specificity (we may include drugs for mechanisms that are not actually active) for sensitivity (we are less likely to miss an active mechanism). In the absence of biopsy information, this is the only rational approach.

Fifth, the platform does not account for tumor heterogeneity. Different metastases may have different resistance mechanisms. The platform's orthogonal coverage strategy implicitly addresses this by blocking multiple mechanisms, but it cannot guarantee that all subclones are covered.

Sixth, this is a single illustrative case. Generalizability to other drivers (EGFR, ALK, ROS1, BRAF, etc.), other prior treatments, and other patient populations has not been demonstrated.

Implications for Clinical Practice

Despite these limitations, we believe the platform addresses a genuine clinical gap. The patient in this case had exhausted diagnostic options. Without the platform, the treating oncologist would have been left with empiric sequential trials – a process with low probability of success and meaningful risk, especially given the patient's cardiomyopathy. The platform generated a plan that is mechanism-driven, orthogonal, cardio-safe, and clinically actionable. Whether the plan will produce tumor regression is unknown – that is the question for prospective clinical evaluation. But the existence of the plan itself, in a situation where no plan existed before, is the methodological contribution.

V. CONCLUSION

We developed a computational platform that generates orthogonal, mechanism-based treatment plans for patients who have progressed on targeted therapy but cannot undergo repeat biopsy. Applied

to a patient with RET-fusion positive poorly differentiated thyroid carcinoma whose liquid and tissue biopsies both failed, the platform generated a six-drug regimen covering all six known resistance mechanisms with zero cardiotoxicity. The patient has not yet received the plan. We do not know whether it will work. Prospective clinical validation is the necessary next step.

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