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CASE-6

Prioritizing the Dominant Pathway When Two Active Molecular Targets Co-Exist in CASE OF Metastatic leiomyosarcoma

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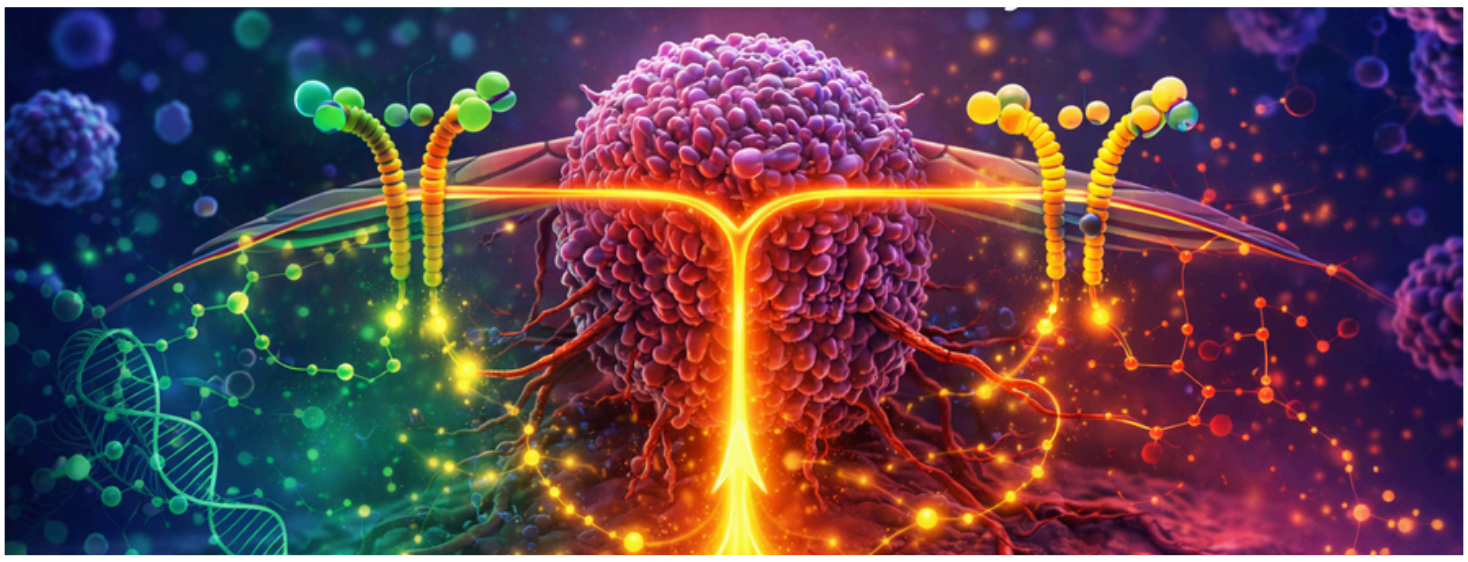

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Prioritizing the Dominant Pathway When Two Active Molecular Targets Co-Exist in CASE OF Metastatic leiomyosarcoma

Case Overview

AT-A-GLANCE CASE SUMMARY	
Metastatic Leiomyosarcoma: When All Actionable Pathways Are Exhausted	
Domain	**Key Information**
Case	47-year-old male | ECOG 2 | Metastatic leiomyosarcoma (lung) | post-surgery + radiotherapy
Prior Therapies	Gemcitabine-docetaxel → Adriamycin-trabectedin → Pembrolizumab + Olaparib (all progressed)
NGS Platform	Guardant360 Tissue | >100 gene panel | 70% tumour content
Key Biomarkers	MSI-High | TMB >10 mut/Mb | BRCA2 biallelic loss (VAF 33%) | MSH2 frameshift (VAF 89%) | HRD positive | PD-L1 CPS <1
Additional Alterations	ATRX, TP53, NF1, TSC2, ERCC6L2–THADA fusion (no standard actionable targets)
Family History	Lynch syndrome pedigree (mother: MSI-H bladder cancer)
Dominant Pathways	dMMR / MSI-H → prior ICI exposure with progression | HRD / BRCA2 → prior PARP exposure with progression
vMTB Focus Question	What is the rational next step when all actionable molecular pathways have been exploited and the patient has progressed?
vMTB Recommendation	Platinum re-sensitisation strategy → olaparib maintenance if response achieved | Mandatory germline testing

A 47-year-old male with ECOG performance status 2 was diagnosed with metastatic leiomyosarcoma involving bilateral lung metastases. Initial management included surgery and radiotherapy in 2024. The disease was subsequently treated across three lines of systemic therapy: gemcitabine–docetaxel, Adriamycin–trabectedin, and pembrolizumab combined with olaparib. PET-CT confirmed progressive disease after each line. Family history was significant for Lynch syndrome (mother with MSI-H bladder cancer), raising the clinical question of a germline MMR defect. The case was referred to the virtual Molecular Tumour Board (vMTB) to address a fundamentally important precision oncology question: what constitutes rational next-line therapy when both available tumour-agnostic molecular pathways — MMR deficiency and BRCA2 biallelic loss — have been exploited and the patient has progressed on both?

MOLECULAR LANDSCAPE

The ladder below classifies all detected alterations by actionability tier — from actively exploited tumour-agnostic targets (Tier I) through investigational targets (Tier III) to permissive biology-only events (Tier IV). This case illustrates the clinical scenario in which both Tier I pathways (dMMR/MSI-H and HRD/BRCA2) have been sequentially exploited with disease progression, leaving only biology-context and investigational options. Evidence ratings are based on current FDA approvals and NCCN guidelines.

FIGURE 1: Molecular Hierarchy Framework

TIER	PATHWAY	ALTERATION	ACTIONABILITY	STATUS AT PRESENTATION
I	MMR Deficiency	MSH2 L762Gfs*2 (VAF 89%) | MSI-High	FDA tumour-agnostic (pembrolizumab) (1)	EXPLOITED — Progressed on ICI
I	Homologous Recombination Deficiency	BRCA2 biallelic loss (VAF 33%) | HRD+/LOH	FDA tumour-agnostic (olaparib) (2,3)	EXPLOITED — Progressed on olaparib
II	DNA Damage Response	HRD positivity (LOH)	Platinum sensitivity; PARP maintenance rationale (4,5)	RESIDUAL STRATEGY — Platinum re-sensitization
III	MAPK Signaling	NF1 loss	MEK inhibition (investigational in sarcoma) (6)	NO STANDARD THERAPY — Trial only
III	mTOR Pathway	TSC2 alteration	mTOR inhibition (investigational in sarcoma) (6)	NO STANDARD THERAPY — Trial only
IV	Tumour Suppressor / Chromatin	ATRX, TP53	Permissive genomic instability — not directly targetable	BIOLOGY CONTEXT ONLY
IV	Fusion	ERCC6L2–THADA	Unknown clinical significance in leiomyosarcoma	BIOLOGY CONTEXT ONLY

Comprehensive genomic profiling (Guardant360 Tissue, >100 gene panel, 70% tumour content) identified a complex mutational landscape. MSI-High status and a TMB of >10 mut/Mb confirmed defective mismatch repair biology. A pathogenic MSH2 frameshift mutation (L762Gfs*2, VAF 89%) was the dominant MMR driver, with a high variant allele frequency strongly suggesting germline origin in the context of a Lynch syndrome family history. (7,8) BRCA2 biallelic inactivation was confirmed through a frameshift mutation (I605Nfs*11) and copy number deletion (VAF 33%), with a positive HRD score and LOH indicating a functionally deficient homologous recombination pathway. [4,5] PD-L1 CPS was <1.

Additional alterations included ATRX truncation (chromatin remodeler, not directly targetable), TP53 mutation (tumour suppressor loss, permissive genomic instability), NF1 loss (MAPK pathway — MEK inhibition investigational in sarcoma), TSC2 alteration (mTOR pathway — mTOR inhibition investigational), and an ERCC6L2–THADA fusion of unknown clinical significance.(6) None of these secondary alterations had validated therapeutic implications in leiomyosarcoma at the time of vMTB discussion.

DECISION FORK – CLINICAL REASONING

With Tier I targets exhausted, the vMTB deliberated between re-engaging residual HRD biology through platinum re-sensitisation (Path A) versus pivoting to sarcoma-standard cytotoxic strategies (Path B). In-text citations within the table indicate the primary trial evidence underpinning each choice.

CLINICAL DECISION FORK: When Actionable Pathways Are Exhausted	
PATH A: Platinum Re-Sensitisation Strategy (vMTB Preferred)	**PATH B: Sarcoma-Standard Cytotoxic Therapy (Alternative)**
Rationale HRD+/LOH biology may restore PARP sensitivity after platinum exposure (4,5); BRCA2 biallelic loss supports platinum vulnerability (9)	**Rationale** Evidence-based sarcoma options remain viable irrespective of molecular profile (10,11)
Agent Carboplatin + gemcitabine; olaparib maintenance if ≥PR (4,5)	**Agent** Eribulin (preferred) (10) | Pazopanib (11) | Dacarbazine
Evidence Basis HRD/BRCA2 retrospective sarcoma data (9); platinum-then-PARP maintenance sequence analogous to BRCA-mutated ovarian cancer (4,5)	**Evidence Basis** EORTC E62012 (eribulin OS benefit) (10); PALETTE trial (pazopanib PFS) (11)
Benefit Assumption Molecular pathway re-engagement: potentially durable if platinum response achieved (4)	**Benefit Assumption** Modest PFS/OS benefit; no molecular enrichment (10,11)
Toxicity Haematological; renal (cisplatin); ECOG 2 demands careful agent selection	**Toxicity** Peripheral neuropathy (eribulin) (10); GI/hepatic (pazopanib) (11)
IO Rechallenge? Not recommended — biological resistance presumed after ICI failure (7,12)	**IO Rechallenge?** Not recommended — no evidence supports IO rechallenge after dMMR ICI failure (1)
Indian Context Carboplatin widely available; cost-effective (6); olaparib maintenance rational if funded (6)	**Indian Context** Eribulin costly (10); pazopanib more accessible; generic options limited (6)

VMTB DISCUSSION AND PATHWAY INTERPRETATION

4.1 CLINICAL CONTEXT

The vMTB noted that this patient represented an advanced-disease scenario characterized by rapid progression across three prior lines, an ECOG 2 performance status limiting tolerance for intensive therapy, and a genomic profile in which both available tumour-agnostic biomarkers had been targeted without clinical benefit. The board emphasized that this is an increasingly encountered clinical archetype in molecular oncology: the molecularly rich but therapeutically exhausted patient. The central educational message was that a positive biomarker report does not guarantee therapeutic benefit, and that prior exposure with progression represents biological — not merely administrative — failure of that pathway.

TEACHING POINT

A comprehensive NGS report listing actionable mutations does not equate to actionable treatment options. Contextual interpretation — including what the patient has already received and at what dose — is essential before recommending targeted therapy.

4.2 MOLECULAR PATHWAY INTERPRETATION

1. Mismatch Repair Deficiency (MSH2 Frameshift, MSI-H): The MSH2 L762Gfs*2 mutation (VAF 89%) with concomitant MSI-High and elevated TMB represents canonical dMMR biology. The board acknowledged that MSI-H is an FDA-approved, tumour-agnostic predictive biomarker for PD-1 blockade, with approval based on the KEYNOTE-158 basket trial demonstrating an ORR of approximately 34% across 10 tumour types.(7) Dostarlimab is an additional approved option for dMMR solid tumours based on the GARNET study (13). However, the patient received pembrolizumab as part of a combination regimen and demonstrated disease progression. The vMTB concluded that progression despite adequate immune checkpoint exposure represents primary or acquired immune resistance — not biomarker failure. The high VAF (89%) of the MSH2 mutation also strongly favoured germline Lynch syndrome origin, mandating formal germline testing. (8,14)

> **TEACHING POINT**
>
> MSI-H predicts ICI response probability but does not guarantee it. In patients progressing on pembrolizumab, presumed biological resistance — through secondary mutations in MMR pathway, antigen loss, or immune exclusion — renders rechallenge irrational without evidence. MSI-H should not be used as justification for indefinite ICI continuation after confirmed progression.

2. BRCA2 Biallelic Loss and HRD (Homologous Recombination Deficiency): BRCA2 biallelic inactivation (frameshift + copy number deletion, VAF 33%) with HRD positivity and LOH identified a functionally impaired DNA repair mechanism, theoretically conferring sensitivity to both platinum salts and PARP inhibitors.(2,3) The key principle from the SOLO-1 and SOLO-2 maintenance trials is that PARP inhibitors function most effectively as maintenance after platinum response rather than as standalone salvage agents.(4,5) However, progression occurred on an olaparib-containing combination regimen in this patient. PARP rechallenge as a standalone strategy was therefore not supported. The board reasoned that platinum compounds, by inducing DNA double-strand breaks through a mechanism distinct from PARP trapping, could potentially re-establish HRD dependency — the rationale for the platinum re-sensitization strategy. (4)

> **TEACHING POINT**
>
> Biallelic loss is more predictive of HRD vulnerability than monoallelic mutation. However, prior PARP inhibitor exposure creates a PARP-resistant subclone landscape. Platinum re-sensitisation attempts to exploit the BRCA2 defect through a mechanistically distinct DNA damaging approach before re-engaging PARP inhibition as maintenance. This sequence — platinum → PARP maintenance — is supported by analogous evidence from BRCA-mutated ovarian and breast cancers.

3.NF1 and TSC2 Alterations — Investigational Targets Only: Both NF1 loss (MAPK/RAS pathway) and TSC2 alteration (mTOR pathway) were identified. Although these alterations activate canonically targetable pathways (MEK inhibitors for NF1, everolimus for TSC2), the board noted the absence of meaningful randomised evidence supporting MEK or mTOR inhibition in leiomyosarcoma.(6) Neither alteration was considered actionable in standard practice. Clinical trial enrolment was noted as the appropriate pathway.

PITFALL

The presence of NF1 or TSC2 mutations in a broad-panel NGS report does not constitute a rationale for MEK or mTOR inhibitor use in leiomyosarcoma. Pathway activation without tumour-type-specific evidence is insufficient justification for off-label use outside a trial

4.3 PRIORITIZING THE DOMINANT PATHWAY WHEN TWO ACTIVE MOLECULAR TARGETS CO-EXIST

General Framework: How to Select the Dominant Pathway

When comprehensive genomic profiling reveals two or more concurrently actionable molecular pathways, the treating oncologist and Molecular Tumour Board face a critical decision: which pathway should be considered biologically dominant and therapeutically prioritised? The selection framework rests on five hierarchical criteria. First, tumour type–specific evidence strength: a pathway with phase III randomised controlled trial evidence in the specific tumour histotype should take precedence over one supported only by tumour-agnostic basket trial data or retrospective series.(1,2,7) Second, driver versus passenger distinction: the alteration with the highest variant allele frequency (VAF), biallelic status, or functional loss—indicating clonal dominance and near-complete pathway abrogation—is more likely to represent the dominant oncogenic driver. Monoallelic, sub-clonal, or low-VAF findings are less likely to be therapeutically decisive.(2,3) Third, predicted response magnitude and durability: immune-mediated responses via MSI-H/PD-1 blockade, when they occur, tend to be durable and potentially long-lasting, whereas PARP inhibitor responses in HRD tumours outside the ovarian/breast context are frequently shorter-lived and subject to acquired resistance through secondary reversion mutations or restoration of fork protection.(4,5,7) Fourth, sequencing feasibility and line of therapy: a pathway for which therapy is best deployed as a first-line or maintenance strategy (e.g., PARP inhibitor after platinum induction) may rationally be sequenced second even if it is biologically co-dominant, in order to first exploit the pathway with greater early response potential. Fifth, the co-mutation context: co-existing alterations that are known to confer resistance to one of the competing therapies (e.g., STK11/KEAP1 mutations predicting ICI resistance, or secondary BRCA reversion mutations predicting PARP inhibitor resistance) can shift the balance toward the other pathway, even if the first pathway's biomarker is present.(12) In practice, no single criterion is determinative; the MTB must weigh all five in the context of the individual patient's disease burden, performance status, prior therapy, and treatment goals. When two pathways are judged genuinely co-equal, combination or sequential strategies may be considered, though the risk of additive toxicity must be modelled against the benefit of dual pathway suppression. (2,6,7)

CRITERION	PRINCIPLE FOR PATHWAY PRIORITISATION
Evidence Strength	Tumour-type-specific phase III RCT evidence takes precedence over tumour-agnostic basket trial data or retrospective series.
Clonal Dominance	High VAF, biallelic status, or homozygous loss indicates clonal driver dominance and is more therapeutically decisive than sub-clonal, monoallelic, or low-VAF findings.
Response Durability	Immune-mediated responses (MSI-H/ICI) tend toward durability; HRD/PARP responses are frequently shorter-lived and subject to acquired resistance through reversion mutations or fork protection restoration.
Sequencing Feasibility	A pathway best deployed in a maintenance or post-induction setting (e.g., PARP inhibitor after platinum) may rationally be sequenced second even if co-dominant, to first exploit the pathway with greater early response potential.
Co-mutation Context	Co-existing alterations known to predict resistance to one therapy (e.g., STK11/KEAP1 for ICI; secondary BRCA reversion for PARP inhibitors) shift the balance toward the competing pathway.

Application to This Case: MSI-H and BRCA2 Biallelic Loss in Leiomyosarcoma

Applying the five-criterion framework to this case clarifies why the vMTB sequenced immunotherapy ahead of PARP inhibition at presentation, and why neither can now be simply re-deployed. At the time of initial NGS reporting, two genuinely actionable tumour-agnostic biomarkers were identified: MSI-High (dMMR, MSH2 frameshift) and BRCA2 biallelic loss (HRD-positive). Applying criterion 1 (evidence strength), both biomarkers carried FDA tumour-agnostic approvals supported by basket trial data (2,7) no tumour-type-specific phase III RCT was available in leiomyosarcoma for either target, placing them at equivalent evidence tiers in this isotype. Criterion 2 (clonal dominance) favoured the MSI-H pathway: the MSH2 frameshift was present at a markedly higher VAF (89%) than the BRCA2 biallelic loss (VAF 33%), indicating that dMMR was a clonally dominant event present in nearly all sampled tumour cells, while BRCA2 loss was a sub clonal or secondary event present in approximately one-third. A clonally dominant driver is more likely to be a bona fide therapeutic target than a sub clonal alteration that may represent tumour heterogeneity.(2,3) Criterion 3 (response durability) also favoured MSI-H: dMMR-driven immune responses, when achieved, can produce long-term complete or partial remissions occasionally exceeding several years,(1,7) whereas PARP inhibitor responses in non-ovarian/breast solid tumours are typically less durable, with acquired resistance developing through BRCA reversion mutations, CDK12 alterations, or upregulation of alternative DNA repair pathways. Criterion 4 (sequencing feasibility) provided the decisive practical rationale: the PARP inhibitor maintenance paradigm —delivering olaparib after platinum induction to consolidate a DNA damage response—is a well-established strategy in BRCA-deficient ovarian and breast cancer.(4,5) Deploying olaparib concurrently with pembrolizumab, however, was intended to capture dual pathway synergy (immune activation + DNA repair inhibition), not a replacement for the sequential platinum-first strategy. Criterion 5 (co-mutation context) revealed no definitive ICI-resistance co-mutations such as STK11 or KEAP1 loss at the time of initial profiling, supporting a first attempt with immunotherapy.(12) The combined pembrolizumab-olaparib regimen was therefore a clinically defensible strategy, grounded in criteria 2, 3, and 5 favoring the immune pathway as the dominant one. Nonetheless, progressive disease on this combination has now foreclosed both pathways simultaneously, bringing this case to the present clinical challenge: pathway-exhausted precision oncology.(2,4,7) The residual biological rationale for the platinum re-sensitisation strategy now rests on criterion 4 revisited: rather than attempting direct PARP rechallenge, exploiting the remaining HRD biology through a mechanistically

distinct DNA damaging agent (platinum) first—and only then consolidating with olaparib maintenance if a meaningful response is achieved—represents the optimal and most evidence-informed pathway sequence available to this patient at this stage of disease.(4,5,9)

4.4 EVIDENCE REVIEW

MSI-H / dMMR Immunotherapy: KEYNOTE-158 established pembrolizumab as tumour-agnostic therapy for MSI-H/dMMR solid tumours, demonstrating an ORR of approximately 34% across 10 tumour types (n=233).(7) KEYNOTE-177 confirmed superiority of pembrolizumab over chemotherapy as first-line treatment in MSI-H metastatic colorectal cancer, reinforcing the predictive value of the biomarker.(1) The GARNET study supported dostarlimab approval for dMMR solid tumours with an ORR of 42.3% in non-endometrial tumours.(13) Neither trial specifically addresses ICI rechallenge after documented clinical progression, and no randomised evidence supports continued PD-1 blockade after confirmed disease progression on ICI therapy.

PARP Inhibitors in BRCA-Altered Tumours: Olaparib demonstrated efficacy in BRCA-mutated prostate cancer in the Profoundly trial (rPFS benefit over enzalutamide/abiraterone, HR 0.34),(2) in BRCA-mutated breast cancer in the Olympia adjuvant trial (invasive DFS benefit, HR 0.42),(3) and in BRCA-mutated pancreatic cancer in the POLO trial (PFS benefit, HR 0.53).(15) Maintenance olaparib following platinum response showed sustained benefit in BRCA-mutated ovarian cancer in SOLO-1 (PFS HR 0.30)(4) and SOLO-2 (PFS HR 0.30).(5) Basket trials including TAPUR and DRUP have shown responses in BRCA-altered non-breast/ovarian solid tumours, though data in leiomyosarcoma specifically remain limited.

Platinum in HRD/BRCA2-Altered Sarcomas: Retrospective data from BRCA-mutated sarcomas suggest platinum sensitivity in selected cases.(9) The mechanistic rationale parallels BRCA-mutated ovarian cancer, where platinum is the backbone of treatment with PARP inhibitor maintenance.(4,5) Prospective sarcoma-specific randomised data are absent; this recommendation was therefore graded as expert consensus with mechanistic biological rationale.

Sarcoma Later-Line Standard Therapy: Eribulin improved overall survival versus dacarbazine in previously treated leiomyosarcoma and liposarcoma (EORTC E62012; median OS 13.5 vs. 11.5 months, HR 0.77).(10) Pazopanib improved progression-free survival in non-adipocytic soft tissue sarcoma in the PALETTE trial (median PFS 4.6 vs. 1.6 months, HR 0.35).(11) These remain the evidence-based cytotoxic alternatives when all molecular targeting has been exhausted and are not biomarker-enriched strategies.

4.5 THERAPEUTIC CONSIDERATIONS

Immunotherapy Continuation: The vMTB did not support IO rechallenge. Despite MSI-H status, the biological case for continued PD-1 blockade after documented progression is weak. (7,12) Presumed immune escape — through secondary somatic reversion mutations in the MMR pathway, loss of MHC class I expression, or upregulation of alternative immune checkpoints — cannot be confirmed without tumour prebiopsy but was the working hypothesis. Re-challenge within a clinical trial (e.g., with anti-CTLA-4 addition for dual checkpoint blockade) was noted as scientifically interesting but non-standard.(12)

PARP Inhibitor Re-Strategy: Rather than direct PARP rechallenge, the vMTB endorsed a sequential platinum → PARP maintenance strategy, contingent on achieving a meaningful objective response to platinum.(4,5,9) This strategy is grounded in the hypothesis that platinum-induced DNA double-strand breaks restore HRD-driven replication stress, re-engaging olaparib sensitivity in residual tumour cells. Carboplatin-based regimens (carboplatin + gemcitabine) were preferred given ECOG 2 performance status, and the available evidence supporting this sequence in analogous BRCA-deficient cancers.

Cytotoxic Alternatives: Eribulin (10) and pazopanib (11) remain viable options without requiring molecular enrichment. Their benefit is disease-isotype-based rather than pathway-driven. These represent the evidence-based fall-back when all molecular targeting has been exhausted. NCCN guidelines for soft tissue sarcoma support both as later-line options.(6)

Germline Testing — Mandatory: The MSH2 frameshift at VAF 89% in a patient with a Lynch syndrome family history constitutes near-certain germline origin. Formal confirmatory germline testing is mandatory, not optional, under NCCN Hereditary Colorectal Cancer guidelines.(8) BRCA2 germline confirmation was also recommended. Cascade testing for first-degree relatives must be recommended regardless of somatic treatment decisions. (8,14)

Indian Practice Considerations: Carboplatin is widely available and cost-effective across all Indian oncology centres, and NCCN guidelines support platinum-based regimens in this setting.(6) Olaparib maintenance, if required, is more cost-rational as a post-response strategy than empirical rechallenge without prior platinum exposure. Eribulin, while expensive, remains accessible at tertiary centres. Pembrolizumab rechallenge without evidence of potential benefit was considered wasteful in the Indian cost-effectiveness context.

PITFALL

MSI-H biomarker positivity does not override clinical evidence of ICI failure. Continuing pembrolizumab after confirmed progression citing MSI-H status is a common error in practice — it conflates predictive biomarker status with guaranteed ongoing therapeutic efficacy. KEYNOTE-158 established initial response probability, not indefinite benefit.(7)

vMTB CHAIR'S NOTE

This case exemplifies one of the most challenging paradigms in modern precision oncology: the patient with a genomically enriched tumour — dual tumour-agnostic biomarkers — who has nonetheless progressed on both corresponding therapies.(2,7) The vMTB's task was not to discover an overlooked targetable mutation, but to reason through how residual molecular biology could guide sequencing of non-targeted therapies. The platinum re-sensitisation strategy applied here reflects mechanism-driven thinking — exploiting BRCA2/HRD biology through a mechanistically distinct DNA damaging modality (4,5,9) — rather than a reflexive return to cytotoxic chemotherapy. The distinction matters for trainee education: precision oncology does not always mean novel targeted agents; sometimes it means using conventional agents in a biologically informed sequence.

FINAL RECOMMENDATION (MTB CONSENSUS)

- **Preferred Next Line:** Platinum-based chemotherapy (carboplatin + gemcitabine preferred given ECOG 2). If significant objective response is achieved, olaparib as maintenance therapy is recommended based on BRCA2 biallelic loss and HRD positivity.
- **Evidence Basis:** HRD/BRCA2 molecular rationale (retrospective sarcoma data); platinum-then-PARP maintenance sequence analogous to BRCA-mutated ovarian cancer; PARP inhibitor maintenance concept.
- **IO Rechallenge:** Not recommended outside clinical trial. Biological resistance to PD-1 blockade is presumed after documented progression on pembrolizumab
- **Germline Testing:** Mandatory — MSH2 germline confirmation + BRCA2 germline confirmation + cascade testing for first-degree relatives
- **If Platinum Fails:** Eribulin (standard of care, later-line leiomyosarcoma) or pazopanib. Clinical trial enrolment (NF1/TSC2-targeting trials, novel sarcoma immunotherapy) should be considered proactively.

KEY LEARNING POINTS

- Biomarker present ≠ therapy effective after prior progression: A positive tumour-agnostic biomarker (MSI-H, BRCA2 biallelic loss) does not guarantee persistent therapeutic benefit after documented progression on the corresponding targeted therapy. Prior exposure context is mandatory before recommending re-challenge.
- Do not continue ICI after confirmed progression on ICI: MSI-H status should not justify continuation of PD-1 blockade after confirmed clinical progression. Biological immune resistance supersedes biomarker positivity.
- Platinum re-sensitization is the rational HRD strategy post-PARP failure: In BRCA2-deficient tumours that have progressed on PARP inhibitors, a platinum → PARP maintenance sequence exploits HRD through a mechanistically distinct DNA damaging approach.
- Combination regimen failure requires mechanistic analysis: Progression on pembrolizumab + olaparib does not automatically confirm resistance to all components. Sequential re-deployment of the same mechanism without an intervening platinum response is not evidence-supported.
- Investigational targets require trial evidence: Secondary alterations (NF1, TSC2) may activate targetable pathways but lack tumour-type-specific evidence in leiomyosarcoma and should not be actioned outside clinical trials.
- High VAF + family history = presumptive germline: A high VAF (>50–80%) of a cancer predisposition gene mutation combined with family history constitutes presumptive germline origin. Formal germline confirmation with cascade testing must be triggered proactively.

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Precision oncology includes mechanism-informed cytotoxic sequencing: When all molecular pathways are

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