MedEdge Series

100 MOLECULAR TUMOR BOARD CASES

Learning Precision Oncology, One Case at a Time

CASE – 1

Navigating Molecular Complexity in MSI-High Metastatic Intrahepatic Cholangiocarcinoma

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Preface

As we complete six months of bi-weekly Virtual Molecular Tumor Board (vMTB) meetings and reach the milestone of 100 complex oncology cases, this compilation reflects a collective commitment to precision oncology, multidisciplinary reasoning, and continuous learning. Moving forward, we will be releasingc two curated cases every month, summarizing key discussions and decision pathways from the vMTB.

We sincerely thank all expert panelists, case presenters, coordinators, technical teams, and statisticians whose dedication and rigor have made this initiative possible. Their collaborative spirit has been central to maintaining the scientific depth and clinical relevance of every discussion.

In parallel, we are conducting a research study based on structured feedback to evaluate the effectiveness and real-world impact of AI integration into the vMTB process, with the goal of strengthening evidence-based, context-appropriate cancer care.

This work stands as a shared achievement, driven by teamwork, curiosity, and a common purpose to advance precision oncology for our patients.

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CHAPTER 1

Navigating Molecular Complexity in MSI-High Metastatic Intrahepatic Cholangiocarcinoma

Case Overview

Table 1: At-a-Glance Case Summary

MSI-High Metastatic Intrahepatic Cholangiocarcinoma	
Domain	**Key Information**
Age / Performance Status	75 years / ECOG 1
Primary Cancer	Metastatic intrahepatic cholangiocarcinoma
Disease Burden	Liver (primary), abdominal lymph nodes, lung
Initial Therapy	Gemcitabine + Carboplatin
Immunotherapy Exposure	Nivolumab 40 mg (Low dose)
Radiologic Response	Necrosis of primary liver lesion; nodal enlargement
Biochemical Trend	Initial CA19-9 decline → subsequent rise
Dominant Molecular Driver	MSI-High / dMMR (MSH2, MSH6 truncating mutations)
Key Co-drivers	**BRCA1 biallelic loss**, STK11, CDKN2A, PTEN
Clinical Dilemma	Mixed response after low-dose PD-1–based treatment: resistance vs(iUPD)
MTB Priority	Optimize PD-1–based treatment before declaring failure
Final MTB Recommendation	Escalate to **full-dose PD-1 inhibitor** → reassess at 4–6 weeks → escalate only if refractory

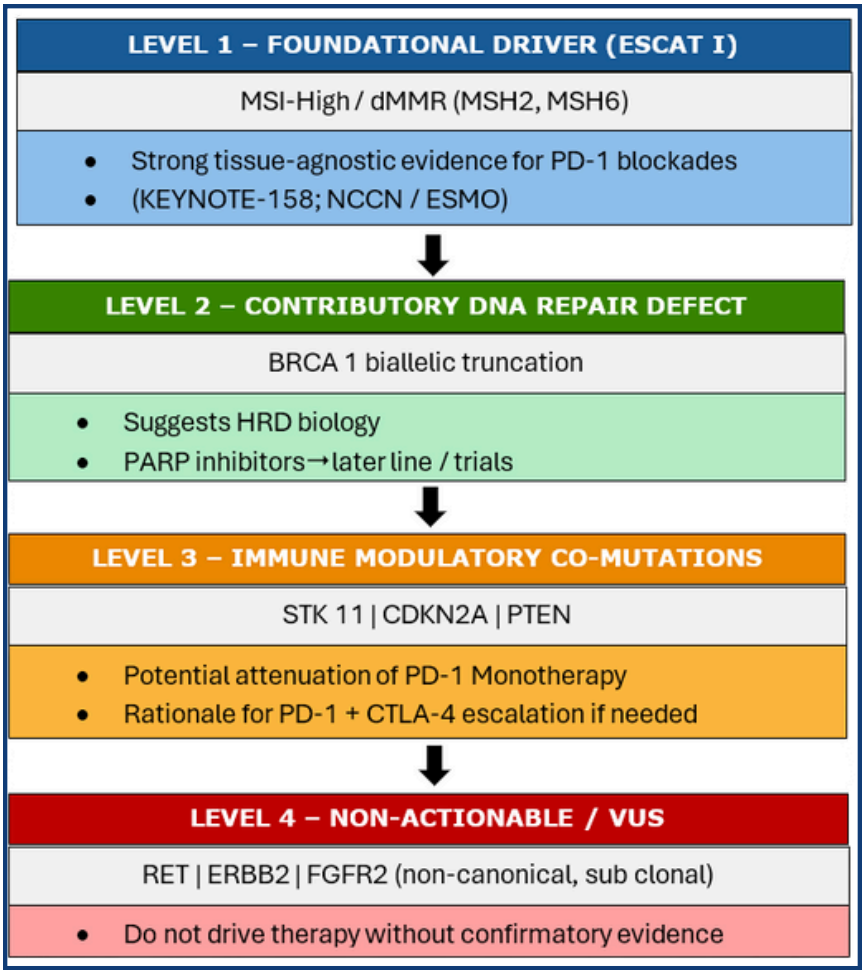
A 75-year-old man with hypertension and preserved functional status (ECOG performance status 1) presented in January 2025 with metastatic intrahepatic cholangiocarcinoma involving the liver, abdominal lymph nodes, and lung. Liver biopsy confirmed poorly differentiated adenocarcinoma with immunohistochemical markers consistent with biliary origin (CK7+, CK19+, CA19-9+) and focal TTF1 positivity. PD-L1 expression by combined positive score was 1.

Initial treatment consisted of gemcitabine-carboplatin doublet chemotherapy. Nivolumab 40 mg was added from cycle 3 onward, and the patient completed six cycles with good tolerance and clinical improvement. However, restaging PET-CT revealed a mixed response pattern: necrosis of the primary hepatic lesion contrasted with enlargement and increased FDG avidity in regional abdominal lymph nodes. Serum CA19-9, which had initially declined, began to rise modestly. This discordant radiologic-biochemical picture, emerging shortly after initiation of checkpoint inhibition at a clearly subtherapeutic dose, prompted presentation to the virtual molecular tumor board.

Molecular Landscape

Comprehensive next-generation sequencing using a 126-gene panel on the tumor tissue identified multiple therapeutically relevant alterations:

FIGURE 1: Molecular Hierarchy Ladder (Flow Diagram)



MISMATCH REPAIR DEFICIENCY (PRIMARY DRIVER)

The tumor demonstrated MSI-high status with pathogenic truncating variants in MSH2 p.E48Wfs*12 and MSH6 p.R248Tfs*8, confirming mismatch repair deficiency.

HOMOLOGOUS RECOMBINATION DEFECT

Two distinct BRCA1 frameshift mutations (p.K339Rfs*2 and p.K654fs*47) were identified in exon 10 at differing variant allele fractions, strongly suggesting biallelic inactivation and an underlying defect in homologous recombination repair.

TUMOR SUPPRESSOR CO-MUTATIONS

Additional pathogenic alterations included:

- TP53 p.R273H (hotspot missense).
- CDKN2A p.R58* (truncating).
- STK11 p.P281Rfs (frameshift).
- PTEN p.N323Mfs (sub-clonal frameshift).
- CIC frameshift.

VARIANTS OF UNCERTAIN SIGNIFICANCE

Tier III variants were noted in RET (p.P799L), ERBB2 (p.P780S), and FGFR2 (p.G793V, subclonal). These non-canonical alterations lack established predictive significance in biliary tract cancer.

Tumor mutational burden and formal homologous recombination deficiency scores were not reported

Clinical Questions Posed to the Molecular Tumor Board (MTB)

- Response interpretation: Does the discordant pattern—necrotic primary with nodal enlargement and rising CA19-9 after subtherapeutic-dose nivolumab—represent true progression or immune-related pseudoprogression (iUPD)?
- MSI-H management: What is the optimal next-line systemic strategy for MSI-H cholangiocarcinoma that has received inadequately dosed immunotherapy alongside platinum doublet chemotherapy?
- BRCA1 actionability: Do biallelic BRCA1 truncating mutations justify PARP inhibitor therapy, either as monotherapy or in combination with immunotherapy, and at what timing?
- Immune resistance modifiers: How should co-existing STK11, CDKN2A, and PTEN alterations influence expectations from PD-1 blockade and inform the choice between PD-1 monotherapy versus dual checkpoint blockade with CTLA-4 inhibition?
- Additional targets: Are the ERBB2 and FGFR2 variants actionable, and do they warrant confirmatory testing with IHC, FISH, or repeat NGS?

MTB DISCUSSION: CLINICAL CONTEXT AND DISEASE TRAJECTORY

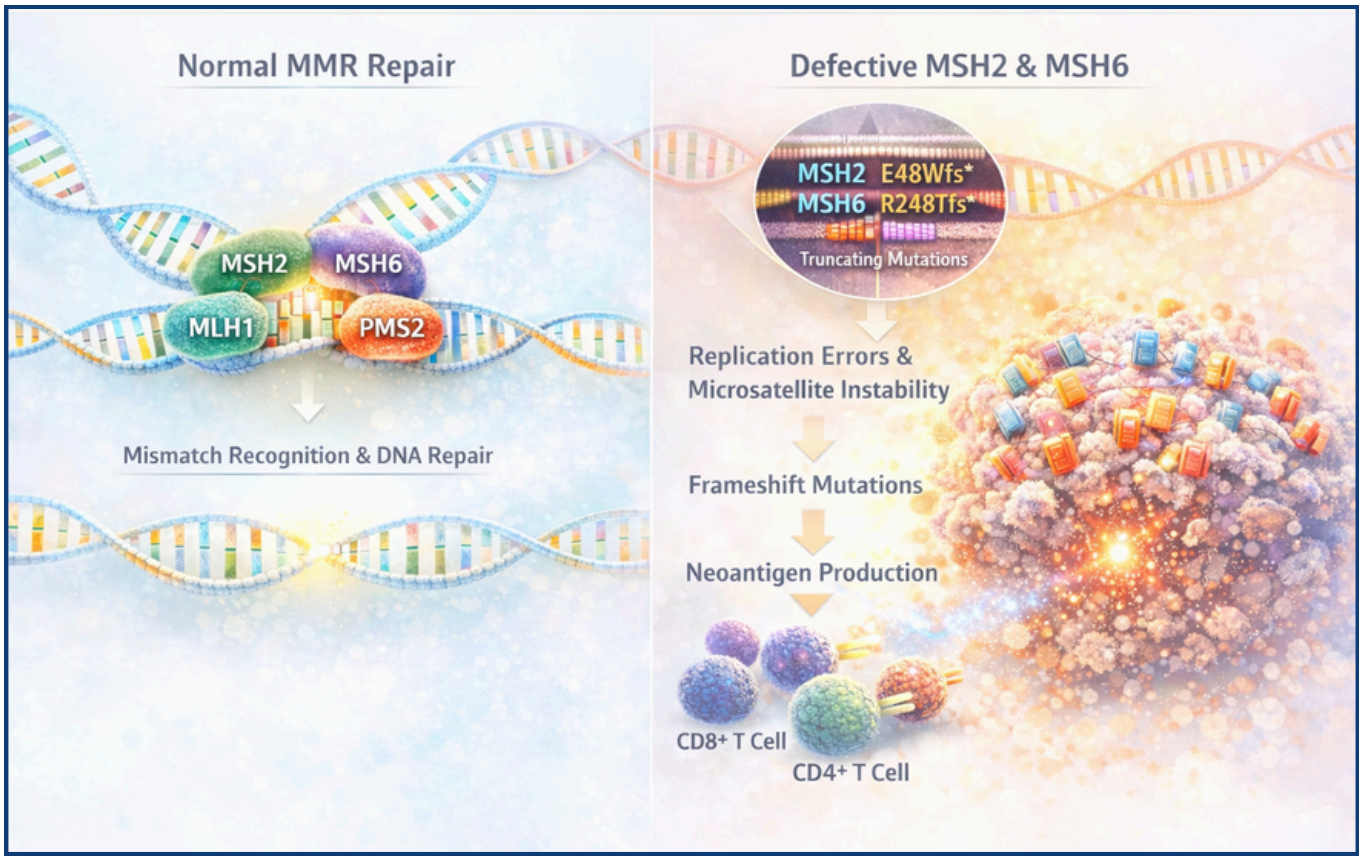
The patient is a 75-year-old male with stage IV cholangiocarcinoma who has demonstrated clinical benefit from first-line therapy without significant immune-related toxicity.

MOLECULAR PATHWAY ANALYSIS

MutSα (MSH2&MSH6 Complex) Disruption as a Determinant of Extreme Immunogenicity in MSI-High Tumors

Truncating pathogenic variants in MSH2 (p.E48Wfs*12) and MSH6 (p.R248Tfs*8; VAF ~16%) result in functional abrogation of the MutSα mismatch recognition complex, establishing DNA mismatch repair deficiency (dMMR) as the dominant oncogenic context driving the microsatellite instability–high (MSI-H) phenotype. As MutSα is essential for the initial sensing of base–base mismatches and short insertion–deletion loops, its loss precipitates pervasive replication slippage across the genome, particularly within coding microsatellites.

FIGURE 2: MutSα Disruption and MSI-High Tumorigenesis

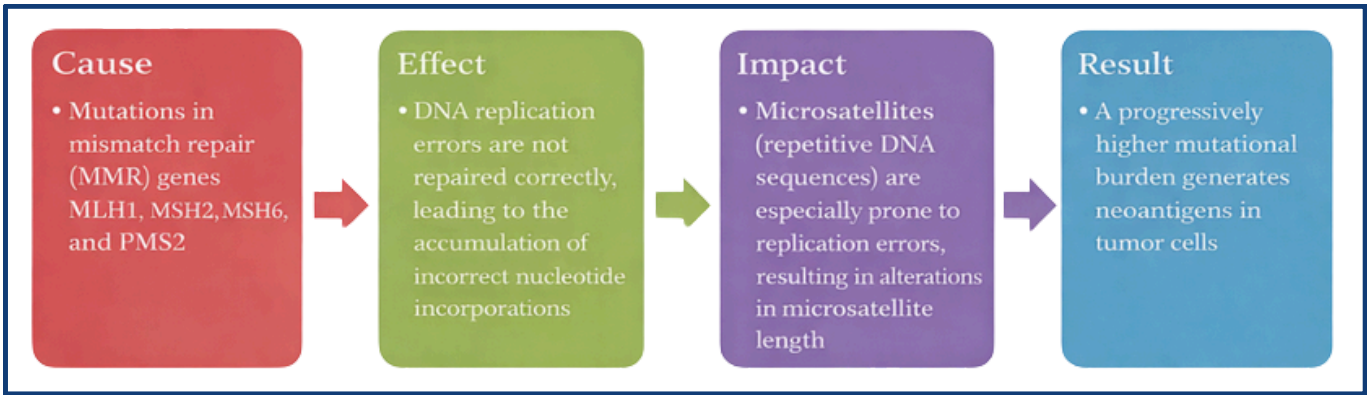


This defect leads to a marked enrichment of frameshift mutations, generating a diverse repertoire of highly immunogenic, tumor-specific neoantigens. These neoantigens are preferentially processed and presented via MHC class I and II pathways, resulting in enhanced T cell priming and sustained antitumor immune surveillance. Consistent with this mechanistic framework, MutS-deficient tumors demonstrate increased immune infiltration, interferon-associated transcriptional programs, and adaptive immune activation, molecular features that are strongly predictive of sensitivity to immune checkpoint blockade.

Notably, comparative clinical analyses reveal that co-loss of MSH2/MSH6 (MutS deficiency) is associated with prolonged median overall survival relative to MLH1/PMS2 (MutL) deficiency across both colorectal and endometrial cancers, suggesting that distinct dMMR genotypes confer differential degrees of tumor immunogenicity. These observations indicate that MutSα disruption confers a quantitatively and qualitatively superior neoantigen landscape, translating into deeper and more durable responses to PD-1/PD-L1–directed immunotherapies.

Together, these data position MSH2/MSH6 truncating alterations as mechanistic drivers of extreme tumor immunogenicity, extending their role beyond MSI-H classification to define a biologically privileged subset of dMMR tumors with heightened and sustained responsiveness to immune checkpoint inhibition.

FIGURE 3: Mechanistic Pathway Linking Mismatch Repair Gene Mutation to Increased Neoantigen Load



MSI-H/dMMR status represents one of the most powerful agnostic biomarkers for benefit from PD-1/PD-L1 blockade across solid tumors.[1,10,12] Within the ESCAT (European Society for Medical Oncology Scale for Clinical Actionability of Molecular Targets) framework, MSI-H/dMMR is categorized as a tier I alteration for immune checkpoint inhibition, conferring level I actionability in biliary tract cancers through tissue-agnostic regulatory approvals.

BRCA1 Loss and Homologous Recombination Deficiency

The presence of two distinct pathogenic BRCA1 (p.K339Rfs*2 and p.K654fs*47) frameshift mutations at different variant allele fractions strongly supports biallelic inactivation, indicating an underlying defect in homologous recombination repair. By analogy to ovarian, breast, pancreatic, and prostate cancers, such tumors frequently exhibit platinum sensitivity and may derive substantial benefit from PARP inhibition.

However, several factors tempered enthusiasm for immediate PARP-based therapy in this case:

- Prospective evidence for PARP inhibitors in cholangiocarcinoma remains sparse, limited to small basket cohorts and case reports.
- The patient demonstrated only modest and mixed benefit from platinum therapy.
- The clearly immunogenic MSI-driven biology represents a more compelling therapeutic target with stronger evidence.

The Variant Allele Frequency (VAF) of BRCA1 K339Rfs*2 and K654fs*47 were 2% and 14% respectively, while the VAF of MSH2 E48Wfs*12 and MSH6 R248Tfs*8 were both 16%. BRCA1 includes one low-VAF (likely subclonal) and one moderate-VAF event; MSI/MMR remains the therapeutic anchor irrespective of VAF. Mismatch repair (MMR) deficiency represents a primary oncogenic driver by inducing a pervasive mutator phenotype that fuels early tumorigenesis, whereas homologous recombination repair (HRR) deficiency predominantly serves as a genomic destabilizer and often require co-driver mutations to drive the cancer, thus it holds more of therapeutic liability rather than an initiating driver of cancer.

Thus MTB consensus held that BRCA1 loss is contributory to the tumor's biology but should not displace dMMR/MSI-H as the primary therapeutic anchor.

Tumor Suppressor Co-mutations: Potential Immune Resistance Signatures

The constellation of CDKN2A truncation, STK11 frameshift, and PTEN loss represents a cluster of tumor suppressor alterations with important implications for immunotherapy response. In lung cancer and melanoma, these alterations are associated with an immune-"cold" tumor microenvironment and primary resistance to PD-1 monotherapy.

STK11-mutant tumors typically exhibit:

- Attenuated T-cell infiltration.
- Lower PD-L1 expression.
- Reduced response rates to single-agent checkpoint inhibition.

In the context of MSI-H disease, these adverse modifiers may be partially counterbalanced by the strong neoantigen-driven immunogenicity. Nevertheless, they provide mechanistic rationale for considering intensified immune checkpoint regimens—specifically PD-1 plus CTLA-4 dual blockade—rather than prolonged reliance on PD-1 monotherapy alone, particularly if initial responses prove suboptimal.

Variants of Uncertain Significance

RET p.P799L, ERBB2 p.P780S, and subclonal FGFR2 p.G793V were classified as tier III variants of uncertain significance. These do not correspond to canonical activating alterations or fusions with established drug sensitivity in biliary tract cancers.

The MTB recommended formal HER2 assessment by immunohistochemistry (and FISH if indicated), recognizing that HER2 amplification or overexpression represents an emerging therapeutic target in cholangiocarcinoma. The FGFR2 variant, being both non-canonical and subclonal, was deemed not clinically actionable.

TEACHING POINT

In genomically complex tumors, therapeutic prioritization should focus on high-impact biomarkers with reproducible predictive value across histologies, alterations with strong guideline-level endorsement, and the alteration most plausibly dominating disease biology in the specific histologic context. Co-mutations frequently modulate but rarely override the implications of a tier I biomarker.

Standard Chemotherapy in Later Lines:

For MSI-H-negative biliary tract cancers, the phase III ABC-06 trial established FOLFOX as a valid second-line regimen after cisplatin-gemcitabine, yielding modest but statistically significant overall survival benefit compared with active symptom control.

In this molecularly enriched, MSI-H context where immunotherapy is strongly indicated and fluoropyrimidine benefit uncertain, the MTB deemed maximizing PD-1-directed therapy more biologically coherent than switching immediately to FOLFOX. Fluoropyrimidine-based regimens therefore remain a backup option if checkpoint blockade is exhausted, contraindicated, or inaccessible.

THERAPEUTIC STRATEGY

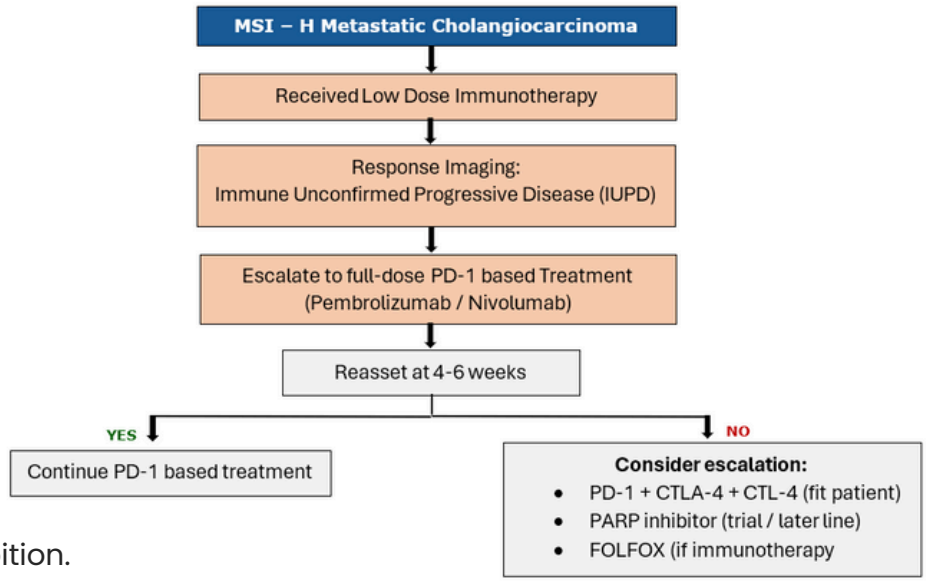
Assessment of Current Disease Status

The MTB interpreted the clinical scenario as immune-related unconfirmed progressive disease (iUPD) under iRECIST, rather than definitive treatment failure. This distinction is critical, as premature declaration of resistance in MSI-H disease exposed only to subtherapeutic PD-1 dosing risks forfeiting the most evidence-backed therapeutic opportunity.

- Necrotic transformation of the primary hepatic lesion suggesting local treatment effect.
- Short interval from introduction of checkpoint inhibition.
- Preserved clinical performance status.
- Markedly subtherapeutic nivolumab dosing (40 mg versus standard 240-480 mg).

The inadequate checkpoint inhibitor dose was recognized as a critical confounder precluding definitive conclusions about intrinsic resistance.

FIGURE 4: Treatment Decision Fork (Flow Diagram)



Optimizing PD-1-Based Therapy

The board identified optimal exploitation of the MSI-H biomarker via full-dose PD-1 inhibition as the central therapeutic priority.

The consensus strategy comprised:

- Maintain checkpoint inhibition.
- Escalate to guideline-concordant PD-1 dosing.
- Reassess clinically, biochemically, and radiologically within 4-6 weeks before declaring primary refractory disease.

Role of PARP Inhibition and Combination Strategies

Despite biologically compelling BRCA1 alterations, the committee deemed immediate PARP inhibition premature. Biallelic BRCA1 loss does not uniformly translate into functional homologous recombination deficiency or PARP inhibitor sensitivity, particularly in the absence of clear platinum responsiveness or validated HRD scoring in cholangiocarcinoma.

- Absence of robust biliary tract cancer-specific efficacy data.
- Suboptimal platinum response suggesting limited homologous recombination dependency.
- Investigational status of PARP-immunotherapy combinations.

The agreed plan deferred PARP-based approaches to later lines, preferably within clinical trials, or to contexts where platinum sensitivity and/or homologous recombination deficiency scoring on repeat NGS provide stronger justification.

Managing Tumor Suppressor Co-mutations

Given the potential for STK11, CDKN2A, and PTEN alterations to attenuate PD-1 monotherapy responses, the MTB discussed escalation to dual checkpoint blockade (PD-1 plus CTLA-4) if the patient demonstrates inadequate benefit on optimized PD-1 monotherapy and remains sufficiently fit to tolerate increased immune-related toxicity.

Owing to limited cholangiocarcinoma-specific evidence and higher toxicity profile, this option was positioned as a subsequent escalation strategy rather than immediate next-line therapy.

FINAL RECOMMENDATION

The MTB interpreted the current radiologic and biomarker pattern as immunotherapy-unconfirmed progression in an MSI-H, dMMR intrahepatic cholangiocarcinoma that has received only inadequately dosed nivolumab.

Primary Recommendation: Pursue immune checkpoint blockade as the principal next-line strategy using full, guideline-concordant dosing of a PD-1 inhibitor (pembrolizumab or nivolumab), with close clinical, biochemical, and radiologic reassessment at 4-6 weeks to determine true sensitivity. [1,2,3,4,10]

Reserved Strategies:

- PARP-based regimens for later lines or clinical trial settings.
- Dual checkpoint blockade (PD-1 plus CTLA-4) for subsequent escalation if inadequate response on optimized PD-1 monotherapy.

Ancillary Testing:

- HER2 evaluation by IHC ± FISH.
- Repeat NGS at progression with HRD scoring and fusion analysis.

FROM THE VMTB CHAIR

"This case illustrates how premature abandonment of immunotherapy—often driven by anxiety over mixed response in imaging—can undermine the most powerful biomarker in oncology. Molecular hierarchy and dose adequacy must always precede escalation."

KEY LEARNING POINTS

- **MSI-H/dMMR represents the dominant actionable biomarker** in this case and should be therapeutically prioritized via adequately dosed PD-1 blockade before considering empiric chemotherapy or experimental strategies. [1,3,4,10,11]

- **Subtherapeutic or delayed immunotherapy introduction can obscure on immunotherapy response interpretation.** Mixed radiologic-response in an MSI-H tumor warrant consideration of immune-related unconfirmed progressive disease (iUPD) under iRECIST criteria and short-interval reassessment rather than reflexive treatment change.

- **Biallelic BRCA1 inactivation implies homologous recombination deficiency**, but given limited and low-level data for PARP inhibition in cholangiocarcinoma, PARP-based therapy is best positioned in later lines or clinical trials, particularly when platinum sensitivity is equivocal. [6]

- **Co-mutations in STK11, CDKN2A, and PTEN may attenuate responses** to PD-1 monotherapy and provide biological rationale for escalation to dual checkpoint blockade in selected, fit patients with suboptimal benefit on PD-1 alone. [8,9]

- **Standard second-line chemotherapy** (FOLFOX per ABC-06) remains valid in biliary tract cancer but may reasonably be deferred in MSI-H disease where immunotherapy has not been fully exploited. [5,7]

- **Variants of uncertain significance** in genes such as RET and FGFR2 should not drive off-label targeted therapy without compelling functional or clinical evidence. HER2 status should be formally evaluated, as amplification/overexpression may enable access to HER2-directed treatments or trials. [3,4].

- **For trainees, this case exemplifies** how molecular hierarchy (MSI-H > BRCA1 > co-mutations), therapeutic evidence level, and real-world constraints (access, cost, toxicity) must be integrated within MTB deliberations to construct a rational, sequence-aware treatment plan.

DISCLAIMER

All recommendations were explicitly contextualized to Indian real-world practice, incorporating drug access, out-of-pocket costs, and patient preferences into shared decision-making.

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