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Montelukast as a Novel Therapeutic Approach in Metastatic Uveal Melanoma Harboring a *CYSLTR2* Mutation: A Translational Case Report

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Introduction[1-4]

- Uveal melanoma (UM) is the most common primary intraocular malignancy in adults, the prognosis is often poor, primarily due to the high risk of liver metastases and the limited systemic treatment options available
- Molecular profiling of UM has revealed distinct genetic alterations, including mutations in *GNAQ*, *GNA11*, *BAP1*, *CYSLTR2*, and *PLCϐ4*
- The cysteinyl leukotriene receptor 1 (CysLT1-R) is overexpressed in various tumor types, and its pharmacologic blockade has shown antitumor effects in several preclinical models. In UM, high expression of CysLT1-R correlates with reduced melanoma-specific and overall survival
- *CYSLTR2* mutations -found in approximately 2–4% of UM cases- represent an early oncogenic event. These mutations lead to constitutive activation of the receptor and downstream endogenous Gαq signaling, the same pathways that are activated by GNAQ/11 mutations
- Montelukast, an FDA-approved, low side effects, CysLT1-R antagonist, commonly used for the treatment of asthma, has demonstrated dose-dependent antiproliferative, pro-apoptotic, and immunomodulatory *effects in vitro* and *in vivo* across various cancer models
- We present the first clinical evidence supporting a durable response to montelukast in a patient with metastatic uveal melanoma harboring a *CYSLTR2* mutation

Case Presentation

- A 59-year-old male was diagnosed with UM in 2010 after visual disturbances enucleation followed, no metastasis at that time point
- 07/21 left flank pain, CT scan revealed abdominal mass, histologically confirmed as UM metastasis
- HLA-A*02:01 negativity, ipilimumab/nivolumab was initiated with partial remission but severe side effect (ir-hepatitis grade 3-4)
- Following disease progression, subsequent lines of therapy were initiated (see timeline); however, no objective response or durable disease stabilization was achieved
- In November 2022, NGS revealed a *CYSLTR2* mutation. Our institutional molecular tumor board recommended off-label therapy with montelukast (10 mg orally, once daily)
- 03/24 initiation montelukast, CT imaging revealed pulmonary, peritoneal, renal, and lymph node metastases. LDH and S100 levels were elevated, the patient was in good general condition, ECOG performance status of 0
- Imaging performed at three-month intervals has demonstrated stable disease. The therapy has been well tolerated, with no adverse events reported to date
- 03/25 minor progression of a single supraclavicular lymph node metastasis
- 06/25 minimal cervical progression and of a subcutaneous metastases

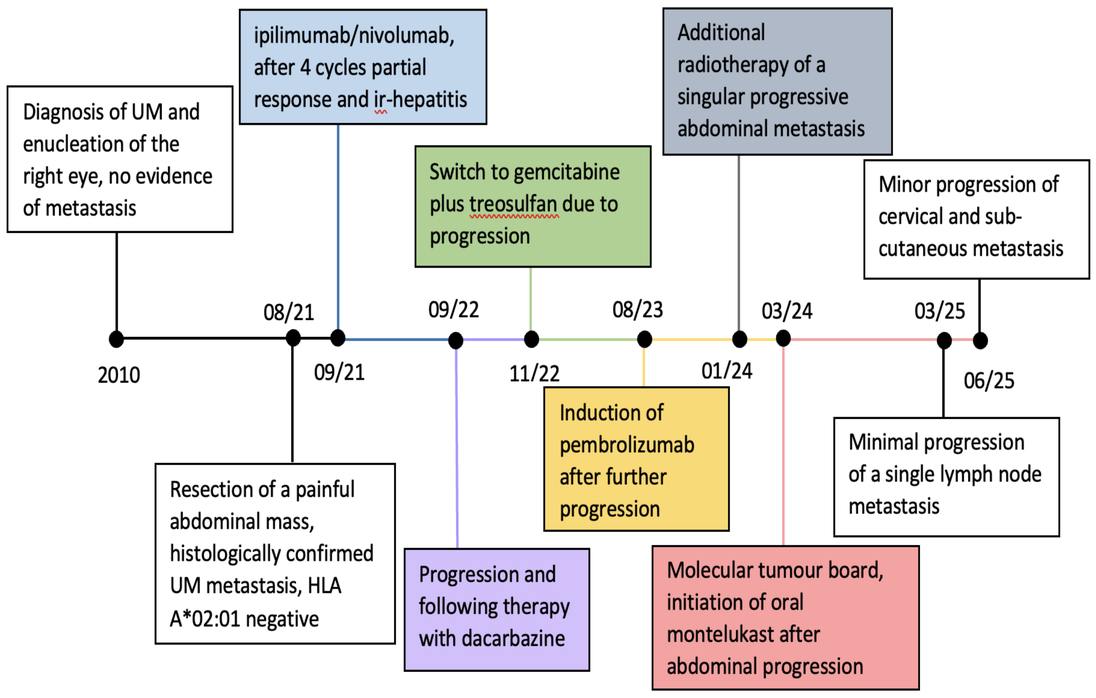


Figure 1. Therapy timeline

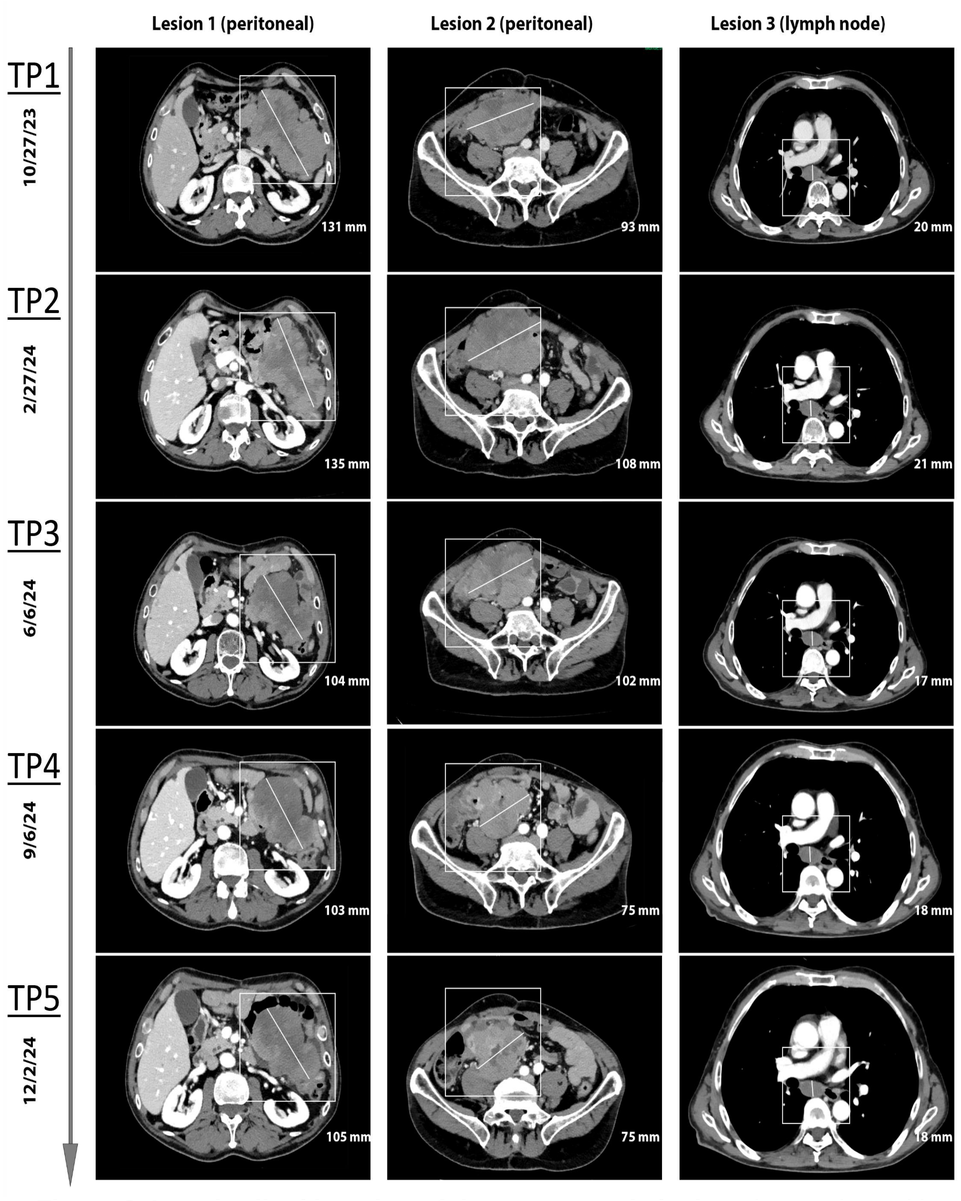


Figure 2. Longitudinal imaging of three metastatic lesions in a patient with uveal melanoma harboring a CYSLTR2 mutation, refractory to standard therapies, receiving Montelukast. Time point (TP) 1 represents the second-latest follow-up prior to therapy initiation with Montelukast, TP2 the baseline immediately before Montelukast, and TP3–TP5 follow-up examinations during treatment. The first column depicts a large peritoneal metastasis in the right lower abdominal quadrant, which increased in size between TP1 and TP2, then decreased after treatment initiation and remained stable thereafter. The second column shows a large peritoneal metastasis in the left upper abdominal quadrant with initial growth from TP1 to TP2, mild regression at TP3, pronounced shrinkage at TP4, and subsequent stability at TP5. The third column illustrates a subcarinal lymph node metastasis demonstrating subtle regression at TP3 followed by stable size through the remaining follow-ups.

Discussion[4, 6-8]

Montelukast achieved sustained disease stabilization over at least 14 months in a patient with heavily pretreated *CYSLTR2*-mutant UM, no side effects recorded until today

Preclinical data suggest that montelukast may suppress tumor growth through two potential mechanisms:

1. antagonizing CysLT1-R signaling pathways involved in tumor proliferation, survival, and inflammatory signaling—independent of mutational background
2. modulating or indirectly antagonizing CysLT2-R expression, which may be particularly relevant in *CYSLTR2*-mutant tumors

From immunological perspective:
Leukotriene signaling via CysLT1-R has been associated with the recruitment of immunosuppressive myeloid cells, increased Th2 cytokine production, and regulatory T cell infiltration—mechanisms that contribute to immune evasion and reduced cytotoxic T cell function
CysLT2-R deficiency enhances Th2-type immune responses in vivo, implying an immunosuppressive capacity

Conclusion[9]

This is the first reported case of montelukast treatment in a patient with heavily pretreated UM. This case suggests that montelukast—a well-tolerated, orally available CysLT1-R antagonist—may offer clinical benefit in patients with metastatic UM, particularly those with *CYSLTR2* mutations.

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