MedEdge Series

100 MOLECULAR TUMOR BOARD CASES

Learning Precision Oncology, One Case at a Time

CASE – 1

Navigating High TMB and Angiogenic Resistance in Metastatic Esophageal Squamous Cell Carcinoma: A Pathway-Informed Approach

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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 2

Navigating High TMB and Angiogenic Resistance in Metastatic Esophageal Squamous Cell Carcinoma: A Pathway-Informed Approach

Case Overview

Table 1: At-a-Glance Case Summary

Navigating Angiogenic Immune Resistance in Metastatic Oesophageal Squamous Cell Carcinoma	
Domain	**Key Information**
Patient Profile	62-year-old male
Performance Status	ECOG 1–2
Cancer Type	Metastatic oesophageal squamous cell carcinoma (ESCC)
Disease Sites	Primary oesophagus; brain metastases
Prior Therapies	Perioperative FLOT → Definitive chemoradiation → WBRT → Toripalimab (Sub-Therapeutic dose) + S-1 + temozolomide
Key Immune Biomarkers	PD-L1 >1%; TMB 16.4 mut/Mb; MSS
Dominant Molecular Features	TP53 biallelic loss; PTEN truncation; NFE2L2 activation
Pathway Convergence	FGF19, MET, PDGFRA amplifications (angiogenic signalling)
Central Clinical Dilemma	Incomplete response to PD-1 blockades despite favourable immune biomarkers
MTB Focus	Overcoming angiogenic immune resistance
Primary Recommendation	**Continue PD-1 blockade (Full dose) + add Lenvatinib**
Escalation Option	Dual checkpoint blockade (PD-1 + CTLA-4) if inadequate response

A 62-year-old male with preserved functional status (ECOG performance status 1–2) and no significant comorbidities presented with metastatic, poorly differentiated oesophageal squamous cell carcinoma (ESCC). Following diagnostic workup, he received multimodal treatment including perioperative FLOT chemotherapy (1,2) for locally advanced disease. Despite this intensive approach, surveillance imaging revealed brain metastases necessitating whole-brain radiotherapy (1).

In the setting of systemic progression with high tumour mutational burden (16.4 mutations/Mb) and PD-L1 expression (>1%), immune checkpoint inhibition with toripalimab was initiated (4,5,6). The patient received toripalimab (Suboptimal dose due to financial constraints) in combination with tegafur (S1) and temozolomide (5,13), representing a creative approach to combine immunotherapy with oral fluoropyrimidine and alkylating agents. However, despite stable local disease, continued brain progression prompted re-evaluation.

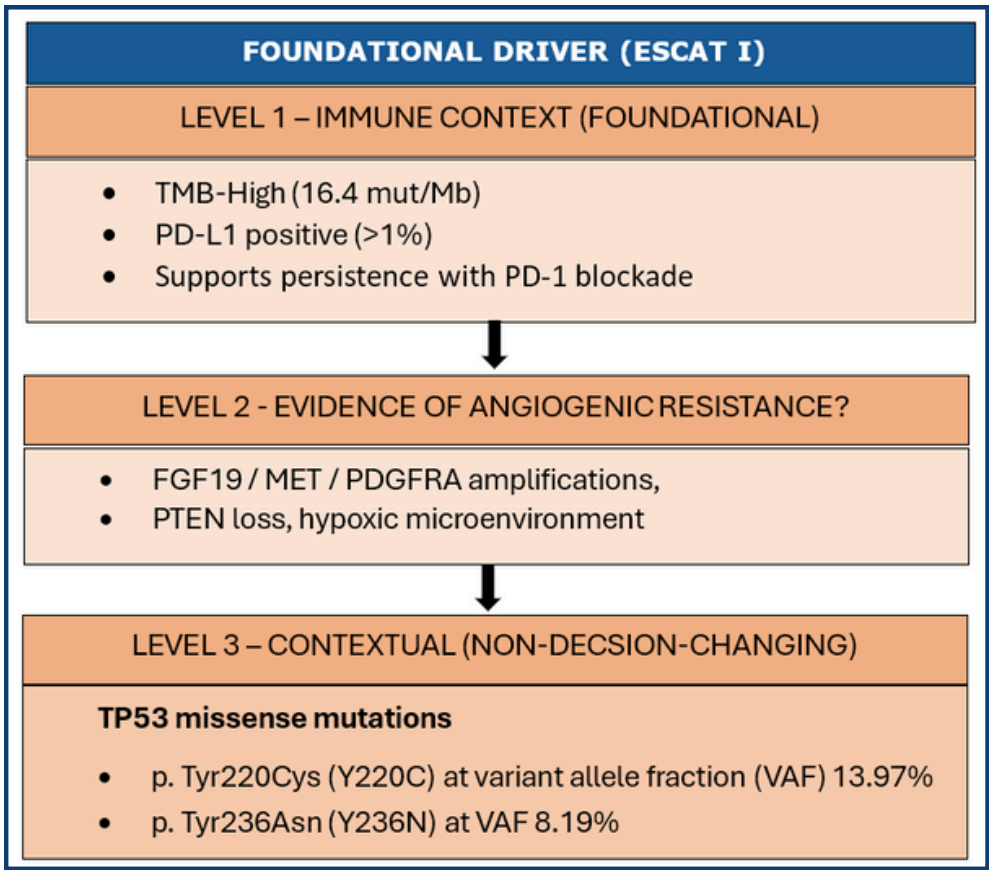
DISCLAIMER

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

MOLECULAR LANDSCAPE

Comprehensive next-generation sequencing using a 161-gene panel (Oncomine CGP) (11) with tumour mutational burden assessment was performed on tissue obtained from the primary esophageal tumor. Tumor cellularity was adequate (10%), with average sequencing coverage of 755× and passing quality control metrics.

FIGURE 1: Molecular Hierarchy Ladder (Flow Diagram)



MISMATCH REPAIR DEFICIENCY (PRIMARY DRIVER)

The tumour demonstrated microsatellite stability (MSS) with an elevated tumour mutational burden of 16.4 mutations/Mb—falling into the intermediate-high range that may predict benefit from checkpoint inhibition (4,6). PD-L1 expression was positive (>1%) by immunohistochemistryt

TUMOUR SUPPRESSOR ALTERATIONS: THE GENOMIC FOUNDATION

The molecular profile was dominated by inactivation of key tumour suppressor genes (10):

TP53 Biallelic Inactivation

Two distinct TP53 missense mutations were identified:

- p. Tyr220Cys (Y220C) at variant allele fraction (VAF) 13.97%
- p. Tyr236Asn (Y236N) at VAF 8.19%

Both variants localize to the DNA-binding domain (exons 6-7), the functional core of p53's tumour suppressive activity (3). Y220C is a well-characterized structural mutant affecting protein stability, while Y236N disrupts DNA contact residues. The presence of two distinct mutations at substantial VAFs strongly suggests biallelic inactivation and complete loss of wild-type p53 function (10,11).

PTEN LOSS OF FUNCTION

A truncating frameshift mutation, p. Glu7Ter (E7Ter), was detected at VAF 6.81%. This early truncation abolishes the lipid phosphatase domain, resulting in complete loss of PTEN tumour suppressor activity (11) and constitutive activation of the PI3K-AKT-mTOR pathway (11). PTEN loss, and the PI3K/AKT pathway activation is associated with increased in M2 TAM infiltration, increase in Micro vessel density, and lymphatic-related metastasis in ESCC specimens. Therefore, PTEN loss could be a useful biomarker to predict high risk for lymphatic-related metastasis in ESCC (24-26).

NFE2L2 ACTIVATION

The p. Asp29Gly (D29G) missense mutation in NFE2L2 (VAF 7.90%) affects the Neh2 domain responsible for KEAP1-mediated degradation. This alteration stabilizes NRF2 protein, enhancing cellular antioxidant responses and conferring resistance to oxidative stress and chemoradiation (11,14). Nuclear NRF2 activation and PD-L1 positivity independently predict aggressive biology and shortened survival in advanced ESCC, serving as robust adverse prognostic biomarkers (20).

NOTCH1 DELETION

An in-frame deletion spanning exon 8 (p. Thr445_Cys449del) was identified. NOTCH1 alterations in ESCC are context-dependent (11) and may function as either oncogenic drivers or tumour suppressors depending on mutation type and location. NOTCH1 mutation was identified as a predictive biomarker for improved outcome with Tislelizumab monotherapy over ICC (RATIONALE-302 Trial). RATIONALE-302 also provided the clinical data, while TMB-H analysis explored biomarkers (like TMB-H and NOTCH1) to better understand who benefits most from tislelizumab, moving towards personalized treatment for ESCC (23).

COPY NUMBER AMPLIFICATIONS: CONVERGING ON ANGIOGENESIS

Three receptor tyrosine kinase pathway genes demonstrated copy number gains (11):

- FGF19 amplification (chromosome 11q13 amplicon, copy number 14)
- MET amplification (chromosome 7q31, copy number 8.9)
- PDGFRA amplification (chromosome 4q12, specific copy number not quantified)

Clinical Questions Posed to the Molecular Tumor Board (MTB)

- Actionability of copy number amplifications: Do the identified FGF19, MET, and PDGFRA amplifications represent therapeutically exploitable pathways in advanced ESCC, and if so, through what mechanism—direct oncogene inhibition or vascular normalization? (3)
- Immunotherapy persistence rationale: Is continuation of PD-1 blockade biologically justified despite incomplete radiologic response, given the high TMB and PD-L1 positivity? At what point should immunotherapy be considered to have failed? (4,6)
- Combination versus escalation strategies: What is the evidence-based rationale for adding anti-angiogenic therapy versus escalating to dual immune checkpoint blockade (anti-PD-1 plus anti-CTLA-4)? (4,7,9)
- Impact of co-mutations: How should PTEN loss, NFE2L2 mutation, and TP53 biallelic inactivation influence expectations from immunotherapy and inform therapeutic selection? (11,13,14)
- Treatment sequencing in limited reserve: How should therapy be individualized in a heavily pretreated patient with brain metastases, prior cranial irradiation, and limited remaining lines of evidence-based treatment? (1,2)

MTB DISCUSSION: CLINICAL CONTEXT AND DISEASE TRAJECTORY

The MTB recognized this case as representing end-stage standard-of-care exhaustion in metastatic ESCC (1,2) while acknowledging the patient retained sufficient functional status (ECOG 1–2) to tolerate additional systemic intervention. The treatment history was notable for:

- Perioperative chemotherapy (FLOT regimen)
- Definitive concurrent chemoradiation (paclitaxel/carboplatin)
- CNS-directed radiotherapy for oligometastatic brain disease
- Combination immunotherapy with toripalimab, S1, and temozolomide

Toripalimab was administered at a reduced dose due to financial constraints, raising the possibility of subtherapeutic PD-1 pathway inhibition rather than true primary immunotherapy resistance.

Despite this intensive multimodal approach, the patient demonstrated progressive disease, indicating exhaustion of conventional cytotoxic strategies and emergence of therapy-resistant biology. Several factors constrained further therapeutic decision-making:

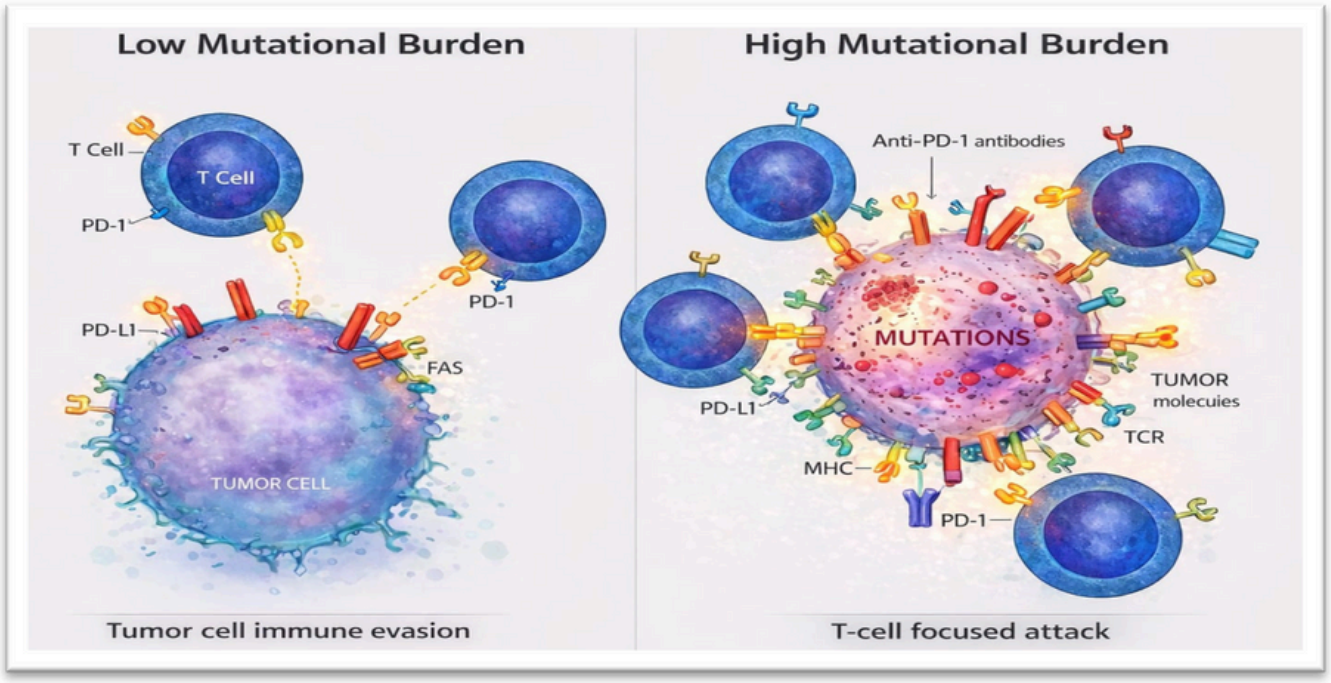
- Cumulative toxicity burden from sequential platinum-based regimens and radiation.
- Diminishing marginal benefit from additional lines of conventional chemotherapy.
- Blood-brain barrier penetration challenges limiting systemic drug delivery to CNS disease.
- Need to preserve quality of life in a patient with finite performance status and organ reserve.

The MTB emphasized that in this clinical context, immunotherapy represented the most biologically rational therapeutic backbone (4,5,6), supported by:

- PD-L1 expression >1% (predictive of checkpoint inhibitor benefit).
- Elevated TMB (16.4 mut/Mb), falling into the range associated with immunotherapy responsiveness.
- Squamous histology (generally more immunogenic than adenocarcinoma).

However, incomplete disease control despite checkpoint inhibition necessitated a conceptual shift from traditional sequential line-of-therapy thinking toward pathway-informed combination strategies designed to overcome specific resistance mechanisms.

Figure 2: Tumor Mutational Burden



A tumour mutational burden of 16.4 mut/Mb places this tumour above histology-specific medians for ESCC and within the range associated with checkpoint inhibitor responsiveness in tissue-agnostic and squamous-enriched datasets.

Tumour mutational burden (TMB) quantifies the total number of somatic mutations per megabase of sequenced DNA, serving as a surrogate marker for neoantigen load. This patient's TMB of 16.4 mutations/Mb falls into the intermediate-high range, substantially exceeding the typical burden in squamous cell carcinomas (median ~5-8 mut/Mb). Elevated TMB arises from defective DNA repair mechanisms, carcinogen exposure (tobacco, environmental mutagens), or—as in this case—loss of tumour suppressor genes like TP53 that coordinate genomic stability. Each somatic mutation has the potential to generate novel peptide sequences (neoantigens) that are displayed on MHC molecules and recognized as "non-self" by the adaptive immune system, rendering tumours with high TMB inherently more immunogenic.

The clinical significance of elevated TMB lies in its predictive value for checkpoint inhibitor benefit across multiple tumour types: TMB-high cancers (typically defined as ≥10 mut/Mb in the KEYNOTE-158 trial, though thresholds vary by assay and histology) demonstrate superior response rates, progression-free survival, and overall survival with PD-1/PD-L1 blockade compared to TMB-low tumours, independent of histology. The KEYNOTE-158 study established TMB ≥10 mut/Mb as a tissue-agnostic biomarker, leading to FDA approval of pembrolizumab for TMB-high solid tumours that have progressed after prior treatment and have no satisfactory alternative options (14). In this patient, the elevated TMB provided strong biological rationale for maintaining PD-1 inhibition as the therapeutic backbone despite incomplete radiologic response, as high neoantigen burden increases the likelihood of eventual T-cell recognition and durable immune control.

TP53 BIALLELIC INACTIVATION: THE PERMISSIVE CONTEXT

TP53 biallelic inactivation functions as a landscape-defining alteration that shapes genomic instability, angiogenic dependence, and treatment resistance, rather than as a direct therapeutic target. At immunomodulatory doses, anti-angiogenic agents promote transient vascular normalization rather than vascular ablation, facilitating immune cell trafficking and restoring sensitivity to checkpoint inhibition.

The presence of two distinct TP53 mutations (Y220C and Y236N) at substantial variant allele fractions indicates complete loss of wild-type p53 tumor suppressor function. In the MTB discussion, this finding was interpreted not as a direct therapeutic target, but as a permissive driver creating downstream biological consequences that shape treatment strategy.

Loss of p53-mediated cell cycle checkpoint control promotes genomic instability (11), contributing to the observed TMB elevation and generating immunogenic neoantigens. Simultaneously, loss of p53's suppression of VEGF expression (9,11) and HIF-1α stabilization removes critical brakes on angiogenesis, mechanistically linking to the observed FGF19, MET, and PDGFRA amplifications. The failure of prior chemoradiation to achieve durable control is consistent with p53 loss impairing apoptotic responses to genotoxic stress.

While TP53 mutations are not directly targetable in routine practice, they inform treatment strategy by explaining prior therapy failures, directing focus toward non-DNA-damaging mechanisms (immunotherapy, targeted agents), and revealing dependencies on compensatory pathways (angiogenesis, PI3K-AKT) that may be therapeutically exploitable.

TEACHING POINT

In advanced solid tumours, TP53 alterations should be viewed as landscape-defining features that shape tumor biology and treatment resistance patterns rather than as isolated targetable events. The clinical value lies in understanding what dependencies TP53 loss creates, not in attempting direct TP53 restoration.

PTEN LOSS AND PI3K PATHWAY ACTIVATION

PTEN loss is associated with an immunologically cold microenvironment and is linked to reduced depth and durability of response to PD-1 monotherapy rather than absolute resistance.

The truncating PTEN E7Ter mutation results in complete loss of the tumor suppressor's lipid phosphatase activity, leading to constitutive activation of the PI3K-AKT-mTOR signalling axis. The MTB discussion highlighted several implications of PTEN loss in the immunotherapy context:

PTEN-DEFICIENT TUMOURS DEMONSTRATE:

- Increased recruitment of myeloid-derived suppressor cells (MDSCs) (13).
- Enhanced regulatory T-cell (Treg) infiltration.
- Upregulation of immunosuppressive cytokines.
- Potential primary resistance to PD-1 monotherapy.

CONTRIBUTION TO ANGIOGENIC PHENOTYPE

At immunomodulatory doses, anti-angiogenic agents promote transient vascular normalization rather than vascular ablation, facilitating immune cell trafficking and restoring sensitivity to checkpoint inhibition.

PTEN loss activates AKT, which stabilizes HIF-1α (9,12) even under normoxic conditions, driving constitutive expression of VEGF and other pro-angiogenic factors. This mechanistically links PTEN loss to the angiogenic amplifications (FGF19, MET, PDGFRA), suggesting convergent pathway activation.

PTEN loss is associated with an immunologically cold microenvironment and is linked to reduced depth and durability of response to PD-1 monotherapy rather than absolute resistance.

At immunomodulatory doses, anti-angiogenic agents promote transient vascular normalization rather than vascular ablation, facilitating immune cell trafficking and restoring sensitivity to checkpoint inhibition.

THERAPEUTIC VULNERABILITY

While PI3K/AKT inhibitors show limited single-agent activity in solid tumours, PTEN loss may create synthetic lethal opportunities when combined with other targeted agents or immunotherapy.

NFE2L2 MUTATION, LYMPHATIC METASTASIS AND THERAPEUTIC RESISTANCE

In ESCC, NRF2 overexpression is strongly associated with lymph node metastasis, tumour recurrence following surgery, and poorer overall survival outcomes (22). The NFE2L2 D29G mutation disrupts the Neh2 domain responsible for KEAP1-mediated proteasomal degradation, resulting in constitutive stabilization and nuclear accumulation of NRF2 transcription factor.

In advanced oesophageal squamous cell carcinoma (ESCC), activation of the NRF2 signalling pathway and PD-L1 expression are associated with significantly inferior survival outcomes. Patients with NRF2 overexpression demonstrated markedly reduced median overall survival (OS) compared with those lacking expression (24.0 vs 48.0 months). This adverse effect was more pronounced in tumours exhibiting predominant nuclear NRF2 localization (>20%), where median OS declined to 17.0 months, highlighting transcriptionally active NRF2 as a driver of aggressive disease biology. Similarly, PD-L1 positivity (CPS ≥10) correlated with shortened survival (22.0 vs 48.0 months). Multivariate Cox regression confirmed nuclear NRF2 expression and PD-L1 CPS as independent prognostic factors, underscoring their combined role in defining a high-risk ESCC subset characterized by immune evasion, therapeutic resistance, and poor clinical outcomes (19).

NRF2 SIGNALLING AND LYMPHATIC METASTASIS:

NRF2 may promote lymph angiogenesis by governing both basal and inducible expression of genes that modulate endothelial cell proliferation, e.g., NOTCH1, PDGFRA and VEGF signaling pathways (22).

OXIDATIVE STRESS RESISTANCE

Enhanced expression of antioxidant response element (ARE)-regulated genes including glutathione synthesis enzymes, NADPH-generating enzymes, and drug efflux pumps.

CHEMORADIATION RESISTANCE

NFE2L2-mutant ESCC demonstrates reduced sensitivity to platinum agents (14) and ionizing radiation—mechanistically consistent with this patient's progression through definitive chemoradiation.

CLINICAL CORRELATION

NFE2L2-mutant ESCC demonstrates reduced sensitivity to platinum agents (14) and ionizing radiation—mechanistically consistent with this patient's progression through definitive chemoradiation.

Evidence Base: Studies in ESCC cohorts demonstrate that NFE2L2 mutations predict inferior outcomes with chemoradiation and may identify patients requiring alternative first-line approaches or treatment intensification. [References: PMID 34358647, 32759723]

COPY NUMBER AMPLIFICATIONS: THE ANGIOGENIC CONVERGENCE

These copy number gains are best interpreted not as isolated oncogenic drivers, but as convergent amplifications reinforcing an angiogenic, immune-excluded tumour microenvironment.

At immunomodulatory doses, anti-angiogenic agents promote transient vascular normalization rather than vascular ablation, facilitating immune cell trafficking and restoring sensitivity to checkpoint inhibition.

The MTB devoted substantial discussion to interpreting the biological significance of FGF19, MET, and PDGFRA co-amplification—a pattern that emerged as the central therapeutic opportunity in this molecularly complex case.

FROM ISOLATED ALTERATIONS TO PATHWAY CONVERGENCE

Rather than viewing these amplifications as independent events, the MTB interpreted them as convergent activation of overlapping signalling networks. FGF19 amplification (chromosome 11q13) drives ligand-dependent FGFR4 activation in gastrointestinal epithelia, triggering RAS-RAF-MEK-ERK, PI3K-AKT, and STAT3 signalling while promoting VEGF production and abnormal vasculature. MET amplification causes ligand-independent receptor dimerization and constitutive pathway activation, stimulating endothelial proliferation, recruiting pericytes, promoting lymph angiogenesis, and creating hyperpermeable vessels.

PDGFRA amplification drives platelet-derived growth factor receptor alpha activation, recruiting cancer-associated fibroblasts, depositing dense extracellular matrix, enhancing pericyte coverage of tumour vessels, and remodelling stroma in ways that physically exclude immune cells from tumour parenchyma. Collectively, these three amplifications converge on a shared biological outcome (9,11): creation of an immunosuppressive, angiogenesis-driven tumor microenvironment that impedes effective immune surveillance and checkpoint inhibitor activity.

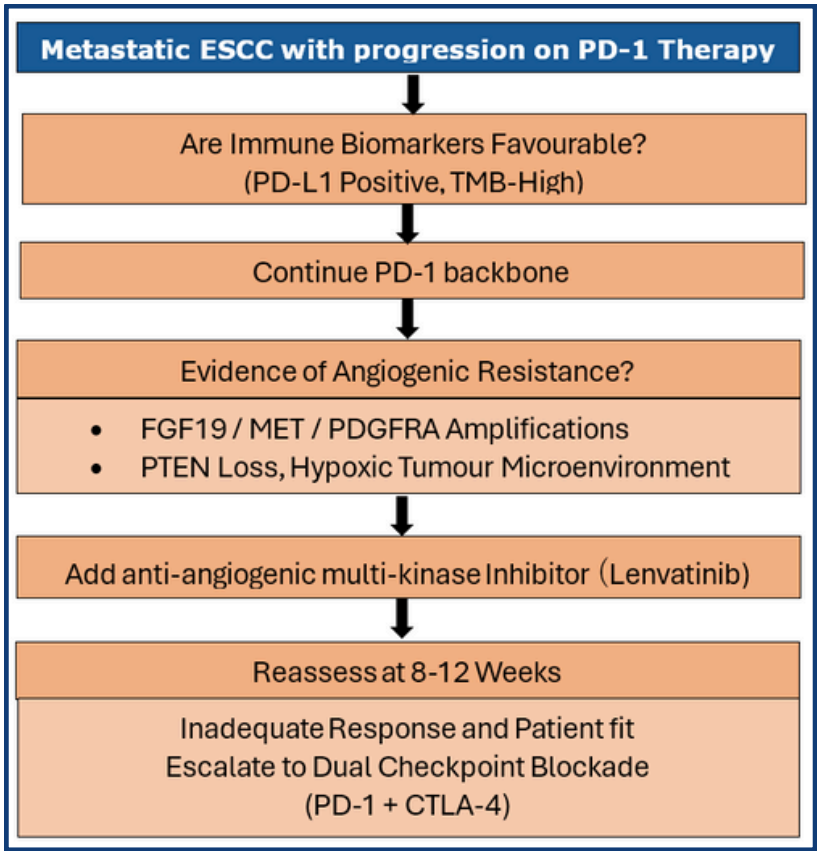
MECHANISTIC LINK TO IMMUNE RESISTANCE

The MTB emphasized that in squamous malignancies, angiogenic amplifications function primarily as immune resistance modifiers rather than classic oncogene drivers. Abnormal tumour vasculature creates chaotic vessels with poor perfusion, generating hypoxic and acidotic conditions that impair T-cell trafficking and physically exclude effector immune cells.Simultaneously, VEGF-mediated recruitment of myeloid-derived suppressor cells and regulatory T cells, polarization of tumour-associated macrophages toward M2 phenotype, and immunosuppressive cytokine production reinforce immune evasion. The therapeutic rationale centres on vascular normalization rather than vascular starvation: at appropriate doses, anti-angiogenic agents prune immature vessels while normalizing remaining vasculature through improved pericyte coverage and reduced permeability, enhancing tumour perfusion to facilitate T-cell infiltration and restore checkpoint inhibitor activity (9,10).

TEACHING POINT

The therapeutic goal with anti-angiogenic agents in this context is not direct tumor shrinkage through vascular starvation (the classic anti-VEGF paradigm), but rather vascular normalization to restore immune cell access. This represents a paradigm shift in how oncologists should conceptualize anti-angiogenic therapy in the immunotherapy era. At immunomodulatory doses, anti-angiogenic agents promote transient vascular normalization rather than vascular ablation, facilitating immune cell trafficking and restoring sensitivity to checkpoint inhibition.

Figure 4: Treatment Decision Fork (Flow Diagram)



IMMUNOTHERAPY IN ADVANCED ESCC

The MTB's recommendation to continue immunotherapy was anchored in robust clinical trial evidence establishing checkpoint inhibition as standard-of-care in biomarker-selected ESCC. The landmark CheckMate-648 Phase III trial fundamentally transformed treatment paradigms by comparing three arms in first-line advanced disease: nivolumab plus platinum-fluoropyrimidine chemotherapy, nivolumab plus ipilimumab dual checkpoint blockade, and chemotherapy alone. In the PD-L1 ≥1% population, both immunotherapy-containing regimens demonstrated substantial overall survival benefit—nivolumab plus chemotherapy achieved median OS of 15.4 months versus 9.1 months with chemotherapy alone (HR 0.54, p<0.001), while nivolumab plus ipilimumab yielded median OS of 13.7 months versus 9.1 months (HR 0.64, p<0.001). In Checkmate 648, Comprehensive biomarker analyses shown that, NIVO + chemo arm, patients with TMB-high tumours had numerically longer median OS (MOS) compared with TMB-low tumours, although the number of patients with TMB-high tumours was small (n=32). Higher inflammation and lower β-catenin GES scores were associated with improved OS benefit of NIVO + chemo or IPI vs chemo. fibroblast GES scores were associated with improved OS benefit of NIVO + Chemo vs chemo (4). Critically, both immunotherapy arms demonstrated durable benefit with separation of long-term survival curves, establishing that PD-L1-positive ESCC derives significant benefit from PD-1-based

therapy and validating both chemo-immunotherapy and dual checkpoint blockade approaches in biomarker-selected patients. (5).

Multiple confirmatory trials with different PD-1 inhibitors have subsequently validated checkpoint inhibition benefit in ESCC, establishing this as a class effect rather than drug-specific phenomenon. The JUPITER-06 trial specifically evaluated toripalimab—the agent this patient was receiving—demonstrating that first-line toripalimab plus chemotherapy versus chemotherapy alone improved median progression-free survival from 5.6 to 11.3 months, thereby establishing toripalimab as a viable PD-1 option with regulatory approval in several Asian markets.

This evidence was particularly relevant to the MTB discussion given the patient's current therapy, providing strong biological rationale for maintaining PD-1 blockade as the therapeutic backbone while addressing resistance mechanisms through complementary pathway inhibition (5)

EMERGING EVIDENCE: ANTI-ANGIOGENIC PLUS IMMUNOTHERAPY SYNERGY

The MTB's rationale for adding Lenvatinib was informed by convergent evidence from translational research and clinical trials. Preclinical studies demonstrate that anti-angiogenic agents overcome immune resistance (9) through vascular normalization—anti-VEGF therapy transiently normalizes tumour vasculature, improving immune cell trafficking, reducing MDSC and Treg infiltration, and enhancing T-cell tumour penetration. A landmark review by Fukumura and colleagues synthesized this mechanistic basis, providing theoretical foundation for the MTB's recommendation. (9)

The CLEAR trial provided proof-of-principle (7) for Lenvatinib plus pembrolizumab feasibility and efficacy in advanced renal cell carcinoma. Compared to sunitinib, the combination achieved median PFS of 23.9 versus 9.2 months (HR 0.39, $p<0.001$) and ORR of 71% versus 36%, with manageable toxicity through dose modifications. This established pharmacologic feasibility and dramatic synergy in solid tumours.

Most directly relevant, the ongoing LEAP-014 Phase III trial (8) prospectively evaluates pembrolizumab plus Lenvatinib plus chemotherapy versus pembrolizumab plus chemotherapy in first-line advanced ESCC, with PFS and OS as primary endpoints. Investigators hypothesized that Lenvatinib’s multi-RTK inhibition would overcome angiogenic immune resistance and target FGFR-amplified subsets enriched in ESCC. While data are not mature, the trial design validates the biological hypothesis and reflects expert consensus on this combination's promise.

TEACHING POINT

The MTB decision exemplifies evidence-informed practice, synthesizing biological rationale (angiogenic amplifications driving immune resistance), proof-of-concept from RCC (CLEAR trial), and ongoing prospective validation (LEAP-014) to justify therapy in a patient with limited alternatives

ALTERNATIVE STRATEGY: DUAL CHECKPOINT BLOCKADE

The MTB also considered escalation to dual checkpoint blockade (PD-1 + CTLA-4) as an alternative intensification strategy. This patient's TMB of 16.4 mut/Mb falls into the predictive range for benefit, as TMB-high tumours demonstrate greater neoantigen burden (4,17), enhanced T-cell recognition, and improved responses to CTLA-4 blockade which enhances T-cell priming.

The dual checkpoint blockade arm of CheckMate-648 (nivolumab + ipilimumab) demonstrated median OS of 13.7 versus 9.1 months (HR 0.64) in PD-L1 ≥1% patients with durable responses in a subset, though Grade 3-4 treatment-related adverse events occurred in 32% versus 18% with nivolumab plus chemotherapy, including colitis, hepatitis, pneumonitis, and endocrinopathies.

Despite biological rationale and clinical evidence, dual checkpoint blockade was reserved as second-line escalation rather than immediate next step due to patient-specific factors—prior brain metastases (risk of catastrophic CNS immune-related AEs), age 62 with limited organ reserve, and cumulative treatment burden affecting quality of life—and strategic reasoning to exhaust the angiogenic strategy first (addressing a specific resistance mechanism with manageable toxicity) while preserving dual blockade as an escalation option if Lenvatinib fails, prioritizing toxicity-conscious sequencing with better therapeutic index.

TEACHING POINT

In heavily pretreated patients with comorbidities, the MTB balanced efficacy against quality of life. While TMB-high status supports dual blockade, thoughtful sequencing that preserves options and minimizes cumulative toxicity is essential in palliative settings.

FINAL RECOMMENDATION

The MTB interpreted this case as a molecularly complex, TMB-high, PD-L1-positive metastatic ESCC with copy number-driven angiogenic resistance to immunotherapy. The patient has exhausted standard cytotoxic approaches but retains favorable molecular features (TMB-high, PD-L1+) supporting continued checkpoint inhibition.

PRIMARY RECOMMENDATION

Continue PD-1 blockade with toripalimab and add Lenvatinib (1,3,7) (starting dose 20 mg daily, or 14 mg daily with escalation based on tolerance) to target angiogenic and receptor tyrosine kinase-driven immune resistance pathways.

RESERVED STRATEGIES

- Dual checkpoint blockade (nivolumab + ipilimumab): Consider if inadequate response after 3-6 months on toripalimab + Lenvatinib, provided patient remains fit (ECOG 0-1) and has not developed contraindications to intensified immunotherapy

- Clinical trial enrolment: Pursue concurrently, particularly FGFR-targeted or novel checkpoint combination trials

FROM THE VMTB CHAIR

"This case exemplifies modern precision oncology in squamous malignancies—where treatment decisions are rarely dictated by a single driver mutation.

Instead, the therapeutic strategy emerges from recognizing pathway convergence, immune context, and resistance biology.

The decision to add Lenvatinib reflects a deliberate shift from line-of-therapy thinking to mechanism-of-resistance thinking, using vascular normalization to restore immunotherapy efficacy while preserving future escalation options."

KEY LEARNING POINTS

- Pathway-level thinking in squamous cancers: Metastatic ESCC commonly exhibits convergent pathway dysregulation (angiogenesis, immune evasion, oxidative stress response) rather than single dominant oncogenic drivers.
- TP53 biallelic inactivation functions as a landscape-defining alteration that shapes genomic instability, angiogenic dependence, and treatment resistance, rather than as a direct therapeutic target.
- PTEN loss is associated with an immunologically cold microenvironment and is linked to reduced depth and durability of response to PD-1 monotherapy rather than absolute resistance.
- At immunomodulatory doses, anti-angiogenic agents promote transient vascular normalization rather than vascular ablation, facilitating immune cell trafficking and restoring sensitivity to checkpoint inhibition.
- Copy number amplifications as immune modifiers: In squamous malignancies, angiogenic RTK amplifications (FGF19, MET, PDGFRA) are critical modulators of immunotherapy response rather than classic oncogene drivers. Their therapeutic relevance lies in vascular normalization to restore immune cell trafficking rather than direct oncogene inhibition.
- TMB-high supports immunotherapy persistence: Elevated tumour mutational burden (>10 mut/Mb) provides strong biological rationale for persistence with checkpoint inhibition despite incomplete early responses. Deep, durable responses may require 6-12 months to manifest; premature switching forfeits potential late benefit. This case illustrates the importance of distinguishing inadequate drug exposure from true resistance.

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