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100

MOLECULAR TUMOR BOARD CASES

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CASE – 3

Navigating Biallelic ARID1A Loss and TMB High in Heavily Pretreated Metastatic Breast Cancer

Feedback & Suggestion : +91 63746 46112 dr.arunseshachalamtalks@gmail.com

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EDITOR & CONVENER

Dr. Arun Seshachalam
Head of Oncology,
Dr. GVN Cancer Institute, Trichy.

CO-EDITORS

Dr. Krupa Shankar
Director & Consultant,
NSR Cankure Hospital, Coimbatore.

Dr. K. Niraimathi
Director,
Evidentia Research Solutions, Chennai.

Dr. Arun Kumar
Molecular Geneticist,
GSK Pharmaceutical Pvt Ltd, Bengaluru.

Dr. Silambarasan
Clinical Geneticist/Genome Analyst,
Datar Cancer Genetics, Mumbai

CO-ORDINATORS

Dr. Narendran
Medical Oncologist,
Silverline Hospital, Trichy.

Dr. Chandralekha
Medical Oncology,
Stanely Medical College, Chennai.

Dr. Saju
Medical Oncologist,
Meenakshi Mission Hospital &
Research Centre, Madurai.

PANEL EXPERTS

Dr. Pushpa Singh
Genomic Scientist,
Chennai.

Dr. Darshana Patil
Datar Cancer Genetics,
Maharashtra.

Dr. Aparna Devi
Kauvery Hospital,
Trichy.

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Care, Delhi

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Neuberg centre for
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AMPATH,
Hyderabad.

Dr. Chandramouleswari
VS Hospital, Chennai.

Dr. Brindha Ramanatha
Nishta Integrated
Neurodevelopment Centre,
Chennai.

RESEARCH & ANALYSIS TEAM

Dr. Sindhu Priya
Oncology & Palliative Care,
Ramana Health Care, Trichy.

Ms. Tamilarasi Dharaniraj
Research Associate,
Evidentia Research Solutions, Chennai.

Mr. Akash Rajendran
Technical Support,
Ramana Health Care, Trichy.

CHAPTER 3

Navigating Biallelic ARID1A Loss and TMB High in Heavily Pretreated Metastatic Breast Cancer

Case Overview

Table 1: At-a-Glance Case Summary

Domain	Key Information
Case Title	Navigating TMB-High Biology and Chromatin Remodelling Defects in Metastatic Hormone Receptor-Positive Breast Cancer
Patient Profile	36-year-old premenopausal woman
Performance Status	ECOG 1
Cancer Type	Metastatic ER-positive, PR-low, HER2-negative invasive ductal carcinoma
Disease Sites	Liver, bone, mediastinal nodes, chest wall
Prior Therapies	Anthracycline–taxane → Platinum → Endocrine + CDK4/6i → Fulvestrant → Eribulin ± carboplatin → Olaparib (off-label)
Key Molecular Biomarkers	TMB 17 muts/Mb; MSS; PD-L1 CPS 1; HRD score 37%
Dominant Molecular Features	Biallelic ARID1A frameshift; FGFR1 amp (10 copies); MDM2 amp (19 copies); GATA3 frameshift
Pathway Convergence	Chromatin remodelling defect (ARID1A) + Angiogenic amplicon (12q13-15)
Central Clinical Dilemma	Justifying PARP inhibitor in BRCA wild-type; assessing immunotherapy eligibility in "immune-cold" breast cancer
MTB Focus	Evidence-based sequencing in exhaustion-line setting with complex genomics
Primary Recommendation	Continue Olaparib; reserve pembrolizumab for progression

A 36-year-old premenopausal woman with no significant comorbidities and preserved performance status (ECOG 1) presented with an aggressive clinical course of metastatic hormone receptor-positive breast cancer. Initially diagnosed in September 2020 with ER-positive, PR-low (10%), HER2-negative grade III invasive ductal carcinoma of the right breast, she developed locoregional recurrence within one year (2021) despite adjuvant systemic therapy, followed by distant metastatic relapse in 2024 involving liver, bone, mediastinal lymph nodes, and chest wall.

Her treatment trajectory reflected aggressive biology: anthracycline–taxane backbone, platinum-based chemotherapy, endocrine therapy with CDK4/6 inhibitor (palbociclib), fuluestrent and eribulin with carboplatin. Despite achieving a partial response to eribulin–carboplatin, disease control was short-lived (~4 months), prompting initiation of off-label Olaparib based on emerging data regarding ARID1A-associated DNA damage response vulnerabilities.

At presentation to the virtual Molecular Tumour Board (MTB), the patient had completed two cycles of Olaparib with radiologic stability. Comprehensive genomic profiling revealed biallelic ARID1A loss-of-function, TMB-high status (17 muts/Mb), and MDM2 amplification—raising questions regarding PARP inhibitor continuation, the role of immunotherapy in luminal breast cancer, and optimal sequencing in a heavily pretreated young patient.

DISCLAIMER

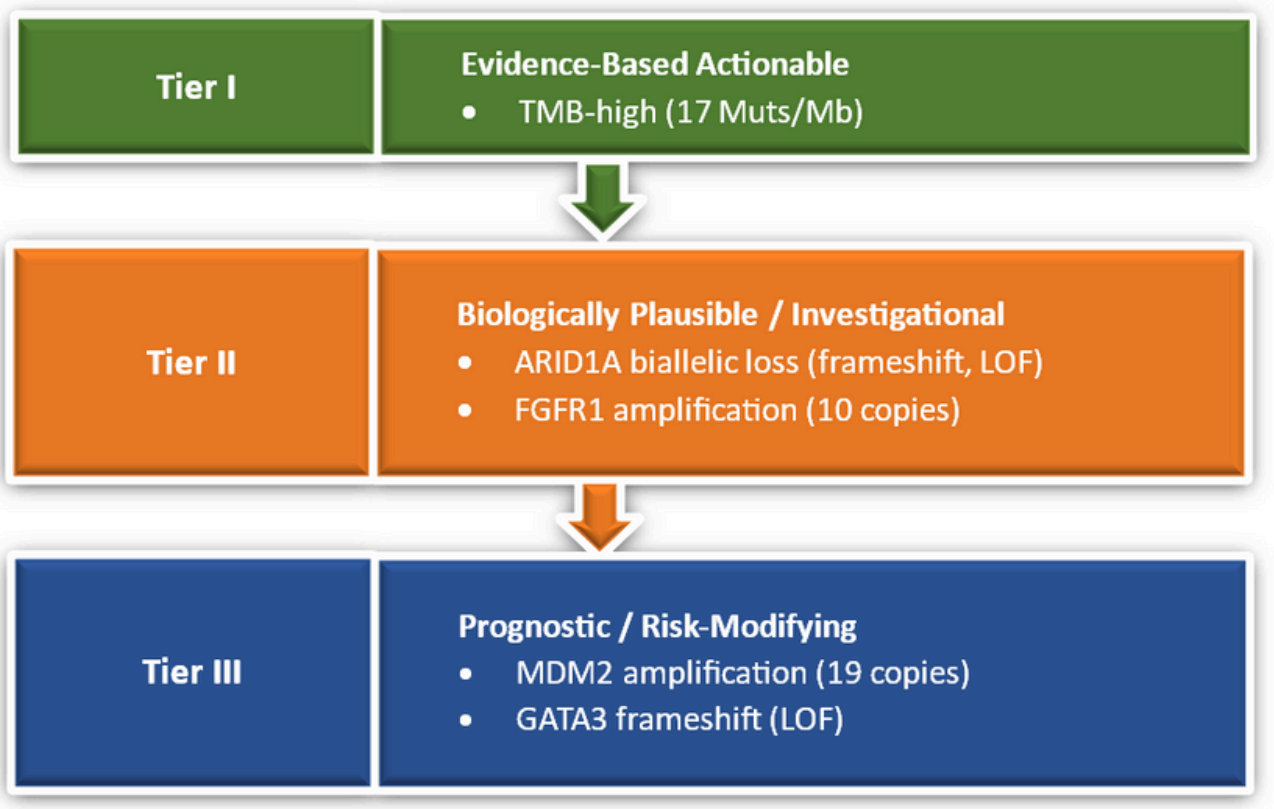
All recommendations were contextualized to Indian real-world practice, incorporating drug accessibility, out-of-pocket costs, prior authorization requirements for immunotherapy, availability of generic versus branded targeted agents, and local treating team expertise. Shared decision-making and quality-of-life preservation were emphasized in a patient with finite organ reserve and multiple prior systemic therapies.

Molecular Landscape

Comprehensive next-generation sequencing was performed using a tissue-based panel covering 324 cancer-related genes with concurrent liquid biopsy analysis. Tumour cellularity was adequate (30%), with mean sequencing coverage exceeding 800×. The profile demonstrated chromatin remodelling dysfunction, genomic instability, and co-amplifications within the 12q13-15 region.

FIGURE 1: Molecular Hierarchy Ladder (Conceptual Framework)

(Flow Diagram)



MOLECULAR RESULTS (ABERRATIONS ONLY; CONSOLIDATED)

BIOMARKER STATUS

- Microsatellite status: MSS
- TMB: 17 muts/Mb
- PD-L1: CPS 1
- HRD score: 37%

VARIANT-LEVEL SUMMARY (KEY ABERRATIONS)

Gene / Region	Alteration	Type	Quant / VAF
ARID1A	p. Glu1849Argfs*8	Frameshift (LOF)	VAF 28%
ARID1A	p. Lys1577Argfs*12	Frameshift (LOF)	VAF 19%
GATA3	p. Asp336Glyfs*17	Frameshift (LOF)	VAF 22%
FGFR1	Amplification	CNV	~10 copies
MDM2	Amplification	CNV	~19 copies
12q13–15 region	Co-amplified genes	CNV cluster	—
Gene / Region	Alteration	Type	Quant / VAF
ARID1A	p. Glu1849Argfs*8	Frameshift (LOF)	VAF 28%
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MDM2	Amplification	CNV	~19 copies

PATHWAY CONVERGENCE (GENOME-TO-BIOLOGY MAP)

- Chromatin remodelling / DDR vulnerability: ARID1A biallelic LOF.
- Immune biomarker axis: TMB-high with PD-L1 low and MSS.
- 12q13–15 amplicon biology: FGFR1 + co-amplifications (signal redundancy / angiogenic context).
- Risk modifier: MDM2 high-level amplification.

TEACHING POINT

Molecular Profiling: Comprehensive NGS interpretation should prioritize patterns of aberrations rather than isolated variants. In heavily pretreated breast cancer, convergence of chromatin remodelling loss, mutational load, and regional co-amplifications often provides more biologic insight than any single mutation.

Clinical Questions Posed to the Molecular Tumor Board (MTB)

- ARID1A loss and PARP inhibitor rationale: Does biallelic ARID1A loss-of-function provide sufficient biological justification for continuing PARP inhibitor therapy in a BRCA wild-type, HRD-low breast cancer, and does the observed disease stability on olaparib represent true synthetic lethality or simply indolent disease biology?
- TMB-high immunotherapy eligibility: Given TMB 17 muts/Mb with PD-L1 CPS 1 in a hormone receptor-positive breast cancer (typically "immune-cold"), is there evidence-based rationale to pursue immune checkpoint inhibitor therapy, and at what line should it be considered?
- MDM2 amplification risk stratification: How should MDM2 amplification modify the risk-benefit assessment for immunotherapy, and what monitoring strategy should be implemented to detect hyper progression?
- FGFR1 amplification actionability: Is there clinical evidence supporting FGFR-directed therapy (selective inhibitors or multi-kinase inhibitors like Lenvatinib) in FGFR1-amplified breast cancer, and how should this be prioritized relative to immunotherapy?
- Treatment sequencing strategy: In a heavily pretreated patient with preserved performance status but limited remaining evidence-based options, how should molecularly guide therapies be sequenced to maximize benefit while preserving quality of life?
- HER2 reassessment: Should HER2 testing be repeated to assess for HER2-low status (IHC 1+ or IHC 2+/ISH-negative) and potential eligibility for antibody-drug conjugates (trastuzumab deruxtecan)?
- Expanded germline testing: Does the young age, aggressive phenotype, and absence of pathogenic BRCA1/2 mutations warrant expanded germline testing including multiplex ligation-dependent probe amplification (MLPA) to detect large genomic rearrangements?

MTB Discussion: Clinical Context and Disease Trajectory

The MTB recognized this as an end-stage standard-of-care exhaustion scenario in aggressive luminal breast cancer, while noting preserved functional status (ECOG 1) and sufficient organ reserve to consider molecularly guided strategies.

TREATMENT HISTORY ANALYSIS

- Rapid exhaustion of endocrine-based therapy: Progression within 12 months on CDK4/6 inhibitor plus aromatase inhibitor, suggesting intrinsic endocrine resistance driven by low PR expression, GATA3 loss, and proliferative biology.
- Chemotherapy responsiveness followed by rapid relapse: Partial response to eribulin–carboplatin lasting ~4 months, indicating chemo sensitive but rapidly adaptive biology.
- Current stability on off-label PARP inhibitor: Two cycles of Olaparib with radiologic stability, raising the question of whether ARID1A loss creates true PARP dependence.

DISEASE BIOLOGY ASSESSMENT

Several features supported atypical luminal biology:

- Young age at diagnosis (<40 years).
- Grade III histology with low PR expression.
- Early recurrence within one year.
- GATA3 frameshift (loss of luminal differentiation).
- High TMB (genomic instability exceeding typical ER+ breast cancer).

Collectively, these features suggested a luminal–basal hybrid phenotype with reduced hormone dependency and increased proliferative drive, explaining aggressive behaviour despite ER positivity.

CONSTRAINTS ON FURTHER THERAPY

- Cumulative toxicity and limited tolerance for further cytotoxic therapy.
- Diminishing benefit from conventional approaches in the sixth-line setting.
- Financial and access constraints in the Indian setting.
- Need to preserve quality of life in a young patient.

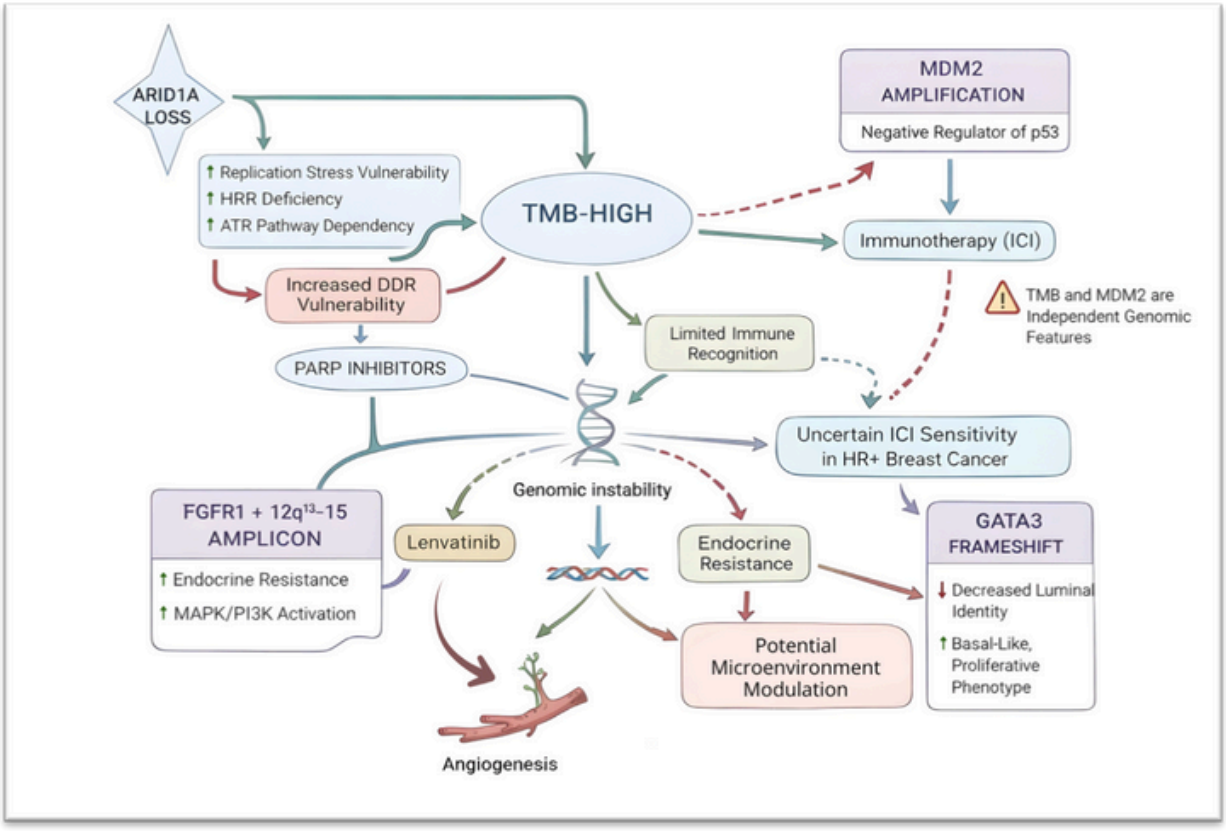
TEACHING POINT

Clinical-Genomic Integration: Aggressive behaviour in ER-positive breast cancer should prompt reassessment of lineage biology. Early endocrine resistance, rapid relapse, and high-grade disease often reflect luminal-basal hybridization, reframing expectations from standard endocrine sequencing.

Molecular Pathway Analysis

FIGURE 2: Molecular Hierarchy Ladder (Conceptual Framework)

(Flow Diagram)



1) ARID1A LOSS: CONTEXT-DEPENDENT DNA DAMAGE RESPONSE VULNERABILITY

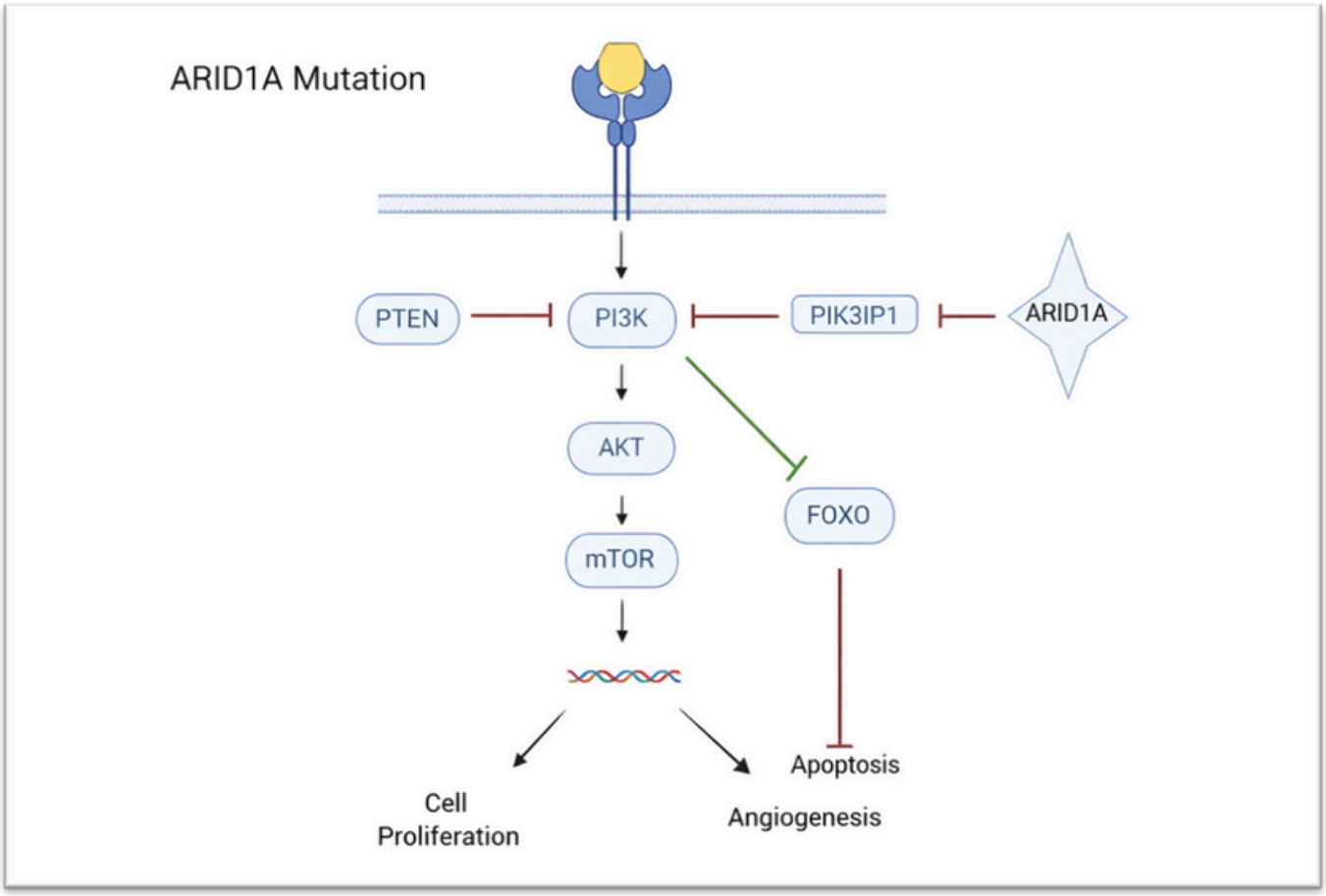
The detection of two independent truncating ARID1A variants (substantial VAFs) supports biallelic loss and functional disruption of the SWI/SNF (BAF) chromatin remodeling complex

CORE MECHANISTIC THEMES DISCUSSED BY THE MTB:

- Replication stress checkpoint impairment (ATR–CHK1 axis): ARID1A loss can impair ATR recruitment at stalled replication forks and attenuate S-phase checkpoint signaling under replication stress (1,2,3).
- Reduced HR efficiency at DSB sites: SWI/SNF dysfunction can limit chromatin accessibility at DNA damage sites, reduce RAD51 focus formation, and lower homologous recombination efficiency—creating a functional HRR deficiency that may not be reflected by genomic scar-based HRD scores (4,5,6).
- Convergent DDR vulnerability: When checkpoint control and HR-mediated repair are simultaneously compromised, accumulated replication-associated lesions can progress to lethal genomic instability under sustained DNA damage pressure (1,2,7).
- Cross-Tumour evidence context (biologic plausibility): Mechanistic and limited clinical response signals have been described most prominently in ovarian clear cell carcinoma and endometrioid endometrial cancers; breast cancer clinical evidence remains limited and largely preclinical (3–5).

Figure 3: Signalling Through the PI3K-AKT-mTOR Pathway

(Flow Diagram)



Beyond its role in chromatin remodelling and DNA damage response, ARID1A loss has critical implications for growth factor signalling through the PI3K-AKT-mTOR pathway (1). ARID1A normally functions as a transcriptional regulator of PIK3IP1 (PI3K-interacting protein 1), a negative regulator of PI3K activity. When ARID1A is lost, PIK3IP1 expression is reduced, removing a critical brake on PI3K signalling. This leads to constitutive activation of the PI3K→AKT→mTOR cascade, driving cell proliferation and survival. Additionally, ARID1A loss dysregulates FOXO transcription factors, which normally promote apoptosis and suppress angiogenesis. The net result is a pro-proliferative, anti-apoptotic, and pro-angiogenic cellular state that mechanistically links ARID1A loss to aggressive tumour biology, endocrine resistance, and the angiogenic amplifications (FGFR1, 12q13-15 amplicon) observed in this patient's tumour. This pathway convergence explains why ARID1A-mutant breast cancers often exhibit rapid progression despite hormone receptor positivity and may benefit from PI3K pathway inhibitors in combination with other targeted therapies.

WHY ARID1A LOSS DOES NOT TRANSLATE INTO HRD POSITIVITY?

Commercial HRD assays measure permanent "genomic scars" such as loss of heterozygosity, telomeric allelic imbalance, and large-scale chromosomal transitions that accumulate over time when homologous recombination is profoundly and chronically defective, as seen with BRCA1/2 loss. ARID1A inactivation, in contrast, produces a more functional and context

DNA damage response weakness by impairing chromatin accessibility and replication stress checkpoint signaling rather than completely abolishing homologous recombination. This defect may be partial, compensable, or acquired later in Tumour evolution, leading to ongoing repair fragility without generating the classic chromosomal scarring pattern detected by HRD assays. As a result, Tumours with ARID1A loss may demonstrate biologic PARP vulnerability despite having low or negative HRD scores.

TEACHING POINT

"BRCAness" encompasses multiple routes to functional HRR deficiency beyond BRCA1/2 mutations. Genomic scar assays capture only a subset of HRR defects; a normal/low HRD score does not exclude alternative DDR vulnerabilities.

2) TMB-HIGH BIOLOGY IN LUMINAL BREAST CANCER

Hormone receptor-positive breast cancers are commonly immune-excluded, with low Tumour-infiltrating lymphocyte density and multiple microenvironmental mechanisms contributing to an "immune-cold" phenotype (7). The MTB discussion focused on whether TMB-high status can act as a tissue-agnostic predictor of immune checkpoint inhibitor responsiveness even in PD-L1–low disease, referencing cross-Tumour evidence from KEYNOTE-158 demonstrating clinically meaningful responses in TMB-high Tumours independent of PD-L1 status (8,9).

Interpretive emphasis: In this case, TMB-high functions as the most evidence-anchored biomarker among the reported alterations, while PD-L1 CPS 1 is recognized as a contextual variable rather than an exclusion criterion in a tissue-agnostic framework.

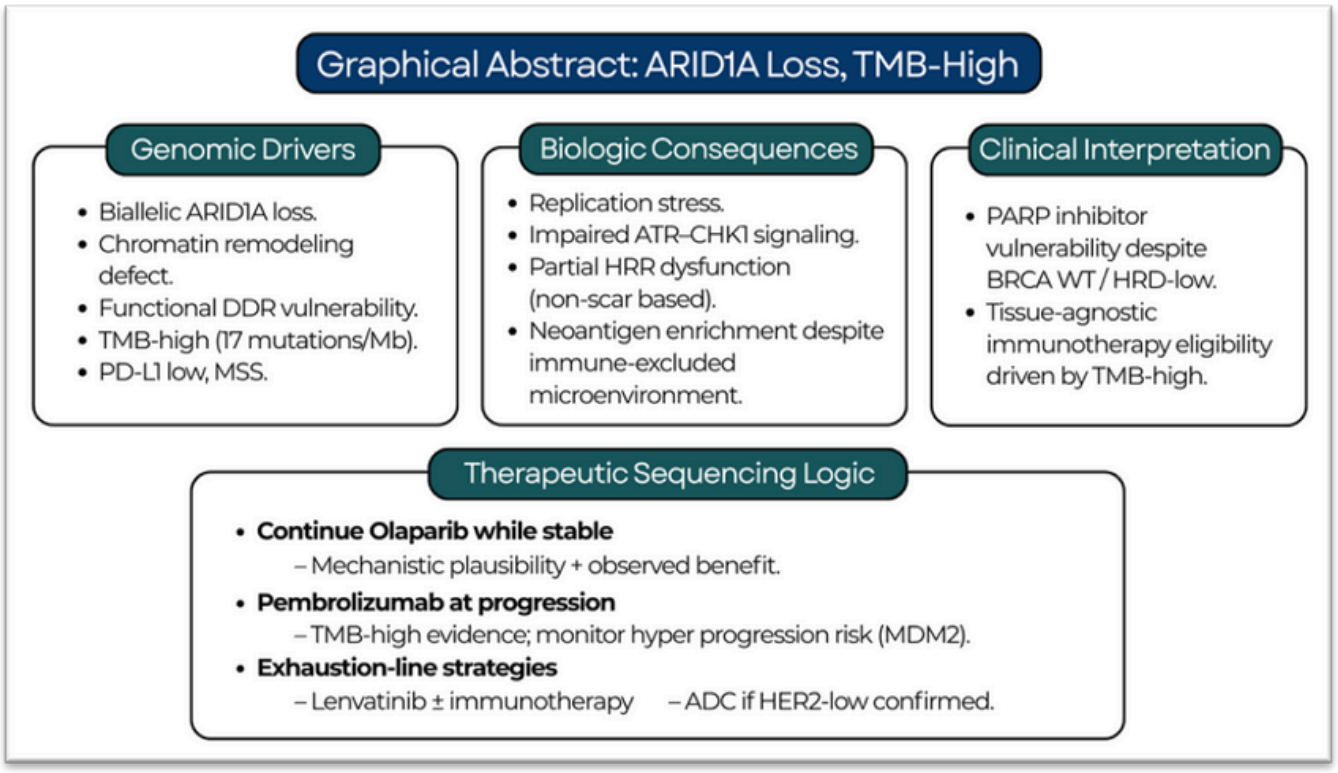
CLINICAL IMPLICATION:

ARID1A LOSS IN HR+ METASTATIC BREAST CANCER: LUMINAL IDENTITY EROSION, ENDOCRINE RESISTANCE, AND THERAPEUTIC VULNERABILITIES

ARID1A loss in HR+ metastatic breast cancer represents a chromatin-level disruption of luminal lineage identity, destabilizing the ER–FOXA1–GATA3 transcriptional network that defines hormone-dependent breast epithelium. ARID1A deficiency shifts tumours toward a more plastic, less lineage-committed state where classical luminal gene-expression patterns weaken and alternative survival programs emerge. Clinically, this creates a phenotype that "behaves less luminal than the IHC suggests," often manifesting as discordant receptor biology, evolving histology, or unexpectedly aggressive endocrine-refractory progression. Mechanistically, ARID1A loss disrupts ER-driven transcription at scale by weakening ER's cooperative chromatin binding with pioneer factors like FOXA1 and remodelling enhancer accessibility, enabling tumour cells to bypass oestrogen signalling and persist under aromatase inhibitor, SERM, or SERD pressure. Practically, ARID1A deficiency should raise suspicion for epigenetically driven endocrine escape, justify comprehensive reassessment of resistance drivers including ESR1 mutations and PI3K/AKT activation, and strengthen the rationale for combination strategies rather than sequential single-agent endocrine manipulation (10,11,12,13).

ARID1A-deficient tumours demonstrate enrichment for elevated tumour mutational burden and immune-related transcriptional signatures, suggesting that a subset may evolve toward a hypermutated, immune-reactive phenotype (14,15). Although high TMB remains uncommon in breast cancer overall, detection of ARID1A alteration—particularly in heavily pretreated metastatic disease—should prompt comprehensive genomic profiling including TMB quantification, MSI/MMR assessment, and immune signature evaluation to identify patients with non–endocrine-driven biology who may benefit from immunotherapy-based strategies (16,17).

ARID1A loss also represents a mechanistically supported non-BRCA DNA repair vulnerability that may confer context-dependent PARP inhibitor sensitivity, especially when combined with agents targeting compensatory survival pathways (14,16). Given the frequent co-occurrence of PI3K/AKT pathway activation in endocrine-resistant HR+ disease, PARP inhibitor–based combinations—such as PARPi plus AKT or PI3K inhibition—represent rational therapeutic strategies in ARID1A-deficient tumours, even in the absence of canonical homologous recombination deficiency. These converging biological rationales position ARID1A loss as a clinically actionable biomarker signalling potential eligibility for both immune checkpoint inhibitor and synthetic lethality approaches, though prospective validation and co-mutation–guided patient selection remain essential to translate these vulnerabilities into durable clinical benefit (14,16).



3) MDM2 AMPLIFICATION: RISK MODIFIER FOR HYPER PROGRESSION

High-level MDM2 amplification was treated as a risk-modifying feature rather than a biologic contraindication. The MTB discussion referenced retrospective associations between MDM2/MDM4 amplification and hyper progressive disease patterns on immune checkpoint blockade (17-20), while emphasizing variability in definitions and reporting.

4) FGFR1 AMPLIFICATION AND THE 12Q13–15 AMPLICON

FGFR1 amplification, endocrine resistance, and CDK4/6 inhibitor resistance in HR+ metastatic breast cancer

MOLECULAR MECHANISMS OF RESISTANCE

FGFR1 amplification drives luminal pathway reprogramming in HR+ metastatic breast cancer through activation of MAPK/PI3K network signalling, creating endocrine bypass mechanisms that reduce transcriptional dependence on oestrogen receptor activity. Foundational preclinical studies established FGFR1 amplification and overexpression as active resistance drivers rather than neutral genomic passengers, demonstrating that FGFR1-altered luminal models exhibit intrinsic endocrine therapy resistance.

MULTI-ESCAPE SIGNALLING PLATFORM

Clinical cohort studies in metastatic HR+ breast cancer reveal that FGFR1-amplified tumours demonstrate resistance not only to endocrine therapy but also to CDK4/6 inhibitors, establishing FGFR1 amplification as a "multi-escape" signalling node. This cross-resistance pattern suggests that FGFR1-driven tumours have fundamentally altered growth dependencies that cannot be fully suppressed by standard ER or cell cycle targeting alone.

TRIAL-LINKED BIOMARKER EVIDENCE
MONALEESA PROGRAM

Circulating tumour DNA analyses from MONALEESA-2 demonstrated that patients harbouring FGFR1 amplification experienced significantly shorter progression-free survival compared to FGFR1-wild-type patients on ribociclib-based therapy. Expanded pooled ctDNA analyses across the MONALEESA phase III program have positioned FGFR1 alterations as clinically relevant biomarkers with prognostic value and potential treatment-shaping implications depending on co-alteration context.

PALOMA-3 INSIGHTS

Genomic profiling within PALOMA-3 identified molecular markers associated with early progression on palbociclib plus fulvestrant, confirming that endocrine-resistant disease contains definable genomic subgroups with bypass signalling mechanisms. These findings support biomarker-driven escalation strategies when resistance pathways are molecularly evident.

GENOMIC CONTEXT: 12Q13-15 CO-AMPLIFICATION

FGFR1 amplification in ER+ breast cancer frequently occurs within broader 12q13-15 chromosomal co-amplification events. This amplicon typically encompasses multiple genes, creating polygenic resistance biology rather than single-driver dependence. The key clinical principle: when multiple genes across a large chromosomal region are co-amplified, tumours rarely depend on a single amplified target, making responses to mono-targeted therapy unpredictable and often clinically insufficient.

CLINICAL IMPLICATIONS BY METASTATIC SITE

FGFR1 amplification in HR+ metastatic breast cancer drives endocrine resistance through MAPK/PI3K activation, creating ER-independent growth pathways that confer cross-resistance to both endocrine therapy and CDK4/6 inhibitors (21,22,23). Clinical data from

MONALEESA-2 and PALOMA-3 demonstrate that FGFR1-amplified tumours exhibit shorter progression-free survival on standard CDK4/6-based regimens, establishing FGFR1 as a multi-escape signalling node rather than a neutral passenger alteration (22,23,24). FGFR1 amplification frequently occurs within 12q13-15 co-amplification events encompassing multiple genes, creating polygenic resistance that limits single-agent targeting efficacy. Mechanistically, FGFR1 signalling enhances VEGF-axis output and vascular remodelling, particularly relevant in liver and chest wall metastases where rapid lesion expansion requires robust neovascular support. This biology supports rational combination strategies including triple blockade (fulvestrant + CDK4/6 inhibitor + erdafitinib) and FGFR-directed therapy plus anti-angiogenic agents (22-24). Current evidence positions FGFR1 amplification as a clinically actionable biomarker warranting biomarker-driven escalation and trial enrolment, particularly in patients with visceral metastases progressing on standard endocrine-CDK4/6 therapy, as FGFR1-amplified disease increasingly appears to require multi-pathway blockade rather than sequential single-agent approaches. (24-26)

Therapeutic Strategy

1) TMB-HIGH AS TISSUE-AGNOSTIC BIOMARKER (KEYNOTE-158)

- KEYNOTE-158 supported pembrolizumab activity in TMB-high (≥10 muts/Mb) solid Tumours after prior therapy, with durable responses among responders and activity observed irrespective of PD-L1 status (27,28).

2) ARID1A DEFICIENCY AND DDR VULNERABILITY

- Preclinical literature supports ARID1A-associated replication stress, impaired checkpoint signalling, and reduced HR efficiency, creating a biologically plausible DDR vulnerability context (3–5,12,13).

3) MDM2 AMPLIFICATION AND HYPER PROGRESSION

- Retrospective series reported enrichment of MDM2/MDM4 amplification in hyper progressor cohorts, though HPD incidence varies widely by definition and Tumour type (17-20).

4) FGFR1 AMPLIFICATION IN BREAST CANCER

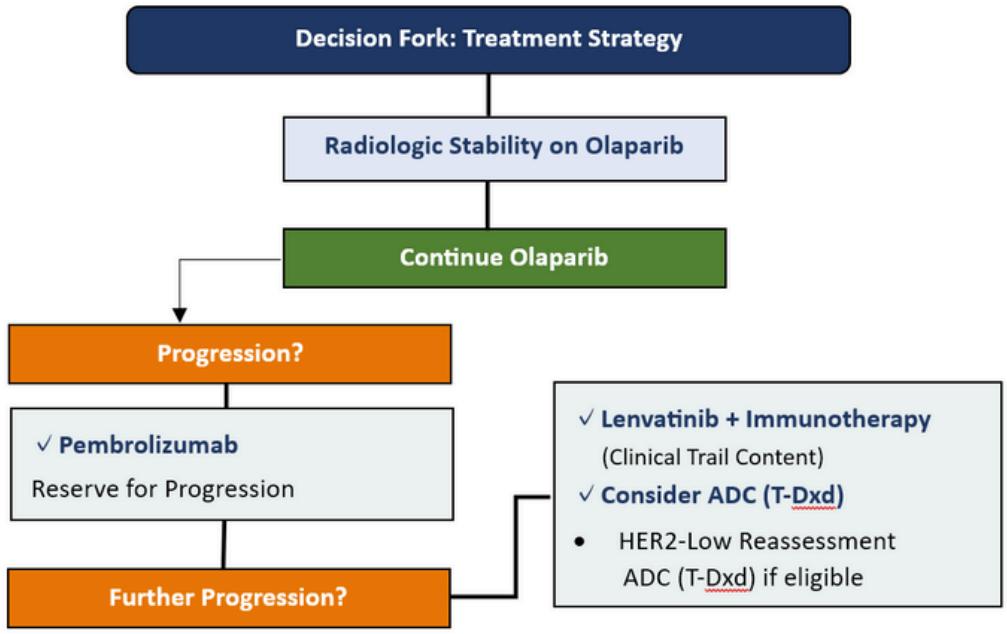
- Translational and clinical trial experience suggests modest and inconsistent activity of FGFR-targeted strategies in FGFR1-amplified breast cancer, with challenges attributable to co-amplification biology and pathway redundancy (29-31).

5) HER2-LOW AND TRASTUZUMAB DERUXTECAN (DESTINY-BREAST04)

- DESTINY-Breast04 established clinically meaningful benefit for trastuzumab deruxtecan in HER2-low metastatic breast cancer after prior therapy (32).

Figure 4: Therapeutic Considerations

(Flow Diagram)



SEQUENCING LOGIC:

The MTB emphasized that in heavily pretreated patients, therapeutic decision-making must balance evidence strength, mechanistic rationale, toxicity, and preservation of future options.

CURRENT STRATEGY: CONTINUE OLAPARIB

- Rationale for continuation:
- Biologic plausibility: Biallelic ARID1A loss creates synthetic lethal vulnerability
- Observed clinical benefit: Disease stability after 2 cycles
- Tolerability: No grade 3–4 toxicities; patient maintaining QOL
- Absence of superior alternative at this line

RESERVED FOR PROGRESSION ON OLAPARIB: PEMBROLIZUMAB MONOTHERAPY

- Supported by TMB-high criteria and cross-Tumour evidence; requires careful monitoring for hyper progression risk given MDM2 amplification.

EXHAUSTION-LINE OPTION: LENVATINIB ± IMMUNOTHERAPY

- Consider only after progression on both Olaparib and pembrolizumab monotherapy, ideally in a clinical trial setting.

CONCURRENT PRIORITY: HER2 REASSESSMENT

- Repeat HER2 IHC on recent tissue to assess HER2-low eligibility for trastuzumab deruxtecan.

EXPANDED GERMLINE TESTING

- Consider MLPA and extended panel testing given young age and aggressive phenotype.

TEACHING POINT

Sequencing Discipline: In exhaustion-line settings, continuing a working therapy and reserving molecularly guided escalation preserves future options, avoids unnecessary toxicity, and allows clearer attribution of benefit.

FINAL RECOMMENDATION

The MTB interpreted this case as a gnomically complex, TMB-high, aggressive luminal breast cancer with biallelic ARID1A loss creating PARP inhibitor vulnerability and co-amplifications driving angiogenic biology.

Primary Recommendation:

Continue Olaparib (300 mg twice daily) as current therapy while disease remains radiologically and clinically stable.

Reserved for Progression on Olaparib

Pembrolizumab monotherapy (200 mg IV Q3W), with enhanced monitoring given MDM2 amplification.

Exhaustion-line Strategy

Lenvatinib (14–20 mg daily) ± pembrolizumab after progression on both olaparib and pembrolizumab monotherapy, ideally in a clinical trial context.

Concurrent Action

- Repeat HER2 IHC on most recent tissue to assess HER2-low status for trastuzumab deruxtecan eligibility
- Expanded germline testing with MLPA and extended panel given young age and aggressive phenotype
- Initiate pembrolizumab prior authorization 2–3 months before anticipated progression

FROM THE MTB CHAIR

"This case exemplifies the evolution of precision oncology beyond simple 'mutation–drug matching' toward a more sophisticated interpretation of biological context. The patient's ARID1A loss doesn't appear in any guideline as an indication for PARP inhibitors in breast cancer, yet the mechanistic rationale is sound, the preclinical data compelling, and the clinical evidence in other Tumour types convincing.

What distinguishes modern MTB deliberation is the ability to weigh evidence hierarchies—recognizing when level-one evidence provides clear guidance (TMB-high supporting pembrolizumab), when mechanistic extrapolation from other Tumour types is justified (ARID1A loss supporting olaparib), and when exploratory strategies must be reserved for exhaustion settings (FGFR1 amplification with Lenvatinib).

The sequencing logic here is critical: we don't abandon working therapy based on molecular findings alone, we don't combine treatments without evidence of synergy, and we preserve future options by thoughtful escalation only when needed. This is precision oncology in its most nuanced form—using molecular data to inform, not dictate, clinical judgment."

KEY LEARNING POINTS

- ARID1A biallelic loss creates context-dependent DDR vulnerability: Chromatin remodeling defects can generate functional HRR deficiency not captured by genomic scar-based HRD scores.
- TMB-high status can override histology-specific immune context: Elevated TMB (≥10 muts/Mb) supports tissue-agnostic ICI consideration even in PD-L1–low disease.
- MDM2 amplification modifies but does not preclude immunotherapy: View as a risk-modifying feature requiring enhanced monitoring rather than an absolute contraindication.
- Amplifications vs fusions in targetability: Large-region amplifications often have lower oncogene addiction than kinase fusions; clinical predictability differs.
- Sequencing discipline preserves future options: Continue active therapy until clear progression; sequential strategies preserve mechanistically distinct options.
- HRD score does not capture all DNA repair deficiencies: Alternative DDR mechanisms can exist despite low/normal HRD scores.
- Evidence hierarchies must be calibrated to context: In exhaustion-line settings, mechanistically sound extrapolation may be reasonable when standard options are exhausted.

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ABBREVIATIONS

ADC, antibody-drug conjugate; AE, adverse event; ARID1A, AT-rich interaction domain 1A; ATR, ataxia telangiectasia and Rad3-related; CDK, cyclin-dependent kinase; CPS, combined positive score; DDR, DNA damage response; DSB, double-strand break; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; GATA3, GATA binding protein 3; HER2, human epidermal growth factor receptor 2; HPD, hyper progressive disease; HRD, homologous recombination deficiency; HRR, homologous recombination repair; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; ISH, in situ hybridization; MDM2, mouse double minute 2 homolog; MLPA, multiplex ligation-dependent probe amplification; MSS, microsatellite stable; NGS, next-generation sequencing; ORR, overall response rate; PARP, poly(ADP-ribose) polymerase; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, progesterone receptor; QOL, quality of life; RCC, renal cell carcinoma; SWI/SNF, Switch/Sucrose Non-Fermentable; T-DXd, trastuzumab deruxtecan; TIL, Tumour-infiltrating lymphocyte; TMB, Tumour mutational burden; VAF, variant allele fraction; VEGF, vascular endothelial growth factor; MTB, virtual molecular Tumour board.