CODEN: WJAPAC | Impact Factor: 5.48 | ISSN: 3049-3013

World Journal of Advance Pharmaceutical Sciences

Volume 3, Issue 11, Page: 23-31 | Review Article | www.wjaps.com

BEYOND TUMOUR VISIBILITY: A BIOMARKER-DRIVEN PHARMACOLOGICAL REVIEW OF CUTANEOUS, ORAL CAVITY AND BREAST MALIGNANCIES

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How to cite this Article: Devanssh Mehta[1]*. (2026). Beyond Tumour Visibility: A Biomarker-Driven Pharmacological Review Of Cutaneous, Oral Cavity And Breast Malignancies. World Journal of Advance Pharmaceutical Sciences, 3(11), 23-31.

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Article Info

Article Received: 08 August 2026,

Article Revised: 28 Sept. 2026,

Article Accepted: 18 Oct. 2026.

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DOI: https://doi.org/10.5281/zenodo.23850631

ABSTRACT

Cancer pharmacotherapy is increasingly guided by molecular characteristics that distinguish biologically heterogeneous tumours and predict their susceptibility to specific interventions. Externally accessible malignancies, including cutaneous melanoma, keratinocyte carcinomas, oral squamous cell carcinoma and breast cancer, offer opportunities for clinical inspection, tissue sampling and longitudinal assessment; however, accessibility does not establish tumour biology or predict therapeutic response. This narrative review examines the molecular pathogenesis, pharmacological vulnerabilities and clinical applications of biomarkers across these malignancies. Evidence was synthesised conceptually from established clinical guidelines, peer-reviewed studies and authoritative oncology resources, with emphasis on clinically actionable biomarkers and recognised limitations of emerging assays. BRAF alterations inform targeted treatment selection in melanoma, while Hedgehog pathway dysregulation provides a therapeutic rationale for selected advanced basal cell carcinomas. In breast cancer, oestrogen and progesterone receptors, HER2, PIK3CA and BRCA1/2 alterations inform distinct endocrine, targeted and DNA repair-directed strategies. PD-L1 assessment contributes to treatment selection in defined head and neck and breast cancer settings. The review also evaluates pharmacokinetic and pharmacodynamic principles, immune-mediated toxicity, acquired resistance, intratumour heterogeneity and circulating tumour DNA. A central finding is that biomarker utility depends on assay validity, tumour context and demonstrated clinical benefit rather than the mere detection of a molecular alteration. Integrating histopathology, validated molecular diagnostics, pharmacological assessment and patient-centred decision-making offers a rational foundation for precision oncology. Future advances require prospective validation, equitable diagnostic access and evidence that biomarker-guided interventions improve survival, treatment tolerability or quality of life.

KEYWORDS: Precision oncology; Pharmacological biomarkers; Molecularly targeted therapy; Tumour heterogeneity; Immunotherapy.

1. INTRODUCTION

Cancer represents a heterogeneous group of diseases characterised by dysregulated proliferation, genomic instability, altered differentiation, evasion of apoptosis, immune escape and the capacity for local invasion and distant dissemination. Contemporary pharmacology increasingly seeks to identify the molecular dependencies that sustain malignant growth and exploit these vulnerabilities through targeted inhibitors, endocrine agents, immunotherapies, cytotoxic medicines and antibody–drug conjugates. The transition from predominantly histology-based treatment towards biomarker-informed treatment selection represents a major development in translational oncology.[1,2]

The expression *externally accessible cancers* is used in this review as a descriptive clinical term rather than a formally recognised oncological classification. It encompasses selected malignancies that can be inspected directly or sampled relatively readily, including cutaneous melanoma, basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (cSCC), oral squamous cell carcinoma (OSCC) and breast cancer. These malignancies are not biologically equivalent. Their inclusion provides a comparative framework for understanding how tissue accessibility, histopathology, molecular diagnostics and pharmacological interventions interact.

Accessible lesions may facilitate early recognition, biopsy, repeated clinical examination and selected pharmacodynamic investigations. Nevertheless, external visibility cannot reliably establish tumour depth, metastatic potential, molecular phenotype or therapeutic sensitivity. Melanoma may disseminate despite originating in a visible lesion, oral carcinoma may invade deeply or involve cervical lymph nodes, and breast cancer may develop systemic disease before becoming clinically apparent. Diagnosis and treatment therefore require appropriate staging and disease-specific assessment rather than visual examination alone.[1–3]

Biomarkers provide measurable information about tumour biology, disease prognosis or treatment response. Their clinical roles must be distinguished carefully. A diagnostic biomarker assists disease identification; a prognostic biomarker provides information about disease outcome; a predictive biomarker helps identify the likelihood of benefit or harm from a particular intervention; and a pharmacodynamic biomarker indicates a biological response to treatment. These categories may overlap, but they are not interchangeable. A protein associated with aggressive disease, for example, is not necessarily a validated predictor of response to a drug directed against that protein.[1]

The present review examines selected externally accessible malignancies through an integrated pharmacological framework. Its objectives are to explain relevant molecular pathways, evaluate established and emerging biomarkers, analyse drug mechanisms and resistance, and identify translational priorities for precision oncology.

2. REVIEW METHODOLOGY

This article is a narrative review based on selected clinical practice guidelines, peer-reviewed clinical studies, authoritative oncology resources and established principles of pharmacology and molecular diagnostics. The synthesis focuses on melanoma, keratinocyte carcinomas, OSCC and breast cancer, with particular attention to the relationship between biomarker status and treatment selection.

The literature was interpreted according to the intended clinical role of each biomarker. Tests with established treatment-selection applications were distinguished from markers used primarily for prognosis, monitoring or research. Mechanistic evidence was not considered sufficient, by itself, to establish clinical utility.

No original experiments, patient recruitment, quantitative meta-analysis or exhaustive systematic database search were performed. The article therefore represents a narrative scientific synthesis rather than a systematic review. References were selected to support the principal clinical and pharmacological statements, and the bibliography should be expanded through a documented literature search before formal journal submission.

3. MOLECULAR BASIS OF BIOMARKER-GUIDED PHARMACOLOGY

3.1 Oncogenic signalling and therapeutic dependence

Malignant transformation frequently involves persistent activation of pathways controlling cellular growth, survival and differentiation. The RAS–RAF–MEK–ERK cascade, commonly termed the mitogen-activated protein kinase (MAPK) pathway, is particularly relevant to melanoma. Activating BRAF alterations can produce sustained downstream signalling and create a therapeutically actionable dependency in selected tumours.[2,3]

BRAF and MEK inhibitors interfere with sequential components of this pathway. Their effectiveness depends on the specific molecular alteration, tumour context and treatment indication. The presence of an alteration should not be interpreted as proof that a tumour will respond or that the same treatment will be effective in another malignancy carrying a superficially similar alteration.

The PI3K–AKT–mTOR pathway provides another important therapeutic target, particularly in selected breast cancers. Alterations affecting pathway regulation may support tumour growth and contribute to endocrine resistance. Pharmacological inhibition of PI3K, AKT or mTOR can therefore be useful in defined clinical settings, although eligibility requirements and expected toxicities differ among agents.[4,5]

3.2 Receptor-mediated growth and hormone dependence

Cell-surface receptors and intracellular hormone receptors provide opportunities for biomarker-directed treatment. Human epidermal growth factor receptor 2 (HER2) amplification or overexpression can support tumour growth in a subset of breast cancers. Oestrogen receptor (ER) and progesterone receptor (PR) expression identify tumours in which hormone signalling may contribute to malignant proliferation.[4,6]

HER2-directed antibodies, kinase inhibitors and antibody–drug conjugates act through different pharmacological mechanisms. Endocrine agents interfere with oestrogen synthesis or receptor activity, while cyclin-dependent kinase 4/6 (CDK4/6) inhibitors interfere with cell-cycle progression in appropriately selected hormone receptor-positive disease.

These examples illustrate an essential principle: the presence of a molecular target is clinically useful only when the assay, disease context and therapeutic evidence establish how the result should influence management.

3.3 DNA repair and synthetic lethality

Tumour-suppressor proteins and DNA repair systems preserve genomic integrity. Pathogenic alterations affecting BRCA1 or BRCA2 can impair homologous recombination repair, creating susceptibility to poly(ADP-ribose) polymerase (PARP) inhibition in selected cancers. Olaparib and talazoparib exploit this vulnerability through interference with PARP-associated DNA repair processes.[5]

This relationship is commonly explained through synthetic lethality, in which the combined disruption of two biological processes becomes lethal to a cell even though either defect alone may be tolerated. However, the presence of a DNA repair alteration does not establish universal eligibility for PARP inhibition. The specific cancer, alteration, disease setting and drug indication must be considered.

3.4 Immune evasion and checkpoint inhibition

Malignant cells can evade immune destruction through multiple mechanisms, including inhibitory signalling through programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1). Checkpoint inhibitors disrupt these inhibitory interactions and may restore antitumour T-cell activity.

Pembrolizumab and nivolumab target PD-1, whereas ipilimumab targets cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Their clinical effects depend on the tumour microenvironment, antigen presentation, immune-cell activity and other biological factors. Durable responses occur in some patients, but primary resistance, acquired resistance and immune-mediated toxicity remain important limitations.[2,7]

4. BIOMARKER CLASSIFICATION AND ANALYTICAL VALIDITY

4.1 Clinically relevant biomarker categories

Biomarkers used in oncology include DNA mutations, gene amplification, protein expression, immune-cell characteristics, DNA repair defects and circulating tumour-derived material. Their interpretation requires distinction between analytical validity, clinical validity and clinical utility.

Analytical validity concerns the reliability with which a test measures its intended target. Clinical validity concerns the association between the result and a clinically relevant outcome. Clinical utility concerns whether using the result improves treatment decisions or patient outcomes sufficiently to justify the test.

Biomarker	Principal clinical relevance	Important limitation
BRAF V600	Identifies eligibility for selected melanoma-targeted regimens	Does not guarantee response or durability
PTCH1/SMO pathway alterations	Clarify Hedgehog pathway biology in BCC	Routine treatment selection is not based on a universal mutation-panel requirement
PD-L1	Informs selected immunotherapy indications	Assay, scoring method and cancer-specific indication matter
ER and PR	Inform endocrine treatment in breast cancer	Expression does not guarantee response
HER2	Informs HER2-directed treatment selection	Interpretation requires validated testing and indication-specific thresholds
PIK3CA	Identifies selected PI3K-directed treatment opportunities	Clinical relevance depends on mutation and regimen
BRCA1/2	May inform PARP inhibitor eligibility and inherited-risk assessment	Germline and tumour findings have different implications
ctDNA	May support molecular monitoring in selected settings	A negative result does not exclude tumour alterations

The table summarises selected examples rather than providing a comprehensive testing guideline. Biomarker interpretation must be aligned with validated assays and the intended therapeutic decision.[1,4–6]

4.2 Tissue-based diagnostics

Histopathology remains central to cancer diagnosis because it establishes tumour morphology, differentiation, invasion and other clinically important

characteristics. Immunohistochemistry can assess protein expression, including ER, PR and HER2. In situ hybridisation may help establish gene amplification, while polymerase chain reaction and next-generation sequencing can identify selected genomic alterations.

Each technique has limitations. Immunohistochemistry depends on specimen quality, antibody performance, scoring methodology and interpretation. Sequencing may be affected by insufficient tumour content, degraded nucleic acids, assay sensitivity and the inability of a particular platform to detect certain alterations.

Tissue accessibility can facilitate repeat sampling, but a biopsy represents only a portion of a heterogeneous tumour. Repeat sampling is most valuable when the expected information could meaningfully alter diagnosis or treatment.

4.3 Liquid biopsy and circulating tumour DNA

Circulating tumour DNA (ctDNA) comprises tumour-derived DNA fragments detectable in biological fluids, particularly plasma. Depending on the assay and clinical context, ctDNA analysis may identify genomic alterations, track molecular response or reveal emerging resistance.

Its principal advantage is the potential for repeated sampling without an additional tumour biopsy. However, ctDNA shedding varies according to tumour burden, site, biological characteristics and treatment status. Some small or low-shedding tumours may not produce detectable ctDNA. Consequently, a negative plasma result does not necessarily exclude an actionable alteration.

Clonal haematopoiesis can also introduce variants originating from blood cells rather than the tumour. Appropriate assay design and interpretation are therefore important. ctDNA should complement, rather than automatically replace, established pathology, imaging and clinical assessment unless its use has been validated for the specific indication.[1,5]

5. PHARMACOLOGICAL PROFILE OF CUTANEOUS MELANOMA

5.1 Molecular characteristics

Cutaneous melanoma is a malignant neoplasm of melanocytes characterised by substantial molecular heterogeneity. Relevant alterations include BRAF and NRAS mutations and selected KIT alterations. BRAF V600 is particularly important because it can identify patients eligible for specific BRAF/MEK inhibitor regimens.[2,3]

Other markers, including PD-L1 expression, tumour mutational burden (TMB) and ctDNA, provide additional biological information, but their clinical roles differ. BRAF testing has an established treatment-selection role in appropriate advanced melanoma settings, whereas immune-related biomarkers should not be treated as universal prerequisites for checkpoint inhibition.

5.2 BRAF and MEK inhibition

Vemurafenib, dabrafenib and encorafenib inhibit susceptible BRAF alterations. Trametinib, cobimetinib and binimetinib inhibit MEK, a downstream component of the MAPK pathway. Combined BRAF/MEK inhibition can suppress pathway signalling and delay some resistance mechanisms compared with BRAF inhibitor monotherapy.[2,3]

Resistance may arise through pathway reactivation, secondary genomic alterations, alternative receptor signalling or changes in tumour-cell state. Combination treatment does not eliminate resistance but can impose additional barriers to tumour adaptation.

Potential adverse effects include fever, fatigue, skin reactions, gastrointestinal symptoms and agent-specific ocular or cardiac complications. Treatment requires appropriate clinical monitoring and should be selected according to disease stage, molecular status, previous treatment and patient-specific risk.

5.3 Immune checkpoint inhibition

Anti-PD-1 therapy with pembrolizumab or nivolumab is an established treatment approach in selected melanoma settings. Ipilimumab and nivolumab plus relatlimab provide additional immune-directed strategies in appropriate circumstances.[2,3]

Checkpoint inhibition differs from kinase inhibition because its principal effect is mediated through immune regulation rather than direct blockade of an oncogenic kinase. Responses may be durable, but immune-mediated adverse events can affect the gastrointestinal tract, liver, lungs, endocrine organs and other tissues.

PD-L1 expression and TMB may contribute to biological understanding, but neither independently predicts every response. Tumour antigen presentation, immune infiltration, immune suppression and the development of resistant tumour populations also influence treatment outcomes.

5.4 Pharmacological implications

Melanoma demonstrates why biomarker-guided treatment requires integration rather than a single-marker approach. BRAF status identifies a targeted treatment opportunity, but it does not independently determine the optimal treatment sequence. Immune checkpoint inhibition may be appropriate regardless of BRAF status, while the relative roles of targeted therapy and immunotherapy depend on the clinical situation and evidence-based guidance.[2,3]

6. BASAL CELL CARCINOMA AND CUTANEOUS SQUAMOUS CELL CARCINOMA

6.1 Basal cell carcinoma and Hedgehog signalling

BCC frequently involves abnormal Hedgehog pathway activation, often associated with alterations affecting PTCH1 or SMO. This pathway provides a therapeutic rationale for Smoothened inhibitors in selected advanced disease.[8]

Vismodegib and sonidegib inhibit SMO and can produce tumour responses in appropriate locally advanced or metastatic BCC settings. Their use is generally considered when established local treatment options are inappropriate or inadequate, according to the relevant indication.

Resistance may involve changes affecting SMO or downstream signalling. Adverse effects can include muscle spasms, altered taste, alopecia, fatigue and weight loss, which may limit long-term tolerability.

Selected superficial lesions may be suitable for topical treatment, including imiquimod or 5-fluorouracil in appropriate indications. These treatments must not be extrapolated indiscriminately to invasive or high-risk disease. Histology, depth, anatomical location and clinical risk remain important determinants of treatment selection.

6.2 Cutaneous squamous cell carcinoma

cSCC differs biologically from BCC and may demonstrate substantial ultraviolet-associated genomic damage. Although many lesions can be managed with local treatment, selected advanced cases require systemic therapy.

PD-1 inhibitors, including cemiplimab and pembrolizumab, have roles in defined advanced cSCC settings. The biological rationale includes the potential for immune recognition of tumour-associated antigens, but response cannot be guaranteed from mutational burden alone.

The principal biomarker challenge is that no single molecular marker universally captures the likelihood of response. Histopathology, disease extent, immune status, treatment history and clinical eligibility remain essential. Immune-mediated toxicities require appropriate recognition and management.[7,9]

7. PHARMACOLOGICAL PROFILE OF ORAL SQUAMOUS CELL CARCINOMA

7.1 Molecular pathogenesis and EGFR

OSCC arises from the squamous epithelium of the oral cavity. Carcinogenesis may involve tobacco exposure, alcohol and other environmental or host factors, together with alterations affecting TP53, cell-cycle regulation, EGFR signalling and PI3K pathway components.

The epidermal growth factor receptor (EGFR) participates in cellular proliferation and survival. Cetuximab, an EGFR-directed monoclonal antibody, has an established role in selected head and neck squamous cell carcinoma regimens. However, EGFR expression alone is not a universally reliable predictor of cetuximab benefit. Target abundance and tumour dependence are not equivalent, and alternative signalling pathways may sustain malignant growth despite receptor blockade.[7]

Cetuximab-associated adverse effects include acneiform rash, infusion reactions and electrolyte disturbances. Neither the presence nor the severity of skin rash should be used as a standalone measure of tumour response.

7.2 PD-L1 and immunotherapy

PD-L1 assessment contributes to treatment selection in defined recurrent or metastatic head and neck squamous cell carcinoma settings. The combined positive score (CPS) is one established scoring approach used in specified indications. It incorporates staining in tumour cells and specified immune cells relative to the number of viable tumour cells.

Pembrolizumab and nivolumab have roles in particular treatment settings, with selection depending on disease context, previous therapy, the relevant indication and applicable clinical guidance.[7] A PD-L1 result cannot be interpreted independently of the assay and scoring system used.

The oral cavity's accessibility may facilitate biopsy and repeat tissue assessment, but it does not eliminate the need for imaging, nodal evaluation or systemic staging. Platinum compounds, taxanes and fluoropyrimidines may also be used in selected regimens. Their mechanisms and toxicities differ, requiring treatment-specific evaluation.

8. PHARMACOLOGICAL PROFILE OF BREAST CANCER

8.1 ER, PR and HER2

Breast cancer is a heterogeneous group of epithelial malignancies in which biomarker classification has substantial therapeutic consequences. ER, PR and HER2 status inform treatment selection, while Ki-67 may provide additional information about cellular proliferation.[4,6]

ER-positive tumours may respond to endocrine therapy. HER2-positive tumours may benefit from HER2-directed treatment. Triple-negative breast cancer lacks conventional ER, PR and HER2 positivity and requires a different therapeutic assessment.

8.2 Endocrine treatment and CDK4/6 inhibition

Tamoxifen modulates ER activity, aromatase inhibitors reduce oestrogen synthesis, and fulvestrant antagonises and promotes degradation of ER. Treatment selection

depends on menopausal status, disease stage, previous therapy and other clinical characteristics.

In selected hormone receptor-positive, HER2-negative breast cancer, CDK4/6 inhibitors such as palbociclib, ribociclib and abemaciclib may be combined with endocrine therapy. These agents inhibit cell-cycle progression and can improve disease control in appropriate settings.

Adverse effects vary by agent and may include neutropenia, diarrhoea, fatigue, hepatic abnormalities and, for selected medicines, QT-interval prolongation. Resistance can involve ESR1 alterations, growth-factor signalling, cell-cycle adaptation and other mechanisms. Biomarker testing should be performed when the result can inform a validated treatment decision.[4,5]

8.3 HER2-directed pharmacology

Trastuzumab and pertuzumab are monoclonal antibodies that interfere with HER2-associated signalling. Small-molecule inhibitors target HER-family kinase activity, while antibody–drug conjugates such as trastuzumab emtansine and trastuzumab deruxtecan deliver cytotoxic payloads through antibody-mediated targeting.

HER2 testing requires validated methods and careful interpretation. HER2-positive disease must be distinguished from other expression categories because therapeutic eligibility and evidence differ among agents. HER2-low expression does not imply that all conventional HER2-directed treatments will be effective.[6]

The pharmacological activity of an antibody–drug conjugate depends on target binding, internalisation, linker stability, payload release and susceptibility to the cytotoxic component. Such agents can be effective in appropriate settings but have distinct toxicity profiles; trastuzumab deruxtecan, for example, requires particular attention to the risk of interstitial lung disease or pneumonitis.

8.4 PI3K–AKT–mTOR pathway

The PI3K–AKT–mTOR pathway regulates cellular growth, metabolism and survival. In selected hormone receptor-positive, HER2-negative advanced breast cancers, PIK3CA testing can inform eligibility for alpelisib combined with endocrine treatment. Capivasertib and everolimus provide additional pathway-directed options in specified clinical settings.[4,5]

These medicines differ in their molecular targets, eligibility criteria and adverse effects. Hyperglycaemia, diarrhoea, skin reactions, stomatitis and metabolic disturbances may be clinically important, depending on the regimen.

Pathway inhibition can overcome selected resistance mechanisms, but it does not guarantee durable control. Treatment decisions should integrate the molecular result with clinical status, previous treatment, expected benefit and toxicity.

8.5 BRCA1/2 and PARP inhibition

Pathogenic BRCA1/2 alterations may identify selected patients eligible for PARP inhibitors such as olaparib or talazoparib. By exploiting defects in homologous recombination repair, these agents can produce antitumour activity in appropriately selected breast cancers.[5]

Germline and tumour-derived BRCA findings must be distinguished because they have different implications for inherited risk and family counselling. Resistance can develop through restoration of DNA repair or other cellular adaptations. Testing should therefore be interpreted within the relevant clinical indication and accompanied by appropriate counselling where inherited risk is implicated.

8.6 Triple-negative breast cancer

Triple-negative breast cancer lacks conventional ER, PR and HER2 therapeutic targets, but selected cases may still be eligible for biomarker-informed interventions. PD-L1 assessment can guide treatment in defined immunotherapy regimens, while germline BRCA1/2 alterations may inform PARP inhibitor eligibility in appropriate settings.[4,5]

No single biomarker fully captures the heterogeneity of triple-negative breast cancer. Treatment may include chemotherapy, immunotherapy and selected antibody–drug conjugates, depending on disease stage and clinical indication.

9. COMPARATIVE PHARMACOLOGICAL INTERPRETATION

The reviewed malignancies illustrate different relationships between molecular alterations and therapeutic vulnerabilities. BRAF V600 has a defined treatment-selection role in melanoma; Hedgehog pathway dysregulation underpins selected targeted approaches in advanced BCC; PD-L1 contributes to treatment decisions in specified head and neck cancer settings; and ER, PR, HER2, PIK3CA and BRCA1/2 inform distinct breast cancer strategies.[2,4–9]

These relationships cannot be generalised across cancer types without evidence. A drug that inhibits a particular pathway in melanoma may not be effective in another tumour carrying an alteration in that pathway. Biological dependence, tumour microenvironment, drug exposure and resistance all affect clinical response.

The therapeutic index is equally important. Targeted therapy may improve selectivity but can still affect normal tissues using the same signalling pathways. Immunotherapy can generate durable responses but may induce inflammatory injury to healthy organs. Cytotoxic

treatment may damage normal proliferating cells. Biomarker selection improves the rationale for treatment but does not remove the need for toxicity monitoring.

10. PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS

Pharmacokinetics describes absorption, distribution, metabolism and excretion, whereas pharmacodynamics concerns the biological effects of a drug and the relationship between exposure and response. These principles are central to interpreting biomarker-directed treatment.

Oral small-molecule inhibitors may be affected by absorption, hepatic metabolism, organ function and drug interactions. Monoclonal antibodies have different distribution and elimination characteristics. Antibody–drug conjugates introduce additional determinants, including target binding, internalisation, linker stability and payload release.

Topical treatment depends on formulation, skin integrity, application technique, lesion depth and local penetration. Topical administration does not automatically eliminate systemic exposure.

Pharmacodynamic measurements may demonstrate target engagement, reduced pathway activity or altered immune-cell behaviour. However, target engagement does not guarantee clinical benefit. A drug may inhibit its intended target while tumour cells survive through alternative pathways. Molecular measurements must therefore be interpreted alongside pathology, imaging and clinical outcomes.

Dose selection must balance efficacy, exposure, toxicity and adherence. The presence of an actionable biomarker does not justify disregarding dose-limiting adverse effects or established prescribing requirements.

11. RESISTANCE AND TUMOUR HETEROGENEITY

Primary resistance occurs when a tumour does not respond adequately to treatment from the outset; acquired resistance develops following an initial response or period of disease control. Mechanisms include secondary genomic alterations, pathway reactivation, alternative receptor signalling, epigenetic adaptation, altered drug handling and immune escape.

A single biopsy may not represent all tumour subpopulations. Primary and metastatic lesions may differ in mutation profile or protein expression, and treatment pressure can change the relative abundance of resistant clones. Historical biomarker results may therefore require reassessment when the result could alter management.

Liquid biopsy may provide complementary information about tumour evolution, but it is not free from limitations. Low ctDNA shedding and clonal haematopoiesis can complicate interpretation. Repeat tissue sampling, ctDNA, imaging and clinical assessment should be integrated selectively rather than applied indiscriminately.

Resistance also limits immunotherapy. Impaired antigen presentation, poor immune infiltration, immunosuppressive signalling and tumour antigen changes may prevent effective immune recognition. PD-L1 and TMB provide only partial information about this complex system. Future biomarkers may combine genomic, proteomic, spatial and immune features, but clinical implementation requires prospective validation.

12. SAFETY PHARMACOLOGY

Targeted agents, immunotherapies and cytotoxic medicines have distinct adverse-effect profiles. BRAF/MEK combinations can cause fever, skin reactions and selected cardiac or ocular complications. Hedgehog inhibitors may cause muscle spasms, altered taste and weight loss. CDK4/6 inhibitors may cause neutropenia or other agent-specific effects, while PI3K pathway inhibitors can produce clinically significant hyperglycaemia.

Checkpoint inhibitors may cause immune-mediated colitis, hepatitis, pneumonitis, endocrinopathies and other inflammatory complications. Such events may emerge during treatment or after discontinuation and require prompt clinical assessment. Their occurrence should not automatically be interpreted as evidence of antitumour response.

Cytotoxic agents may produce myelosuppression, mucositis, neuropathy, renal injury or other organ-specific toxicities. Monitoring should reflect the particular medicine, regimen, baseline organ function, concomitant treatment and individual risk.

Tumour genomic testing and host pharmacogenomic testing answer different questions. The former characterises malignant tissue to inform diagnosis or treatment selection; the latter investigates genetic characteristics that may influence drug handling or toxicity. Both may contribute to precision pharmacology when supported by validated clinical indications.

13. TRANSLATIONAL OPPORTUNITIES AND INDIAN RESEARCH PRIORITIES

Accessible lesions offer opportunities for serial tissue sampling and pharmacodynamic research. Paired biopsies can help assess changes in pathway activity, proliferation, apoptosis and immune infiltration. Such investigations can clarify whether a drug engages its intended target and whether the expected biological effect occurs.

Patient-derived organoids and ex vivo drug testing may help investigate resistance and generate hypotheses about

therapeutic vulnerabilities. However, these models do not fully reproduce systemic pharmacokinetics, vascular supply or the immune microenvironment. Laboratory sensitivity cannot automatically be equated with clinical benefit.

Artificial intelligence and multimodal analysis may integrate digital pathology, imaging, genomic data and longitudinal clinical information. Their clinical value depends on external validation, reproducibility, transparent evaluation of errors and demonstration of benefit beyond established predictors.

In India, the practical value of precision oncology depends on diagnostic infrastructure, pathology quality, affordability, trained personnel and access to the corresponding medicines. Research priorities include validated low-cost assays, reliable turnaround times, clinical evaluation of biomarker panels and prospective studies of real-world effectiveness and toxicity. Greater molecular detection alone does not establish improved patient outcomes. Testing programmes should demonstrate that the information obtained changes management appropriately and provides meaningful clinical value.

14. LIMITATIONS

This review uses a descriptive category of externally accessible cancers rather than a unified disease classification. The malignancies discussed differ in biology, staging and treatment requirements, so their comparison is intended to illuminate shared pharmacological principles rather than imply biological equivalence.

The article is a narrative synthesis and does not include an exhaustive systematic search, formal risk-of-bias assessment or quantitative meta-analysis. Biomarker indications and treatment recommendations also evolve over time and may differ across jurisdictions. Emerging technologies such as ctDNA monitoring, spatial profiling and artificial intelligence require indication-specific validation.

The review does not provide patient-specific dosing or treatment recommendations. Clinical management depends on confirmed histopathology, stage, molecular findings, prior treatment, organ function and applicable clinical guidance.

15. CONCLUSION

The pharmacological management of externally accessible malignancies demonstrates that anatomical visibility and molecular treatability are distinct concepts. Skin, oral cavity and breast lesions may facilitate inspection and tissue sampling, but their therapeutic vulnerabilities are determined by tumour biology, validated biomarkers, disease extent and clinical context.

BRAF alterations can identify targeted treatment opportunities in melanoma; Hedgehog pathway dysregulation supports selected interventions in advanced BCC; PD-L1 informs particular immunotherapy decisions; and ER, PR, HER2, PIK3CA and BRCA1/2 guide defined breast cancer treatment strategies. None of these biomarkers independently guarantees response or eliminates resistance and toxicity.

The future of precision oncology depends on integrating histopathology, molecular diagnostics, pharmacokinetics, pharmacodynamics and longitudinal clinical assessment. Equitable access to validated tests and evidence-based treatments is essential if these advances are to improve outcomes across healthcare settings.

The ultimate objective is not simply to obtain more molecular data, but to identify clinically meaningful information that improves treatment selection, reduces avoidable harm and extends survival or quality of life. Such progress requires rigorous validation, disease-specific interpretation and responsible clinical application.

ACKNOWLEDGEMENTS

I would like to acknowledge Dr. Mohd. Shuaib and Dr. Shamim Ahmed for this study.

CONFLICT OF INTEREST

There exists no conflict of interest while publishing this work.

FUNDING

This is a self studied work. No funding was taken for this study.

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