**Title:**
How can we effectively integrate emerging immunotherapies and targeted therapies into existing treatment protocols to improve patient outcomes?

**Full Name:**
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**Name of the Institution:**
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**State:**
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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
1) Steroid free premedication
2) ctDNA guided treatment
3) SC/PO formulations
4) Timing of administration
5) Single agent Chemo + IO combination
6) Introduce IO after 3-4 cycles of ChT in palliative setting.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**
1) Steroid suppresses inflammation and immunity. We can try dexa free premedications for ChT + IO combination
2) Instead of indefinite treatment, baseline ctDNA --> Initiate IO --> monitor ctDNA every 3 months to decide continuation of the drug
3) SC/PO formulation decreases hospital time and saves admission cost to the hospital so finances of the patient can go for buying more drugs
4) Some trials for cisplatin in CTRT shows it works better when administered in afternoon/evening. Same can be tried with IO - afternoon administration
5) In palliative settings, we see use dual ChT with IO combination. Since anyway it is palliative, for low volume of disease we can offer single agent ChT and IO and save that 2nd ChT for next line
6) 3-4 cycles of ChT --> Evaluate --> if good response -->1-2 more cycles with IO + ChT and then IO maint can be tried to decrease out of pocket expenditure

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
Key objective is to enhance patient outcomes by integrating IO and targeted therapy in standard of care protocols. In this way, patients get the benefit of durable long-lasting response of IO and rapid cell kill precision of targeted therapies. By using recent biomarker testing methods, the goal is to shift from one size fits all chemotherapy to precision medicine that improves overall survival and quality of life.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**
Policymakers and stakeholders should take necessary steps to bring recent phase 3 trials involving IO & targeted therapies to the Indian population, as much as possible, to improve the standard of care. Provision should be made to open day care centres in each district, based on "hub and spoke model", so that patient can get treatment nearby to their home, and those centres can be controlled remotely from tier 1 cities. Standardised drug infusion & workup & toxicity assessment and management training can be given for those local doctors and nurses taking care of the daycare centres. Also, strict monitoring of iRAE is advised, and immediate referral of patients with grade 3 or more toxicity to apex centres is advised.
Online platforms can be created for transparent pricing of drugs and associated biomarker tests, allowing for accurate financial calculation and planning of intended therapy. Also, steps can be taken to give updated guidelines online, protocol administration guidelines, toxicity management protocols.

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**Full Name:**
Rahul Kumar

**Name of the Institution:**
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**State:**
Delhi

**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
Promoting clinical trial to include multicentre collaboration.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**
Integrating emerging immunotherapies and targeted therapies into existing oncology protocols requires a biomarker-driven, adaptive framework that prioritizes the right treatment for the right patient at the right time. By leveraging molecular profiling, including PD-L1 expression, MSI status, and actionable mutations, clinicians can rationally sequence or combine therapies to maximize efficacy while minimizing toxicity. Strategic combinations such as immune checkpoint inhibitors with chemotherapy or anti-angiogenic agents can enhance tumor immunogenicity and overcome resistance. Additionally, incorporating these approaches into neoadjuvant and adjuvant settings may improve long-term outcomes. Multicentre collaboration and real-world data are essential to validate effectiveness across diverse populations. Ultimately, a dynamic, response-adapted model supported by precision medicine and evolving clinical trials will redefine standard cancer care and significantly improve patient survival and quality of life.
We need Indian solutions in Indian problems.

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**Full Name:**
Avinash Ranjan

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
To ensure that each cancer patient receives the most appropriate immunotherapy or targeted therapy based on their tumor biology and clinical condition, leading to better outcomes, fewer unnecessary treatments, and improved access without financial burden.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**

1. Immunotherapy activates the immune system for durable responses, while targeted therapy blocks specific mutations for rapid tumor control. They offer better precision and outcomes than chemotherapy but are limited by high cost, toxicity, resistance, and benefit only in selected patients.
2. Key biomarkers include PD-L1, MSI-H/dMMR, TMB, and mutations like EGFR, ALK, ROS1, BRAF, HER2, NTRK, RET, MET, KRAS, BRCA, HRD, helping select patients most likely to benefit.
3. Major barriers are high cost, limited access to testing and drugs, late presentation, poor performance status, resistance, and need for specialized toxicity monitoring.
4. Improve affordable molecular testing, use tumor boards, follow biomarker-based protocols, expand insurance coverage, negotiate prices, and promote biosimilars and patient support programs.

**Goal**: right patient gets the right treatment on time without financial or access barriers.

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**Full Name:**
Reshma Abraham

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
Immunotherapy and targeted therapies have shown better responses in global studies, yet their use in clinical practice is neither uniform nor accessible to all eligible patients, how can we expand their utilization, and what biomarker gaps need to be addressed to guide their appropriate use?
What are the key barriers and challenges—clinical, biological, economic, and systemic—that limit the effective use of immunotherapy and targeted therapies in everyday practice?

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**

a) Immunotherapy in the current day and age should be viewed as a backbone modality across malignancies, not as a later line option. The main advantage is durable complete responses even in certain advanced diseases. The debate is no longer about whether to adopt it, but why adoption has not yet occurred. The absence of evidence in certain tumor types represents a gap in research; not necessarily an always an absence of benefit. This shows the need for exploring combination strategies or strategic search for biomarkers (eg how keynote B96 in ovarian cancer got approved now in 2026 compared to other cancers).

Clinicians must remain aligned with emerging global data rather than being constrained only to regulatory approvals atleast as to offering the options to the patient. In carefully selected patients, a well-informed, shared decision-making approach may support such use.

Similarly targeted therapies in the form of biologicals, TKIs, ADC and there are known to cause deeper responses, lesser side effects than chemotherapy and improved quality of life.

Biomarker-driven selection gives us double assurance-dMMR/MSI-H (strong, tumor-agnostic), PD-L1 (useful but imperfect—negativity doesn't exclude benefit in some cases), TMB with specific cutoffs, NGS-derived driver mutation and resistance markers like STK11 to guide monotherapy versus combination.

**b) Key challenges-** Cost and affordability remain the major challenge, even with emerging newer drugs and generics.

Underutilization of Asian/Chinese evolving data in view of Western guidelines;

Lack of availability of drugs in India (e.g., NHL drugs) and DCGI lag period for approvals.

Drug-related challenges: absence of better predictive biomarkers for optimal patient selection, resistance mechanisms, Tcell exhaustion, heterogeneous toxicity profiles (some permanent and disabling), and the complexity of managing adverse events even with coordinated multidisciplinary care.

**Solution-**

Integrated NCG, ICMR-NCDIR, and DCGI approach to review and release approvals for Asian trials and home trials and expedited drugs approvals.

Tax exemption on essential drugs and state-wise bulk procurement to reduce cost.

Increased global visibility and representation; more global phase 3 clinical trial sites to be opened up, to benefit patients.

Exploring beyond biomarkers with biological stratification: hot tumors (immune-rich) respond well to checkpoint blockade, while cold tumors require microenvironment modulation first. Cold-to-hot conversion strategies include anti-angiogenics (bevacizumab, lenvatinib), PARP inhibitors in BRCA-mutant disease, radiation therapy exploiting the abscopal effect, and hyperthermia—especially in dismal-prognosis diseases like aggressive sarcomas.

A simple IHC-based MMR testing across all tumour types, with our population as the data-generating source for Indian prevalence data.

Dedicated irAE clinics with standardized management approaches.

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**Full Name:**
Foram Joshi

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**

Oncological research has made cancer care and treatment highly dynamic, with newer therapies and innovations continuously emerging. Access to these evolving treatment modalities should be a major priority. New advancements become meaningless if we fail to integrate them into real-world practice and make them accessible to all patients.

Next-generation sequencing (NGS) and hotspot panel testing have revolutionized cancer diagnosis, treatment modification, and therapeutic expansion, especially in metastatic disease. These technologies have also enabled the development and use of tumor-agnostic therapies, significantly changing the landscape of precision oncology.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**

In today's era of molecular oncology and immuno-oncology, we must realize that chemotherapy-free regimens are increasingly becoming possible, and judicious utilization of these treatment modalities should be a priority. Many patients refuse chemotherapy because of fear regarding treatment-related side effects and, at times, may even choose palliative care over definitive treatment. Therefore, incorporation of immuno-oncology and precision oncology into routine cancer care is extremely important.

Targeted therapies and immunotherapy are also not free from adverse effects, and therefore patients must be properly counselled regarding the potential toxicities and expected outcomes of these treatments. Another major advantage of these modalities is the availability of oral and subcutaneous formulations, which improve patient compliance while maintaining treatment efficacy and quality of life.

One of the biggest challenges in incorporating immunotherapy and practicing precision oncology is financial toxicity. The high cost associated with these therapies often limits accessibility for the common patient. Therefore, the most important priority is bridging the gap between innovation and access to quality cancer care.

Implementation of cost-reduction strategies, wider availability of biosimilars, expansion of clinical trial access, and incorporation of patient assistance programs can significantly improve accessibility to immunotherapy in resource-limited settings. These measures can help bridge the gap between innovation and affordability, allowing a larger population of cancer patients to benefit from precision oncology and immunotherapy-based treatment approaches.

Increased use of biosimilars and low-dose immunotherapy strategies may further reduce financial toxicity for both patients and healthcare systems while maintaining treatment efficacy. Encouraging clinical trial participation and developing supportive healthcare policies can strengthen equitable cancer care delivery and ensure that advanced cancer therapies are not limited only to economically privileged populations. Ultimately, these strategies can help create a more accessible, affordable, and patient-centered oncology care system focused on delivering quality cancer care for all.

With advances in cancer care and availability of advanced molecular techniques, biomarker identification has become a crucial aspect of practicing precision medicine. However, one of the major challenges is the dynamic nature of cancer biomarkers along with the financial burden and prolonged turnaround time associated with these investigations. Therefore, strategies must be developed to ensure availability of diagnostic testing at subsidized costs in order to improve accessibility for larger populations.

An important and emerging concept in molecular oncology is liquid biopsy and ctDNA analysis. At times, biomarker testing in tissue samples becomes difficult because of inadequate tissue availability. In such situations, incorporation of liquid biopsy, ctDNA, and cell-free DNA testing can help guide precision oncology practice.

The role of ctDNA is rapidly emerging as an important prognostic biomarker. However, further clinical trial validation is required before it can be routinely used as a predictive and treatment decision-guiding tool.
In 2026, with rapid advancements in oncology, artificial intelligence, molecular oncology, and immuno-oncology, it is crucial that these innovations are effectively incorporated into treatment strategies and made accessible to all patients to ensure equitable and high-quality cancer care.

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**Full Name:**
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**State:**
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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
To develop a ctDNA-guided precision immunotherapy protocol for Primary Mediastinal B-Cell Lymphoma (PMBCL) that identifies patients at high risk of relapse after DA-R-EPOCH and integrates adjuvant pembrolizumab in ctDNA-positive patients to improve event-free survival, reduce overt clinical relapse, and personalize post-treatment management using biomarker-driven decision making.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**
**PEMBRO-ctDNA PMBCL Protocol**
Primary mediastinal B-cell lymphoma (PMBCL) is biologically characterized by frequent PD-L1/PD-L2 overexpression and 9p24.1 amplification, making it highly sensitive to PD-1 blockade. Although DA-R-EPOCH cures many patients, a subset relapse despite achieving radiologic remission. Emerging evidence shows that persistent circulating tumor DNA (ctDNA) after treatment predicts molecular residual disease and future relapse with high accuracy.
We propose a ctDNA-guided adjuvant pembrolizumab strategy integrating immunotherapy into standard PMBCL treatment protocols.
**Proposed Workflow**

- All newly diagnosed PMBCL patients receive standard DA-R-EPOCH.
- ctDNA is assessed:
  - at baseline,
  - during therapy,
  - and after completion of treatment.
- Patients who become:
  - PET-negative and ctDNA-negative →observation.
  - ctDNA-positive post-treatment →classified as molecular high-risk.

These ctDNA-positive patients receive:

- Pembrolizumab 200 mg IV every 3 weeks
- for up to 1 year as adjuvant consolidation.

**Biomarker Integration**

Key biomarkers include:

- ctDNA kinetics,
- PD-L1 expression,
- 9p24.1 amplification,
- PET-CT response.

**Advantages**

- Detects relapse earlier than imaging.
- Provides personalized escalation only for high-risk patients.
- Avoids unnecessary immunotherapy in low-risk patients.
- May prevent overt clinical relapse and reduce need for salvage chemotherapy/transplant.

**Challenges & Solutions**

Challenges include ctDNA availability, cost, and lack of standardization. Proposed solutions include centralized molecular testing platforms, risk-adapted testing, and prospective multicentre validation trials.

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**Full Name:**
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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**

To ensure the right cancer patient receives the right precision therapy at the right time to improve survival, treatment precision, and equity in cancer care by integrating biomarker-driven immunotherapy and targeted therapy, prioritising therapeutics, optimizing access, monitoring toxicity, and adaptive treatment sequencing in to routine clinical practice through a scalable resource-adapted framework.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**

**Problem statement:** Modern oncology has developed highly effective immunotherapies and targeted therapies, yet healthcare systems continue to struggle with delivering these advances to the right patients at the right time. The major barrier is not therapeutic availability, but implementation failure. Without structured biomarker triage, rational sequencing, access navigation, and toxicity governance, precision oncology remains inaccessible to many patients. PRAGATI Framework addresses this gap through a practical implementation framework tailored for real world and resource-constrained oncology practice.

**Solution:** Precision Resource Adapted Genomic & Adaptive Therapy Integration (PRAGATI).

The key challenge in Government hospitals/Limited resource hospitals is not scientific ignorance. It is resource asymmetry.

**Constraints include:**

* Delayed pathology
* Limited IHC
* No routine NGS
* Drug stock availability
* Overcrowding
* Poor follow-up continuity
* Out of pocket burden
* Limited immunotherapy access

**So, the framework must be resource adaptive, not idealistic.**

P: Precision triage-High-yield biomarker selection only
R: Resource stratification—Categorize patients by affordability/resources
A: Access enablement—PMJAY/state schemes/NGO pathways
G: Genomic prioritization—NGS only when high clinical yield
A: Adaptive treatment—switch based on response/toxicity
T: Toxicity surveillance—nurse-led toxicity protocols
I: Iterative review-MDT every week.
Tier 1 (must-do)- ER/PR/HER2, MSI/MMR,EGFR (lung adenoca),ALK (selected),PDL1(where actionable)
Tier 2 (selective)- BRCA,HER2 mutation, KRAS G12C, BRAF
Tier 3 (high-select yield)-broad NGS

**CASE 1:** 58-year-old woman, Non smoker, diagnosed with Metastatic lung adenocarcinoma with bone metastases, planned for 6 cycles pemetrexed, carboplatin, Bone supportive care.
Traditional errors:
*Empiric chemotherapy
*No biomarkers
*Delayed mutation testing
*Progression
*Lost opportunity
PRAGATI workflow for this case 1:
P = Precision triage—Never smoker + adenocarcinoma
High mutation probability. Mandatory:EGFR, ALK
R = Resource Stratification-Patient cannot afford NGS. So focused testing only.
A = Access-Use
* Hospital molecular subsidy
* State cancer fund
* NGO assistance

G = Genomic prioritization-EGFR positive: Exon 19 deletion
A = Adaptive treatment- Instead of chemotherapy:
Osimertinib.If unavailable- Gefitinib/erlotinib through public pathway.
T = Toxicity surveillance-Monthly:
* CBC, LFTs, RFTs
* Rash management

I = Iterative reassessment-CT at 12 weeks
Without PRAGATI: wrong chemotherapy
With PRAGATI: biomarker Directed therapy
Cheap focused testing prevents expensive wrong treatment.

**CASE 2:** 46-year-old woman, Metastatic HER2+ breast cancer, Financially constrained.
Traditional Problem
Ideal therapy: dual anti-HER2, Reality: unaffordable.
PRAGATI workflow for case 2:-
P- HER2 confirmation mandatory, Repeat if doubtful
R- Categorize affordability.
Tier A: full access
Tier B: partial subsidy
Tier C: minimal support
A- Explore: biosimilars, NGO funding, state schemes
G- No need broad NGS upfront, Known actionable target
A- If trastuzumab accessible: taxane + trastuzumab
If later access improves: escalate sequence.
T-Cardiac monitoring via echo.
I- Progression review for next line
Perfect should not become enemy of good, Use scalable access pathways.
PRAGATI works through a public private precision oncology partnership where government hospitals provide clinical care, and Esteemed Pharma companies like Roche supports diagnostics, access, training, and implementation infrastructure to ensure eligible patients receive biomarker-matched immunotherapy or targeted therapy on time.
* Government Hospital Clinical Leadership
* Pharma Supported Biomarker Testing Access
* Affordable Patient Access Programs
* Molecular Tumor Board Collaboration
* Clinician & Nurse Capacity Building
* Digital Decision Support Integration
* Toxicity Monitoring & Safety Pathways
* Real-World Data & Outcome Tracking
* Clinical Trial Access Expansion
* Biosimilar & Sustainable Drug Access Model
* NGO / Insurance / Public Scheme Linkage
* Adaptive Treatment Review & Escalation Pathway

**PRAGATI Workflow:**

Patient enters government hospital
↓
Doctor identifies cancer type
↓
PRAGATI biomarker checklist applied
↓
Pharma-supported diagnostic testing
↓
MDT treatment decision
↓
Eligible patient directed to immunotherapy / targeted therapy
↓
If affordability issue: patient assistance activation
↓
Treatment starts
↓
Nurse led toxicity monitoring
↓
Response reassessment
↓
Adaptive next-line therapy.

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
**Deliver precision, biomarker-driven oncology care by selecting the right therapy for the right patient**

- Improve survival, quality of life, and treatment tolerability through personalized immunotherapy and targeted therapy integration
- Standardize upfront molecular and immunotherapy biomarker testing in routine cancer practice
- Optimize therapy sequencing, monitoring, and multidisciplinary decision-making to maximize long-term outcomes
- Enhance accessibility and affordability through rational treatment use, biosimilars, and government-supported healthcare models

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**

Effectively integrating immunotherapy and targeted therapy into routine oncology care means choosing the right drug for the right patient at the right time. In diseases like Non-Small Cell Lung Cancer, a PD-L1—high patient often achieves superior outcomes with immunotherapy and lower toxicity than chemotherapy. Similarly, EGFR exon-19—mutated tumors respond dramatically to targeted TKIs, offering oral convenience and improved quality of life. Immunotherapy also provides a unique "immune memory" effect, leading to durable responses even after treatment discontinuation.

The backbone of integration is biomarker-driven selection. Immunotherapy biomarkers include PD-L1, MSI-H/dMMR, tumor mutational burden, and tumor-infiltrating lymphocytes. Targeted therapy relies on alterations such as EGFR, ALK/ROS1, HER2, BRAF V600E, BRCA1/2, and NTRK fusions. These markers help avoid ineffective therapy and ensure personalized treatment.

A practical integration pathway is:

Biomarker testing → Therapy selection → Sequencing/combination → Monitoring → Outcome optimization.

For example, EGFR-mutant NSCLC is best treated with upfront TKI, followed by chemotherapy or immunotherapy later, whereas PD-L1-high tumors may benefit from first-line immunotherapy± chemotherapy.

Challenges remain significant. Clinically, only a subset responds, resistance develops, and immune-related toxicities require expertise. Diagnostically, limited molecular labs, tissue inadequacy, and delayed reports affect timely decisions. Economically, high drug costs, repeated testing, and poor insurance coverage are major barriers. Systemically, rural access gaps and dependence on Western data limit applicability in India.

Solutions must be multi-level: mandatory upfront biomarker testing (including cfDNA), multidisciplinary tumor boards, rational sequencing strategies, and digital monitoring tools for toxicity prediction. Expanding Indian clinical trials will generate local evidence. Cost reduction through biosimilars, generics, and government support such as Ayushman Bharat is essential.

Ultimately, integration is not about using all therapies, but using them intelligently to maximize survival, quality of life, and affordability.

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
At high volume centre with majority patients from low socio-economic backgrounds, accessing standard-of-care immunotherapies or targeted therapies is prohibitive due to high costs. Our objective is to develop a localized, evidence-based framework to safely and affordably implement these advanced therapies. This requires overcoming systemic barriers—such as the high costs of both the drugs and essential biomarker testing (like NGS, IHC)—and addressing critical clinical challenges, including differing pharmacokinetics and pharmacodynamics (PK/PD) in our demographic. We aim to democratize access through tailored protocols and policy advocacy.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**
To effectively integrate emerging immunotherapies and targeted therapies and improve outcomes for the vast majority of our patients, we must address the glaring disconnect between Western trial data and our local clinical realities**.**

1. **Navigating Clinical Challenges and PK/PD Differences**

While these therapies offer undeniable survival advantages, utilizing them in our clinic presents unique hurdles. Western-based trial dosing often results in high toxicity due to distinct population pharmacokinetics and pharmacodynamics (PK/PD). For instance, standard tyrosine kinase inhibitor (TKI) dosing frequently fails locally; when initiating Lenvatinib for HCC, even lower doses like 4mg show poor tolerance, with patients experiencing higher-than-reported rates of Hand-Foot Skin Reaction (HFSR). Addressing this requires adopting population-specific dosing protocols rather than blindly mirroring Western guidelines.

**2. Overcoming Biomarker and Utilization Bottlenecks**

Therapy decision-making depends heavily on biomarkers, yet the financial infrastructure does not support this. Next-Generation Sequencing (NGS) is rarely covered by insurance, and even basic Immunohistochemistry (IHC) in government setups creates prohibitive out-of-pocket costs (e.g., HER2 testing for non-breast indications). Consequently, the combined cost of prerequisite testing and the therapy itself marginalize our patients.

**3. Actionable Solutions: Low-Dose Trials and Market Expansion**

The primary solution lies in validating and standardizing cost-effective alternatives. We must aggressively pursue and publish low-dose trials—such as utilizing ultra-low-dose nivolumab (40mg at Rs 13,000)—to establish affordable, evidence-based regimens that maintain efficacy while opening the market to the majority. Additionally, advocating for subsidized diagnostic panels within government insurance schemes is crucial so testing does not preclude treatment. Ultimately, generating local Real-World Evidence (RWE) on both efficacy and altered toxicities will force a shift toward volume-based, localized pricing rather than relying on restrictive assistance programs.

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
Effective integration of Immuno and targeted therapy into treatment protocols

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**

**1. Effectiveness, Advantages, and Clinical Challenges**

- Immunotherapies activate the immune system to destroy cancer cells and can produce long-lasting responses.
- Targeted therapies act on specific mutations such as EGFR, HER2, BRAF, and ALK, improving precision in treatment.
- Their use improves survival, reduces unnecessary toxicity, and supports personalized medicine.
- Clinical challenges include immune-related side effects, drug resistance, tumor escape mechanisms, and variable patient response.

**2. Biomarkers Supporting Therapy Decision-Making**

- PD-L1 expression, Microsatellite Instability (MSI-H/dMMR), POLE/POLD1 ultramutated and Tumor Mutational Burden (TMB) predicts response to checkpoint inhibitors.
- Negative predictors of response include KEAP1, LKB and presence of other actionable mutations.
- EGFR, ALK, HER2, and BRAF mutations guide targeted therapy selection.
- Circulating tumor DNA (ctDNA) and immune-cell signatures help monitor treatment response and resistance.

**3. Challenges in Utilizing These Therapies in All Patients**

- Tumor heterogeneity and evolving resistance pathways reduce treatment effectiveness.
- High costs and limited biomarker testing restrict accessibility.
- Some tumors remain immunologically “cold” and fail to respond.
- Limited representation of diverse populations in clinical trials affects treatment applicability.

**4. Possible Solutions**

- Routine testing for not only positive predictors like PD L1 but also negative ones like KEAP 1 using CGP at diagnosis and at progression or recurrence
- AI-driven multi-omics profiling for accurate patient stratification.
- Expand liquid biopsy technologies for serial real-time monitoring.
- Develop combination therapies involving immunotherapy, targeted therapy, and radiotherapy.
- Standardize biomarker testing and improve global access programs.
- Advance personalized approaches such as neoantigen vaccines and microbiome-based therapies
- Large clinical trials studying various combinations of Immunotherapy and targeted therapy with existing treatment

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
To establish a biomarker stratified, sequencing aware integration framework for immunotherapy and targeted agents that explicitly addresses the toxicity interactions and scheduling conflicts arising when these modalities overlap or are used sequentially, replacing ad hoc prescribing with a structured clinical decision pathway.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**
The integration of immunotherapy and targeted therapy is not simply a matter of choosing both when both have evidence. Osimertinib followed immediately by durvalumab produces pneumonitis rates that are clinically unacceptable. Bevacizumab added to atezolizumab in non-squamous NSCLC works precisely because anti VEGF normalizes tumour vasculature and facilitates T cell infiltration, which is the biological rationale behind IMpower150. Ipilimumab combined with nivolumab produces response rates in MSI-H colorectal cancer that neither agent achieves alone. These are not comparable clinical situations and treating them as variations on the same integration problem is where most protocols go wrong.
The framework has three components.
First, a reflex biomarker panel should precede any integration decision. TMB, MSI status, PD-L1 TPS and CPS, and tumour specific driver mutation status need to be known before sequencing is decided. The biomarker result determines which modality leads, and which follows, not institutional habit or drug availability.
Second, a mandatory safety washout protocol should be embedded in every institutional guideline for sequential use of targeted therapy followed by immunotherapy, with organ specific monitoring requirements defined by the known toxicity overlap. EGFR TKI to ICI transitions require at minimum a three-to-four-week washout and baseline pulmonary function documentation because the interstitial pneumonitis and other IRAEs risk from this specific sequence is real and routinely underestimated.
Third, any combination outside a standard approved indication should require molecular tumor board sign off before initiation. This is not bureaucracy. It is recognition that the number of clinically relevant two drug interactions in oncology now exceeds what any individual clinician can reliably hold in working memory, and the consequence of getting it wrong is grade 4 toxicity in someone who was otherwise doing well.

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
Integration of immunotherapy and targeted therapy results in best response.this can be done via molecular driver and precision oncology driven biomarker based personalized treatment.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**
The advantages of immunotherapy includes

- Long term durable response in a subset of population
- Less use of steroids
- Fewer off target toxicities
- Harnessing of one's own immune system
- Can be stopped with limited time
- Response even after re-challenging

The challenges of immunotherapy includes

- Immune related adverse events which may be life threatening sometimes
- High cost
- Reduced accessibility
- Difficult to use in autoimmune disorders
- No long term safety data available
- Knowledge gaps in the predictive and prognostic biomarkers

The advantages of targeted therapy includes

- Predictive biomarker availability
- Very good survival and response rate data
- Long term safety data available
- Mostly oral drugs and easy to administer
- Personalised therapy

Challenges include

- Life long administration /till progression
- Difficulty in adherence
- Can develop resistance in long course
- Off target toxicity

**Various biomarkers in IO includes**

1. PDL1 expression- calculated by various methods like CPS, TAP etc. Most commonly used one but it is considered to be a poor biomarker.
2. MSI-denotes the increase in the neo antigen load and hence better immunotherapy responsiveness
3. Tumour mutation burden-higher the TMB, better the response
4. Tumour infiltrating lymphocytes-higher the TIL, higher the response as shown in many TNBC and Her2+ breast cancer trials. It is approved in Scandinavian breast cancer guidelines for their role in early breast cancer
5. Gut microbiota- Certain microbes in gut increase the immunotherapy responsiveness and some others are unfavourable
6. Multiomics-integrates genomic, transcriptomics and proteomic data to improve the biomarker precision
7. Certain biomarkers like Her2, ALK, ROS, EGFR, MET, RAS etc

**Challenges in using immunotherapy**

- Patient heterogeneity
- Intratumoral heterogeneity
- Cost and accessibility issues
- Infrastructural gaps
- Resistance mechanism
- Toxicity and its management

**To overcome these**

1. for reducing the cost and accessibility- can promote clinical trials and biosimilars, patient support programmes, increase the insurance coverage
2. To prevent resistance- can use combination chemo and IO, use of AI in predicting the resistance mechanisms and overcoming it
3. For heterogeneity issues-can use biomarker driven personalised therapy and AI
4. For toxicity—Address the knowledge gaps and early identification and treatment

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**Full Name:**
Jarfin I M

**Name of the Institution:**
Gleneagles Health City, Chennai

**State:**
Tamil Nadu

**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
To integrate immunotherapy and targeted therapy into routine protocols in a way that improves survival, preserves quality of life and avoids irrational, unaffordable treatment.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**
Immunotherapy can produce durable responses in selected cancers, while targeted therapies can give rapid, biomarker-driven disease control. Their greatest strength is personalization. Their biggest challenge is that benefit is not universal, toxicity can be serious, and cost is often overwhelming.
Biomarkers must guide use. These include PD-L1, MSI-H/dMMR, TMB in selected contexts, EGFR, ALK, ROS1, BRAF, HER2, NTRK, RET, MET, KRAS G12C, BRCA/HRD and others depending on tumour type. Testing should be planned before treatment starts, not after multiple ineffective lines.
Challenges include limited tissue, delayed reports, test cost, drug affordability, immune-related adverse events, resistance, lack of trial access and uneven expertise outside major centres. In Tamil Nadu, hub-and-spoke models can allow district centres to treat standard cases while complex targeted/immunotherapy decisions are reviewed by tertiary tumour boards.
Solutions include reflex biomarker testing, resource-stratified protocols, molecular tumour boards, toxicity-management pathways, patient-assistance programs, registries and real-world audits. CMCHIS and public hospitals can prioritize high-value indications with proven benefit.

Roche can support responsible access through diagnostics, education, affordability programs and transparent outcome registries.
The key is discipline. These drugs should not be used because they are fashionable, but because the biology, evidence and patient's life situation all point in the same direction. That is where modern oncology becomes both scientific and humane**.**

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**Full Name:**
Dr. Rajul Jain

**Name of the Institution:**
Omega hospitals, Hyderabad

**State:**
Telangana

**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
Immunotherapy and targeted therapies represent the most significant advances in oncology, yet their integration into treatment protocols remains suboptimal. Current practice frequently reserves these agents for later lines of therapy - by which point patients in India are financially exhausted, physically depleted, and psychologically overwhelmed. This paradox is stark: our most effective agents are deployed when patients are least equipped to benefit. With cancer burden rising rapidly in India, where out-of-pocket expenditure exceeds 70%, treatment abandonment is common before optimal therapy is ever reached. Evidence already validates earlier use of osimertinib in first-line EGFR+ NSCLC (FLAURA), pembrolizumab in PD-L1-high NSCLC (KEYNOTE-024), and olaparib maintenance in BRCA+ ovarian cancer (SOLO-1). All demonstrated superior outcomes precisely because effective therapy was frontloaded.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**
The solution lies in a three-pronged framework: early access policy, biomarker-guided integration, and cost-efficient testing infrastructure.
First, a policy mandate requiring early-line evaluation of agents that already hold later-line approvals backed by existing cross-tumour trial evidence would systematically shift integration upstream. Regulatory bodies and institutional protocols should incentivize trials testing approved targeted agents and immunotherapies in earlier-stage or first-line settings, where patients retain better performance status, financial capacity, and treatment tolerance.
Second, a biomarker-guided early integration algorithm should replace the current reactive model. Rather than ordering molecular testing piecemeal at each progression, reflex bundled testing - comprehensive NGS and IHC panel at diagnosis -should become standard of care. One upfront panel replacing three to four sequential tests ordered over the treatment course is not only clinically superior but paradoxically more cost-effective. Actionable results at diagnosis allow immediate, personalized therapy selection rather than empiric chemotherapy followed by delayed targeted therapy as salvage. Government subsidy of reflex panels for lung, breast, colorectal, and hematologic malignancies under PMJAY would make this sustainable at scale.
Third, a hub-and-spoke model similar to e-commerce logistics networks like Amazon, where regional fulfilment centres serve surrounding areas. Applied to molecular diagnostics, with central testing laboratories processing courier biopsies from district hospitals, would eliminate travel burden for patients in tier-2 and tier-3 cities, reducing delays, indirect costs, and patient attrition.

Together these measures create a virtuous cycle: early biomarker identification enables early effective therapy, reducing treatment futility and cumulative financial burden -delivering better outcomes per rupee spent across India's growing cancer population.

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**Full Name:**
Livin T

**Name of the Institution:**
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**State:**
Tamil Nadu

**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
We have to mandate a really strict multidisciplinary workflow. When we discuss a tough case at the tumor board, we must lean hard on the ESMO Magnitude of Clinical Benefit Scale

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**
Watching those major ASCO presentations, targeted agents and checkpoint inhibitors honestly look like pure magic. But trying to actually weave them into our daily protocols is just incredibly difficult. You see these wild response rates for MSI-high gastrointestinal cases where the mass essentially melts. And yet, getting the basic biomarker testing done remains this massive bottleneck.
We totally rely on PD-L1 scores or heavy NGS panels just to know who might even react to the drug. But ordering that kind of expensive molecular workup for a family that is already financially exhausted is often a non-starter. The hurdles aren't purely financial, though. We also have to manage these completely unpredictable autoimmune toxicities. Most regional hospital wards are rarely set up to handle a sudden grade 4 pneumonitis safely. Plus, a huge chunk of our patients present with frankly terrible nutritional baselines. Hitting them with full-dose targeted regimens based entirely on Western trial data is usually highly dangerous.
How do we actually fix this mess in practice? We have to mandate a really strict multidisciplinary workflow. When we discuss a tough case at the tumor board, we must lean hard on the ESMO Magnitude of Clinical Benefit Scale. If a new drug doesn't offer a massive, undeniable survival bump, we just walk away from it. We stick to reliable generic chemotherapy or simply push for maximum surgical optimization in the OR. And we desperately need the state to negotiate aggressive risk-sharing contracts with pharma. Because if a ridiculously expensive neoadjuvant immunotherapy fails to shrink a tumor enough for me to achieve a clean R0 resection, our local health system absolutely shouldn't be stuck paying the premium price.

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**Full Name:**
Kiran Narayan Chavan

**Name of the Institution:**
Regional Cancer Centre, Thiruvananthapuram

**State:**
Kerala

**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
Immunotherapy and targeted agents have changed what we can offer but slotting them into protocols built around chemotherapy and radiation is harder than it looks. The questions pile up at the bedside: who actually benefits, in what sequence, alongside or instead of what we already give, and at what cost in toxicity and money. A checkpoint inhibitor that transforms outcomes in one patient does nothing in the next, and a targeted drug works beautifully until resistance arrives a year later. In India the gap is wider still the biomarker testing that should drive these choices is often unavailable or unaffordable, our patients are tested late or not at all, and the same agent that is routine in a metro is out of reach in a district hospital. Integration is therefore not just a scientific problem but a question of selection, sequencing, testing and access.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**
On effectiveness, immunotherapy earns its place where the tumour is immunogenic—melanoma, NSCLC, MSI-high colorectal and renal cancers offering durable, sometimes years-long responses with toxicity that differs from rather than adds to chemotherapy. Targeted therapy gives high, rapid response rates in mutation-driven disease (EGFR or ALK lung cancer, HER2 breast and gastric cancer, BRCA-mutated ovarian cancer) with relatively clean off-target effects. The catch is that benefit is conditional: immune-related adverse events can hit any organ, and resistance to targeted drugs is almost inevitable.
This is why biomarkers must drive the decision. For immunotherapy these are PD-L1 expression, tumour mutational burden and MSI-high/dMMR status; for targeted therapy, EGFR, ALK, ROS1, HER2, BRAF and BRCA, with liquid biopsy increasingly useful for picking up resistance mutations such as EGFR T790M without a repeat invasive sample.
The real difficulty in offering these to every patient is practical. NGS and immunohistochemistry are concentrated in a few cities; the drugs cost more than most families earn; irAEs need expertise that peripheral centres lack; and resistance demands repeat testing and a next line.
The fixes have to work together. Make biomarker testing affordable and reimbursed under PM-JAY rather than gating it behind out-of-pocket cost and expand NGS through hub-and-spoke laboratory networks. Lean on Indian biosimilars and pooled NCG procurement to bring drug prices down. Build irAE competence in district centres through Project ECHO-style tele-mentorship from a tertiary hub. And generate our own sequencing data adaptive, India-relevant trials so we choose and sequence these agents for our patients rather than borrowing thresholds set elsewhere.

**Full Name:**
Rishika Goyal

**Name of the Institution:**
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**State:**
Karnataka

**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
**Objective**: The goal is to ensure that patients who qualify for immunotherapy and targeted treatments receive the appropriate care promptly by minimizing the time between identifying biomarkers and making treatment decisions.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**
**Existing Gap**
Despite significant progress in molecular diagnostics and precision oncology, many patients do not receive the most suitable immunotherapy or targeted therapy even after biomarker testing.
Access to molecular testing alone is not enough. In many cases, biomarker results become available only after treatment has begun.
Patients with aggressive or symptomatic disease often need prompt therapy, leading clinicians to make treatment decisions before molecular data are available.
Consequently, potentially actionable findings may not be incorporated into initial treatment planning, limiting access to the most appropriate first-line precision therapies.
**Solution Offered**
**Molecular Fast-Track Pathway**
This model makes sure that actionable biomarker information if available earlier should impact therapeutic decision-making where it becomes meaningful for altering the outcomes of the patient
At the first instance, biomarker testing can be done for one kind of cancers like advanced non-small cell lung cancer, where predefined molecular testing should be done at the diagnosis point only without waiting for a separate oncology request.
This move considerably testing earlier in the patient journey and reduces diagnostic delays.
A coordinator can monitor various processes like competition of the tests, checking availability of the reports, notify clinician when result becomes available and calling the patient on arrival of results.
This ensures that actionable molecular findings are not overlooked.
Patients who are clinically stable and awaiting for biomarker results can be started on predefined bridging protocols that preserve the chance to start the most suitable targeted therapy or immunotherapy as the first-line treatment.
This model shifts precision oncology from a testing-centered model to a time-sensitive decision pathway, ensuring that the correct biomarker result reaches the right patient before the opportunity to act on it is lost.

**Full Name:**
Devarakonda Srujana

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
Immunotherapies and targeted therapies have transformed outcomes in melanoma, RCC, NSCLC, HER2-positive breast cancer, and hematologic malignancies by improving OS, and QoL. Their greatest advantage lies in precision treating biologically selected patients while reducing unnecessary toxicity. However, resistance mechanisms, immune-related adverse events, high acquisition costs, and variable access to molecular testing limit their real-world impact. Furthermore, some recently approved therapies provide only marginal clinical benefit despite substantial cost, creating low-value care and straining healthcare systems.

**Biomarkers for Therapy Decision-Making:**
The majority of Indian cancer patients are not receiving immunotherapies or targeted agents due to challenges in identifying effective treatments, but also difficulty in accessing.
Drug costs, delayed biomarker testing, and unequal healthcare infrastructure are the main issues. India, needs a framework that integrates innovation with affordability, precision, and quality assurance.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**
A "Biomarker Before Treatment" strategy should become standard practice. Key biomarkers include PD-L1, MSI-H/dMMR, TMB, EGFR, ALK, ROS1, RET, BRAF, HER2, BRCA1/2, NTRK, and ctDNA-based liquid biopsy markers. AI-assisted pathology and centralized molecular testing networks can help identify actionable alterations rapidly and cost-effectively, ensuring patients receive the most appropriate therapy from the outset.

**Challenges:**

1. .Low-Value and Inappropriate Use
   Some treatments achieve regulatory approval based on surrogate endpoints with limited OS & QoL improvement.
2. Geographic and Infrastructure Inequity
   Patients from rural and semi-urban regions frequently travel long distances for biomarker testing and treatment, increasing time toxicity, treatment abandonment, and financial burden.
3. Lack of Standardized Molecular Decision-Making
   Many centers lack Molecular Tumor Boards, resulting in variation in interpretation of genomic reports and treatment recommendations.
4. Resistance and Toxicity: Primary and acquired resistance reduce long-term effectiveness, while immune-related adverse events need timely recognition and management, which may not be available everywhere.
5. Limited Indian Real-World Evidence
   Differences in genetics, comorbidities, affordability, and healthcare delivery mean that efficacy, toxicity, and cost-effectiveness data may not always be directly applicable to Indian patients.
6. Policy and Reimbursement Barriers, high out-of-pocket expenditure**.**

**Solution:** The VALUE BASED-PRECISION ONCOLOGY MODEL (VBPO): addressing four major challenges identified by Tannock et al., meaningful benefit, affordability, access, and quality of care, while ensuring that every rupee invested in cancer treatment delivers the greatest possible patient benefit.

1. Universal “Biomarker-First” Pathway: Standardised testing pathways for EGFR, ALK, ROS1, RET, PD-L1, MSI/MMR, BRCA, and NTRK can prevent inappropriate therapy use and reduce delays. Centralised testing hubs linked to peripheral centers can improve access
2. National AI-Enabled Molecular Tumor Board Network through tele-oncology. AI-assisted clinical decision support systems
3. Value-Based Treatment Prioritisation demonstrates meaningful gains in OS or QoL using tools such as the ESMO-MCBS, ensuring resources are directed toward high-value interventions while reducing expenditure on therapies with marginal benefit.
4. Dose Optimization and Treatment De-escalation with interventional pharmacoeconomics. Low-dose abiraterone administered with food, Biosimilar adoption for monoclonal antibodies, Evidence-based shorter trastuzumab durations, validated low-dose or extended-interval immunotherapy schedules.
5. National Precision Oncology Registry to generate Indian-specific evidence, identify disparities, and accelerate precision medicine research.
6. Reducing Time Toxicity Through Decentralised Care: Expanding subcutaneous formulations (e.g., HER2-directed therapies), tele-oncology follow-up, digital toxicity monitoring, and satellite infusion centres can reduce patient burden, improve adherence, and enhance quality of life.

"Precision oncology should not be defined by access to the newest drug, but by access to the highest-value treatment for every patient, regardless of geography or income."

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**Full Name:**
Dr. Chirag Gajera

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**State:**
Karnataka


**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
To develop an integrated, personalized oncology treatment approach that combines emerging immunotherapies and targeted therapies with existing treatment protocols to improve survival outcomes, optimize treatment selection, and ensure safe and effective use based on individual patient and tumor characteristics.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**

Immunotherapies and targeted therapies have transformed cancer care by providing durable responses and improved outcomes in selected patients. Immunotherapies, including immune checkpoint inhibitors, enhance anti-tumor immune activity and have demonstrated benefit across multiple cancers. Targeted therapies act on specific molecular alterations, providing precision treatment with improved efficacy and reduced toxicity compared with conventional therapies. However, challenges include primary and acquired resistance, immune-related adverse events, tumor heterogeneity, high cost, and limited access to molecular testing.

Biomarker-driven treatment selection is essential for effective integration. Important biomarkers include PD-L1 expression, microsatellite instability (MSI)/mismatch repair deficiency (dMMR), tumor mutational burden (TMB), specific genomic alterations such as EGFR, ALK, ROS1, BRAF, HER2, BRCA mutations, and emerging biomarkers such as circulating tumor DNA (ctDNA) and immune gene signatures.

Major challenges include limited biomarker availability, lack of standardized testing, treatment resistance, financial burden, toxicity management, and unequal access to advanced therapies.

Possible solutions include strengthening molecular diagnostic infrastructure, implementing routine biomarker testing, developing evidence-based combination strategies, improving clinician training, and using multidisciplinary tumor boards for treatment decisions. Health policies supporting reimbursement, affordable diagnostics, and broader access programs can improve availability. Continuous clinical research and real-world evidence generation will further optimize sequencing and combination of immunotherapy and targeted therapy.

A personalized, biomarker-guided approach can maximize treatment benefit while minimizing unnecessary toxicity and healthcare costs.

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**Full Name:**
Pavitra Hegde

**Name of the Institution:**
Regional Cancer Centre, Trivandrum

**State:**
Kerala

**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**

Title: Integrating Immunotherapy and targeted therapy in Oral Cavity Squamous cell carcinoma

Background: Oral cavity squamous cell carcinoma (OCSCC) is one of the most common cancers in India. In patients with OCSCC, nearly 30% of them have PI3K mutation. PIK3CA activation is associated with enhanced invasion, lymph angiogenesis, and cervical nodal dissemination, making it an attractive target in OCSCC where nodal metastasis is the major determinant of survival.

Rationale: PI3K pathway activation may create an immunosuppressive tumour microenvironment by reducing T-cell infiltration and promoting myeloid-derived suppressor cells and regulatory T cells.

Thus, inhibition of PI3K may “re-condition” the tumor microenvironment and improve the efficacy of PD-1 blockade; thus paving way for a combination of a PI3K inhibitor and pembrolizumab/nivolumab to lead to a possibly improved response in biomarker-selected OCSCC patients.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**

**Study Design Overview:**

1. Patients with recurrent/metastatic OCSCC post first line standard approved therapy and planned for standard immunotherapy will undergo NGS testing for PIK3CA mutation and immune profiling, including PD-L1 CPS.
2. Patients with PIK3CA-mutant disease will receive standard PD-1 inhibitor therapy with the addition of a PI3K inhibitor such as alpelisib.
3. Patients will be stratified based on:
    - PD-L1 CPS <1
    - CPS 1-19
    - CPS ≥20 and
    - PIK3CA mutation subtype.
4. Response will be monitored using clinical assessment, imaging, toxicity scoring, and ctDNA where available.

   Endpoints:
5. Objective response rate
    - Progression-free survival
    - Overall survival
    - Duration of response
    - ctDNA clearance
    - Safety and tolerability

**Expected Impact:**

This proposal integrates targeted therapy with immunotherapy in a genomically selected subgroup of OCSCC, potentially converting partial or non-responders of PD-1 therapy into durable responders.

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**Full Name:**
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Regional Cancer Centre, Trivandrum

**State:**
Kerala

**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**

To evaluate efficacy and safety of adjuvant FGFR-targeted therapy in patients with FGFR3-altered intermediate- and high-risk non-muscle-invasive bladder cancer following standard treatment, with goal of reducing recurrence and disease progression.

**Describe your solution / proposal: Provide a detailed account of your solution/ proposal to this challenge. You could type your solution/ proposal here. (Disclaimer: Solution/proposal should not exceed more than 300 words.):**

Title: Adjuvant FGFR Inhibition in FGFR3-altered Intermediate- and High-Risk Non-Muscle-Invasive Bladder Cancer: A Randomized Phase II Study

Background:

Non-muscle-invasive bladder cancer (NMIBC) accounts for 75% of newly diagnosed bladder cancers. Following the standard treatment of complete transurethral resection of bladder tumor (TURBT) and intravesical therapy, the recurrence rates are still high, 50% of patients recur within five years. Current treatment strategies are dependent on clinicopathological risk factors and not on targeted molecular approaches.

FGFR3 alterations are the most frequent genomic abnormalities in NMIBC and have an important role in the early stages of bladder carcinogenesis. These alterations promote tumor cell proliferation, survival, and recurrence through activation of the FGFR signalling pathway. FGFR inhibitors have showed efficacy in metastatic urothelial carcinoma with FGFR alterations, but their role in earlier-stage disease has not been adequately studied.

Rationale:

We aim to evaluate whether targeting FGFR3-altered tumors in the adjuvant setting can reduce recurrence and progression in patients with intermediate- and high-risk NMIBC.

Study Design Overview

1. Patients with intermediate- or high-risk NMIBC who have undergone complete TURBT will undergo FGFR3 testing using a validated molecular assay (IHC if Confirmed by PCR/NGS).
2. Patients with FGFR3 alterations will be randomized in a 1:1 ratio to:
   - Standard management (intravesical therapy and surveillance)
   - Standard management plus adjuvant FGFR inhibitor therapy
3. Scientific Basis:
   - FGFR3 mutations are early oncogenic drivers in NMIBC.
   - Persistent FGFR signalling leads to tumor recurrence and disease progression.
   - Inhibition of FGFR signalling may eliminate residual microscopic disease and delay recurrence.
   - Clinical activity of FGFR inhibitors in advanced urothelial carcinoma supports their basis of use in earlier disease stages.
4. Primary Endpoint:
   2-year Recurrence-Free Survival (RFS)
5. Secondary Endpoints:
   - Progression-Free Survival (PFS)
   - Time to First Recurrence
   - Cystectomy-Free Survival
   - Overall Survival
   - Safety and Tolerability
6. Biomarker Strategy:
   Correlation of specific FGFR3 alterations with treatment response.
   - Identification of molecular predictors of recurrence and resistance.

**Expected Impact:**

This study tries to incorporate the precision oncology into the early management of bladder cancer by targeting a key molecular driver of NMIBC -FGFR3. If successful, this strategy could establish a new biomarker-driven adjuvant treatment paradigm, reduce recurrence rates, and improve long-term clinical outcomes.