**Title:**
Navigating Immunotherapy Resistance in Oncology

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

1. Resistance - Primary vs Acquired, Intrinsic & extrinsic, physical & vascular barrier
2. Overcome resistance - PD1/CTLA4 combination, VEGFi/IO combination, Using IO with RT, ChT/IO combination
3. Knowledge gap
4. Predict and overcome resistance

**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) Resistance:
A) Primary - occurs in cold tumors due to absence of tumor antigens invisible to adaptive immunity
B) Acquired - seen in patients who initially respond to therapy but later relapse.
C) Intrinsic-
a. Genetic Alterations- Mutations in signaling pathways- eg dysregulated KRAS signaling
b. Tumors downregulate HLA genes or proteins like TAP1 and TAP2
c. DNA repair can lead to a lower mutational burden
D) Extrinsic-

- Hypoxia and Metabolic Reprogramming
- Immunosuppressive Cell Recruitment
- Alternative Checkpoints such as LAG-3, TIGIT, TIM-3, and VISTA

E) Physical and Vascular Barriers
a. Neovascularization
b. Stroma Density- fibrous stroma can act as a physical wall, trapping T-cells on the periphery of the tumor
2) Overcome resistance:
a) Combining anti-PD-1/PD-L1 with anti-CTLA-4 → Overcomes compensatory checkpoint upregulation.
b) VEGF inhibitors inhibits angiogenesis
c) Chemotherapy & Radiotherapy → Tumor cell death → Release of neoantigens → Antigen presentation → Immune activation → IO detects and targets tumor cells.
3) Knowledge gap- Tumor cells and T cells depend on glucose for ATP generation and function. Starving tumor cells without halting glucose supply to immune cells
-Lack of consistent predictive biomarkers. Some patients with high PDL1 responds to IO & some don't.
4) Predicting resistance by liquid biopsy for ctDNA, TMB. Overcoming by using combination treatment. Fecal Microbiota transplant.

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
**Resistance mechanisms seen in ICI are -**
**Primary resistance** - d/t cold tumors - tumor never respond to ICI, d/t low TMB, lack of neoantigen formation
**Secondary resistance** - initial response, but eventual progression. By stopping expressing antigen, expression of inhibitory molecules - TIM3, LAG-3, VISTA and mutation in signaling pathways
**Extrinsic resistance** - involving the TME. By presence of immunosuppressive cells (Tregs, MDSC, M_2-macrophages) & inhibitory cytokines (TGF-\beta) (IL-10) - acts as a protection to tumors.
Combination therapy to overcome resistance using dual checkpoint blockade are

1. PD-L1/CTLA inhibitors (Nivo + Ipilimumab)
2. ICI + anti-angiogenics (Pembro + Lenvatinib) normalize tumor vasculature, reduce recruitment of immunosuppressive cells---- making environment more hospitable for T-cells.
3. ICI + chemotherapy - chemotherapy induce 'immunogenic cell death', release tumor antigens & prime immune system.
4. ICI + targeted therapy - using BRAF or MEK inhibitors along with ICI - alter signaling pathway which helps in tumor evasion.
5. ICI + radiotherapy - RT - release antigens & pro-inflammatory signals - leading to abscopal effect. Tumors outside radiation field also shrink.

There is currently a vast gap in knowledge about the resistance mechanisms in immunotherapy. We need to know about role of immune cells, apart from T-cells, role of microbiomes, how to convert cold tumor to hot tumor, methods to improve specificity of ICI - targeting only tumor cells and avoiding normal cells (identifying receptors specific only to tumor cells), maximum duration ICI to be used for maximal response and reducing adverse effects at same time.
Also, PD-L1 is not a effective receptor tested to assess ICI efficacy. Further receptor testing to be tested and refined to now the efficacy and mechanism of immunotherapy.

**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.):**
I cannot tell much about the scientific & research aspects, as I am just a student, doing my final year residency. As far as to my knowledge, after reading theories and articles, ways to predict & overcome resistance according to me are

1. Designing effective biomarker test to assess ICI response.
2. Develop more specific molecules, that target only tumor cells and avoid normal cells, thereby reducing irAE as much as possible.
3. Doing more research on microbiome signatures and making them as a way to treat cancer
4. Development of ICI with chemokine attracting properties, so that it can be used even for cold tumors - where immune cells are attracted towards the tumor & enhance killing.
5. To discover molecules, that eliminate the immunosuppressive molecules like Tregs, MDSC, M_2 macrophages and make the tumor microenvironment viable for immune molecules to attack the tumors.

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
Novel cancer treatment modalities such as immunotherapy, CAR-T therapy, bispecific antibodies, and gene therapy are not free from drug resistance mechanisms. Therefore, there is a need for strategic utilization and proper policies to effectively prevent and manage treatment resistance. It is crucial to have adequate understanding of tumour biology, tumour microenvironment, and treatment response mechanisms.
In the era of molecular oncology, precision medicine, and artificial intelligence, identification of novel biomarkers predicting resistance pathways has become extremely important. Since newer therapies are associated with significant financial toxicity, careful and vigilant patient selection is essential.

**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 resistance can be broadly divided into primary resistance and secondary resistance. Primary resistance occurs when the tumor is intrinsically resistant to immunotherapy. This is commonly associated with genetic alterations such as STK11 and KEAP1 mutations. Therefore, molecular profiling and genomic panels before treatment initiation can help guide patient selection, reduce irrational use of immunotherapy, and minimize unnecessary financial toxicity.
Secondary resistance occurs when there is an initial response to immunotherapy followed by disease progression and resistance. Mechanisms of secondary resistance are complex and may involve loss of tumor antigens, alterations in the tumor microenvironment, and activation of alternative signaling pathways. This highlights the importance of precision medicine and advanced imaging techniques, which can help identify resistance mechanisms early and support proactive tailoring of treatment strategies to delay disease progression. Managing secondary resistance is extremely important because treatment options after progression are often limited.
Recognizing immunotherapy resistance can sometimes be difficult because of pseudo progression observed on imaging studies. Therefore, there should be an optimal and individualized duration for response assessment to avoid false interpretation of disease progression. Clinical improvement and overall patient status should also be carefully considered while assessing treatment response.
Immunotherapy resistance may be reduced through careful immuno-profiling, genomic analysis, biomarker assessment, and precision medicine approaches that evaluate the tumor microenvironment and identify alternative resistance pathways. These profiling strategies may also help guide combination treatment approaches involving targeted therapies, chemotherapy, radiotherapy etc ,that can synergistically overcome resistance mechanisms.
Artificial intelligence may also serve as a useful prognostic tool for predicting resistance patterns. However, wider clinical validation of AI-based predictive models is still required, and its use currently remains investigational.
Inappropriate utilization of immunotherapy should not automatically be considered immunotherapy resistance. Therefore, there should be multidisciplinary discussions combining evidence from clinical trials and real-world data to better understand resistance patterns and optimize treatment strategies, including exploration of low-dose immunotherapy approaches when appropriate. Tumor heterogeneity is complex and so are resistance pathways and hence navigating these is thus challenging.

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

- Identify and overcome primary and acquired mechanisms of immunotherapy resistance
- Enable precision immuno-oncology through integrated biomarker-driven and personalized treatment strategies
- Develop rational combination therapies to restore and enhance antitumor immune response
- Implement early resistance detection and real-time monitoring using advanced molecular and AI-based tools
- Improve durability of response, survival outcomes, and long-term treatment adaptation for cancer 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.):**

Immunotherapy has transformed oncology, yet resistance remains a major clinical challenge. In practice, resistance is either primary—where tumors like Non-Small Cell Lung Cancer fail to respond despite PD-L1 expression—or acquired, where an initial response (e.g., in Melanoma treated with Nivolumab) is followed by progression. Biologically, this reflects breakdowns in the cancer immunity cycle: poor antigen presentation (loss of MHC-I/B2M), low neoantigen load, defective IFN-Î³ signaling, T-cell exhaustion, and a suppressive tumor microenvironment (Tregs, MDSCs, TAMs). Alternative checkpoints (LAG-3, TIGIT), metabolic barriers, and even the microbiome further contribute.

To overcome this, oncology is shifting toward rational combination strategies. Chemotherapy and radiotherapy can increase antigen release and “heat up” cold tumors. Dual checkpoint blockade (e.g., nivolumab + ipilimumab) helps reverse T-cell exhaustion. Anti-angiogenic agents improve immune-cell trafficking, while vaccines and cellular therapies aim to bypass weak endogenous immunity. The principle is simple: identify the broken step and fix it.

However, key knowledge gaps remain. Why do some "hot” tumors still fail? Which biomarkers are truly predictive rather than prognostic? How does resistance evolve over time, and what is the exact role of tumor heterogeneity and the microbiome? Importantly, reliance on single markers like PD-L1 is often insufficient.

The future lies in predicting and overcoming resistance early. Tumor biomarkers (PD-L1, TMB, MSI), tumor microenvironment profiling, and host factors (inflammation markers, steroid use) must be integrated. Emerging tools like ctDNA monitoring, spatial omics, organoid testing, and AI-driven models can detect resistance early and guide therapy.

A practical approach is:

Mechanism → Biomarker → Combination Strategy → Monitoring → Adaptation.

Ultimately, the goal is precision immuno-oncology—moving from trial-and-error to predictive, personalized, and adaptive treatment for every patient.

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
The primary objective is to delineate the transformative role of Artificial Intelligence (AI) and Machine Learning (ML) in deciphering and predicting immunotherapy resistance in oncology. Despite the profound clinical success of immune checkpoint inhibitors, heterogeneous patient responses and resistance remain significant therapeutic barriers. By leveraging high-dimensional, multi-omics **data** encompassing radiomics, genomics, and transcriptomics—AI and ML frameworks offer unprecedented capabilities in discovering novel biomarkers and evaluating the tumor microenvironment. This approach aims to accurately predict intrinsic and acquired resistance, tailor combination therapies, and ultimately optimize precision immunotherapy strategies to improve long-term clinical outcomes.

**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. Current Landscape & Resistance Mechanisms**

The contemporary immuno-oncology landscape is heavily reliant on immune checkpoint inhibitors, though both innate (primary) and acquired resistance frequently hinder long-term efficacy across various malignancies.

Resistance mechanisms are highly multifaceted, involving defective antigen presentation, the absence of tumor antigens, epigenetic alterations, and a profoundly immunosuppressive tumor microenvironment.

Furthermore, tumor cells can evade lymphocyte-mediated cytotoxicity through specific intracellular adaptations, such as the disruption of interferon-gamma signaling pathways.

**2. Combination Therapies Overcoming Resistance**

To counteract monotherapy failure and tumor heterogeneity, clinical strategies are shifting toward combination therapies that target multiple mechanistic pathways simultaneously.

Chemo-immunotherapy regimens have established improved clinical outcomes in non-small-cell lung cancer (NSCLC).

Advanced combinations now focus on concurrently targeting T-cell exhaustion (e.g., via PD-1, CTLA-4, and LAG3 inhibition) while actively modulating the suppressive tumor environment, such as by targeting TREM2 on immunosuppressive macrophages.

**3. Current Knowledge Gaps**

A critical translational gap exists in implementing identified resistance mechanisms into routine clinical workflows; for instance, there are limited reliable methodologies to seamlessly screen patients for specific molecular evasion tactics, like disabled interferon-gamma pathways.

In the realm of predictive modeling, there is a prominent "validation gap," wherein AI algorithms that demonstrate high accuracy in internal, single-institution cohorts often fail to maintain their predictive power when tested on independent, external patient populations.

**4. Predicting and Overcoming Resistance via AI/ML**

Multi-Omics Integration: AI models integrate genomics, transcriptomics, pathomics, and radiomics to comprehensively map spatial and temporal tumor heterogeneity, accurately predicting clinical endpoints and therapeutic benefit without relying solely on traditional, single biomarkers.

Digital Pathology: Deep learning networks applied to histopathology can automatically quantify PD-L1 expression and tumor-infiltrating lymphocytes (TILs), achieving robust predictive precision for patient stratification.

Dynamic Mechanistic Modeling: Next-generation AI and systems biology models simulate real-time tumor-immune interactions and checkpoint blockade dynamics, facilitating adaptive dosing and the rational design of personalized combination protocols.

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

Discuss how to prevent and manage resistance to Immunotherapy better

**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. Current Landscape of Immunotherapy Resistance**

- Immune checkpoint inhibitors (PD-1/PD-L1, CTLA-4), CAR-T, TIL therapy, neoantigen vaccines, bispecific antibodies, and oncolytic viruses dominate modern oncology treatment paradigms in both curative and palliative settings
- Only about 20-40% of patients achieve durable responses due to "primary" or "acquired" resistance

Tumor-intrinsic resistance:

- Loss of antigen presentation (B2M, HLA defects)
- IFN-γ/JAK-STAT pathway mutations
- Neoantigen depletion and tumor heterogeneity
- Epigenetic silencing and metabolic rewiring

Tumor microenvironment (TME)-mediated resistance:

- Tregs, MDSCs, TAMs causing immune suppression
- Hypoxia, lactate accumulation, adenosine signaling
- T-cell exhaustion (TIM-3, LAG-3, TIGIT upregulation)
- Microbiome dysbiosis and stromal fibrosis.

**2. Combination Therapies Overcoming Resistance**

- Dual checkpoint blockade: PD-1 + CTLA-4
- Immunotherapy + anti-angiogenic agents (VEGF inhibitors normalize TME)
- CAR-T + checkpoint inhibitors
- Oncolytic viruses + ICIs to convert “cold” tumors into “hot” tumors.
- Radiotherapy + ICIs for antigen release and immune priming and abscopal effect
- Epigenetic drugs + ICIs to restore antigen expression
- Microbiome engineering/fecal microbiota transplantation
- Emerging: CCR5 blockade, STING agonists, mRNA neoantigen vaccines, AI-designed adaptive combinations.

**3. Current Knowledge Gaps**

- Lack of universal predictive biomarkers
- Poor understanding of temporal evolution of resistance
- Limited insight into non-genetic cellular plasticity
- Incomplete mapping of microbiome–immune interactions
- Sparse longitudinal multi-omics datasets
- Unclear mechanisms behind hyper progression and immune-related toxicity.

**4. Future Strategies to Predict & Overcome Resistance**

- AI-driven multi-omics resistance prediction platforms
- Real-time liquid biopsy monitoring (ctDNA, exosomes, CTCs)
- Personalized neoantigen vaccines
- Synthetic biology-engineered CAR-T/NK cells
- Adaptive immunotherapy guided by digital twins
- Metabolic reprogramming of T cells
- Precision microbiome therapeutics
- Nanoparticle-mediated immune delivery systems
- Dynamic biomarker surveillance instead of static PD-L1 testing
- Invitro cell culture models.

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
To characterise the mechanistic distinction between primary and acquired immunotherapy resistance, identify combination strategies with the strongest current evidence for overcoming each resistance phenotype, and propose a clinical framework for early resistance detection using dynamic biomarker monitoring that enables timely therapeutic adaptation before radiological 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.):**
Not all immunotherapy failures are the same and treating them as though they are is why resistance remains so poorly managed clinically. Primary resistance, where a tumour never responds from the outset, and acquired resistance, where a tumour responds and then escapes, are driven by mechanistically distinct processes that require fundamentally different interventions.
Primary resistance is predominantly a tumour microenvironment problem. Non inflamed and excluded tumour phenotypes lack the T cell infiltration that checkpoint inhibition requires to function. In NSCLC, STK11 and KEAP1 co mutations drive an immunosuppressive microenvironment that makes PD-L1 expression a meaningless predictive biomarker in that molecular context. KRAS G12C mutant tumours carrying STK11 co mutations consistently underperform in immunotherapy trials regardless of PD-L1 positivity. Loss of beta-2 microglobulin abrogates MHC class I antigen presentation, making CD8+ T-cell killing mechanistically impossible regardless of checkpoint status. These genomic resistance predictors are identifiable at diagnosis using standard NGS and should alter the initial treatment decision, not the second line salvage decision.

Acquired resistance operates through different mechanisms. T cell exhaustion driven by TOX and NR4A transcription factor accumulation, upregulation of alternative checkpoints including LAG-3, TIM-3, and TIGIT, and loss of IFN-gamma signalling through acquired JAK1/2 mutations are the dominant escape pathways. The LAG-3 plus PD-1 combination, relatlimab plus nivolumab, received FDA approval in 2022 for melanoma specifically because LAG-3 upregulation is a validated acquired resistance mechanism to anti-PD-1 monotherapy, and this represents the first approved strategy mechanistically targeted at the resistance pathway rather than a second empirical immune checkpoint.
The most important knowledge gap is the absence of a validated dynamic biomarker for early resistance detection. Circulating tumour DNA kinetics during ICI treatment correlate with outcome across multiple tumour types. A rising ctDNA on treatment represents a resistance signal that precedes radiological progression by weeks to months, and that window is currently wasted in routine practice. Prospective ctDNA monitoring during ICI should become a research priority, because the ability to detect resistance early enough to act on it differently is the clinical opportunity that static biomarkers at baseline simply cannot provide.

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
Understanding the knowledge gaps, use combination approaches, optimize the treatment sequence and use of AI and real time biomarker driven approaches.

**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.):**
IO resistance can be primary or secondary. Primary occurs in those who are never exposed and secondary is the acquired one. It can also be divided into tumour intrinsic and extrinsic. Umor intrinsic includes loss of antigen presentation, genetic or epigenetic mutations, altered interferon signalling etc. Extrinsic mechanisms include immunosuppressive cells like Tregs, MDSc etc, up regulation of alternative check points like TIGIT and unfavourable gut microbiome.
Various combination therapies to overcome the resistance includes:

- CTLA4+CPI - Eg Nivolumab ipilimumab shown results in various malignancies
- IO+ anti Vegf eg- Atezolizumab + Bevacizumab in HCC
- IO+ anti LAG3 in melanoma
- Braf + Met inhibitors in melanoma
- IO+ Chemo in ca lung
- IO+ Rt/SBRT under trials
- IO+ targeted therapy in RCC
- IO+ probiotics supplementation under various trials

Knowledge gaps in resistance mechanisms

- Lack of knowledge about the predictive biomarkers
- Complexity of microbiome and cellular mechanisms
- Complexity of Resistance pathway and its evolution
- Tumour heterogeneity
- Optimal sequencing of therapies.

Possible solutions include

- Improvement in research and better understanding of biomarker driven precision oncology.
- AI driven predictive models
- Combination treatment approaches
- Early optimal sequencing of therapy.
- Real time biomarker monitoring like ctDNA to adjust therapy.
- Steroid sparing irAE management strategies to prevent the reduction in the efficacy.

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
To understand immunotherapy resistance early and develop rational strategies so that patients are not exposed to ineffective treatment for too long.

**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 has transformed several cancers, but primary and acquired resistance remain major limitations. Resistance may occur through low tumour immunogenicity, absent T-cell infiltration, poor antigen presentation, β2-microglobulin loss, JAK mutations, STK11/KEAP1 alterations, alternate checkpoints, immune-excluded microenvironment, Treg/MDSC dominance and gut microbiome effects.
Combination strategies are trying to overcome this. These include IO with chemotherapy, anti-CTLA-4, anti-VEGF therapy, radiation, PARP inhibitors, targeted therapy, cancer vaccines, oncolytic viruses and newer checkpoints like LAG-3, TIGIT and TIM-3. However, combinations should be adopted only when survival benefit and toxicity balance are proven.
Knowledge gaps remain: why some PD-L1-negative patients respond, why some biomarker-positive patients progress, how microbiome influences response, how best to sequence IO after IO, and how to distinguish pseudoprogression from true progression.
Prediction needs better biomarkers: PD-L1, MSI-H/dMMR, TMB in selected settings, gene signatures, circulating tumour DNA, immune-cell profiling and radiomics. Overcoming resistance requires re-biopsy where feasible, molecular reassessment, clinical-trial referral, rational combinations and early switch when progression is clear.
In Tamil Nadu, tertiary centres can create immunotherapy resistance registries and virtual review boards for complex progression cases. Roche can support translational research, biomarker access, registry platforms and responsible clinical-trial collaboration.
Resistance is not failure of the patient. It is biology challenging us to think deeper, treat smarter and never sell false hope.

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
**Problem statement:** Immunotherapy has transformed cancer care, but many cancer patients either never respond or lose response after initial benefit. In routine practice, resistance is often recognised only after radiologic progression, when valuable time is lost.
**Objective:** To create Clinically feasible framework that predicts, identifies and redirects immunotherapy resistance through biomarker guided decision making and adaptive strategies and to deliver more rational treatment decisions, avoidance of unnecessary switching and improved personalisation of immunotherapy care.

**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.):**
Solution: COMPASS-IO-Practical decision Navigation Model for patients who develop resistance or uncertainty during immunotherapy treatment. Don't abandon immunotherapy, Decode the resistance, Redirect response.
C: Classify resistance-Differentiate primary resistance, acquired resistance, pseudo progression, hyper progression.
O: Observe patient fitness-Asses performance status, organ function, symptom burden, steroid dependence and treatment tolerance.
M: Map Tumour biology: Review PDL1, TMB /MSI, ctDNA Trends if available, repeat biopsy if feasible and molecular escape pathways.
P: Profile Practical Barriers-Identify affordability constraints, insurance gaps, travel burden, caregiver limitations and access barriers.
A: Align precision strategy, Match intervention to resistance mechanism: Cold tumour?-IO+ RT, VEGF driven suppression?- IO+Anti angiogenic therapy, Low Antigenicity?-chemo immunotherapy T cell Exhaustion?- Dual checkpoint strategies, Local ablative therapy, Driver mutation escape?-Targeted+ IO sequencing, Symptom led care for frail patients.
S: Support Access Navigation- Connect patients to financial aid, pharma assistance programs, trial options and closer to home care.
S: Surveillance and Reassessment-Track response dynamically and adapt early.
PROBLEM CASE: Mr.X 58-year-old man, diagnosed with metastatic Non-small cell lung cancer and PDL1 85% started on pembrolizumab. After 4 months, Reassessment scan showed progression in liver lesions. Standard practice may label this as immunotherapy failure and switch treatment.
COMPASS-IO review identifies: ECOG PS 1, isolated progression, prolonged Dexamethasone exposure for brain edema, financial inability for expensive next line therapy. Treated by tapering steroids and stop, deliver liver directed radiotherapy, continue benefit preserving combination systemic rescue rather than switching therapy blindly and activate financial navigation support.
>>Learn continuously: Build Institutional real world resistance registry to identify resistance patterns and improve future prediction. Pharma companies like roche can support for biomarkers guided care, navigation access can improve treatment continuity, better therapy utilisation, retention of patients. They can generate real world evidence on immunotherapy resistance, treatment sequencing and patient outcomes while strengthening meaningful engagement with oncologists through practical decision support tools.

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
We really need to run serial liquid biopsies. Tracking circulating tumor DNA dynamically lets us see the resistance building long before it ever shows up on a routine MRI.

**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.):**
Checkpoint inhibitors honestly seem like a wonder until they suddenly stop working. We see this constantly in our clinics between Madurai and Chennai. You get a locally advanced GI case and start them on a neoadjuvant PD-1 blockade. The mass actually starts downstaging beautifully. But then the tumor just hits this brutal biological wall. The T-cells essentially get exhausted. Or the tumor stroma throws up a dense physical shield that our systemic drugs simply cannot penetrate anymore.
But we aren't completely helpless when that happens. Mixing immunotherapy with traditional cytotoxic chemo is showing real promise to break through that primary resistance. We are also looking closely at trial data pairing VEGF inhibitors directly with checkpoint drugs. This essentially normalizes those chaotic tumor blood vessels so the immune cells are forced right back into the active fight.
And yet, our actual clinical knowledge gaps remain embarrassingly wide. We still cannot reliably explain why a perfectly "hot" tumor suddenly flips cold halfway through a standard NCCN or ESMO protocol. The genomic plasticity of these advanced malignancies just constantly outpaces whatever standard molecular panels we manage to order.
So how do we actually catch this resistance early on the ground? Relying on a single baseline tissue biopsy is a massive mistake. We really need to run serial liquid biopsies. Tracking circulating tumor DNA dynamically lets us see the resistance building long before it ever shows up on a routine MRI. And honestly, as a surgical oncologist, we have to recognize exactly when the medical window is shutting. If the immunotherapy stops shrinking the disease, we need to pivot immediately. We have to take them straight to the OR for a radical resection—applying strict JCOG lymphadenectomy principles—before the chance for a clean R0 margin completely vanishes.

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
We really need to run serial liquid biopsies. Tracking circulating tumor DNA dynamically lets us see the resistance building long before it ever shows up on a routine MRI.

**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.):**

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But we aren't completely helpless when that happens. Mixing immunotherapy with traditional cytotoxic chemo is showing real promise to break through that primary resistance. We are also looking closely at trial data pairing VEGF inhibitors directly with checkpoint drugs. This essentially normalizes those chaotic tumor blood vessels so the immune cells are forced right back into the active fight.

And yet, our actual clinical knowledge gaps remain embarrassingly wide. We still cannot reliably explain why a perfectly "hot" tumor suddenly flips cold halfway through a standard NCCN or ESMO protocol. The genomic plasticity of these advanced malignancies just constantly outpaces whatever standard molecular panels we manage to order.

So how do we actually catch this resistance early on the ground? Relying on a single baseline tissue biopsy is a massive mistake. We really need to run serial liquid biopsies. Tracking circulating tumor DNA dynamically lets us see the resistance building long before it ever shows up on a routine MRI.

And honestly, as a surgical oncologist, we have to recognize exactly when the medical window is shutting. If the immunotherapy stops shrinking the disease, we need to pivot immediately. We have to take them straight to the OR for a radical resection—applying strict JCOG lymphadenectomy principles—before the chance for a clean R0 margin completely vanishes.

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

While ICIs have revolutionised outcomes, some patients either never respond or develop resistance after some response. Currently, resistance is often seen only after radiological progression, by which time valuable treatment opportunities may have been lost. There is a need for proactive, biomarker-driven strategies that can predict and overcome immunotherapy resistance before clinical failure occurs.

**Objective**: Move from reactive management of resistance to proactive prediction and prevention of resistance, enabling precision immuno-oncology for every patient.

**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.):**

**Resistance:**

Tumor-intrinsic (Primary resistance): antigen loss, defective MHC-I presentation, interferon-Î³ pathway disruption, and clonal evolution.

Tumor-extrinsic mechanisms: immunosuppressive microenvironments, myeloid-derived suppressor cells, TGF- β, IL-10, and adenosine. (1)

Chronic immune stimulation (adaptive & acquired resistance) also induces T-cell exhaustion with upregulation of PD-1, TIGIT, TIM-3, CTLA-4, and LAG-3.

co-occurring TP53 (2)

NF1, STAT5B, and STK11 alterations

Intratumoral dysbiosis (Fusobacterium - activating PI3K/AKT)

**Combination stratifies:**

The most promising strategy is combining immunotherapy with targeted therapies that convert "cold" tumors into "hot" tumors.

PD-1 + CTLA-4 blockade (NADINA, CheckMate studies).

PD-1 + ADCs (T-DXd in breast cancer).

PD-1 + VEGF inhibition (atezolizumab–bevacizumab in HCC).

PD-1 + PARP inhibitors in HR-deficient tumors.

Radiotherapy + Immunotherapy, leveraging the abscopal effect.

Personalized neoantigen vaccines + ICIs (mRNA platforms).

Microbiome modulation, including fecal microbiota transplantation (FMT), showing activity in resistant melanoma.

**Current knowledge gaps:**

1. There are no validated antigen-expression thresholds, biomarkers for detecting resistance and methods to integrate tumor genomics with immune profiling.
2. There is no defined optimal sequencing of ADCs, ICIs, T-cell engagers, cellular therapies
3. RECIST criteria inadequately captures responses
4. The role of ctDNA-guided treatment adaptation
5. Limited understanding of microbiome–immune interactions in Asian populations.
6. Poor understanding of resistance mechanisms in common cancers (oral cavity, gallbladder, cervical cancer).
7. The reciprocal signaling of novel checkpoint loops, such as the leukemic stem cell-extrinsic TIM-3/Gal-9 autocrine axis, remain unmapped.

**Predicting resistance:**

1. Serial ctDNA monitoring to detect emerging mutations and molecular progression before changes in imaging (better than RECIST).
2. AI-driven spatial transcriptomics maps immune-cell distribution and tumor-infiltrating lymphocyte (TIL) architecture to predict response
3. Immune Signature Scores (ISS): Gene-expression panels to identify immune-active versus immune-suppressed tumors for better patient selection.
4. Microbiome profiling: Gut and intratumoral microbial signatures may serve as novel biomarkers of resistance.
5. Indian Immunotherapy Resistance Registry should be maintained, focusing on breast, lung, cervical, oral cavity, and hepatobiliary cancers.

**Overcoming resistance:**

1. ADC–Immunotherapy combinations: generate a bystander effect against resistant clones. Anti-VEGF + Immunotherapy: Converts "cold" tumors into "hot" tumors
2. Microbiome-directed therapies: FMT, probiotics, and dietary interventions may restore immune responsiveness.
3. Multi-checkpoint blockade + myeloid reprogramming: Targeting PD-1, CTLA-4, LAG-3 alongside TREM2-mediated macrophage suppression can restore antitumor immunity.
4. Ultra-low-dose immunotherapy: The Tata Memorial DELII strategy demonstrates a cost-effective approach particularly relevant for resource-constrained settings such as India.

**References**


1. Cancer Discovery Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. 2017.
2. Nature Reviews Clinical Oncology Schoenfeld AJ, Hellmann MD. Acquired resistance to immune checkpoint inhibitors. 2020.
3. Nature Medicine Davar et al. FMT overcomes anti-PD-1 resistance in melanoma.
4. European Society for Medical Oncology Immunotherapy Resistance Consensus Guidelines.
5. https://www.esmo.org/oncology-news/ultra-low-dose-nivolumab-significantly-improves-os-over-chemotherapy-in-pretreated-patients-with-solid-tumours
6. Frontiers | AI-driven immunotherapy: synergizing with radiotherapy to reconfigure the tumor microenvironment and treatment landscape https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2025.1747638/full


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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
Integrating AI in detection of resistance 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.):**
As now we have a good literature in resistance pathway in oncology.
We can take help of AI in identification and formatting the plan for combination resistance.
Rational use of chemo-immuno can also be guided.

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**Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):**
To develop effective strategies for predicting, preventing, and overcoming resistance to cancer immunotherapy by understanding tumor-immune interactions, identifying reliable biomarkers, and optimizing combination treatment approaches to improve patient outcomes.

**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, particularly immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4, has significantly improved outcomes in several cancers. However, primary and acquired resistance remain major challenges. Resistance mechanisms include loss of tumor antigen presentation, reduced T-cell infiltration, immunosuppressive tumor microenvironment, activation of alternative immune checkpoints, genetic alterations in interferon signaling pathways, and immune cell exhaustion.
Combination therapies are being explored to overcome resistance. These include dual checkpoint blockade (PD-1/PD-L1 plus CTLA-4 inhibitors), immunotherapy combined with chemotherapy, radiotherapy, targeted therapies, anti-angiogenic agents, cancer vaccines, adoptive cell therapies, and novel immune modulators. These approaches aim to enhance immune activation, increase tumor antigen release, and modify the tumor microenvironment.
Current knowledge gaps include incomplete understanding of tumor-immune evolution, limited predictive biomarkers, mechanisms of acquired resistance, optimal sequencing of therapies, and identification of patients who benefit from combination strategies.
Potential solutions include development of predictive biomarkers such as PD-L1 expression, MSI/dMMR status, TMB, tumor-infiltrating lymphocytes, gene expression profiles, and circulating tumor DNA. Serial monitoring using liquid biopsy and advanced immune profiling may help detect emerging resistance. Strategies to overcome resistance include personalized combination therapies, early identification of non-responders, rational treatment sequencing, clinical trial participation, and integration of artificial intelligence-based predictive models.
A comprehensive, biomarker-driven approach is essential to maximize the benefit of immunotherapy and achieve durable cancer control.