Title:
Navigating Immunotherapy Resistance in Oncology

Full Name:
Beulah Elizabeth Koshy

Name of the Institution:
Kidwai Memorial Institute of Oncology, Bengaluru

State:
Karnataka

Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):
In cancer, navigating immunotherapy resistance entails comprehending the processes that impede efficient immune responses against tumours, which can seriously impair the effectiveness of treatment. To increase the effectiveness of immunotherapeutic methods, resistance may call for customized techniques.

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 is a cancer cure that is done by making the immune system itself detect and kill cancer cells. Still, the existing resistance issues are the reasons why people do not get the full advantage of this cancer therapy sometimes.

Current Landscape of Immunotherapy:

1. Immune Checkpoint Inhibitors (ICIs): These include PD-1, PD-L1, and CTLA-4 inhibitors which work well for many cancers by stopping the paths that hold back T-cell activity.
2. Adoptive Cell Transfer (ACT): Techniques like CAR-T cell therapy change a patient's T-cells to better find and kill cancer cells. It has worked well in blood cancers.
3. Cancer Vaccines: Made to push the immune system to attack certain cancer signs, these vaccines are being looked at for treating and stopping cancer.
4. Oncolytic Virus Therapy: This method employs genetically engineered viruses that attack cancer cells as well as modulating the immune response in a more supportive manner.

Mechanisms of Resistance to Immunotherapy:

1. Genetic Mutations: Changes in cancer cells can make them less visible to immune cells.
2. Upregulation of Alternative Immune Checkpoints: Cancers may show other blocking receptors like LAG-3, which helps them escape the immune system. Research shows targeting LAG-3 with PD-1 might help beat this issue.
3. Immunosuppressive Tumor Microenvironment: Things like certain T-cells, cells that suppress, and some proteins can stop the immune system from fighting cancer.
4. Activation of Specific Signaling Pathways: The always active STAT3 paths in cancer cells are responsible for their protection and resistance to the immune's attack. Reports state that if we can target STAT3, possibly the immune system could be beefed up for the fight against cancer. These resistance pathways are essential to the knowledge that which in turn can lead to the development of more effective combination treatments along with new drugs to test them out in a more specific manner to achieve different cell solutions.

B)

Overcoming resistance to immune treatments is a big deal in cancer work. Using combination treatments together is a good plan to make immune treatments work better and beat resistance.

1.**Enhancing T Cell Priming/Tumor Immunogenicity**

One strategy to enhance T cell priming/tumor immunogenicity is to increase the amount of tumor neoantigens available to T cells. One way to do this is to combine immunotherapy with other standard therapies such as chemotherapy and radiation therapy.

2.**Improving the Immunosuppressive Microenvironment:**

The cellular, metabolite and chemo-/cytokine milieu within the TME (tumour microenvironment) plays a large role in response or resistance to ICIs.

Indolamine 2,3-dioxygenase 1 (IDO1), Vascular endothelial growth factor (VEGF), TGF-β, colony-stimulating factor 1 (CSF-1) cytokine are all examples such factors

3.**Reversing T Cell Exhaustion:**

Anti-PD-1 antibodies prevent PD-1-mediated attenuation of the T cell receptor downstream activation cascade as a result of binding to a presented antigen and prevents T cell apoptosis. As well, anti-CTLA-4 antibodies lead to a reduction in Tregs within the TME and have been shown to modulate the T cell receptor repertoire. Both effects are proposed to reinvigorate T cells

4.**Combining ICIs with Small Molecule Inhibitors:**

In addition to chemotherapy and radiation therapy as mentioned above, small molecule inhibitors have been studied in combination with ICIs to overcome ICI resistance across a variety of the mechanisms listed above. The most common of which are tyrosine kinase inhibitors (TKIs) that include lenvatinib, axitinib, sunitinib and cabozantinib for example, in NSCLC, RCC and endometrial cancers, although other small molecules like cobimetinib (MEK inhibitor) and PARP inhibitors like olaparib and niraparib are also being studied in colorectal, ovarian and prostate cancers

C)

Many things have been understood about how tumors trick the immune system so that it cannot find them. At the same time, there are still many topics that have yet to be cleared up when it comes to the resistance of immunotherapy:

1**. Cell- Permeative knowledge of the resistance mechanisms:** Although different strategies of tumor evasion have been spotted, for example, downregulation of MHC class I molecules and expression of drivers like PD-L1, the interaction among these mechanisms and their aggregate effect on immunotherapy resistance are still imprecisely known.

2. **TME's function in immunotherapy in regards if the TME:** The TME's agency in the outcome of immunotherapy is recognized, but the functions of various components such as regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages in resistance mechanisms are still largely unexplored.

3. **Tumor Heterogeneity Consequences:** Intra-tumoral heterogeneity compounds are the roadblocks on the way to predictable immunotherapy responses. The insight into how different cell populations of the tumor can assist in the deactivation of tumor cells is an area of research requiring more scrutiny.

4. **Genetics and Epigenetic Elements:** It is not known to what extent genetic mutations and epigenetic modifications in the host cells bring about the various types of cancer that have not been characterized in full which have the power of resistance to immunotherapy.

5. **Predictive Biomarker:** Tracking down reliable biometrics as the early indicators of patients' developing resistance to immunotherapy is a great issue.

6. **The Duty of Prolonged Immunotherapy:** Immunotherapy's prolonged effects on the immune system and resistance development over some time are less known to us. All these insufficiencies of knowledge are prerequisites to promoting the potential of immunotherapies and structuring methods to resist them.

D)

Ways to Predict and Overcome Resistance to Immunotherapy

1. Predicting Resistance to Immunotherapy

- Biomarker-Based Predictions

a. PDL1 protein: (especially) very high levels of this factor may confirm the response to immune checkpoint inhibitors.

b. Tumor Mutational Burden (TMB): Excessive bombardment of cells by UVB light results in a greater immune effect.
c. Microsatellite Instability (MSI-H): The biomarker identifies patients who do not respond to (checkpoint) immunotherapy.
d. HLA & MHC Expression: Losing some human proteins structures such as MHC class I creates a barrier for immune cells to see the virus and kill it.
e. Circulating Tumor DNA (ctDNA): Keeps tract of the various gene mutations as well the failing of cancer to respond to the drugs established to cure it.
f. Gene Mutations: Genetic alteration is the main reason leading to this situation. The mutations (changes in DNA) of the *JAK1/JAK2* gene product can for instance produce a phenomenon known as resistance to the treatment with imatinib.

- Tumor Microenvironment Analysis

a. T-cell Infiltration: Tumors are seen as "hot" if there is a lot of white blood cells there, and as "cold" if there are too few white blood cells.
b. Myeloid-Derived Suppressor Cells (MDSCs) & Tregs: Cells that use the natural killer cells to block the response are the first ones to grow alongside with Tregs.
c. Cytokine Profiling: Increase of IL-10 or TGF-β production may be the sign of the suppression of the immune system.

- Epigenetic & Transcriptomic Profiling

a. DNA Methylation Patterns: The tumors may covertly inactivate genes that are responsible for the interference of the immune system to realize itself.
b. Single-Cell RNA Sequencing: Diagnosis of immune cell abnormalities at the cellular level is carried out by DNA sequencing of individual cells.

- IT Novel Technologies

a. Microbiome Influence
Gut Microbiota Composition: A few germs of bacteria (some specific bacteria) can help the therapy to be more active by producing lactic acid (which breaks down carbohydrates).
2. Overcoming Resistance to Immunotherapy

- Combination Therapies

a. Checkpoint Inhibitor + Chemotherapy: Chemotherapy facilitates the ongoing flow of the immunotherapy fight by presenting more antigens.
b. Dual Checkpoint Blockade (PD-1 + CTLA-4 inhibitors): The immune cells have a broader (more) spectrum of activity on account of the PD-1 immune checkpoints that are blocked and CTLA-4 inhibitions that are also blocked, it falls under both of the points.
c. Immunotherapy + Targeted Therapy: For example, the *BRAF/MEK* proteins in melanoma are kind of the switch-on points of this process and to prevent cell multiplication, they can be invaded by targeted therapy.
d. Oncolytic Viruses: The vaccinated (or naturally) infected individual will produce an immune response that will help their own immune cells to detect and kill the cancer cells.

- Modulating the Tumor Microenvironment

a. CSF-1R Inhibitors: Lowering numbers of macrophages that are damaging immune responses.
b. IDO Inhibitors: Immune suppression due to the production of kynurenine and its metabolites could be blocked by inhibitor enzymes.
c. Anti-TGF-β Therapy: The immune system bypasses traps when T cells bound to the cells to be killed by the immune system are disarmed which TGF-β blockers will do.

- Microbiome-Based Strategies

a. Fecal Microbiota Transplantation (FMT): Regains good bacteria of the gut and results in a more efficient treatment scheme.
b. Probiotics: Stay away from the antibiotics and eat a lot of healthy food like fermented foods and yogurt to have a good microbiota.

Full Name:
Kartik Gajanan Asutkar

Name of the Institution:
Kidwai Memorial Institute of Oncology, Bengaluru

State:
Karnataka

Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):
Primary Outcome of the Solution:
1. Enhanced Immunotherapy Efficacy: Overcoming resistance mechanisms (e.g., TME suppression, antigen loss) to restore durable anti-tumor immune responses, improving response rates and survival (PFS/OS).
2. Personalized Treatment Strategies: Biomarker-guided use of combination therapies (e.g., checkpoint inhibitors + *PARP* inhibitors/VEGF blockers) tailored to tumor biology and resistance drivers.
3. Proactive Resistance Management: Early prediction via biomarkers (TMB, ctDNA) and emerging tools (single-cell sequencing) to preempt or reverse resistance.
4. Expanded Therapeutic Options: Integration of novel approaches (oncolytic viruses, microbiome modulation) to address evolving resistance pathways.

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.):
Current Landscape of Immunotherapy & Resistance Mechanisms
Immunotherapies: Checkpoint inhibitors (anti-PD-1/PD-L1, CTLA-4), CAR-T, cancer vaccines, and bispecific antibodies.
1. Primary Resistance Mechanisms:
- Tumor-Intrinsic: Low tumor mutational burden (TMB), antigen loss, defects in antigen presentation (MHC-I downregulation).
- Immune Microenvironment (TME): Immunosuppressive cells (T-regs, MDSCs), inhibitory cytokines (TGF-ϒ, IL-10), and metabolic barriers (IDO, adenosine).
- Acquired Resistance:

a. Upregulation of alternative checkpoints (LAG-3, TIM-3).
b. T-cell exhaustion or clonal depletion.
c. Tumor evolution (antigen escape variants).

2. Combination Therapies to Overcome Resistance
- Checkpoint Inhibitor Combinations: Anti-PD-1 + anti-CTLA-4 (melanoma) or anti-LAG-3 (relapsed Hodgkin).
- Immunotherapy + Chemo/Radiation: Induce immunogenic cell death (e.g., pembrolizumab + platinum chemo in NSCLC).
- Targeted Therapy Synergy:
  a. *PARP* inhibitors + anti-PD-1 (*BRCA*-mutated cancers).
  b. *VEGF* inhibitors (e.g., bevacizumab) to normalize TME.
  c. Oncolytic Viruses: T-VEC (talimogene laherparepvec) to enhance tumor immunogenicity.
  d. Epigenetic Modulators: HDAC inhibitors to re-express tumor antigens.

3. Current Knowledge Gaps:
- Heterogeneity of TME: Spatial/temporal variation in immune cell subsets and suppressive factors
- Biomarkers: Lack of validated predictors for which resistance pathway dominates per patient
- Non- immune Factors: Role of microbiome, metabolism, and stromal components in resistance
- Dynamic Evolution: Real time monitoring of tumor adaptation under immunotherapy pressure

4. Strategies to Predict & Overcome Resistance

- **Prediction:**

a. Biomarkers: TMB, PD-L1, MSI-H, IFN-Ɣ gene signatures.
b. Emerging Tools: Single-cell sequencing, ctDNA for clonal evolution.
c. Imaging: PET-CT radiomics to assess TME changes.

- **Overcoming Resistance:**

a. Target Alternative Pathways: Anti-TIM-3/LAG-3 antibodies.
b. Prime Immune Response: Neoantigen vaccines, CAR-T/NK cells.
c. Modulate TME: CSF-1R inhibitors (target MDSCs), IDO inhibitors.
d. Microbiome Interventions: Fecal microbiota transplantation (FMT).
e. Adaptive Trials: Basket trials testing combinations (e.g., anti-PD-1 + PARPi).

Full Name:
Soumya BM

Name of the Institution:
Manipal Hospitals Bengaluru

State:
Karnataka

Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):
Immunotherapy offers immense promise; resistance mechanisms remain a major challenge. By combining therapies, better understanding the tumor environment, and identifying predictive biomarkers, we can enhance the effectiveness of immunotherapy and overcome resistance, ultimately improving outcomes 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 revolutionized cancer treatment, but resistance remains a significant hurdle. Tumors can evade immune detection through mechanisms like immune evasion (e.g., by downregulating PD-L1 expression), antigen loss, or creating an immunosuppressive tumor microenvironment (TME). Additionally, patients with pre-existing immune dysfunction or tumors upregulating other inhibitory receptors (like TIM-3 or LAG-3) can also develop resistance to immunotherapy. To combat this, combination therapies are being explored. For example, combining checkpoint inhibitors (such as PD-1 inhibitors) with CTLA-4 inhibitors has shown promise in overcoming resistance by enhancing immune activation. Other approaches include combining immunotherapy with chemotherapy, targeted therapies, or even oncolytic viruses that specifically target and kill cancer cells, further enhancing immune responses. However, there are significant knowledge gaps in understanding resistance. We still lack comprehensive insights into how the tumor microenvironment influences resistance, and there are no universally reliable biomarkers to predict which patients will develop resistance. Also, long-term resistance mechanisms remain poorly understood, especially in patients who initially respond to treatment but later relapse. To predict and overcome resistance, a more personalized approach is needed. Biomarker profiling, including PD-L1 expression and mutational burden, could help identify patients who will benefit from immunotherapy. Additionally, analyzing the TME for key factors like TGF-β and MDSCs may guide tailored treatment plans. Liquid biopsies and monitoring immune cell profiles could also provide real-time insights to adapt treatments and address resistance early on.

Full Name:
Vishwanath M

Name of the Institution:
Madras Medical College

State:
Tamil Nadu

Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):
To decode the evolving puzzle of immunotherapy resistance in oncology by mapping its underlying mechanisms, exploring innovative combination strategies, and identifying predictive tools that can guide adaptive treatment.
This proposal aims to illuminate both the current landscape and the unknown bridging gaps in understanding while building a foundation for more durable, individualized immunotherapeutic responses. By integrating molecular insights with clinical innovation, it seeks to transform resistance from a barrier into a blueprint for smarter, stronger cancer 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.):
Addressing immunotherapy resistance in oncology requires a comprehensive approach to understand its mechanisms, develop combination therapies, and predict resistance early to optimize treatment outcomes.

1. Understanding Resistance Mechanisms:
Resistance to immunotherapy arises from various mechanisms, such as tumor cells evading immune detection by upregulating immune checkpoint proteins (e.g., PD-L1) or altering tumor antigen presentation. The tumor microenvironment (TME) plays a significant role by harboring immunosuppressive cells (e.g., regulatory T cells) and cytokines (e.g., TGF-β) that inhibit immune response. Tumor heterogeneity, including mutations and metabolic changes, further complicates immune recognition.

2. Combination Therapies:
Combining immunotherapies with other treatment modalities shows promise in overcoming resistance. For example:

- Checkpoint inhibitors combined with targeted therapies, such as anti-angiogenesis agents, to enhance immune infiltration and activity.
- Immunotherapy combined with chemotherapy or radiotherapy can increase tumor antigen exposure and stimulate a stronger immune response.
- Targeting the tumor microenvironment through agents that block immunosuppressive signals like IDO or TGF-β has shown potential to improve responses to immunotherapy.

3. Knowledge Gaps:
There are still significant gaps in understanding the full spectrum of resistance mechanisms across different cancers. A better understanding of tumor-specific mutations, immune evasion strategies, and the dynamics of TME are needed. Moreover, the development of reliable biomarkers to predict resistance remains an area of active research.

4. Predicting and Overcoming Resistance:
To better predict resistance, biomarkers such as tumor mutational burden (TMB) and immune gene signatures are valuable tools. Incorporating regular monitoring of the tumor's immune profile through liquid biopsies could help in adjusting treatment strategies before resistance fully develops.

Full Name:
Prabhu Pandian

Name of the Institution:
Madurai Medical College

State:
Tamil Nadu

Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):
Improved prediction and personalized treatment strategies for cancer immunotherapy, leading to enhanced efficacy and reduced 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.):

Current Landscape & Resistance Mechanisms

1. Primary Resistance: "Cold" tumors (low T-cell infiltration, TME immunosuppression via TGF-Ɣ, Tregs).
2. Secondary Resistance: Loss of antigen presentation (B2M mutations), upregulation of alternative checkpoints (LAG-3, TIM-3).
3. Microbiome Impact: Antibiotic use → gut dysbiosis → 50% lower IO response (Science, 2018).

Current combination therapies aiming to overcome resistance include:

1. Combining immune checkpoint inhibitors (ICIs) with other ICIs targeting different pathways; Combining ICIs with chemotherapy or targeted therapies to enhance tumor cell killing and reduce immunosuppression
2. Employing oncolytic viruses to directly lyse tumor cells and stimulate anti-tumor immunity; and
3. Incorporating therapies that modulate the tumor microenvironment, such as immune modulators or anti-angiogenic drugs. for e.g., T-cell Exhaustion- LAG-3 + PD-1- RELATIVITY-047 (melanoma)
Hypoxic TME – HIF-2α inhibitor (Belzutifan) + IO - NCT04976634
Low Neoantigens- Oncolytic Virus (T-VEC) + Pembrolizumab-MASTERKEY-265

Critical Knowledge Gaps

1. Spatial Heterogeneity: How do resistant clones evade immune surveillance in specific niches (e.g., bone marrow)?
2. Epigenetic Drivers: Can demethylating agents (azacitidine) reverse resistance?
3. Host Factors: Role of circadian rhythms, chronic stress in IO response

Predictive & Therapeutic Breakthroughs

1. Resistance Radar: AI-Powered Early Warning
a. Liquid Biopsy + Exosome Profiling: Detects TME-derived exosomal PD-L1 months before radiographic progression.
b. Digital Twins: Simulates tumor-immune dynamics to predict resistance timelines.
2. TME Reprogramming Cocktails
a. Faecal Microbiota Transplant (FMT): From IO responders to re-sensitize resistant patients (NCT03353402).
b. Ultrasound-Guided STING Agonist Injections: Converts cold pancreatic tumors to hot.
3. Resistance Vaccine
a. Neoantigen Booster Shots: For patients with acquired resistance due to antigen loss (BioNTech pipeline).
4. Immuno-Metabolic Reset: Ketogenic Diet + IO: Preclinical data shows ketosis enhances CD8+ T-cell infiltration.

Full Name:
Joseph Joy

Name of the Institution:
CMC, Vellore

State:
Tamil Nadu

Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):
The solutions aim to enhance immunotherapy efficacy by identifying resistance mechanisms, leveraging combination strategies, addressing knowledge gaps, and implementing predictive tools—ultimately leading to better patient selection, improved response rates, and prolonged survival in 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.):

1. Current Landscape of Immunotherapy Resistance: Resistance to immune checkpoint inhibitors (ICIs) can be primary (non-response from the outset) or acquired (relapse after initial benefit). Key mechanisms include:

- Low tumor mutational burden or absence of neoantigens
- Deficient antigen presentation (e.g., β2M or HLA mutations)
- Immunosuppressive tumor microenvironment (Tregs, MDSCs, TAMs)
- Checkpoint upregulation beyond PD-1/PD-L1 (e.g., TIM-3, LAG-3)

2. Combination Therapies Overcoming Resistance:

- Chemo-immunotherapy (e.g., NSCLC regimens)
- Anti-angiogenic + ICIs (e.g., IMpower150: atezolizumab + bevacizumab + chemo)
- Dual checkpoint blockade (nivolumab + ipilimumab in melanoma, RCC) Radiotherapy + ICIs (induces immunogenic cell death)
- Targeted agents + ICIs (e.g., *EGFR* inhibitors in T790M-altered NSCLC—ongoing trials)

3. Knowledge Gaps:

- Lack of validated predictive biomarkers beyond PD-L1 and TMB
- Heterogeneity in resistance pathways across tumor types
- Limited understanding of microbiome-immunity interactions
- Few prospective studies validating resistance reversal strategies

2. Predictive and Overcoming Strategies:

- Multi-omics profiling (genomics, transcriptomics, immunophenotyping)
- Liquid biopsies (ctDNA, exosomal PD-L1)
- AI-based prediction models integrating clinical and molecular data
- Personalized immunotherapy combinations
- Microbiome modulation (e.g., faecal transplants)

Full Name:
Baghath Singh L A

Name of the Institution:
Madras Medical College

State:
Tamil Nadu

Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):
Overcoming immunotherapy resistance by using better predictive markers and steps to Overcome them with combinations..

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. How Resistance Develops in Immunotherapy

Immunotherapy resistance, impacting 40-60% of patients with cancers like NSCLC, stems from tumor-intrinsic and extrinsic factors. Primary resistance arises from low PD-L1 expression or lack of tumor antigens, limiting drugs like pembrolizumab. Acquired resistance occurs when tumors lose MHC class I or upregulate checkpoints (e.g., TIM-3). Immunosuppressive tumor microenvironment (TME) elements, like Tregs or TGF-β, and genetic mutations (e.g., *JAK1/2*) reduce T-cell activity. In India, late-stage diagnoses (60%) and limited PD-L1 testing (<20% centers) worsen resistance, hindering effective therapy.

2. Overcoming Resistance with Chemo-Immunotherapy

Chemo-immunotherapy combinations enhance immunotherapy by inducing immunogenic cell death, releasing antigens, and reducing TME suppression. Trials like KEYNOTE-189 show pemetrexed-pembrolizumab improve NSCLC response (48%) over monotherapy. In India, generics like carboplatin (₹5,000/cycle) make combos feasible, though immunotherapy costs (₹1-4 lakh) challenge affordability. Tailoring to biomarkers (e.g., PD-L1) optimizes outcomes, but toxicity (e.g., neutropenia) demands supportive care, scarce in rural areas with only 1,500 oncologists nationwide.

3. Prognostication and Prediction of Resistance

Predictive biomarkers like high PD-L1 (>50%) forecast pembrolizumab success in NSCLC (45% response), while prognostic biomarkers like high TMB (>10 mutations/Mb) indicate better nivolumab outcomes. TME analysis (e.g., Treg levels) and liquid biopsies for *JAK1/2* mutations predict resistance. In India, NGS (₹50,000- ₹1 lakh) is limited to 10-15% of centers. Subsidized testing and AI models can improve early identification of resistant cases, guiding therapy adjustments.

4. Overcoming Challenges of Resistance

High costs, scarce biomarkers, and infrastructure gaps (1 oncologist per 900,000) limit immunotherapy. Solutions include biosimilars to cut costs by 30-40%, Ayushman Bharat subsidies for NGS, and CMEs to train oncologists. Regional hubs and telemedicine extend rural access. Trials for dual inhibitors (e.g., anti-PD-1/CTLA-4) and India-specific guidelines addressing oral/cervical cancers can counter resistance. Tumor boards and community health workers ensure personalized, early interventions, improving outcomes for 1.5 lakh Indian cancer patients.

Full Name:
Bala Manikandan

Name of the Institution:
GKNM Hospitals

State:
Tamil Nadu

Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):
To enumerate methods to overcome resistance to 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.):

1. Mechanisms of Resistance

- Tumor-Intrinsic Factors:

a. Low Antigenicity: Reduced neo-antigen expression or defects in antigen presentation (e.g., MHC class I downregulation).

b. Genetic Alterations: Mutations in IFN-Ɣ signaling or epigenetic silencing of immunogenic genes.

c. Adaptive Immune Resistance: Upregulation of alternative checkpoints (e.g., TIM-3, LAG-3) post-PD-1 blockade

- Tumor Microenvironment (TME):

a. Immunosuppressive Cells: Infiltration of Tregs, or tumor-associated macrophages.

b. Metabolic Barriers: Hypoxia, nutrient depletion (e.g., tryptophan via IDO1), or adenosine accumulation.

2. Strategies to Overcome Resistance

- Combination Therapies:

a. Checkpoint Inhibitor Combinations: Anti-PD-1 + anti-CTLA-4 (e.g., nivolumab/ipilimumab in melanoma).

b. With Targeted Therapy: BRAF/MEK inhibitors + immunotherapy (e.g. in metastatic melanoma vemurafenib and cobimetinib given as 28 day run in followed by atezolizumab has improved outcomes)

- Modulating the TME:

a. Target Immunosuppression: Inhibit IDO1 (e.g. Epacadostat, Indoximod under trials), adenosine (A2AR antagonists), or TGF-Î².

b. Metabolic Modulation: Block arginase or use OXPHOS inhibitors to disrupt MDSC function.

c. Vascular Normalization: VEGF inhibitors (e.g., bevacizumab in HCC) to enhance T-cell infiltration

- Adoptive Cell Therapies:

a. CAR-T/TCR-T Cells: Engineered to target tumor antigens (e.g., BCMA-CAR-T in myeloma).

b. TIL Therapy: Expanded tumor-infiltrating lymphocytes for melanoma.

3. Emerging Biomarkers for Patient Stratification:

- Gut microbiota profiles, TCR clonality, IFN-Î³ signatures, and spatial transcriptomics are used to stratify patient response to immunotherapy.
- Utilizing other immune Checkpoint proteins: TIM-3, LAG-3, TIGIT studies are ongoing to overcome PD1/PDL1 resistance (e.g. sabatolimab for AML and Relatlimab first LAG3 Inhibitor in combination with atezolizumab approved for advanced melanoma based on RELATIVITY-047 Trial)
- AI-Driven Solutions: Predicting resistance mechanisms or optimal drug combinations.
- Microbiome Engineering: usage of antibiotics is associated with reduced response to immunotherapy so use of Probiotics/dietary interventions to boost efficacy can be done

---

Full Name:
Dr. Senthamizhan. VS

Name of the Institution:
RCC Trivandrum

State:
Kerala

Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):
Metastatic colorectal cancer is one of the leading causes of cancer related mortality globally. Anti-*EGFR* therapy, in combination with chemotherapy, remains a cornerstone in the treatment of left sided

colorectal cancer with *RAS/BRAF* wild type status, achieving response rates approximately 60%. However, resistance frequently develops during anti-*EGFR* treatment through multiple mechanisms, including mutations in the *PIK3CA/AKT* signaling pathway. The tumor microenvironment is inherently pro-inflammatory, promoting the activation of prostaglandin E2 (PGE2), which subsequently stimulates downstream signaling cascades such as *PI3KCA/AKT*. Celecoxib, a selective COX-2 inhibitor, has demonstrated the ability to reduce PGE2 production and may thereby mitigate the oncogenic effects of these signaling pathways.

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.):
Patients with metastatic left-sided colon cancer with RAS/BRAF wild-type status who are scheduled to receive anti-EGFR therapy in combination with chemotherapy will be randomized to receive either celecoxib 200 mg twice daily or a placebo throughout the treatment course. Patients with contraindications to celecoxib or a recent history of cardiovascular disease or stroke will be excluded from the study. Celecoxib has significantly fewer gastrointestinal side effects compared to other prostaglandin E2 inhibitors. The primary endpoint will be disease-free survival. This study aims to evaluate whether celecoxib can reduce the development of acquired resistance to anti-EGFR-based therapy in metastatic left-sided colorectal cancer (CRC).

Full Name:
Dr. Senthamizhan. VS

Name of the Institution:
RCC Trivandrum

State:
Kerala

Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):
Background
Metastatic colorectal cancer (mCRC) remains one of the leading causes of cancer-related mortality worldwide. For patients with left-sided colorectal cancer harboring *RAS/BRAF* wild-type status, anti-*EGFR* therapy in combination with chemotherapy is a mainstay of treatment, achieving response rates of approximately 60%. However, acquired resistance frequently develops, often mediated by activation of the *PIK3CA/AKT* signaling pathway.
The tumor microenvironment in colorectal cancer is characterized by chronic inflammation, with elevated prostaglandin E2 (PGE2) levels promoting downstream oncogenic signaling, including the *PIK3CA/AKT* axis. This provides a rationale for exploring anti-inflammatory interventions to overcome or delay therapeutic resistance.
Rationale
Celecoxib, a selective COX-2 inhibitor, effectively reduces PGE2 production, potentially mitigating the activation of the *PIK3CA/AKT* pathway and its contribution to resistance against anti-*EGFR* therapy. Compared to other prostaglandin inhibitors, celecoxib demonstrates a more favorable gastrointestinal side effect profile.

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
Patients with metastatic left-sided colorectal cancer, confirmed to be *RAS/BRAF* wild-type, and scheduled for anti-EGFR therapy in combination with chemotherapy will be randomized into two arms:

Arm A: Celecoxib 200 mg twice daily
Arm B: Placebo
Treatment will continue throughout the chemotherapy and anti-EGFR regimen.
Patients with contraindications to celecoxib, or a recent history of cardiovascular disease or stroke, will be excluded from the trial.

Objectives and Endpoints

Primary Endpoint: Disease-Free Survival (DFS)
Secondary Endpoints: Response rate, overall survival, and time to acquired resistance

Conclusion

This study aims to determine whether the addition of celecoxib to standard anti-EGFR-based therapy can reduce or delay the development of resistance mediated by the PIK3CA/AKT pathway in patients with metastatic left-sided colorectal cancer.

Full Name:
Mohamed Aaseem Arshad VS

Name of the Institution:
Madras Medical College

State:
Tamil Nadu

Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):
To identify and treat immunotherapy 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. Current immunotherapy approaches:

- ICI
- Car T cell therapy
- Cancer vaccines
- Oncolytic viruses
- Adoptive T cell therapy

2. Mechanisms of Immunotherapy resistance:

- Tumor-Intrinsic Factors:

a. Loss of tumor antigen expression
b. Defects in antigen presentation (e.g., B2M, MHC mutations),
c. Activation of oncogenic pathways (e.g. TEN losses, *MAPK* activation).

- Tumor Microenvironment (TME):

a. Immunosuppressive cells upregulation: Tregs, MDSCs.
b. Checkpoint upregulation: PD-L1, TIM-3, LAG-3.
c. Cytokine milieu: High TGF-β, IL-10 suppress T-cell function.

- Host-Related Factors:

a. Microbiome composition
b. HLA diversity
c. Corticosteroid or immunosuppressant use

3. Combination Strategy for overcoming resistance:

- Checkpoint Inhibitors + Chemotherapy -Chemo increases neoantigen release
- Dual Checkpoint Blockade: CTLA-4 + PD-1 (e.g., ipilimumab + nivolumab in melanoma)

- ICIs + Anti-VEGF - Normalizes vasculature and increases immune infiltration (e.g., atezolizumab + bevacizumab in HCC)
- ICIs + RT - Radiation promotes immunogenic cell death and antigen release
- ICIs + STING/TLR agonists - Boosts innate immune activation
- ICIs + Oncolytic Viruses - Enhance tumor lysis and immune priming

4. Current knowledge gaps in resistance mechanisms:

- Lack of reliable predictive biomarkers
- Heterogeneity in resistance patterns
- Limited understanding of TME remodelling post immunotherapy
- Incomplete mapping of immune escape mechanisms
- Impact of host microbiome in ICI resistance

5. Predictive tools to overcome resistance:

- Liquid biopsy for early detection of resistance mutations
- Microbiome profiling to predict ICI response and toxicity
- Imaging and radiomics to predict tumor immunophenotype and response / resistance to ICI

Full Name:
Amol Sitaram Rathod

Name of the Institution:
PD Hinduja National Hospital and Medical Research Centre

State:
Maharashtra

Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):
Combining with different modalities of cancer 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.

1.

A- Intrinsic mechanism of
a. Loss of neo-antigen
b. Alteration of signalling and metabolic pathway
c. Impaired processing a neo-antigen production
d. Epigenetic modification
e. Low T lymphocyte infiltrating tumour
B-Extrinsic
a. Immunosuppressive Tumor microenvironment
b. Gut micro biome
c. alternative immune checkpoints
d. Epithelial Mesenchymal transition

2.

- Enfortumab vedotin with Pembrolizumab overcame resistance of Pembrolizumab and increased PFS & OS in metastatic Urothelial carcinoma
- Gemcitabine-Cisplatin-Nivolumab in Urothelial carcinoma.
- Adding Axitinib or Lenvatinib with Pembrolizumab in metastatic RCC
- Adding Cabozantinib with Nivolumab in RCC
- Chemoradiotherapy with Pembrolizumab in Ca cervix

3. Knowledge gaps are

- Role of Tumor infiltrating lymphocytes (TIL)
- Role of Tumour Microenvironment
- Mechanism behind primary resistance
- Sequencing of IO and targeted therapy

4. Strategies to Overcome

- IO with chemotherapy
- IO with Radiation therapy (Ipilimumab with RT Melanoma)
- IO with targeted therapy
- IO with other Checkpoint inhibitor (Nivolumab + Ipilimumab)
- IO with immunostimulatory agents (ICOS agonist, GITR agonist)
- IO with Adoptive T cell transfer (After CART)
- IO With cancer vaccines or oncolytic viruses (Talimogene laherparepvac)
- IO with Epigenetic modulator (HDAC inhibitor, DNMT inhibitors)
- IO with gut micro biome (bifidobacterium, bacteroides fragilis, burkholderia capacia with bacteroides thetaiotamicron)
- Bispecific antibodies
- Antibody drug conjugates
- IO with Targeting co-inhibitory signals (with Tiragolumab an anti-TIGIT), (LAG-3 inhibitor Relatlimab, TIM-3 inhibitor cobolimab, VISTA inhibitor)

Full Name:
Pearl

Name of the Institution:
KMC Medical College

State:
Uttar Pradesh

Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):
Navigating Immunotherapy Resistance in Cancer: A Patient-Centered Perspective
Immunotherapy has changed the face of cancer care. Bringing hope to many patients who previously had limited options. However, not all patients benefit equally. Some cancers fail to respond, while others develop resistance over time. Understanding this resistance isn't just about science: It's about ensuring patients don't lose their chance at a better life.
Immunotherapy resistance isn't a dead end — it's a challenge we're learning to outsmart. Each setback reveals something new about the complex dialogue between tumors and the immune system. By combining scientific insight with a patient-centered mindset, we can turn resistance into resilience and give more patients a real chance at durable remission.

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.):
Understanding and Overcoming Resistance to Immunotherapy in Cancer
Immunotherapy has brought new hope to many cancer patients, offering long-lasting responses where traditional treatments often fail.
Yet not all patients benefit, some don't respond at all (primary resistance), while others initially improve but later relapse (acquired resistance). Understanding why this happens is key to improving outcomes.
Current Landscape & Resistance Mechanisms

Immunotherapy works by activating the immune system to target cancer. Resistance can arise when:

- Tumors stop presenting antigens (e.g., B2M mutations), The immune system is actively suppressed by the tumor microenvironment (Tregs, MDSCs),
- Alternative immune checkpoints (like LAG-3 or TIM-3) take over.

Promising Combination Therapies

To overcome resistance, combinations are being explored:

- Checkpoint inhibitors + chemotherapy (e.g., in NSCLC),
- Dual checkpoint blockades (PD-1 + CTLA-4 in melanoma),
- Immunotherapy + anti-angiogenics (renal cancer),
- Radiotherapy + immunotherapy, leveraging the abscopal effect.

These combinations aim to wake up the immune system or make tumors more visible.

Knowledge Gaps

We still don't fully understand:

- Why some patients relapse,
- How the microbiome or epigenetics affect immune response,

The best way to personalize immunotherapy combinations.

Predicting and Overcoming Resistance

We can improve outcomes by:

- Using biomarkers (PD-L1, MSI, TMB) and liquid biopsies,
- Monitoring immune cell activity and tumor microenvironment,
- Exploring new checkpoint targets,
- Personalizing therapy using AI and real-world data.

Bottom line: Resistance is a challenge but one we're learning to navigate with smarter science and deeper personalization.

Full Name:
Viji V Julian

Name of the Institution:
Madras Medical College

State:
Tamil Nadu

Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):
Overcoming resistance mechanisms 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.):

1. Immunotherapy has transformed cancer treatment, especially with immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 and CTLA-4. However, many patients experience primary or acquired resistance. Resistance mechanisms include lack of tumor immunogenicity, impaired antigen presentation (loss of MHC I), T-cell exhaustion, suppressive tumor microenvironment (Tregs, MDSCs), metabolic reprogramming, and upregulation of alternative checkpoints (e.g., TIM-3, LAG-3, TIGIT).

2**. Combination therapies overcoming resistance**: Several combinations show promise:

- ICIs with chemotherapy/radiotherapy: Enhance neoantigen release. ICIs with anti-angiogenic agents (e.g., bevacizumab): Normalize vasculature, reduce immune suppression.
- Dual checkpoint blockade (e.g., PD-1 + CTLA-4): Broaden T-cell activation.
- ICIs with targeted therapies (e.g., BRAF/MEK inhibitors in melanoma): Modulate tumor microenvironment.
- ICIs with oncolytic viruses or vaccines: Boost tumor immunogenicity.
- ICIs with microbiome modulation: Alter gut flora to enhance response.

3. Current knowledge gaps
- Complete mapping of tumor-immune interactions.
- Biomarkers predicting resistance vs. response.
- Understanding tumor heterogeneity and clonal evolution.
- Role of microbiome and host genetics in resistance.

4. Predicting and overcoming resistance
- Predictive markers: TMB, PD-L1 expression, gene signatures, T-cell infiltration, circulating tumor DNA.

5. Strategies to overcome resistance:
- Novel checkpoint inhibitors (e.g., LAG-3, TIGIT).
- Personalized cancer vaccines.
- Adoptive cell therapy (e.g., CAR-T, TILs).
- Targeting stromal and metabolic pathways.
- Modulating gut microbiota.

Full Name:
Aishwarya Ghule

Name of the Institution:
Deenanath Mangeshkar Hospital

State:
Maharashtra

Objective of your solution: (Briefly define the primary outcome of your solution to this challenge):
To overcome resistance in 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.):
1. Tumour intrinsic resistance - Mechanism & solution
- Lack of tumour immunogenicity - Radiation induced cell death, personalised neoantigen peptides and mRNA Vaccines
- Aberrations in IFNgamma/JAK/STAT pathway - CLINICAL TRIALS in JAK/STAT inhibition
- Aberrations in RAS, RAF pathway - BRAF, MEK inhibition, RAS G12C with Anti PD1 therapy
- Abnormal PI3K, PTEN pathway - PI3K, AKT inhibition

Tumour extrinsic resistance
- Adaptive immunity Tregs
- Tcell exhaustion - TIGIT, TIM3, LAG 3 & CTLA4 inhibition along with PD1 inhibition
- Tumour associated macrophages - Clinical trials targeting CCL2 & TLR8

- MDSCs – ATRA
- Cancer associated fibroblasts - CAF specific CAR t CELL therapies, FAP 41BB, FAP CD40 bispecific antibodies
- Endothelium - VEGF inhibitors

2. Biomarker to detect tumour heterogenecity - ct DNA based surveillance
Immunocore detecting TILs to detect immunotherapy response

Full Name:
Pankaj deep Rana

Name of the Institution:
Metro Hospital and Cancer Institute

State:
Delhi

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

1. Enhancing Antigen Presentation: Epigenetic therapies, STING agonists, oncolytic viruses
2. Reprogramming the TME: Targeting Tregs, MDSCs, and normalizing vasculature
3. New Checkpoint Targets: LAG-3, TIM-3, VISTA, TIGIT inhibitors
4. Tumor-Intrinsic Targeting: Inhibiting WNT/Î²-catenin, PI3K/AKT pathways
5. Personalized Immunotherapy: Neoantigen vaccines, TCR-T cell therapies

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 and Resistance Mechanisms

Immunotherapy has revolutionized cancer treatment, particularly through immune checkpoint inhibitors (ICIs), adoptive T cell therapy, and cancer vaccines. Immunotherapy Modalities:

- Checkpoint Inhibitors (PD-1/PD-L1, CTLA-4)
- CAR-T Cell Therapy
- Cancer Vaccines
- Oncolytic Viruses
- BiTEs (Bispecific T-cell engagers)

Types of Resistance:

- Primary Resistance: Tumors fail to respond initially
- Acquired Resistance: Response lost after initial success
- Adaptive Resistance: Tumor evolves immune escape mechanisms dynamically

Key Resistance Mechanisms:

- Tumor-Intrinsic Factors:

a. Lack of antigen presentation (e.g., mutations in Î²2-microglobulin or MHC molecules)
b. Oncogenic pathway activation (e.g., WNT/Î²-catenin, PTEN loss, MAPK pathway)
c. Low tumor mutational burden (TMB)

- Tumor-Extrinsic Factors:

a. Immunosuppressive tumor microenvironment (TME)
b. High levels of regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs)

2. Combination Therapies to Overcome Resistance

- Promising Strategies:

a. Checkpoint Inhibitor Combinations: Anti-PD-1 + Anti-CTLA-4 (e.g., nivolumab + ipilimumab), PD-1 + LAG-3 (e.g., relatlimab + nivolumab)

b. Checkpoint Inhibitors + Targeted Therapies: PD-1/PD-L1 + VEGF inhibitors (e.g., atezolizumab + bevacizumab), BRAF/MEK inhibitors + ICIs
c. Checkpoint Inhibitors + Chemotherapy/Radiation: Enhances antigen release and T-cell infiltration
d. Checkpoint Inhibitors + Epigenetic Modifiers: Hypomethylating agents or HDAC inhibitors

3. Current Knowledge Gaps in Resistance Mechanisms

- Incomplete Understanding of TME Complexity: Spatial and temporal dynamics of immune cell infiltration
- Biomarkers for Predicting Response: Lack of reliable predictive biomarkers beyond PD-L1 and TMB
- Understanding Epigenetic and Metabolic Barriers: Epigenetic silencing of immune genes, tumor metabolism

4. Possible Ways to Predict and Overcome Resistance

- Prediction Tools:

a. Biomarkers: PD-L1, TMB, neo-antigen load, gene expression signatures, blood-based biomarkers
b. Imaging and AI-based Radiomics: Detect immune infiltration and response patterns
c. Organoid and Ex Vivo Models: In vitro testing of patient-specific responses

- Overcoming Resistance Approaches:

a. Enhancing Antigen Presentation: Epigenetic therapies, STING agonists, oncolytic viruses
b. Reprogramming the TME: Targeting Tregs, MDSCs, and normalizing vasculature
c. New Checkpoint Targets: LAG-3, TIM-3, VISTA, TIGIT inhibitors
d. Tumor-Intrinsic Targeting: Inhibiting WNT/ β -catenin, PI3K/AKT pathways
e. Personalized Immunotherapy: Neoantigen vaccines, TCR-T cell therapies