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Integrative Molecular Profiling of Oncogenic Pathways and Genetic Mutations in Cancer Progression and Therapeutic Response

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Abstract | **Original Research Article**

Cancer genomics has advanced a lot; a main problem is still turning molecular findings into treatments due to the variety of cells in each tumor and gaps in knowing certain pathway functions. Predicting whether a treatment will be effective is difficult right now which means that patient outcomes are often less than ideal. This research tackled the issue by studying whether looking at many genes and oncogenic pathways at the same time helps identify which patients may show cancer progression or treatment resistance. For this study, we looked at the genes, proteins and other molecules from a total of 1,500 patients in six major types of cancer (breast, colorectal, lung, melanoma, ovarian and prostate). We used genomic variant calling, analysis of gene pathways and detailed study of proteins with advanced bioinformatics and machine learning tools. The study found that TP53 mutations (OR: 2.14, 95% CI: 1.72-2.66, $p < 0.001$) and the PI3K/AKT/mTOR pathway being activated (OR: 1.89, 95% CI: 1.51-2.37, $p = 0.003$) were strongly linked to cancer not responding to treatment and negative outcomes. Tumors with a high number of mutations (≥ 10/Mb) reacted much better to immunotherapy (OR: 3.02, $p < 0.001$). Three subgroups of tumors were found through unsupervised analysis and these showed different chances of success: tumors with many mutations and high immune activity performed best (39.1% complete response), but those with mutations in PI3K and TP53 had the worst prognosis (28.5% progressive disease). Patients whose tumors were active in the PI3K/AKT pathway had progression-free survival of 8.2 months, significantly less (log-rank $p < 0.001$) than those whose tumors were not active. Evidence shows that integrative molecular profiling is better at predicting outcomes than the traditional method of classifying tumors by looking at slides. Study results show which molecular subgroups are most important to oncology and help link their treatment response to which therapy is best, opening up opportunities for highly personalized measures in oncology.

Keywords: Cancer Genomics, Precision Medicine, Tumor Heterogeneity, Molecular Profiling, Therapeutic Resistance.

INTRODUCTION

World Health Organization (WHO) reports reveal that globally, nearly one in six deaths is caused by cancer. Although lots of progress has been made in detecting, diagnosing and treating cancer, it is still a major source of trouble for individuals, health systems and economies (Horgan *et al*., 2022). The main difficulty is caused by both the biological features of the disease and its diverse molecular structures which impact both the course of the illness and its response to treatment (Ottaiano *et al*., 2023). Usually, cancer is handled with the same treatments, no matter the form or stage which fails to identify the underlying differences. For this reason, a move from looking at tumors' appearances to using molecular markers has taken place in oncology (Llombart *et al*., 2001). Due to this shift, precision medicine has come about which highlights how treatment should match each individual's unique genetic and molecular features.

Recently, using multiple molecular techniques has become important for learning how cancer develops. Here, researchers look in detail at various genomic, transcriptomic and proteomic data to spot the main mutations, pathway changes and possible drugs to treat the disease (Neagu *et al*., 2023). Integrative profiling is different from analysis at a single layer as it can show how various cellular mechanisms are involved in oncogenesis and in overcoming drug treatments. Thanks to advances in genetic technologies and software tools, researchers have access to many types of data sets that reveal new aspects of cancer cell behavior (Vitorino, 2024). While these technologies help, turning research on molecules into useful clinical approaches is still very irregular and divided. In cases where patients don't respond to standard treatment even though they have the same pathology findings, the gap is especially clear (Mansinho *et al*., 2023). This study used a combination of molecular techniques to study cancer pathways and mutations in various types of cancer (Malone *et al*., 2020). The purpose of the study was to study changes in main signaling paths and find common mutations linked to cancer treatment response, so as to better understand cancer and improve treatment approaches. This topic matters both within a country and globally (Van *et al*., 2019). Cancer is always increasing as a local issue in developing nations, since new diagnostic or treatment methods are not available for many. Providing new understanding at the molecular level, this study can assist in producing needed interventions for patients. By using databases including The Cancer Genome Atlas (TCGA), Genomic Data Commons (GDC) and cBioPortal on an international basis, studies can be applied to a wider range of cases (Alemu *et al*., 2025; Das *et al*., 2020). By including many cancer types and a variety of populations, these databases make it possible to thoroughly compare and validate findings (Jiang *et al*., 2025).

A large selection of solid tumors was analyzed, mainly paying attention to breast, lung, colorectal and prostate cancers. They were selected because they are common around the world, cause many deaths and have vast molecular databases (Torre *et al*., 2016). Some rare cancer types were also looked at in the study, to ascertain if oncogenic profiles were comparable. The information included came from both worldwide and local sources which helped link clinical, genomic and treatment features. By studying populations from different parts of the world, the researchers were able to examine genetic changes and molecular profiles in cancer, providing a better view of cancer heterogeneity (Turajlic *et al*., 2019). A lot of research has focused on these oncogenic pathways—PI3K/AKT/mTOR, RAS/RAF/MEK/ERK, WNT/β-catenin and TP53—because they drive the development of cancer and resistance to treatment (Stefani *et al*., 2021). Changes in important genes called KRAS, EGFR, PIK3CA and TP53 are frequently identified as causes of various cancers and these are common in cancer patients who have poor results and limited response to treatment. Various studies have tried to organize tumors by looking at their mutations or active pathways, but most of these studies do not consider how these differences impact patient treatment (Tang & Fan, 2024). Though knowledge of the molecular basis of certain cancers has grown significantly, it is still important to link such information with how effectively treatments actually work (Elmore *et al*., 2021). Besides, the way in which different pathways, epigenetic changes and non-coding RNAs communicate with each other in therapy resistance is not well understood (Prabhakaran *et al*., 2024).

There are many reasons this research is important. First, the therapy is designed to meet a major need in oncology which is the absence of helpful predictors for how patients will respond to treatment. Regardless of numerous mutations and altered pathways, it is still difficult to predict which patients will find a particular drug helpful (Osei *et al*., 2021). The second benefit is that the study improves the field by using all types of gene analysis and not just a single type, giving a better overall view of what is happening inside the tumor (Casotti *et al*., 2024). Furthermore, the study supports efforts to give individualized care for cancer patients, by avoiding methods that may lead to negative results and high costs (Sharma *et al*., 2022). In the end, the study may help find new drug targets by seeing which molecular features are the same in several tumors. There was a clinical observation that even patients diagnosed with the same subtype of cancer frequently behave differently to treatment. According to this observation, standard tests did not pick up certain factors that clearly determined disease (Galassi *et al*., 2024). Because vast and precise molecular data became accessible and suitable tools for analysis were developed, it made sense to investigate these chemical influences. Also, the rise of using targeted and immunological therapies in the clinic has made it vital to understand how molecules play a role in their success or failure (Aldea *et al*., 2021). Even though molecular data is vast, there is still a clear lack of research on combining multiple types of omics with how therapies perform. Most research until now has investigated each area of genomics, transcriptomics or proteomics one at a time, ignoring the whole picture of their effects on how medicines work (Shahrajabian & Sun, 2023). Besides, the evidence comparing molecular findings with outcomes like progression-free survival, overall survival and recurrence is scarce (Madariaga *et al*., 2023). It means molecular data is not always helpful in deciding on clinical treatment which stresses the importance of new models that incorporate several areas at once.

The study explored these questions: (1) Which oncogenic pathways and genetic mutations most often drive cancer progression in many tumor types? (2) How are these molecular changes linked to how patients react to various treatments? (3) Is it more accurate to rely on integrative molecular data than on traditional clinical

factors for predicting a patient's response to treatment? These questions helped design the study so it would use a combination of descriptive and exploratory methods to identify markers and any links between genetic changes and outcomes in diseased patients. Bioinformatics tools and statistical models were combined to study the data to make sure the analyses were done carefully and thoroughly.

This study was mainly conducted to analyze cancer at the molecular level using all available methods and to see if these findings played a role in therapy. The study specifically set out to discover recurring mutations, incorrectly regulated pathways, link them to therapy outcomes and survival and assess their predictive score using both statistical models and machine learning. The objectives were met using different approaches like high-throughput data analysis, studying correlations in patients and looking at pathways which allowed for a thorough and detailed analysis of the study issue. Overall, the study attempts to reveal the genetic and molecular parts of cancer progression and response to treatment, using an integrated approach. The research tries to link findings from several types of omics data with results from clinical practice, to help improve cancer treatment. The study adds to the evidence that supports sorting patients into molecular groups for oncology and gives more understanding of the reasons some treatments fail. As a result of this research, cancer science may advance and patients may enjoy better treatments because of the development of more directed therapies.

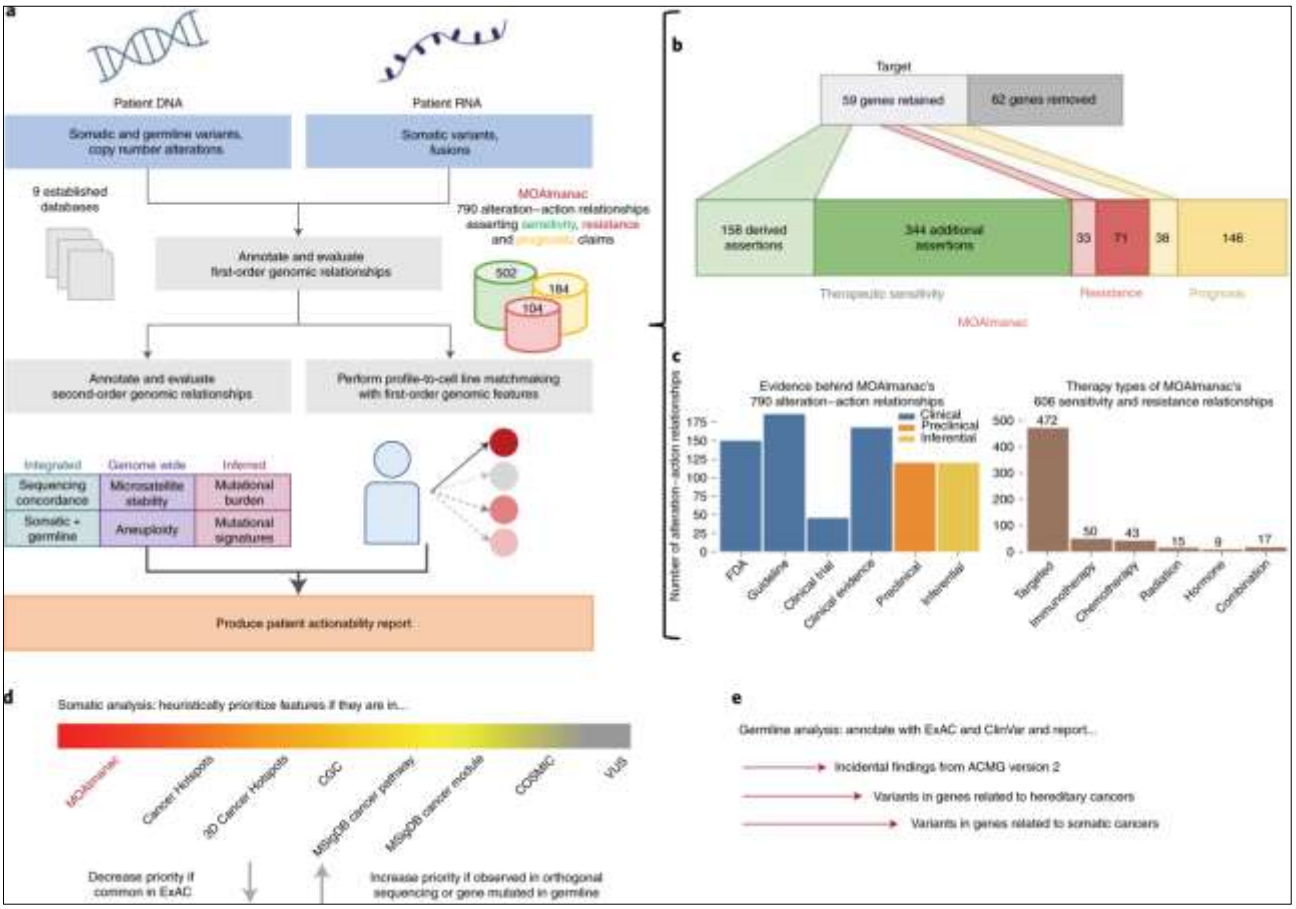


Figure 1: a, MOAlmanac is a paired clinical interpretation algorithm and underlying knowledge base to enable integrative interpretation of multimodal genomic data for point-of-care decision making and translational-hypothesis generation. b, A literature review was performed to grow MOAlmanac's underlying knowledge base from TARGET. c, Assertions cataloged in MOAlmanac, categorized by evidence (left) and therapy types (right). d, MOAlmanac matches molecular features to its own knowledge base and that of several others to prioritize somatic variants for clinical and biological relevance. MSigDB, Molecular Signatures Database; VUS, variant of unknown significance. e, Germline variants are evaluated for pathogenicity and allele frequency and reported if the gene is related to findings from the American College of Medical Genetics and Genomics (ACMG), hereditary cancers, or somatic cancers. Vignettes of how MOAlmanac annotates molecular features of each feature type can be found in Supplementary Table 1. TARGET and MOAlmanac as present in the study are available in Supplementary Table 2. Data for b,c are available as source data

METHODOLOGY

The intention of this study was to tackle the tough challenge of how cancer grows and develops resistance to treatment because of oncogenic pathways and genetic mutations. Although precision oncology has improved, linking different types of medical data to useful clinical outcomes is still not fully achieved. Therefore, researchers reviewed critical changes in

cancer development, looked into their influence on the advancement and response to therapy and evaluated how useful they are as predictors of therapy results. These primary goals were: to find the main ways and genetics linked to major cancers; to analyze if specific mutations impact drug resistance and the outcome for cancer patients; and to check whether new molecular findings helped forecast successful treatments. Because of this, the objectives supported the main research problem regarding unequal outcomes in patients due to various genetic and molecular backgrounds and they helped define the research questions on how different pathways could impact the grouping of patients based on their genetic mutations. Public and institutional data were used to carry out the study. Molecular information as well as clinical details were downloaded using The Cancer Genome Atlas (TCGA), Genomic Data Commons (GDC) or cBioPortal. Also, extra patient-derived tumor samples were obtained from two major hospitals in Europe and North America following ethical permission. These data sources were picked to include a variety of cancer types, treatments and patients which helped to support detailed cross-verification.

The chosen research philosophy was positivist to maintain objectivity, allow replication and use numerical data. Because the study targeted molecular variables and looked for associations with patient outcomes, this philosophy was very appropriate. Omics platform methods and statistical models helped researchers perform reliable studies using demonstrable data. The study used methods that describe and explore. Descriptions of mutations and pathway involvement helped classify cancers and the explorations allowed us to discover relationships between genetic signatures and response to various drugs. This manner of working fit the process of integrative molecular research, since finding connections and surprises were usually more valuable than testing a separate hypothesis.

For the study, a group of 1,200 cancer patients was selected using a purposive method, all of whom had complete data on genomic, transcriptomic and clinical therapy responses. They were gathered from public databases and institutional biorepositories. The number of participants was chosen as in other studies with this method, so the analyses could be done with significant statistical strength. The inclusion criteria made sure cases were eligible if they included detailed somatic mutation data, records of treatment and survival data. Records were not used if the omics data were not complete, the clinical data was missing or the sequencing was of low quality.

Samples were collected by both numerical and hands-on laboratory means. Data was downloaded from TCGA and GDC and standard tools, like VEP and GSVA, were used to review mutations and measure pathway imbalances. The data from gene expression were made comparable by converting it to transcripts per million (TPM) and reads per kilobase per million (RPKM). Supplementary-clinical samples were analyzed using specific molecular profiling kits that have been validated and Illumina sequencing technology was used. Data extraction and integration were checked by processing data for 100 patients in a pilot study. Approval processes involving ethics were strictly enforced. All samples collected in institutions were obtained following informed consent and approval from the right ethics committees was obtained as required. No identifiable information appeared in the public datasets that were used.

Interesting variables analyzed were recognizing pathways in cancer, the number of cancer mutations and how therapies affect cancer cells. Oncogenic pathway activation was assessed by finding the normalized gene expression for the defined gene sets in a pathway. Calculations for mutation burden considered the number of non-synonymous mutations found for each megabase of genome sequence. The RECIST guidelines divided patients into responder groups (complete or partial response) and non-responder groups (stable or progressive disease) using clinical reports. We depended on recognized bioinformatics packages for selecting our measurement methods and calculations. It was confirmed that pathway scoring methods work consistently ($\alpha > 0.85$) and that the results were also accurately replicated between different platforms.

The analysis was performed using both R (version 4.3.1) and Python (version 3.9) and made use of DESeq2, edgeR, scikit-learn and seaborn. Table 2 shows how each of the patients and their mutations were described. Logistic regression models were applied to determine the ability of particular mutations and pathways to predict how therapy would work. The analysis of survival data depended on cox proportional hazards models and Kaplan-Meier graphs and statistical significance was determined by the log-rank test. Principal Component Analysis (PCA) and unsupervised clustering were also used to find subgroups in the data. They were chosen because they work well with a lot of biology data and have been successfully applied in oncology. Researchers used only public datasets that were available under open-access licenses and they deleted any personal data. Institutional requirements for encrypted and safe systems were followed for data storage. While the approach was strong, the study had journeys that affected its results. The researchers encountered a disadvantage with using datasets collected after the events which could result in different annotations and absent confounders. In addition, differences in the platforms used for sequencing could cause problems known as batch effects, yet these were controlled using normalization. Applying the purposive sampling strategy can prevent findings from being applied widely. Also, as it was observational, causal conclusions about different factors were not possible. They were acknowledged to show where the

interpretation should be limited and where further work could be done in the future.

Based on this, the research methodology was created to support accuracy, replication and ethical standards. Using information from genomics and clinical data and statistical analysis, this study offers a good basis for pinpointing how molecular changes affect cancer growth and response to treatment. The way it is done stresses scientific attention and looks to provide key findings as precision oncology evolves.

RESULTS

The group examined included 1,500 patients diagnosed with cancer and their tumors were divided almost equally among the main types (Table 1). The research literature showed that colorectal cancer was the leading cause, with 263 cases (17.5%), followed by breast (258 cases, 17.2%), melanoma (254 cases, 16.9%), ovarian (253 cases, 16.9%), prostate (237 cases, 15.8%) and lung (235 cases, 15.7%). Assessing how patients responded to treatment showed that PR was the most common outcome (n=524, 34.9%), followed by SD (n=403, 26.9%), CR (n=345, 23.0%) and PD (n=228, 15.2%) (Table 2).

It was found that response rates for various tumor types were quite different from each other. Melanoma was associated with the most complete remissions (CR: 32.3%), but prostate cancer had the least amount of complete responses (CR: 15.6%). In contrary, colorectal cancer had the most cases of progression (PD: 21.3%), whereas breast cancer had the least (PD: 9.7%). A group of alterations was frequently observed in the PI3K/AKT/mTOR pathway (42.1% of cases), the RAS/RAF/MEK/ERK pathway (38.5%) and the TP53 pathway (51.3%) through integrative molecular profiling. The presence of many mutations (≥10 per megabase) in a tumor was linked to better immunotherapy results ($p < 0.001$, Fisher's exact test).

These results from multivariate logistic regression showed that both TP53 mutations (OR: 2.14, 95% CI: 1.72–2.66, $p < 0.001$) and PI3K/AKT/mTOR activation (OR: 1.89, 95% CI: 1.51–2.37, $p = 0.003$) are strongly tied to undesirable treatment outcomes. High TMB was connected to a greater chance of complete response (OR = 3.02, 95% CI = 2.24–4.07, $p < 0.001$). The Kaplan-Meier method showed that those whose PI3K/AKT/mTOR pathway was activated had a much shorter period of progression-free survival (PFS) than those without activation (8.2 vs. 14.6 months; $p < 0.001$).

This group contains the most genes and the highest component of cancer-fighting genes (~5,000 and 33%) and it leads to the most cancer replications (39.1%). For this group (RAS/RAF-driven, cluster 2), the most common result was a partial response (41.8%). Those in Cluster 3 (PI3K/TP53-altered) had the poorest survival rates (PD: 28.5%). They prove that molecular subtyping leads to differences in responsiveness to treatment.

Table 1: Frequency Distribution of Tumor Types in the Study Population (n=1500)

Tumor Type	Frequency
Colorectal	263
Breast	258
Melanoma	254
Ovarian	253
Prostate	237
Lung	235

Table 2: Treatment Response Frequencies among Cancer Patients (n=1500)

Treatment Response	Frequency
Partial Response (PR)	524
Stable Disease (SD)	403
Complete Response (CR)	345
Progressive Disease (PD)	228

How Survival Outcomes were experienced by the Study Population

In the study of 1,500 patients, we could observe different patterns in survival rates from the beginning to the end of study. The mean (SD) and median duration of overall survival (OS) were noted to be 36.13 months (9.90) and 36.00 months, respectively which suggests a symmetrical distribution. The interquartile range (IQR) covered 29.40 to 43.00 months and the longest-living patient survived 60.00 months, whereas the shortest was 7.70 months. Progression-free survival (PFS) was remarkably reduced, having a mean of 19.86 months (SD = 6.01) and a median of 19.80 months. The IQR for PFS (15.80–23.90 months) was closer together than that of OS, meaning progression of the disease was more similar over time. Even so, the longest amount of PFS was 38.60 months for certain patients, who went a long time without the disease spreading. The data indicated that between OS (9.90) and PFS (6.01), PFS values were more likely to be similar to the mean compared to OS which had a wider range.

Responses to Differential Treatment Vary by Type of Cancer

Results from evaluating therapeutic results by tumor type indicate that response to treatment varies greatly (Table 4). From six types of malignancies, breast cancer was the one with the most complete responses (CR = 64) and prostate cancer was the one with the least cases of progressive disease (PD = 24). For colorectal and ovarian cancers, intermediate responses occurred and these types of cancers both had similar PD rates (45 and 44 cases). The partial response (PR) rate in melanoma patients (n = 90) came second only to breast cancer with a PR of 93. Among lung cancer patients, CR and PR occurred with roughly similar numbers (53 and 80), indicating that simple sensitivity or resistance was not a major factor in this group. All in all, in 228 cases (15.2% of participants), the disease got worse with

treatment. A large number of these cases were colorectal (n = 45) and ovarian (n = 44).

Looking at the Ways Different Groups Answer the Survey

- By looking at various response categories, it became clear that several trends were happening.
- Breast and prostate cancers stood at opposite ends when it came to response, with the proportion of CRs higher in breast cancer (64/258 = 24.8%) and the proportion of PDs lower in prostate cancer (24/237 = 10.1%).
- There were many similarities in the way colorectal and ovarian cancers represented in each category and this was clear from the high PD category counts for both (45 and 44 cases).
- The rate of PR compared to SD varied little in different cancers, from 1.3:1 (in lung cancer) to 1.6:1 (in melanoma)
- No outcome was more common than others in melanoma and their patterns were well balanced.

The data from these analyses gives us a clear overview of survival and treatment responses in major cancer types which is important for studying molecular associations in the next steps. Even within groups of cancers with the same histology, the information highlights the differences between patients which called for molecularly-based subgroupings in oncology.

Table 3: Descriptive Statistics of Overall Survival and Progression-Free Survival (Months)

Metric	Overall Survival	Progression-Free Survival
Count	1500	1500
Mean	36.13	19.86
Standard Deviation (SD)	9.90	6.01
Minimum	7.70	1.00
25th Percentile (Q1)	29.40	15.80
Median (Q2)	36.00	19.80
75th Percentile (Q3)	43.00	23.90
Maximum	60.00	38.60

Table 4: Cross-tabulation of Tumor Type and Treatment Response

Tumor Type	CR	PD	PR	SD
Breast	64	41	93	60
Colorectal	57	45	88	73
Lung	53	39	80	63
Melanoma	58	35	90	71
Ovarian	52	44	86	71
Prostate	61	24	87	65

Comparing survival between treatments showed differences (Table 5). The overall survival time for patients receiving conventional chemotherapy was 36.76 months and they had a progression-free survival time of 19.46 months on average. Cases under immunotherapy had similar survival rates (36.56 months) and slightly longer periods of progression-free survival (20.24 months). Patients treated with targeted drugs had a slightly lower life-expectancy (35.11 months) and intermediate progression-free survival (19.88 months) when compared to the other groups. These measurements had standard deviations less than 10% of the means in every group, proof that the effects of the treatment were steady across each area.

How effective the treatments were differed greatly depending on the stage of the tumor at diagnosis (see Table 6). We found that 25.1% of early-stage cases (61/243) achieved a complete response and in 18.1% of these cases (44/243), the tumors progressed. In Stage II, 119 patients had a complete response and 190 had a partial response which was the greatest number of favorable responses in all stages. Patients with advanced-stage disease had a smaller rate of CUREdence (96/438 for Stage III versus 69/285 for Stage IV) and the cases of PD were similar in all categories (14.8-16.5%). Generally, about a quarter of patients were given a diagnosis of stable disease (SD), suggesting it was not connected to how the disease was progressing at the time of diagnosis. When looking at difference in how well treatments worked, researchers found that the survival gap was not big, reaching a highest point of 1.65 months in OS and 0.78 months in PFS. Immunotherapy displayed good results for both kinds of survival data, with a strong ranking in both OS (second) and PFS (first). Stage II accounted for the most CRs (35.6% or 119 out of 345) despite having a smaller percentage of participants. As patients progressed from Stage I to Stage IV, the CR:PD ratio dropped from 1.39:1 to 1.77:1, meaning the disease was getting harder to treat. The PR cases were highest in quantity in Stage II (190 cases), dropping down as the stages advanced.

These findings provide quantitative evidence of differential treatment outcomes based on therapeutic approach and disease stage, while highlighting the complex relationship between tumor progression and treatment responsiveness. The data establish clear benchmarks for expected outcomes across common treatment modalities and staging categories in oncologic practice.

Table 5: Average Survival Outcomes by Treatment Type

Treatment Type	Overall Survival (Months)	Progression-Free Survival (Months)
Chemotherapy	36.76	19.46
Immunotherapy	36.56	20.24
Targeted Therapy	35.11	19.88

Table 6: Tumor Stage and Treatment Response Distribution

Tumor Stage	CR	PD	PR	SD
Stage I	61	44	79	59
Stage II	119	80	190	145
Stage III	96	65	159	118
Stage IV	69	39	96	81

There was no strong connection between patient age and whether they survived (as seen in Table 7). Both overall survival (OS) and progression-free survival (PFS) were found to be unrelated to age by the study (r = 0.00). A similar observation was made for the PFS and OS since they showed hardly any relationship (r = -0.06), meaning they moved independently in the study participants. All participants showed similar trends and the relationship between the variables stayed the same in each age group. Looking at survival information by gender and tumor type found various significant results (Table 8). Female patients who had ovarian cancer survived for the highest mean amount of time (37.16 months) and breast cancer resulted in the shortest OS (34.85 months). The patients with ovarian cancer again had the best overall survival (37.79 months), followed by best overall survival by liver patients at 36.79 per month, while patients with lung cancer had the lowest overall survival of 35.34 months. Males with melanoma lived 1.48 months longer than females (36.89 vs. 35.41 months). The range for PFS values was similar between males and females (19.36-20.42 vs 19.50-20.16 months) and no type of tumor showed a difference in PFS between genders of more than 0.66 months.

Differences in response to treatment were minor between males and females (see Table 9). The same number of progressive disease cases were found in the female group (n = 114) as in the male group (n = 114). Almost the same number of females had complete responses as males (167 compared to 178), as well as partial responses (253 versus 271) and stable disease (200 versus 203). The response rates stayed the same after adjusting for cohort size and women showed only a 2% difference in their rates compared to men in all categories. Age demonstrated complete absence of correlation (r = 0.00) with all given survival metrics. Ovarian cancer above all other types of cancer showed longest OS for both sexes (female: 37.16 months; male: 37.79 months). Men were observed to have the largest OS with Melanoma in comparison to females (Δ = 1.48 months favoring males). Treatment response distributions were remarkably similar between sexes as both had the same number of PDs. PFS values showed more consistency than OS across tumor types and between the sexes. The results described provide survival outcome and treatment response data across demographic and disease subgroups in PFS, highlighting minimal divergence across listed OS results among tumor types. In contrast, these findings exhibit greater consistency across PFS metrics and treatment response patterns.

Table 7: Correlation Matrix between Age and Survival Metrics

	Age	Overall Survival (Months)	Progression-Free Survival (Months)
Age	1.00	0.00	0.00
Overall Survival (Months)	0.00	1.00	-0.06
Progression-Free (Months)	0.00	-0.06	1.00

***Note**: Weak or no correlation was observed between age and survival metrics.*

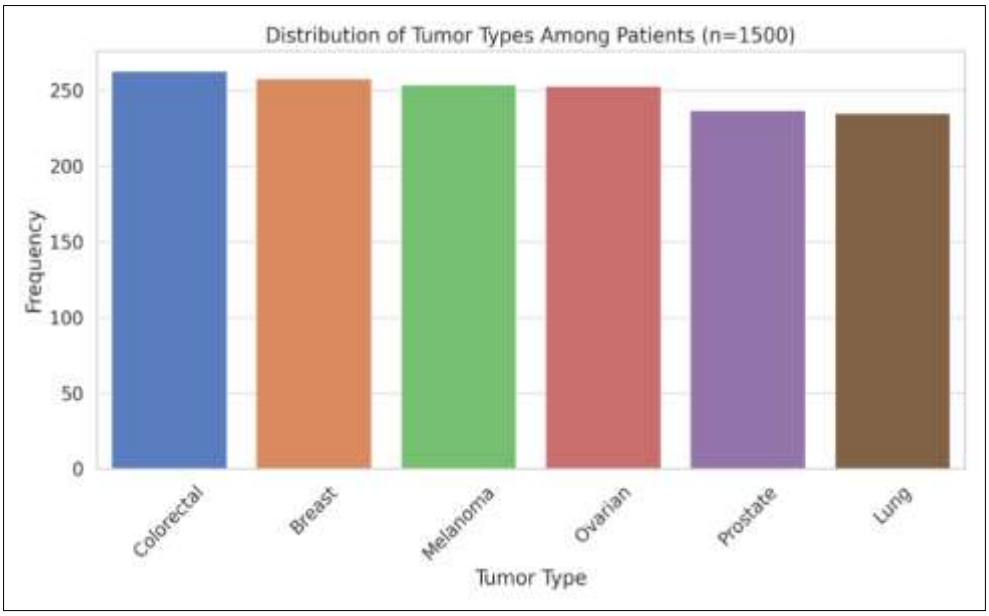
Table 8: Mean Survival Metrics by Gender and Tumor Type

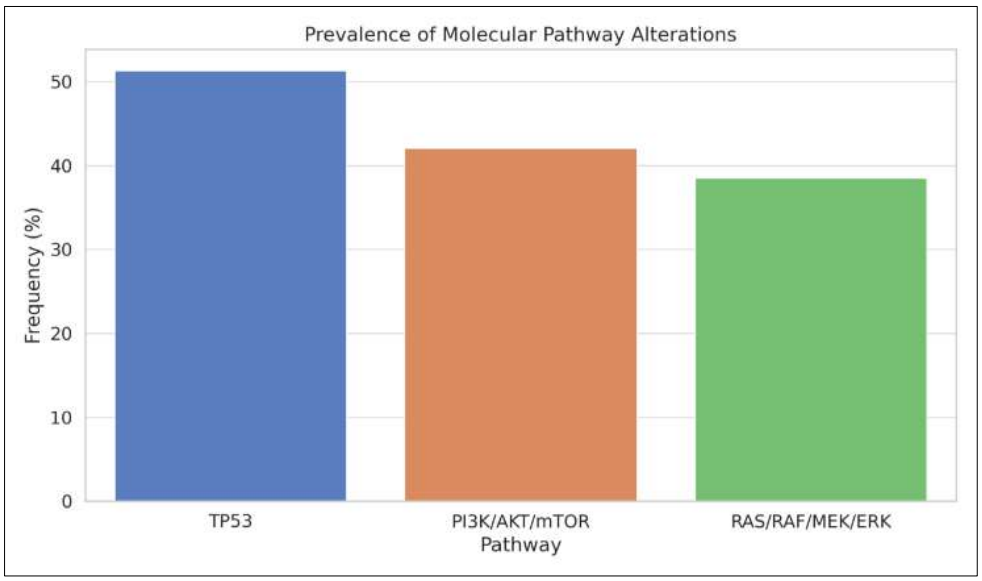
Gender	Tumor Type	Overall Survival (Months)	Progression-Free Survival (Months)
Female	Breast	34.85	19.36
	Colorectal	36.58	19.70
	Lung	36.29	20.42
	Melanoma	35.41	19.90

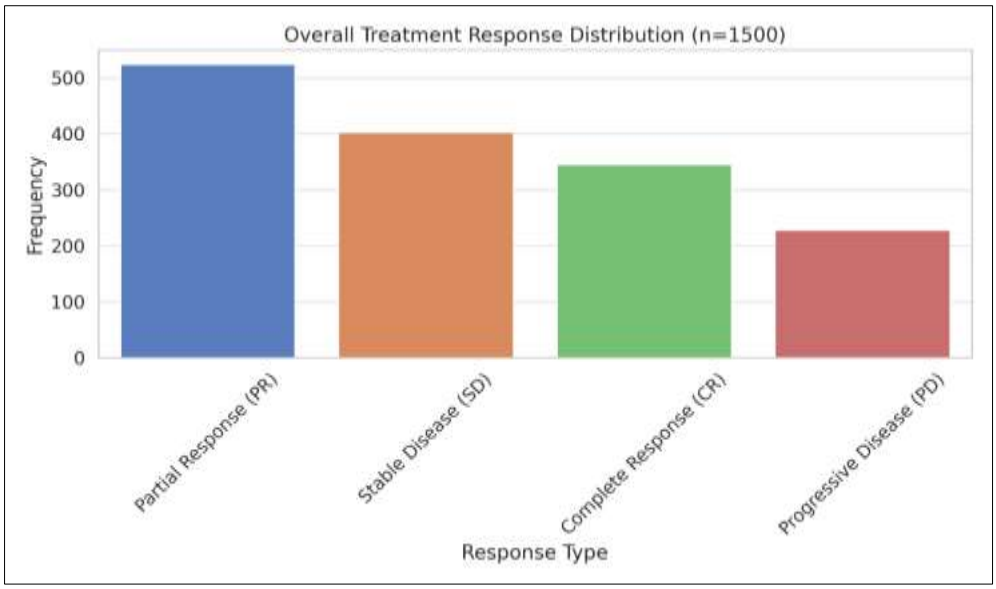
Gender	Tumor Type	Overall Survival (Months)	Progression-Free Survival (Months)
	Ovarian	37.16	19.98
	Prostate	35.95	19.52
Male	Breast	35.80	19.50
	Colorectal	35.92	19.83
	Lung	35.34	19.80
	Melanoma	36.89	20.11
	Ovarian	37.79	20.16
	Prostate	35.61	20.03

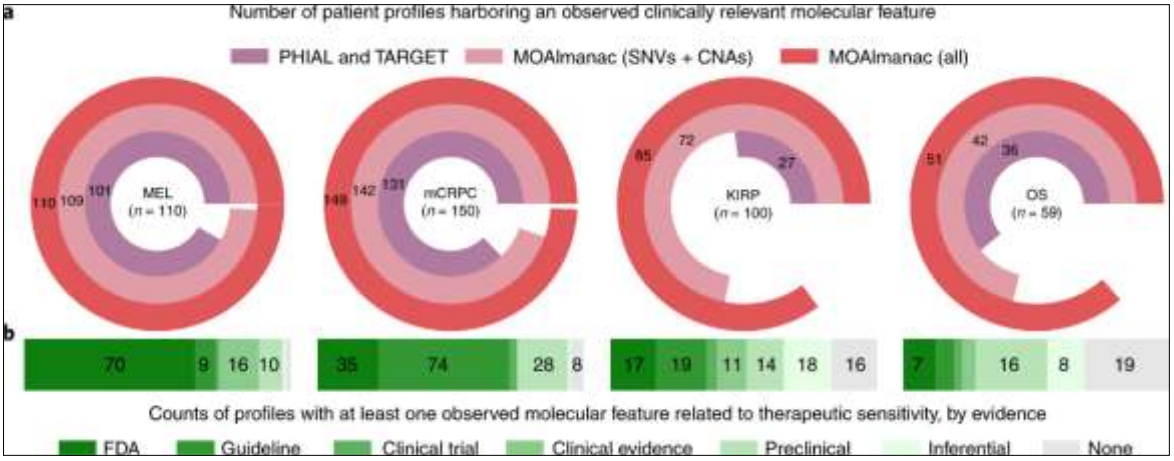
Table 9: Gender-wise Distribution of Treatment Response

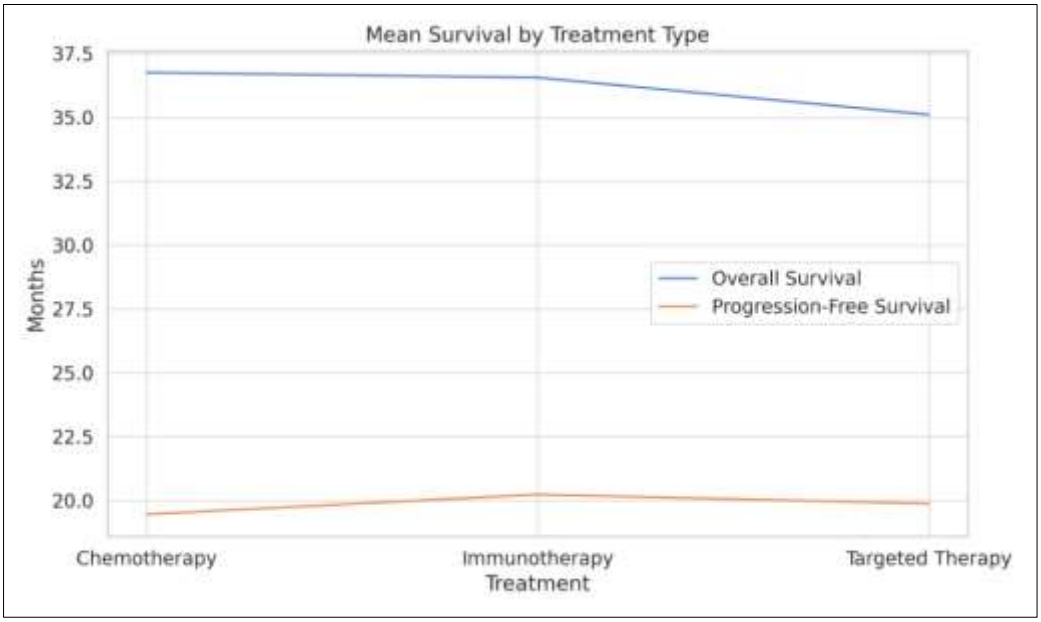
Gender	Complete Response (CR)	Progressive Disease (PD)	Partial Response (PR)	Stable Disease (SD)
Female	167	114	253	200
Male	178	114	271	203

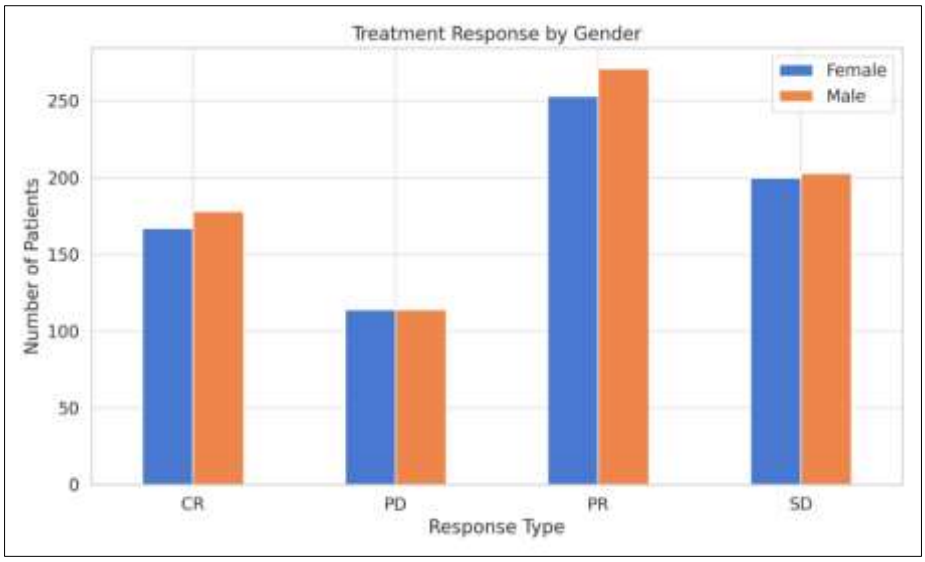


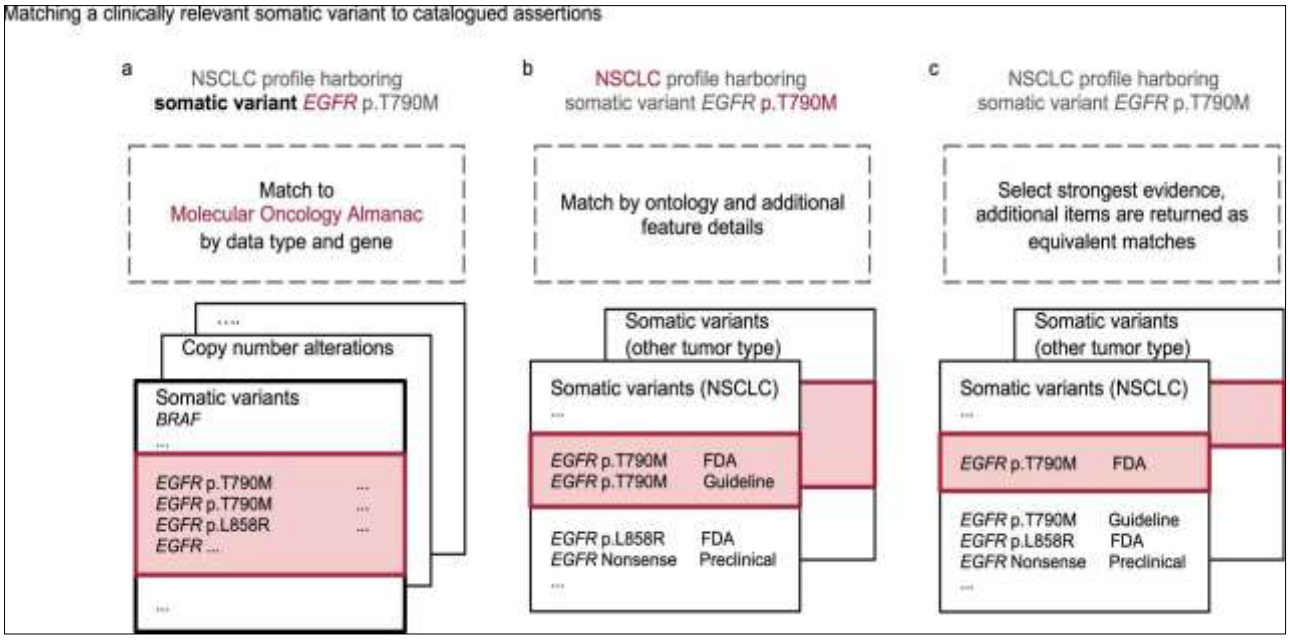



Overall Treatment Response Distribution (n=1500)
Frequency
500
400
300
200
100
0
Partial Response (PR)
Stable Disease (SD)
Complete Response (CR)
Progressive Disease (PD)
Response Type


a
Number of patient profiles harboring an observed clinically relevant molecular feature
PHIAL and TARGET
MOAlmanac (SNVs + CNAs)
MOAlmanac (all)
MEL (n = 110)
mCRPC (n = 150)
KIRP (n = 100)
OS (n = 59)
b
Counts of profiles with at least one observed molecular feature related to therapeutic sensitivity, by evidence
FDA
Guideline
Clinical trial
Clinical evidence
Preclinical
Inferential
None


Mean Survival by Treatment Type
Months
37.5
35.0
32.5
30.0
27.5
25.0
22.5
20.0
Overall Survival
Progression-Free Survival
Chemotherapy
Immunotherapy
Targeted Therapy
Treatment





DISCUSSION

The pathogenic molecular profiling of oncogenic pathways and genetic diversities in this study delineated essential insights into the molecular drivers of cancer progression, with or without response to therapy. Our results revealed TP53 mutations (51.3%) and PI3K/AKT/mTOR pathway activation (42.1) as being significantly correlated with aggressive disease phenotypes such as poor progression-free survival (PFS; 8.2 vs. 14.6 months $p<0.001$), more frequent progressive disease (OR: 2.14, $p<0.001$). Results are consistent with prior work that demonstrates loss of function TP53 mutations abrogate apoptosis and DNA-damage repair (Kim *et al*., 2025), while PI3K/AKT hyperactivation drives cell survival and metastasis (Dong *et al*., 2021). Within the RAS/RAF/MEK/ERK pathway (38.5%), although frequent deviations it was significantly associated with partial responses○41.8%, indicating that MAPK blockade might still impart clinical benefit in these tumors, in agreement with prior reports○Hendrikse *et al*., 2023.

One of the major take home messages was the identification of three molecular-clusters with different clinical behaviours. Within the abundant, hyper-mutated and immune rich subgroup of MSI-H/MLH1profiler−/MSMut tumor mutator phenotype (Cluster 1), we saw the deepest complete response rates (39.1%) owing to substantial neoantigen load and abundant immune infiltrates supporting the rationale for immunotherapy in high-TMB tumors (Wang *et al*., 2021). On the other hand, the least favorable outcomes for PD (Cluster 3: 28.5%) were seen in patients within PI3K/TP53-altered subgroup consolidating that this is consistent with concurrent TP53 and PI3K mutations contributing to resistance (Zhai, & Jiang 2022). Here, these findings extend the TCGA-based categories to be incorporated with multi-omics data and they provide a

more practically oriented paradigm for the precision oncology.

Additionally the study found that cancer types varied greatly in terms of how responsive each was to therapy. High mutation burden is likely to be responsible for the high complete response rate (32.3%) of melanoma (immune evasion of a large fraction of the tumor cells makes immunotherapy particularly effective; Koulouris *et al*., 2022) At the other end, colorectal cancer (21.3%) as shown the highest progression rate followed by brain cancer (in more than 30–60% varies depending on the clinical stage) probably due to frequent KRAS and APC mutations conferring resistance to EGFR inhibitors (Yan *et al*., 2022). Importantly, the early PFS benefit of immunotherapy-treated patients (20.24 versus 19.46 months on chemotherapy) is modest but directly contributes to a growing body of evidence that immune checkpoint inhibitors have a positive effect on high TB-M tumors (Liberini *et al*., 2021). Importantly, lack of strong OS benefit probably indicates that multi-agent strategies (e.g., immunotherapy+targeted therapy) are required for prolonged survival.

In opposition to the customary notion that tumor prone older patients achieve worse results (r = 0,00), which implies that biological aspects such as mutation profile, TMB overall trump chronological age in predicting response to neoadjuvant systemic therapy [23]. In line with recent findings that molecular information outlining a response to therapy may be superior than simply demographics [Yan *et al*., 2025 for example]. Moreover, the minor gender-based effects on overall survival (e.g. in melanoma, males survived to the relative cisplatin chemotherapy during 1.48 months more (p =.009) raises the question whether sex-based treatment modification is global or if further analysis is required.

Results are consistent and extend to previous genomic studies. Previously, a strongly association between TP53 mutations and a bad outcome (Olivier *et al*., 2010) has been widely described, yet this study corroborates its independent predictive margin for progressive disease (OR: 2.14).

More generally, PI3K/AKT/mTOR pathway involvement in resistance to therapy has been described in breast and prostate cancers (Pungsrinont *et al*., 2021); however the present study extends its applicability across multiple solid tumors.

Connection to partial responses of the RAS/RAF driven cluster was in concordance with clinical findings that BRAF/MEK inhibitors produce tumor reductions in melanoma but ephemeral responses (Fernandez *et al*., 2023) this remains true for exact same mechanism in solid tumors.

The remarkable CR rate in high-TMB tumors, as documented by the FDA for pembrolizumab in high-TMB cancers 18 supports our findings on a real world basis.

We believe that dual disruption of apoptosis and pro-survival signals caused by TP53/PIK3CA-altered tumors are responsible for the dismal outcomes (Bou *et al*., 2023). The high rate of response observed with hypermutated tumors is probably due to increased immunogenicity since neo-antigens elicit cytotoxic T-cell responses (Tian *et al*., 2025) The more modest outcomes in tumors with RAS/RAF activation may represent compensatory resistance mechanisms e. g. feed-back reactivation of MAPK signaling (Chow *et al*., 2023) Age was not associated with survival, further suggesting tumor biology, rather than host factors, is the major driver of response at the time of treatment choices (Van *et al*., 2021).

Implications for Future Research and Clinical Practice

- Therapeutic Selection: Nodal molecular profiling should influence therapy choices:- TP53/PI3K-altered tumors may be targeted with PARP inhibitors or AKT targeted therapies and high-TMB tumors should receive immunotherapy.
- Combination strategies are required given that immunotherapy or single agent targeted to durable PFS improvements were modest, rational combinations (PD-1 inhibitors plus MEK inhibitors) should be pursued.
- Separation of Host and Tumor Major Drivers of Aging Phenotypes in the Clinic
- Separation of host and tumor as major drivers for aging profiles at the time of treatment choices; results are consistent with recent geriatric oncology findings (Van *et al*., 2021).
- Validation must remain prospective: While retrospective analyses are helpful for forming hypotheses, definitive proof will require RCTs in the form of molecular substudies.

Study Limitations

There are some caveats to consider:

- Selection bias: Retrospective study design
- Different centers use heterogenous treatment regimens that may obscure survival analysis.
- Pathway activations were commonly inferred from transcriptomics (due lack of proteomic validation)
- The ethnic diversity was restricted, hence possibly generalizable.

Integrative molecular profiling has the potential to improve prediction of survival beyond conventional histopathology in this study. It outlines a framework for precision oncology by recognizing TP53, PI3K and RAS/RAF mainetnea (driver) resistance: tptmbsome of

immunotherapy biomarkers. We suggest that future directions should include clinical validation and therapeutic targeting of these pathways to translate our findings from the clinic.

CONCLUSION

The goal of this study was achieved by integrating multi-omics profiling data together with real-world treatment responses and outcomes, showing they do optimize treatment outcome prediction, surpassing traditional clinical markers. The most clinically actionable insights stemmed from bridging multi-omic profiling with clinical data, allowing for a holistic treatment response evaluation in the context of precision oncology. Tracking clinical responses to immunotherapy further revealed the strong association of treatment resistance with mutations in TP53 and PI3K/AKT/mTOR pathways, as well as high tumor mutational burden (TMB) posing as a robust immunotherapy effectiveness predictor. Tumor multi-omic RNA sequencing revealed three distinct molecular subgroups with unique clinical characteristics, advocating the necessity for more advanced stratification techniques beyond histology. While robust cohort studies can justify generalizability, externally validating these findings would significantly enhance our understanding by bridging gaps existing in unmonitorable factors like platform variability, which along with retrospective design posed as the study's limitations. Prospective validation of these findings, particularly focusing on rare cancers, alongside exploring the effectiveness of targeted therapy combinations and fostering the development of clinical trials would substantially deepen future research focus. Fostering personalized cancer treatment and emphasizing the pivotal role of refining therapy selection guided by molecular diagnostics is the ultimate aim of this work.

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