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Research Article

Real-World Applications of Comprehensive Tumor Profiling for Personalized Cancer Therapy in Metastatic Patients

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Abstract

Objectives: To evaluate the clinical utility of extensive tumor profiling-including DNA, RNA, proteomic, and pharmacogenetic analyses-for guiding personalized therapy in patients with metastatic solid tumors who had exhausted standard treatment options. **Methods:** A real-world, retrospective cohort of 44 metastatic cancer patients underwent comprehensive tumor profiling (mainly EXACTA platform) after failure of guideline-based therapy. Multimodal analysis included next-generation sequencing (NGS), gene expression profiling, immunohistochemistry, and pharmacogenetic screening. Individualized therapy recommendations were generated by an interdisciplinary tumor board. Clinical benefit was assessed via intrapatient comparison of progression-free survival (PFS) before (PFS1) and after (PFS2) profiling-guided therapy, with a target PFS2/PFS1 ratio =1.25. **Results:** A molecularly guided therapy recommendation was feasible in 78% of cases and was implemented in 100% of those patients. Among treated patients, 9% received chemotherapy, 23% received targeted biological therapy, and 68% received combination regimens. The median progression-free survival after molecularly guided therapy (PFS2) was 30 weeks, compared to 22.5 weeks prior to molecular profiling (PFS1), yielding a median PFS2/PFS1 ratio of 1.3. Targeted biological therapies were associated with the most favorable outcomes, achieving a median PFS2 of 61 weeks and a PFS2/PFS1 ratio of 2.06. Notably, the number of molecular targets identified did not correlate with improved clinical outcomes. Therapeutic recommendations informed by gene expression profiling appeared to confer a modest clinical advantage over those based solely on genomic alterations identified by next-generation sequencing; however, this trend did not reach statistical significance. **Conclusion:** Comprehensive molecular tumor profiling enabled treatment recommendations in a substantial proportion of heavily pre-treated patients and was associated with improved progression-free survival. While targeted biological therapies yielded the most favorable outcomes, only a subset of patients had actionable genomic alterations. Interestingly, therapeutic recommendations based on gene expression profiling were associated with a trend toward improved clinical benefit, suggesting that transcriptomic data may provide complementary insights in cases lacking clear genomic drivers. These findings underscore the value of integrative multi-omic approaches and point toward the potential of AI-assisted data interpretation to enhance therapeutic decision-making. Prospective validation in larger cohorts is warranted.

Key words: Comprehensive Tumor Profiling; Precision Oncology; Progression-Free Survival (PFS); Gene Expression Analysis; Targeted Therapy; Real-World Data.

Introduction

Historically, the diagnosis and treatment of malignant tumors have relied on the pathological classification of the primary tumor and, when applicable, its metastases. Increasingly, predictive and prognostic biomarkers at the molecular, cellular, and functional levels are being integrated into decision-making processes for personalized cancer therapy. However, a sole focus on genetic alterations has often resulted in limited clinical benefit.

This illustration highlights the complexity of tumor biology, suggesting that genomic characterization alone is insufficient to fully capture the tumor phenotype and its therapeutic targets.

An attempt to tailor therapy more precisely to tumor characteristics is represented by extensive tumor profiling mainly using EXACTA. This approach includes DNA analyses based on tissue samples involving 511 genes, liquid biopsy (409 genes in ctDNA), gene expression analyses on tissue and exosomal RNA (20,805 genes), signal transduction pathways according to the Kyoto Encyclopedia of Genes and Genomes, immunohistochemistry and immunocytochemistry staining, pharmacogenetics for estimating potential side effects, particularly in combination therapies [1], and interrogating the efficacy of chemotherapies using circulating tumor cells [2, 3]. In principle, this tool facilitates a shift from drug-centered trials to comprehensive patient-centered trials.

Following the comprehensive tumor profiling, bioinformatic analysis is performed to detect actionable targets and potential biomarkers of clinical relevance, based on ranking according to Joint Consensus Recommendations. Subsequently, an intensively collaborative interdisciplinary tumor board is convened to issue an individually optimized therapy recommendation, taking into account patient characteristics. In 78% of the patients, a recommendation could be made. Of these, 27% were based on NGS and 51% on gene expression profiles.

The clinical benefit of extensive tumor profiling in routine oncological practice remains a pertinent question.

Study Population/Methodology

This setting encompasses 44 patients with various solid tumors in metastatic stages with the most frequently represented entities being breast (18 patients), pancreatic (4 pat.), prostate (5 pat.) cancer and NSCLC (5 pat.). Following the failure of standard-of-care therapy, extensive tumor profiling was conducted. Subsequent therapy was guided by the results of this profiling when no further guideline recommendations or opportunities for participation in clinical trials were available, or when the patient expressed a desire for personalized therapy.

The implementation of the interdisciplinary Tumor Board's recommendations was as follows: 9% of patients received chemotherapy (CTX), 23% received biological targeted therapy, and 68% received a combination of chemotherapy and biological targeted therapy, including antibody-drug conjugates. As part of a structured follow-up, clinical and efficiency assessments were conducted, and key outcome parameters such as progression-free survival (PFS1) after the failure of standard-of-care therapy, PFS2 after therapy recommendation based on extensive tumor profiling, and the ratio of PFS2 to PFS1 for intrapersonal comparison were evaluated. A ratio of 1.25 was targeted, which is slightly lower than the highly published data under study conditions, such as the iPredict [4] study with a ratio of 1.3 and the WINTHER trial [5] with a ratio of 1.5. This targeted ratio accounts for the fact that these are real-world data and not a selected study population.

Additionally, factors such as age, sex, smoking status, and ECOG performance status were evaluated after the completion of therapy based on extensive tumor profiling. Other parameters assessed included proliferation index, grading, mutation load, tumor burden, number of prognostically significant mutations, number of targets identified through gene expression profiling, and the number of therapeutically addressed targets.

Results

70% (31 out of 44) of patients demonstrated an improvement in progression-free survival (PFS) with an unchanged ECOG performance status. Patients who received therapy based on extensive tumor profiling exhibited a median PFS2 of 30.0 weeks, (IQR [15.8; 59.5]) compared to a median PFS1 of 22.5 weeks (IQR [8.8; 39.3]). A Wilcoxon signed-rank test indicated a significantly better PFS2 with a moderate to large effect size ($W=208$, $p=0.003$, $r= 0.43$)

Additionally, 59% of patients achieved a PFS2 of over 6 months, indicating that disease progression was prevented for more than six months. The median PFS2 to PFS1 ratio was 1.3 (IQR [1.0; 2.0]), which was significantly greater than previous defined 1.25 with a low to moderate effect size, as tested with a Wilcoxon rank-sum test ($W=576$, $p=0.030$, $r= 0.26$).

The aforementioned parameters, for instance the mutation load, number of prognostically significant mutations etc. didn´t notably improve the efficacy.

Noteworthy aspects emerge regarding the therapeutic modality and its associated key outcomes. Looking at PFS2 weeks between therapies, we can observe that patients with only cytotoxic chemotherapy ($n = 4$) showed a median of MDN = 10.5 weeks (IQR [5.8; 47.2]) and combination therapy (cytotoxic CTX with

targeted biological therapy) (n = 30) of MDN = 29.5 weeks (IQR [16.0; 46.2]) while targeted biological therapies (n = 10) with an average of two medications had a PFS2 median of MDN = 61 weeks (IQR [32.8; 105.3]) (see Table 1). A Kruskal-Wallis test comparing the difference of PFS2 weeks between the three groups yielded a borderline significant effect ($X^2(2) = 5.77$, $p = 0.056$).

	Therapy	n	Min	Max	Median	Q1	Q3
PFS2 weeks	Biolog. Target	10	9	195	61	32.8	105.3
	Chemo	4	5	144	10.5	5.8	47.3
	Combi	30	3	134	29.5	16	46.3
PFS ratio	Biolog.Target	10	0.35	8.43	2.06	1.92	3.45
	Chemo	4	1	1.36	1.05	1	1.16
	Combi	30	0.23	11	1.25	1	1.85

Table 1: Descriptive Statistics of PFS2 and ratio by therapy.

Examining PFS ratio between therapies, we can observe that patients with only chemotherapy showed a median of MDN = 1.04 (IQR [1.0; 1.2]) and combination therapy of MDN = 1.25 (IQR [1.0; 1.84]) while targeted biological therapy with two medications had a PFS ratio median of MDN = 2.06 (IQR [1.9; 3.5]). A Kruskal-Wallis test comparing the difference of PFS ratios between the three groups also yielded a borderline significant effect ($X^2(2) = 5.94$, $p = 0.051$).

Analysis of PFS2 and the PFS2/PFS1 ratio based on the number of administered biological targeted therapies suggests that fewer but more effective targets lead to clinical benefits. Table 2 illustrates descriptive statistics of PFS2 and ratio by recommendations to identify a few effective targets within the specific individual tumor biological context. Kruskal-Wallis tests showed no significant differences in PFS2 ($X^2(2) = 2.05$, $p = 0.359$) or ratio ($X^2(2) = 1.58$, $p = 0.453$) between the different numbers of targets.

	Targets	n	Min	Max	Median	Q1	Q3
PFS2 weeks	1	27	3	195	30	13.5	46
	2	10	16	136	53	21.5	62.5
	3	3	9	108	48	28.5	78
PFS ratio	1	27	0.23	11	1.25	1.14	2
	2	10	0.4	8.43	1.85	0.99	2.02
	3	3	0.31	2.08	0.35	0.33	1.22

Table 2: Descriptive Statistics of PFS2 and ratio by number of targets.

Recommendations based purely on NGS (n = 12) showed a median PFS2 of MDN = 27.5 weeks (IQR [19.0; 50.5]) and a median PFS2/PFS1 ratio of MDN = 1.4 (IQR [1.20; 1.86]). The response based on gene expression recommendations (n = 22) showed a median PFS2 of MDN = 37.5 weeks (IQR [17.0; 51.8]) and a PFS2/PFS1 ratio of MDN = 1.6 [IQR [1.02; 2.34]). Conversely, the response without precision oncology recommendations (n = 10) showed a median PFS2 of MDN = 16.5 weeks (IQR [7.5; 70.0]) and a median ratio of MDN = 1.1 (IQR [0.86; 1.64]). However, a Kruskal-Wallis test showed no statistically significant differences between the efficacy after gene expression based prescriptive guidelines, neither in PFS2 weeks ($X^2(2) = 0.30$, $p = 0.862$) nor in PFS ratio ($X^2(2) = 2.02$, $p = 0.365$).

Discussion

The results of this real-world study underscore the potential clinical impact of comprehensive tumor profiling in metastatic cancer patients, particularly those who have exhausted standard-of-care options. The observed improvement in progression-free survival (PFS2) following precision oncology-guided therapy, as compared to PFS1 under conventional treatment, highlights the feasibility and translational relevance of integrating extensive molecular analyses into therapeutic decision-making. Notably, the differential outcomes associated with biological targeted therapy, combination regimens, and gene expression-driven recommendations suggest that molecular profiling alone may not be a definitive predictor of therapeutic efficacy. These findings necessitate a broader discussion on the interplay between genomic alterations, transcriptional activity, the tumor microenvironment as well as other individualized therapeutic response shaping factors. Furthermore, the significant variation in PFS2/PFS1 ratios across treatment modalities underscores the importance of optimizing patient stratification criteria and refining bioinformatics-driven ranking systems for therapeutic prioritization. In light of these insights, the following discussion contextualizes these findings within the broader landscape of precision oncology, addressing key challenges, potential limitations, and future directions for optimizing patient-centered therapeutic strategies.

Extensive tumor profiling inherently detects more potential targets, including previously uncharacterized variants for which therapies are available. For instance, a young patient with a therapy-resistant breast carcinoma, finally endocrine-sensitive according to hormone receptor status, HER2-negative, underwent extensive tumor profiling after all available therapy modalities failed to show benefit. This profiling revealed an uncharacterized ERBB2pV697L mutation, retrospectively identified as a gain-of-function mutation with high clinical impact.

A fundamental challenge is the translatability of targeted therapy information across different tumor entities. This issue is influenced by several etiological components, such as the functional heterogeneity of alterations with varying sensitivities to targeted therapies, entity-specific transcription and gene expression profiles with diverse efficacies, and epigenetic factors, among others [6-8].

This context of functional heterogeneity of oncogenic alterations across tumor entities is exemplified by the divergent therapeutic response to BRAFpV600E mutations in different tumor types. The efficacy of vemurafenib as a monotherapy in patients with BRAFpV600E-mutated malignant melanoma was substantiated by the phase III BRIM-3 trial [57]. In contrast, colorectal carcinoma with the same mutation shows intrinsic resistance to BRAF inhibition due to feedback activation of EGFR signaling. Effective treatment therefore requires combination regimens targeting multiple nodes of the MAPK pathway, as demonstrated in the BEACON CRC trial.

Similarly, the SUMMIT Basket Trial [12, 13] showed that neratinib elicited responses in HER2-mutated solid tumors with the pS310x alterations in various solid tumors (breast, colon, cervix, cholangiocarcinoma, etc.), but not in bladder carcinoma, despite the presence of the same mutation, indicating significantly varying response rates.

To explain the value of comprehensive tumor testing and the associated individual challenges, while simultaneously demonstrating the insights derived from our approach, we have curated a selection of illustrative case examples.

In cases of solid tumors where a targetable genetic alteration predominates with respect to tumor-biological behaviour and considering additional functionally critical alterations, a purely molecularly guided therapy can achieve high efficacy as exemplified by the following case of a young patient with therapy resistant Her 2 negative breast cancer. The initial tumor profiling, conducted in the 38th month of therapy, revealed the HER2 p.V697L mutation. This mutation was subsequently targeted multiple times, considering various potential resistance factors. For example, the presence of an NF2 mutation can lead to upregulation of EGFR and the mTOR pathway, suggesting a potential benefit from the additional administration of lapatinib and everolimus, sometimes associated with long-lasting remissions [37, 41]. Upon the disappearance of this clinically significant mutation, mutations related to homologous recombination deficiency were targeted, such as a germline BRCA1 and a somatic BRCA1 mutation, alongside a synchronous ARID1A mutation. The therapeutic consequence of this included the use of olaparib and carboplatin to induce a prompt therapeutic response in the setting of extensive tumor progression. Throughout the treatment course, various subclones were detected, with peritoneal and hepatic recurrences influencing therapy choices based on remission driven selective pressure.

This example demonstrates that NGS can reflect clinically significant aspects of the tumor phenotype, effectively guiding treatment over six years with varying targets.

In contrast to the aforementioned example, the complexity of tumor progression presents a distinct challenge in the following context: genome, transcriptome, proteome, signal transduction pathways, interconnected pathways, microenvironment, immune system dysfunction, and cell-cell contacts. All these factors contribute to intra- and intertumoral heterogeneity [7,14-16].

Our data also demonstrate that gene alterations do not necessarily lead to the expected gene expression [17, 18, 20]. For example, a patient with neuroendocrine breast carcinoma developed multiple

therapy-resistant recurrences after adjuvant chemotherapy. In the absence of guideline recommendations and the possibility of participating in a clinical trial, extensive tumor profiling was conducted. This profiling detected a PIK3CApE545K mutation, which is predictive of the potential efficacy of mTOR or PIK3CA inhibitors. However, mTOR inhibition showed limited therapeutic response. Retrospective analysis revealed that mRNA profiles of the mTOR pathway exhibited a downregulation of peripheral effector mechanisms such as S6 Kinase 1 and 2 and eIF4B. Thus, the therapeutic blockade of an already downregulated pathway could explain the treatment failure [21-24].

Additionally, other signal transduction pathways within the PIK3CA pathway, such as cell cycle progression (e.g., MYC, CDK20) and cell survival pathways (e.g., MCL1, BIM, BCL2), were also downregulated. Therefore, PIK3CA inhibition alone appeared insufficient for a therapeutic response.

The combination of alpelisib (in 2020 available through compassionate use) and carboplatin demonstrated, as per the NCT 05472220 study, a therapeutic response for the first time, with improvement in quality of life despite prior extensive tumor progression.

Another example illustrating the indication for extensive tumor profiling shows that co-alterations as potential emerging markers can influence signal transduction pathways and therapy efficacy. In another patient with neuroendocrine breast carcinoma, hepatic metastases were detected immediately after completing adjuvant therapy. Extensive tumor profiling revealed a loss-of-function mutation in STK11 (STK11pY131*) and a TP53pR290fs alteration, which could lead to upregulation of the PIK3CA pathway even in the absence of an activating PIK3CA mutation [19, 38].

The potential discrepancy between molecular genetics and gene expression [17, 18 ,20, 25] necessitated evaluating this pathway at the mRNA level. This analysis revealed an upregulation of S6 kinase 1 and 2, indicating a potential benefit from mTOR pathway inhibitors. Additionally, the synchronous presence of FGFR1/2 amplification, which can be associated with PIK3CA-mTOR pathway stimulation and potential resistance to endocrine therapy, CDK4/6 inhibitors, and PIK3CA inhibitors, while maintaining sensitivity to mTOR inhibitors [26, 27], suggests that mTOR inhibition could be promising in this individual case.

However, there are counterarguments against monotherapy. Everolimus, as an allosteric inhibitor of mTORC1, has a more significant effect on S6 Kinase 1and 2 and less on 4E-BP1/eIF4E axis, which strongly inhibits tumor protein synthesis [22-24]. Thus, complete inhibition of mTOR cannot be expected. Additionally, arguments against Everolimus monotherapy include the potential suppression of negative feedback loops, such as IRS1, leading to subsequent PIK3CA-mTOR activation [28], and the downregulation of S6 Kinase 1 and 2by Everolimus may induce inverse AKT and mTOR activation [29]. Moreover, mTOR inhibition is known to trigger interconnected pathways, such as the MAPK pathway [30].

Based on the literature, a combination of mTOR inhibition and anti-angiogenesis appears reasonable, particularly in the context of upregulated VEGF-A and HIF-alpha at the mRNA level in this patient [31-35]. Given data on the effective combination of an mTOR inhibitor with chemotherapy [29], the administration of Everolimus, Bevacizumab, and 5-FU resulted in a therapeutic response for the first time over four months.

These cases illustrate that the efficacy of targeted therapy does not necessarily correlate with the number of genes or expression parameters addressed. Instead, it highlights the relevance of targeting key oncogenic drivers rather than maximizing the breadth of intervention. Specifically, statistical analysis does not indicate a meaningful association between the extent of targeted NGS or gene expression profiling and improved progression-free survival (PFS), nor with the PFS2/PFS1 ratio.

The integration of artificial intelligence and machine learning in drug ranking could enhance the precision of treatment recommendations by systematically analyzing vast datasets of genomic, transcriptomic, proteomic, and clinical data. This approach can identify complex patterns and interactions that may not be immediately apparent to human experts. Furthermore, AI-driven drug ranking can adapt to new data and evolving knowledge, continuously refining therapeutic strategies.

In conclusion, while interdisciplinary expertise remains crucial, incorporating AI-based methodologies could significantly improve the accuracy and efficacy of personalized cancer therapy. Future research should focus on developing and validating AI models that can integrate diverse biological data to provide robust and individualized treatment recommendations.

These examples raise the question of utilizing a drug ranking system via digital learning processes to better predict individual therapeutic efficacy [42]. It is evident that therapy recommendations based solely on interdisciplinary human expertise or even with AI-assisted prioritization, sometimes necessitate non-evaluated and non-established therapy combinations for clinical benefit. This involves considerations of independent drug actions, additivity, synergism, and other related aspects [43].

In cases of extensive metastasis, complementing cytostatics may be required, potentially following sensitivity testing and considering pharmacogenetic aspects. This dual approach aims to achieve a rapid antiproliferative effect while maintaining a broad therapeutic range, mindful of overlaps in substance classes and targets [1, 44].

A significant challenge lies in estimating the therapeutic index. Often, there is no overlapping toxicity between cytostatics and biological targeted therapies, especially with the application of two antibodies [44]. Key aspects to consider include patient age, organ function, comorbidities, and concomitant medications, as outlined by Borad et al., where a median of eight medications per patient are reported for Phase 2 studies [45].

Pharmacogenetics also plays a crucial role, with extensive tumor profiling providing additional insights into individual toxicity profiles. This comprehensive approach can inform personalized treatment plans, enhancing both efficacy and safety.

In general, combination therapies require dose reduction based on data from Phase 1 studies, where applicable. This dose optimization principle applies to the same substance class, such as small molecules, but does not apply to combinations of antibodies with each other. For drug combinations targeting the same pathway, such as anti-angiogenesis agents dose adjustment is necessary. The combination of mTOR inhibitors affecting DNA repair mechanisms by influencing CDK 1 and cytotoxic agents along with PARP- and HDAC inhibitors, also modulating DNA expression and repair necessitates dose optimizations [46].

The lowest safe additive starting dosage is considered to be 60% of each drug when there is no overlap and no mTOR inhibitor is applied. For combinations with overlap of class and/or target or application of mTOR inhibition, the initial dosage can be reduced to 30% of each drug. The literature review on therapeutic efficacy in the era of biological targeted therapies indicates that patients receiving lower doses in Phase 1 trials do not ultimately fare worse than those treated with the maximum tolerated dose. Efficacy parameters, including response rate, progression-free survival, and overall survival, remain comparable between these dosing cohorts [46].

In the absence of contemporaneous data at the time of patient recruitment and treatment, our therapeutic decision was initially guided by Liu´s recommendations [1].

This approach ensures the preservation of the therapeutic index while mitigating the risk of overlapping toxicity, thereby enhancing the safety and effectiveness of combination therapies in clinical practice.

These encouraging results from our trial, based on a small study population under real-world conditions, indicate at least directional trends in precision oncology. Significant studies such as the WINTHER trial and the I-PREDICT study confirm the clinical benefit of broad-based diagnostics with partially entity-agnostic therapy. Molecular differences in subclones can account for variations in tumor response, necessitating more targeted therapies for resistant subclones. This etiological aspect may explain the significant positive correlation between higher matching scores and improved overall response, progression-free survival, and overall survival, as already noted in the aforementioned studies.

The I-PREDICT study highlights the challenge of using multiple drugs simultaneously, raising the question of whether “more is better.” The study demonstrated improved outcomes in a subset of patients with a high matching score.

Due to ethical and pharmacoeconomic considerations, our trial did not use a matching score. Instead, we focused on extracting clinically relevant information from extensive tumor profiling to identify a few highly effective therapies tailored to the tumor’s biological context where possible information on tumor characteristics was obtained and analysed at prognostically and clinically relevant primary tumor and metastasis sites. Our evaluation suggests that this approach can extend patient survival while maintaining functional status, alongside with reduced side effects.

The integration of extensive tumor profiling, including gene expression analysis, has the potential to enhance clinical outcomes. While recommendations based solely on next-generation sequencing (NGS) exhibit a notable improvement in progression-free survival compared to the absence of precision oncology guidance, the incorporation of gene expression profiling suggests a further, albeit statistically non-significant, increase in therapeutic benefit. These findings underscore the potential value of comprehensive tumor characterization in optimizing treatment strategies, although the extent of its clinical impact requires further validation.

Summary and Outlook

In summary, expanded tumor profiling, when combined with adequate bioinformatic analysis and resulting therapy recommendations, can lead to improved therapeutic outcomes. A problematic aspect remains the complexity due to the enormous amounts of data being generated. This necessitates the selection of relevant information for oncological real-world application using machine learning algorithms [47, 48]. Moreover, practitioners must effectively implement this information in clinical practice.

The appropriate development of modern techniques based on machine learning for diagnostics, bioinformatics, prognostics, and prediction, coupled with closely coordinated interdisciplinary therapy recommendations, offers the potential for a paradigm shift from reactive to proactive oncology.

Abbreviations:

ctDNA: circulating tumor DNA

CTX: Chemotherapy

ECOG: Eastern Cooperative Oncology Group (performance status)

EXACTA: trade name for advanced molecular tumor profiling system

IQR: inter quartile range (statistics)

MDN: median

NGS: Next Generation Sequencing

p: propability of observing a result at least as extreme under the null hypothesis (statistics)

pat.: patients

PFS1: progression-free survival in first therapy line based on standard of care therapy

PFS2: progression-free survival based on NGS navigated therapy

Q1: First quartile (statistics)

Q3: Third quartile (statistics)

r: Pearson correlation coefficient (statistics)

W: sum of ranks of positive or negative differences in Wilcoxon signed rank test

Ethical Considerations: Under the reference number2023-086-f-S, the Ethics Committee of westfalen-Lippe in Münster issued a positive ethics vote on March 14, 2023.

Conflict of Interest: There is no conflict of interest for any of the authors.

References

1. Liu S, Nikanjam M, Kurzrock R (2016) Dosing de novo combinations of two targeted drugs: Towards a customized precision medicine approach to advanced cancers. Oncotarget 7:11310-20.
2. Herzog TJ, Krivak TC, Fader AN, Coleman RL (2010) Chemosensitivity testing with ChemoFx and overall survival in primary ovarian cancer. Am J Obstet Gynecol 203:68.e1-6.
3. 3. Loizzi V, Chan JK, Osann K, Cappuccini F, DiSaia PJ et al. (2003) Survival outcomes in patients with recurrent ovarian cancer who were treated with chemoresistance assay-guided chemotherapy. Am J Obstet Gynecol 189:1301-7.
4. Sicklick JK, Kato S, Okamura R, Schwaederle M, Hahn ME, et al. (2019) Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. Nat Med 25:744-750.
5. Rodon J, Soria JC, Berger R, Miller WH, Rubin E, et al. (2019) Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial. Nat Med 25:751-758.
6. Halim F, Azhar Y, Suwarman S, Hernowo B (2022) p53 Mutation as Plausible Predictor for Endocrine Resistance Therapy in Luminal Breast Cancer. F1000Res 11:330.
7. Bhat GR, Sethi I, Sadida HQ, Rah B, Mir R, et al. (2024) Cancer cell plasticity: from cellular, molecular, and genetic mechanisms to tumor heterogeneity and drug resistance. Cancer Metastasis Rev 43:197-228.
8. Casado-Pelaez M, Bueno-Costa A, Esteller M (2022) Single cell cancer epigenetics. Trends Cancer 8:820-838.
9. Shahjehan F, Kamatham S, Chandrasekharan C, Kasi PM (2019) Binimetinib, encorafenib and cetuximab (BEACON Trial) combination therapy for patients with BRAF V600E-mutant metastatic colorectal cancer. Drugs Today (Barc). 55:683-693.
10. Cutsem EV, Huijberts S, Grothey A, Yaeger R, Cuyle PJ, eta al. (2019) Binimetinib, Encorafenib, and Cetuximab Triplet Therapy for Patients With BRAF V600E-Mutant Metastatic Colorectal Cancer: Safety Lead-In Results From the Phase III BEACON Colorectal Cancer Study. J Clin Oncol 37:1460-1469.
11. Kopetz, S, Murphy DA, Pu J, Ciardiello F, Desai J, et al. (2024) Molecular profiling of BRAF-V600E-mutant metastatic colorectal cancer in the phase 3 BEACON CRC trial. Nat Med 30:3261–3271.
12. Hyman DM, Piha-Paul SA, Won H, Rodon J, Saura C, et al. (2018) HER kinase inhibition in patients with HER2- and HER3-mutant cancers. Nature 554:189-194.
13. Oaknin A, Friedman CF, Roman LD, D'Souza A, Brana I, et al. (2020) Neratinib in patients with HER2-mutant, metastatic cervical cancer: Findings from the phase 2 SUMMIT basket trial. Gynecol Oncol 159:150-156.
14. Lasser SA, Kurt FGO, Arkhypov I, Utikal J, Umansky V (2024) Myeloid-derived suppressor cells in cancer and cancer therapy. Nat Rev Clin Oncol 21:147-164.
15. Adashek JJ, Subbiah V, Westphalen CB, Naing A, Kato S, et al. (2023) Cancer: slaying the nine-headed Hydra. Ann Oncol 34:61-69.
16. Adashek JJ, Subbiah V, Kurzrock R (2021) From Tissue-Agnostic to N-of-One Therapies: (R)Evolution of the Precision Paradigm. Trends Cancer 7:15-28.
17. Boichard A, Lippman SM, Kurzrock R (2021) Therapeutic implications of cancer gene amplifications without mRNA overexpression: silence may not be golden. J Hematol Oncol 14:201.
18. Guo Y, Xiao P, Lei S, Deng F, Xiao GG, et al. (2008) How is mRNA expression predictive for protein expression? A correlation study on human circulating monocytes. Acta Biochim Biophys Sin (Shanghai) 40:426-36.
19. Laderian B, Mundi P, Fojo T, Bates SE (2020) Emerging Therapeutic Implications of STK11 Mutation: Case Series. Oncologist 25:733-737.
20. Adashek JJ, Kato S, Parulkar R, Szeto CW, Sanborn JZ, et al. (2020) Transcriptomic silencing as a potential mechanism of treatment resistance. JCI Insight 5:e134824.
21. https://www.atlasgeneticsoncology.org/
22. Rutkovsky AC, Yeh ES, Guest ST, Findlay VJ, Muise-Helmericks RC, et al. (2019) Eukaryotic initiation factor 4E-binding protein as an oncogene in breast cancer. BMC Cancer 19:491.
23. Formisano L, Napolitano F, Rosa R, D'Amato V, Servetto A, et al. (2020) Mechanisms of resistance to mTOR inhibitors. Crit Rev Oncol Hematol 147:102886.
24. Li S, Kong Y, Si L, Chi Z, Cui C, et al. (2014) Phosphorylation of mTOR and S6RP predicts the efficacy of everolimus in patients with metastatic renal cell carcinoma. BMC Cancer 14:376.
25. Rauluseviciute I, Drabløs F, Rye MB (2020) DNA hypermethylation associated with upregulated gene expression in prostate cancer demonstrates the diversity of epigenetic regulation. BMC Med Genomics 13:6.

26. Drago JZ, Formisano L, Juric D, Niemierko A, Servetto A, et al. (2019) FGFR1 Amplification Mediates Endocrine Resistance but Retains TORC Sensitivity in Metastatic Hormone Receptor-Positive (HR+) Breast Cancer. Clin Cancer Res 25:6443-6451.

27. Turner N, Pearson A, Sharpe R, Lambros M, Geyer F, et al. (2010) FGFR1 amplification drives endocrine therapy resistance and is a therapeutic target in breast cancer. Cancer Res 70:2085-94.

28. Rozengurt E, Soares HP, Sinnet-Smith J (2014) Suppression of feedback loops mediated by PI3K/mTOR induces multiple overactivation of compensatory pathways: an unintended consequence leading to drug resistance. Mol Cancer Ther 13:2477-88.

29. O'Reilly KE, Rojo F, She QB, Solit D, Mills GB, et al. (2006) mTOR inhibition induces upstream receptor tyrosine kinase signaling and activates Akt. Cancer Res 66:1500-8.

30. Porta C, Paglino C, Mosca A (2014) Targeting PI3K/Akt/mTOR Signaling in Cancer. Front Oncol 4:64.

31. Hobday TJ, Qin R, Reidy-Lagunes D, et al. (2015) Multicenter Phase II Trial of Temsirolimus and Bevacizumab in Pancreatic Neuroendocrine Tumors. Journal of Clinical Oncology 33:1551-1556.

32. Marton I, Knezevic F, Ramic S, Milosevic M, Tomas D (2012) Immunohistochemical expression and prognostic significance of HIF-1a and VEGF-C in neuroendocrine breast cancer. Anticancer Res 32:5227-32.Pal K, Madamsetty VS, Dutta SK, Wang E, Angom RS, et al. (2019) Synchronous inhibition of mTOR and VEGF/NRP1 axis impedes tumor growth and metastasis in renal cancer. NPJ Precis Oncol 3:31.

33. Schwaederlé M, Lazar V, Validire P, Hansson J, Lacroix L, et al. (2015) VEGF-A Expression Correlates with TP53 Mutations in Non-Small Cell Lung Cancer: Implications for Antiangiogenesis Therapy. Cancer Res 75:1187-90.

34. Said R, Hong DS, Warneke CL, Lee JJ, Wheler JJ, et al. (2013) P53 mutations in advanced cancers: clinical characteristics, outcomes, and correlation between progression-free survival and bevacizumab-containing therapy. Oncotarget 4:705-14.

35. Yardley DA (2013) Combining mTOR Inhibitors with Chemotherapy and Other Targeted Therapies in Advanced Breast Cancer: Rationale, Clinical Experience, and Future Directions. Breast Cancer 7:7-22.

36. Li X, Ma J, Pan B, Zhao Z, Li M (2019). Acquired NF2 mutations confer resistance to HER2 targeted therapy in HER2-mutant breast cancer. Journal of Clinical Oncology 37:e12518-e12518.

37. Panwar V, Singh A, Bhatt M, Tonk RK, Azizov S, et al. (2023) Multifaceted role of mTOR (mammalian target of rapamycin) signaling pathway in human health and disease. Signal Transduct Target Ther 8:375.

38. Xu D, Yin S, Shu Y (2024) NF2: An underestimated player in cancer metabolic reprogramming and tumor immunity. NPJ Precis Oncol 8:133.

39. Gerdes H, Casado P, Dokal A, et al. (2021) Drug ranking using machine learning systematically predicts the efficacy of anti-cancer drugs. Nat Commun 12:1850.

40. Palmer A, Sorger PK (2017) Combination Cancer Therapy Can Confer Benefit via Patient-to-Patient Variability without Drug Additivity or Synergy. Cell 171:1678-1691.e13.

41. Nikanjam M, Liu S, Kurzrock R (2016) Dosing targeted and cytotoxic two-drug combinations: Lessons learned from analysis of 24,326 patients reported 2010 through 2013. Int J Cancer 139:2135-41.

42. Borad MJ, Curtis KK, Babiker HM, Benjamin M, Tibes R, et al. (2012) The impact of concomitant medication use on patient eligibility for phase I cancer clinical trials. J Cancer 3:345-53.

43. Zou Z, Tao T, Li H et al. (2020) mTOR signaling pathway and mTOR inhibitors in cancer: progress and challenges. Cell Biosci 10:31.

44. Bo Z, Huiping S, Hongtao W (2023) Machine Learning and AI in Cancer Prognosis, Prediction, and Treatment Selection: A Critical Approach. Journal of Multidisciplinary Healthcare 16:1779-1791.

45. https://www.genome.jp/kegg/

46. Fei Y, Lu L, Zou Q (2020) Analysis of gene expression profiles of lung cancer subtypes with machine learning algorithms. Biochimica et biophysica acta. Molecular basis of disease 1866:165822.

47. Jain RK, Lee JJ, Hong D, Markman M, Gong J, et al. (2010) Phase I oncology studies: evidence that in the era of targeted therapies patients on lower doses do not fare worse. Clin Cancer Res 16:1289-97.

48. Chapman PB, Hauschild A, Robert C, Haanen, JB, Ascierto P, et al. (2011). Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. New England Journal of Medicine 364:2507-2516.