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Cancer: slaying the nine-headed Hydra

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Abstract

Modern medicine continues to evolve, and the treatment armamentarium for various diseases grows more individualized across a breadth of medical disciplines. Cure rates for infectious diseases that were previously pan-fatal approach 100% because of the identification of the specific pathogen(s) involved and the use of appropriate combinations of drugs, where needed, to completely extinguish infection and hence prevent emergence of resistant strains. Similarly, with the assistance of technologies such as next-generation sequencing and immunomic analysis as part of the contemporary oncology armory, therapies can be tailored to each tumor. Importantly, molecular interrogation has revealed that metastatic cancers are distinct from each other and complex. Therefore, it is conceivable that rational personalized drug combinations will be needed to eradicate cancers, and eradication will be necessary to mitigate clonal evolution and resistance.

Keywords

mixed response; cancer clinical trials; novel therapeutics

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> The Lernaean Hydra was a monster in Greek mythology. It had many heads and every time someone would cut off one of them, two more heads would grow out of the stump. In order to slay the Hydra, Heracles cut off all off the monster's heads and burned the neck.[1]

Primary cancers and their metastatic sites often have divergent molecular landscapes. Furthermore, there may be tremendous complexity within tumor sites.[2] Recent data suggest that tumor complexity and heterogeneity require a precision medicine paradigm that moves beyond predetermined monotherapies to customized matched combinations.[3] Importantly, N-of-one combination therapies maximized to impact as many deleterious genomic alterations as possible are associated with improved outcomes.[3–7]

While personalized combination therapy may be new to oncology, this approach has been successfully deployed in other conditions, a prime example being human immune-deficiency virus (HIV). Novel HIV drug development has become sophisticated to the level that a single pill now encompasses three[8] or four[9] different drugs with varying mechanisms of action. Further, when the initial regimens stop working, likely due to resistance mutations, HIV genotype resistance assays are often carried out and can further inform treatment decisions.[10,11]

Importantly, the general reluctance to combine medications in oncology may be the exception to the rule in medicine, perhaps due to the legacy of the cytotoxic era, where drug combinations potentially lead to an increase in toxicity. Indeed, drug combinations are routine in medical practice. Cancer patients, who often have multiple comorbidities, were found to be on 'polypharmacy' (defined as ≥5 medications, excluding cancer drugs) in 33% to >80% of cases, depending on the cohort examined.[12] Therefore, physicians prescribe personalized drug combinations routinelydexcept in oncology. Indeed, the cancer patient with diabetes, heart disease, and depression will receive a different drug combination than the one with diabetes, rheumatoid arthritis, and an infection.

Herein, we provide a perspective on addressing tumor heterogeneity by rethinking traditional strategies regarding mixed responses, secondary resistance, treatment beyond progression, and the need for tailored combination therapies.

PATTERNS OF RESPONSE AND RESISTANCE PROVIDE CLUES TO UNDERLYING MOLECULAR HETEROGENEITY

Historically, responses to cancer therapy can be classified as complete or partial response, stable disease, or progressive disease. However, other important patterns of response also are seen. For instance, in patients with more than two sites of metastatic disease, one site may decrease in size while another site increases in size. Similarly, there may be shrinkage at one or more sites, but new lesions may appear. These types of responses are called 'mixed' responses. Traditionally in oncology, such patients are lumped into the progressive disease category (Table 1), and either switched to a different systemic therapy or, when in the refractory, heavily pretreated setting, moved to palliative care. Yet, mixed responses may give us important insights into mechanisms of response and

resistance, and the implications of tumor heterogeneity (Figure 1). These insights may be exploitable for optimizing frontline therapy with combination approaches, as well as for treating progression and secondary resistance and the mixed responses themselves.

Malignant tumors consist of various clones, each of which may potentially respond in a different way to therapeutic agents. A drug might induce regression of a sensitive clone, while the growth of a different resistant clone may be facilitated, manifesting as resistance to therapy and designated disease progression.[13–15] Sometimes, the sensitive clone may become resistant to therapy, perhaps because new genomic alterations emerge under therapeutic pressure. Alternatively, the sensitive clone may still exist, albeit in a quiescent state.[16,17] If therapy is changed, the sensitive clone could re-emerge if it remains latent in the tumor (Figure 1). Alternatively, pausing a specific drug or drug regimen may permit even a clone that has become resistant to revert to a sensitive state, perhaps via epigenetic adaptations and/or plasticity induced by the impact of chromatin remodeling.[18,19] In addition, each metastatic site may contain clones with genomic or other alterations that are sensitive and those that are resistant to the therapy being given. If sensitive and resistant clones exist at different sites, they will give rise to mixed responses, with the tumors containing sensitive clones shrinking and those containing resistant clones growing (Figure 1A). By contrast, if sensitive and resistance clones coexist within the same tumor lesion, one may see shrinkage, or growth, or secondary resistance (shrinkage followed by growth) depending on the kinetics of response of each of the clones to the therapy administered (Figure 1B).

Mixed responses

The hallmark of mixed tumor response is that some tumors shrink, and others grow, or new tumors appear. Mixed responses may occur frequently. For instance, in a study of patients with non-small-cell lung cancer, 21.5% (53/246) had mixed responses.[20] Another study similarly noted that 31% of such patients had mixed responses.[21]

In a recent report of 82 patients with mixed responses, therapy was switched in 30, resulting in a 20% response rate; the same therapy was continued in 50, with no responses; and an additional agent was added to the current treatment in 2 cases (and 1 of the 2 patients responded).[22] Figure 1A illustrates a potential theory of mixed responses in light of a growing understanding of clonal heterogeneity that may exist between metastatic tumor sites.[14]

Other evidence for clonal heterogeneity underlying mixed responses also exists. For instance, in some tumor types, local therapy of metastatic lesions (surgical or locally ablative) can provide a significant survival advantage for patients, as in the resection of liver metastases in colorectal cancer, lung metastasectomy in renal cell carcinoma, and resection of oligometastatic disease from a variety of cancers.[23–25] In fact, considerable heterogeneity in the growth behavior of metastatic sites (rapidly progressive versus stable for prolonged periods) underscores inherent biologic and pathologic differences between metastases. In the same light, it may be worthwhile to resequence resistant or growing metastatic sites to add an appropriately targeted agent or agents to combat these differentially growing metastases.

Immunotherapy and mixed responses—a more complex scenario.—The phenomenon of mixed responses may be especially relevant in the era of immune checkpoint inhibition. The responses can often be capricious in terms of response, mixed response, progression, pseudoprogression, hyperprogression, and oligometastatic progression.[26–29]

Mixed response in tumors treated with immune checkpoint inhibition have been seen in patients with metastatic melanoma.[30] In a long-term longitudinal study, a large cohort of patients (n = 292) who had received ipilimumab and/or nivolumab were enrolled.[30] Overall, 22% of patients (n = 64) had a mixed response; defined in this study as 'simultaneously regressing and progressing metastatic lesions'.[30] The patients with mixed response were further found to have a response upon follow-up (n = 38), having a progression upon follow-up (n = 20), or having a stable mixed response (n = 6).[30]

Mixed responses in the context of immunotherapy may have an underlying biology that is at times distinct from mixed responses with targeted or chemotherapy. In particular, some mixed responses may be due to the false appearance of tumor growth due to a local immune inflammatory reaction, as occurs with pseudoprogression.[27] Of interest, it has now been documented that periods of pseudoprogression can also occur with targeted therapies.[31] Therefore, with multiple therapy types, but especially with immunotherapy, mixed responses may reflect distinct clones in different tumor sites or, alternatively, may suggest an inflammatory process related to the microenvironment.

Retreatment after secondary resistance

It is widely acknowledged that if a complete remission can be achieved and drug(s) discontinued, but the disease later relapses, a second complete remission, albeit of shorter duration, may be attained by readministering the original treatment regimen; this is especially pertinent in lym-phomas and leukemias.[32,33] It is likely that this phenomenon occurs because microscopic deposits of tumor or, in the case of hematologic malignancies, leukemia or lymphoma cells, remain, despite the macroscopic complete remission, and these deposits regrow after therapy discontinuation. By contrast, if the tumor initially responds, but then grows again while the patient is still on therapy, the situation is referred to as secondary resistance. It is a general dogma of oncology that, in the presence of secondary resistance, retreatment is futile. However, secondary resistance of this type may be dynamically analogous to complete remission and later relapse, with the only difference being that the initial remission was incomplete in secondary resistance. We therefore address this prohibition against retreatment in secondary resistance through the lens of emerging literature as well as current knowledge of tumor heterogeneity.

Several publications have contested the dogma that retreatment after secondary resistance is not useful by showing that, in select patients, retreatment after secondary resistance can result in repeat responses. For example, a pilot study of 11 patients with a variety of cancers who had previously received between two and seven therapies found that 73% of them (8/11) experienced stable disease for ≥24 weeks, partial responses, or complete responses when receiving retreatment based on previously applied agents.[13] Of these eight patients, two were retreated with the same drug(s), one with the same class of drug [epidermal growth factor receptor (EGFR) inhibitor gefitinib, then EGFR inhibitor erlotinib], and

five received the same drug in combination with other drugs. These patients had shown secondary resistance (response and then later resistance) to the original therapy, and the median time between stopping the original treatment and restarting was 92 weeks.

Retreatment with the same drugs after a holiday period.—It is plausible that some of the mechanisms of response to retreatment after secondary resistance are similar to those for retreatment after complete remission followed by relapse.[32] Response to retreatment with the same drug or class of drugs to which the patient had originally responded may be explained in both settings based on re-emergence of a suppressed clone after some time off a therapy that had initially been effective, but then lost its effectiveness (Figure 1B). In this case, secondary resistance may be akin to a mixed response, except that the different clones coexist in the same tumor mass, rather than in distinct tumor masses. A new clone that emerges after an initially successful treatment might be suppressed by a new treatment but, the new treatment might, at the same time, permit the re-emergence of the original clone, and therefore retreatment with the original drug(s) may be effective.

Other studies have supported these concepts regarding retreatment after a drug holiday. For instance, successful retreatment with BRAF inhibitors in melanoma has been reported.[34] Individuals with ovarian cancer and even partial sensitivity to platinum drugs and recurrent disease have also demonstrated salutary effects following retreatment with platinum agents.[35,36] Moreover, several studies, based on the pulsatile behavior of RAS clones under EGFR blockade, investigated whether retreatment with EGFR-targeted agents is effective in colorectal cancer. A systematic review retrieved 26 publications on this subject. Rechallenge with anti-EGFR provided clinical benefit in molecularly selected metastatic colorectal cancer patients beyond second line (objective response rate = 2.9%−53.8%; disease control rate = 40.0%−89.7%).[37] Rechallenge trials with anti-EGFR therapy among *RAS* wild-type metastatic colorectal cancer is being conducted and clinical outcomes are pending.[38]

These proof-of-concept studies show that the traditional dogma that discourages retreatment in oncology needs rethinking. In certain situations, retreatment strategies can achieve good results in pretreated patients.

Adding new drugs in the context of reusing the original drugs or treatment past progression[17]

Retreatment with the same drugs, but supplementing the treatment regimen with additional drugs, may have a different mechanism that underlies effectiveness—that is the need for additional therapy to address emerging clones while maintaining the original therapy to suppress the original clones.

Several studies have documented that treating human epidermal growth factor receptor 2 (HER2)-positive breast cancer with continued HER2-targeting antibody trastuzumab after disease progression is beneficial.[39,40] For instance, a German study of patients with HER2-positive breast cancer whose disease progressed on trastuzumab, but then continued receiving trastuzumab with capecitabine, showed a significant improvement in overall response and time to progression as compared with those who discontinued trastuzumab and switched to capecitabine only.[40,41] In addition, in large cohorts of patients with

colorectal carcinoma, individuals who continued to receive bevacizumab (together with new drugs) after disease progression on bevacizumab-containing regimens had significantly longer survival compared with those who did not have bevacizumab included in their post-bevacizumab progression regimen.[41,42] Moreover, in a cohort of patients with colorectal cancer who were refractory to irinotecan, those who received cetuximab and irinotecan beyond progression compared with those who only received cetuximab had significantly better outcomes.[41,43]

SURVEILLANCE OF THE HYDRA FOR THE EMERGENCE OF NEW 'HEADS' (RESISTANCE)

Aside from the initial biopsy of a tumor identifying various genomic alteration to be targeted, an important concept in treating the 'Hydra' is identifying secondary resistance mechanisms early and 'cutting off those heads' when they emerge. The advent of liquid (blood-based) biopsies has enabled early identification of molecular alterations in circulating tumor DNA (ctDNA), before they appear on imaging, without invasive tissue biopsies.[44] Liquid biopsies represent powerful new technology, but still have several challenges including the confounding presence of mutations derived from clonal hematopoiesis of indeterminant potential,[45,46] variations in the amount of shed ctDNA from various sites or cancers,[47] and discordance between tissue and ctDNA, which may be due to biologic factors, but requires ruling out technical factors.[48,49] Other strategies important for following tumors for resistance mutations include interrogating circulating tumor cells and re-biopsying new disease sites as they emerge. Dynamic monitoring of liquid and tissue biopsies may capture new biologically relevant clones that drive progression.

CUSTOMIZED (N-OF-1) COMBINATION THERAPYdTHE KEY TO KILLING THE CANCER HYDRA

Multiple lines of evidence confirm the impact of clonal heterogeneity in the clinic.[3,7,50–56] The result is a variety of response and retreatment patterns that increasingly suggest that multiple pathways and clones drive tumor growth. As a consequence, therapy is often engaged in 'whack-a-mole'[54]—akin to cutting off a Hydra head, only to have two heads grow back (Figure 2).

Therefore, scripted monotherapies are likely inefficient and may not provide durable outcomes for patients. Some drugs in oncology lack efficacy as single agents, but when combined in a rational context produce durable responses, possibly because more than one driver alteration exists in a patient's malignancy.[5,53,55,56] Still the question that arises is whether or not combining drug A with drug B is better than sequentially using drug A followed by drug B. Some studies, such as those showing modest efficacy of single-agent EGFR inhibitors in gastric cancer[57] and single-agent CDK (cyclin-dependent kinase) inhibitors in breast cancer,[58,59] while combinations such as those of CDK inhibitors with antiestrogens are effective,[60] indicate that drug combinations are needed from the beginning (Table 2). But the question of combination versus sequential therapy still needs answering on a larger scale level. Ultimately, however, data from cancers that are cured by therapy,

such as pediatric leukemias, imply that all heads of the cancer hydra must be slayed from the outset.[61–64]

Other important considerations may apply. The combination approach may result in higher response rates, not from either synergy or an additive effect but, when applied to a population without biomarker selection, from targeting different subgroups within that population, as shown by Palmer and Sorger.[65] The latter emphasizes the crucial importance of molecular profiling of each patient to limit the combination of drugs given to them to those that will impact their tumor, hence reducing toxicity from drugs that may only impact other subgroups of the population.

A major challenge involves the method of choosing optimal drug combinations. One approach has been to use systems biology to understand the larger picture, and address convergence pathways for molecular alterations. Challenges with this approach include the fact that single-cell genomics has revealed that some molecular alterations may exist in different clones and, hence, there is no convergent pathway.[66] Furthermore, pathways which may converge may simultaneously diverge through many branches that occur as a result of complex molecular interactions along the conduit to the convergence point. Other approaches include choosing drugs to impact as many alterations as possible directly; this strategy has shown efficacy in clinical trials,[3,7] but may be limited by the number of drugs needed for patients with multiple molecular alterations. Additional strategies include evaluation of real-world data on similar patients, including digital cancer twins,[67] and functional *ex vivo* assessment of drug impact,[68] as well as the use of transcriptomics to determine synthetic lethal and immune interactions.[69–71]

OPTIMIZING TOLERANCE TO MOLECULARLY MATCHED COCKTAILS

An inherent difficulty in the development of combination regimens for precision therapeutics is defining a minimum and maximum range of recommended, biologically effective doses, as well as studying pharmacokinetics, pharmacodynamics, and toxicities. These issues will become more marked in a therapeutic landscape in which various targeted agents will be combined during the disease course. To mitigate this challenge, several approaches are possible. First, multiarm platform trials that address multiple drug combinations simultaneously are increasingly being used.[72] Second, a novel approach of intrapatient dose escalation (starting at lower doses and escalating to tolerance in individual patients) has also been recently utilized for novel combinations of previously approved drugs[3,5,7,55,56]; this approach permits tailoring not only the drugs, but also the dosing to the patient, and was shown to be safe, without any increase in toxicity compared with that seen in patients receiving standard of care, while maintaining efficacy. The latter tactic is predicated on prior knowledge of general outcomes, dosing, and toxicities based on large-scale analysis of drug combinations in over 70 000 patients in published clinical trials.[73–76] Continued prospective exploration of platform clinical trials and intrapatient dosing assessment strategies for novel combinations is warranted.

HEALTH CARE ECONOMICS AND REGULATORY CHALLENGES

There are also payer and regulatory hurdles that will need to be addressed. Real-world data suggest that the costs of more effective, newer therapies is less than that for older, less expensive treatments when productivity (work) is taken into account.[77] Future studies will need to account for patient and caregiver productivity in health economic assessments, in addition to cost per life-year gained. Furthermore, as precision therapeutic combinations are flexibly applied to the patient during the disease course in the personalized medicine model, our traditional methods for running trials, approving drugs, and documenting effectiveness may prove suboptimal. Strategies to address these challenges include master observational protocols,[78] postapproval rolling validation of effectiveness, evaluation of real-world data, and perhaps assessment of the value or lack thereof of specific algorithms for choosing drugs, rather than just assessment of the drug regimens themselves.

CONCLUSIONS AND FUTURE PERSPECTIVES

The ‘whack-a-mole’ paradigm in cancer treatment is akin to the mythical serpentine water monster known as the Hydra, a creature with multiple heads, wherein severing one head inevitably resulted in the regrowth of two heads (Figure 2). Traditionally, clinical trials in cancer have not accounted for the variations seen among patients’ cancers and use a firehose approach, giving everyone within a group of patients the same drug(s) in a trial-and-error fashion. Historically, patients in clinical trials have largely been treated in a genomically agnostic fashion, thus receiving drugs that might or might not hit a target that is pathogenic and driving the disease. In the latter cases, these drugs are deemed to ‘fail’ or have limited to no utility. Within these all-comer trials using targeted agents, a signal might be lost in the noise of nonresponses.[79] More recently, these issues have been addressed in biomarker-based trials for gene-targeted agents. However, these trials are mostly geared toward a single targeted agent and its cognate molecular anomaly. For immunotherapy, clinical trials are still typically applied to populations without a biomarker, and without immunomic analysis.[79]

Taking the concept of tumor heterogeneity into account and aiming to overcome this phenomenon is key.[80] Heterogeneity can occur between patients or within a patient. Accounting for interpatient heterogeneity can potentially be achieved by more in-depth analyses of tumor and patient-specific characterization.[3–5,7,71,79] To account for intrapatient heterogeneity, different approaches, such as liquid biopsies, rebiopsy of progressive disease or radiomics, are needed.[2,81] Therefore the heterogeneity within a patient means that customized combinations may be crucial for response optimization.[6]

Based on the data outlined in the preceding text, it may be reasonable to siphon mixed responding patients or patients with secondary resistance into an additional ‘box’on the trial-schema hierarchy. These mixed responders or secondarily resistant tumors are the outward manifestation of the Hydra, regrowing new heads when one head is amputated. Emerging data suggest the potential for continuing the current regimen past progression or mixed response, assuming tolerable toxicities. In addition, tissue biopsies of progressing lesions or liquid biopsies for comprehensive tumor profiling could be used to understand

mechanisms of resistance and to hope-fully elucidate new actionable targets that could be added onto the existing regimens.

Most importantly, tumors represent a ‘moving target’ driven by clonal evolution due to therapeutic or time pressure.[81–83] Innovative combinational therapies early in the course of the disease may help combat the heterogeneity of cancer and slay the nine-headed Hydra.[7]

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REFERENCES

1. Lernaean Hydra. Available at https://www.greekmythology.com/Myths/Monsters/Lernaean_Hydra/lernaean_hydra.html. Accessed August 9, 2022.
2. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med. 2012;366:883–892. [PubMed: 22397650]
3. Sicklick JK, Kato S, Okamura R, et al. Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. Nat Med. 2019;25:744–750. [PubMed: 31011206]
4. Rodon J, Soria JC, Berger R, et al. Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial. Nat Med. 2019;25:751–758. [PubMed: 31011205]

5. Kato S, Kim KH, Lim HJ, et al. Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-one strategy. Nat Commun. 2020;11:4965. [PubMed: 33009371]
6. Adashek JJ, Subbiah V, Kurzrock R. From tissue-agnostic to N-of-one therapies: (R)evolution of the precision paradigm. Trends Cancer. 2021;7:15–28. [PubMed: 33008795]
7. Sicklick JK, Kato S, Okamura R, et al. Molecular profiling of advanced malignancies guides first-line N-of-1 treatments in the I-PREDICT treatment-naive study. Genome Med. 2021;13:155. [PubMed: 34607609]
8. Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380–1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet. 2017;390:2063–2072. [PubMed: 28867497]
9. Gaur AH, Kizito H, Prasitsueubsai W, et al. Safety, efficacy, and pharmacokinetics of a single-tablet regimen containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in treatment-naive, HIV-infected adolescents: a single-arm, open-label trial. Lancet HIV. 2016;3:e561–e568. [PubMed: 27765666]
10. Clavel F, Hance AJ. HIV drug resistance. N Engl J Med. 2004;350:1023–1035. [PubMed: 14999114]
11. Saag MS. HIV infection – screening, diagnosis, and treatment. N Engl J Med. 2021;384:2131–2143. [PubMed: 34077645]
12. Loeppenthin K, Dalton SO, Johansen C, et al. Total burden of disease in cancer patients at diagnosis – a Danish nationwide study of multi-morbidity and redeemed medication. Br J Cancer. 2020;123:1033–1040. [PubMed: 32632149]
13. Naing A, Agarwal R, Falchook G, et al. Retreatment after secondary resistance or mixed response: a pilot study. Oncology. 2013;85:350–355. [PubMed: 24335388]
14. Naing A, Kurzrock R. Chemotherapy resistance and retreatment: a dogma revisited. Clin Colorectal Cancer. 2010;9:E1–E4. [PubMed: 20378496]
15. Santini D, Vincenzi B, Addeo R, et al. Cetuximab rechallenge in metastatic colorectal cancer patients: how to come away from acquired resistance? Ann Oncol. 2012;23:2313–2318. [PubMed: 22396447]
16. Cara S, Tannock IF. Retreatment of patients with the same chemotherapy: implications for clinical mechanisms of drug resistance. Ann Oncol. 2001;12:23–27. [PubMed: 11249045]
17. Naing A, Kurzrock R. Dodging a dogma: is treating beyond progression beneficial? Cancer Chemother Pharmacol. 2013;71:1385–1386. [PubMed: 23443308]
18. Flavahan WA, Gaskell E, Bernstein BE. Epigenetic plasticity and the hallmarks of cancer. Science. 2017;357.
19. Oronsky BT, Oronsky AL, Lybeck M, et al. Episensitization: defying time's arrow. Front Oncol. 2015;5:134. [PubMed: 26125013]
20. Dong ZY, Zhai HR, Hou QY, et al. Mixed responses to systemic therapy revealed potential genetic heterogeneity and poor survival in patients with non-small cell lung cancer. Oncologist. 2017;22:61–69. [PubMed: 28126915]
21. Rager O, Espinet C, Humm J, Weber W. Mixed response on FDG PET/CT: frequency and prognostic relevance in non-small cell lung cancer (NSCLC). J Nucl Med. 2014;55:514.
22. Baldeo C, Kaleem T, Paz-Fumagalli R, et al. CLO19–026: determining the treatment decision of tumors with mixed response. J Natl Compr Canc Netw. 2019;17:CLO19–CLO26.
23. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. J Clin Oncol. 2020;38:2830–2838. [PubMed: 32484754]
24. Adashek JJ, Aydin AM, Kim P, Spiess PE. The role of metastasectomy in the treatment of metastatic renal cell carcinoma. AME Med J. 2019;4.
25. Adam R, Pascal G, Azoulay D, et al. Liver resection for colorectal metastases: the third hepatectomy. Ann Surg. 2003;238:871–883. discussion 883–874. [PubMed: 14631224]

26. Kato S, Goodman A, Walavalkar V, et al. Hyperprogressors after immunotherapy: analysis of genomic alterations associated with accelerated growth rate. Clin Cancer Res. 2017;23:4242–4250. [PubMed: 28351930]
27. Borcoman E, Kanjanapan Y, Champiat S, et al. Novel patterns of response under immunotherapy. Ann Oncol. 2019;30:385–396. [PubMed: 30657859]
28. Adashek JJ, Kato S, Ferrara R, et al. Hyperprogression and immune checkpoint inhibitors: hype or progress? Oncologist. 2019. In press.
29. Adashek JJ, Subbiah IM, Matos I, et al. Hyperprogression and immunotherapy: fact, fiction, or alternative fact? Trends Cancer. 2020;6:181–191. [PubMed: 32101722]
30. Rauwerdink DJW, Molina G, Frederick DT, et al. Mixed response to immunotherapy in patients with metastatic melanoma. Ann Surg Oncol. 2020;27:3488–3497. [PubMed: 32472413]
31. Kurzrock R, Atkins J, Wheler J, et al. Tumor marker and measurement fluctuations may not reflect treatment efficacy in patients with medullary thyroid carcinoma on long-term RET inhibitor therapy. Ann Oncol. 2013;24:2256–2261. [PubMed: 23676418]
32. Lee S, Tallman MS, Oken MM, et al. Duration of second complete remission compared with first complete remission in patients with acute myeloid leukemia. Eastern Cooperative Oncology Group. Leukemia. 2000;14:1345–1348. [PubMed: 10942227]
33. Buchanan GR, Rivera GK, Boyett JM, et al. Reinduction therapy in 297 children with acute lymphoblastic leukemia in first bone marrow relapse: a Pediatric Oncology Group Study. Blood. 1988;72:1286–1292. [PubMed: 3167209]
34. Seghers AC, Wilgenhof S, Lebbe C, Neyns B. Successful rechallenge in two patients with BRAF-V600-mutant melanoma who experienced previous progression during treatment with a selective BRAF inhibitor. Melanoma Res. 2012;22:466–472. [PubMed: 22584957]
35. Leitao MM Jr, Hummer A, Dizon DS, et al. Platinum retreatment of platinum-resistant ovarian cancer after nonplatinum therapy. Gynecol Oncol. 2003;91:123–129. [PubMed: 14529671]
36. Morgan RJ Jr, Alvarez RD, Armstrong DK, et al. Ovarian cancer. Clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2008;6:766–794. [PubMed: 18926089]
37. Mauri G, Pizzutilo EG, Amatu A, et al. Retreatment with anti-EGFR monoclonal antibodies in metastatic colorectal cancer: systematic review of different strategies. Cancer Treat Rev. 2019;73:41–53. [PubMed: 30616224]
38. Strickler JH, Ou F-S, Bekaii-Saab TS, et al. PULSE: a randomizedphase II open label study of panitumumab rechallenge versus standard therapy after progression on anti-EGFR therapy in patients with RAS wild-type metastatic colorectal cancer (mCRC). J Clin Oncol. 2021;39:TPS143–TPS143.
39. Extra JM, Antoine EC, Vincent-Salomon A, et al. Efficacy of trastuzumab in routine clinical practice and after progression for metastatic breast cancer patients: the observational Hermine study. Oncologist. 2010;15: 799–809. [PubMed: 20671105]
40. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a German Breast Group 26/ Breast International Group 03–05 study. J Clin Oncol. 2009;27:1999–2006. [PubMed: 19289619]
41. Kuczynski EA, Sargent DJ, Grothey A, Kerbel RS. Drug rechallenge and treatment beyond progression–implications for drug resistance. Nat Rev Clin Oncol. 2013;10:571–587. [PubMed: 23999218]
42. Grothey A, Sugrue MM, Purdie DM, et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). J Clin Oncol. 2008;26:5326–5334. [PubMed: 18854571]
43. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med. 2004;351:337–345. [PubMed: 15269313]
44. Adashek JJ, Janku F, Kurzrock R. Signed in blood: circulating tumor DNA in cancer diagnosis, treatment and screening. Cancers (Basel). 2021;13:3600. [PubMed: 34298813]
45. Chan HT, Chin YM, Nakamura Y, Low SK. Clonal hematopoiesis in liquid biopsy: from biological noise to valuable clinical implications. Cancers (Basel). 2020;12:2277. [PubMed: 32823942]

46. Okamura R, Piccioni DE, Boichard A, et al. High prevalence of clonal hematopoiesis-type genomic abnormalities in cell-free DNA in invasive gliomas after treatment. Int J Cancer. 2021;148:2839–2847. [PubMed: 33497479]
47. Keller L, Belloum Y, Wikman H, Pantel K. Clinical relevance of blood-based ctDNA analysis: mutation detection and beyond. Br J Cancer. 2021;124:345–358. [PubMed: 32968207]
48. Mardinian K, Okamura R, Kato S, Kurzrock R. Temporal and spatial effects and survival outcomes associated with concordance between tissue and blood KRAS alterations in the pan-cancer setting. Int J Cancer. 2020;146:566–576. [PubMed: 31199507]
49. Chae YK, Davis AA, Jain S, et al. Concordance of genomic alterations by next-generation sequencing in tumor tissue versus circulating tumor DNA in breast cancer. Mol Cancer Ther. 2017;16:1412–1420. [PubMed: 28446639]
50. Adashek JJ, Kurzrock R. Balancing clinical evidence in the context of a pandemic. Nat Biotechnol. 2021;39:270–274. [PubMed: 33547424]
51. Kato S, Weipert C, Gumas S, et al. Therapeutic actionability of circulating cell-free DNA alterations in carcinoma of unknown primary. JCO Precis Oncol. 2021;5.
52. Kato S, Alsafar A, Walavalkar V, et al. Cancer of unknown primary in the molecular era. Trends Cancer. 2021;7:465–477. [PubMed: 33516660]
53. Adashek JJ, Kato S, Gumas S, et al. 86MO personalized molecularly matched therapies for carcinomas of unknown primary is associated with improved outcomes. Ann Oncol. 2020;31:S275–S276.
54. Groisberg R, Subbiah V. Combination therapies for precision oncology: the ultimate whack-a-mole game. Clin Cancer Res. 2021;27:2672–2674. [PubMed: 33707180]
55. Kato S, Adashek JJ, Shaya J, et al. Concomitant MEK and cyclin gene alterations: implications for response to targeted therapeutics. Clin Cancer Res. 2021;27:2792–2797. [PubMed: 33472910]
56. Kato S, Okamura R, Adashek JJ, et al. Targeting G1/S phase cell-cycle genomic alterations and accompanying co-alterations with individualized CDK4/6 inhibitor-based regimens. JCI Insight. 2021;6.
57. Adashek JJ, Arroyo-Martinez Y, Menta AK, et al. Therapeutic implications of epidermal growth factor receptor (EGFR) in the treatment of metastatic gastric/GEJ cancer. Front Oncol. 2020;10:1312. [PubMed: 32850413]
58. Adashek JJ, Aguiar PN, Castelo-Branco P, et al. PALOMA-3 clinical trial: is there a significant benefit in overall survival for breast cancer? Is it worth it? Future Oncol. 2019;15:1407–1410. [PubMed: 31066287]
59. Fernandes MT, Adashek JJ, Barreto CMN, et al. A paradigm shift for the treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2−) advanced breast cancer: a review of CDK inhibitors. Drugs Context. 2018;7:212555. [PubMed: 30416529]
60. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med. 2018;379:1926–1936. [PubMed: 30345905]
61. Cooper SL, Brown PA. Treatment of pediatric acute lymphoblastic leukemia. Pediatr Clin North Am. 2015;62:61–73. [PubMed: 25435112]
62. Wijaya J, Gose T, Schuetz JD. Using pharmacology to squeeze the life out of childhood leukemia, and potential strategies to achieve breakthroughs in medulloblastoma treatment. Pharmacol Rev. 2020;72:668–691. [PubMed: 32571983]
63. Freireich EJ. The road to the cure of acute lymphoblastic leukemia: a personal perspective. Oncology. 1997;54:265–269. [PubMed: 9216848]
64. Frei E 3rd, Karon M, Levin RH, et al. The effectiveness of combinations of antileukemic agents in inducing and maintaining remission in children with acute leukemia. Blood. 1965;26:642–656. [PubMed: 5321112]
65. Palmer AC, Sorger PK. Combination cancer therapy can confer benefit via patient-to-patient variability without drug additivity or synergy. Cell. 2017;171:1678–1691 e1613. [PubMed: 29245013]
66. Saadatpour A, Lai S, Guo G, Yuan GC. Single-cell analysis in cancer genomics. Trends Genet. 2015;31:576–586. [PubMed: 26450340]

67. Kamel Boulos MN, Zhang P. Digital twins: from personalised medicine to precision public health. J Pers Med. 2021;11:745. [PubMed: 34442389]
68. Spinner MA, Aleshin A, Santaguida MT, et al. *Ex vivo* drug screening defines novel drug sensitivity patterns for informing personalized therapy in myeloid neoplasms. Blood Adv. 2020;4:2768–2778. [PubMed: 32569379]
69. Aharonov R, Dinstag G, Shulman E, et al. ENLIGHT: pancancer response prediction to targeted and immunotherapies via tumor transcriptomics. J Clin Oncol. 2022;40:e13556–e13556.
70. Szeto CW, Kurzrock R, Kato S, et al. Association of differential expression of immunoregulatory molecules and presence of targetable mutations may inform rational design of clinical trials. ESMO Open. 2022;7:100396. [PubMed: 35158206]
71. Adashek JJ, Kato S, Parulkar R, et al. Transcriptomic silencing as a potential mechanism of treatment resistance. JCI Insight. 2020;5.
72. Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. N Engl J Med. 2017;377:62–70. [PubMed: 28679092]
73. Nikanjam M, Liu S, Kurzrock R. Dosing targeted and cytotoxic two-drug combinations: Lessons learned from analysis of 24,326 patients reported 2010 through 2013. Int J Cancer. 2016;139:2135–2141. [PubMed: 27389805]
74. Liu S, Nikanjam M, Kurzrock R. Dosing *de novo* combinations of two targeted drugs: towards a customized precision medicine approach to advanced cancers. Oncotarget. 2016;7:11310–11320. [PubMed: 26824502]
75. Nikanjam M, Patel H, Kurzrock R. Dosing immunotherapy combinations: analysis of 3,526 patients for toxicity and response patterns. Oncoimmunology. 2017;6:e1338997. [PubMed: 28920006]
76. Nikanjam M, Liu S, Yang J, Kurzrock R. Dosing three-drug combinations that include targeted anti-cancer agents: analysis of 37,763 patients. Oncologist. 2017;22:576–584. [PubMed: 28424323]
77. Kurzrock R, Goldberg R, Ceacareanu AC, Wintrob ZAP. HSR19–096: The impact of new oncology drugs on disability and health care spending: an assessment of real-world evidence. J Natl Compr Canc Netw. 2019;17:HSR19–096-HSR019–096.
78. Dickson D, Johnson J, Bergan R, et al. The master observational trial: a new class of master protocol to advance precision medicine. Cell. 2020;180:9–14. [PubMed: 31951522]
79. Adashek JJ, Goloubev A, Kato S, Kurzrock R. Missing the target in cancer therapy. Nat Cancer. 2021;2:369–371. [PubMed: 34368781]
80. McGranahan N, Swanton C. Clonal heterogeneity and tumor evolution: past, present, and the future. Cell. 2017;168:613–628. [PubMed: 28187284]
81. Pisapia DJ, Salvatore S, Pauli C, et al. Next-generation rapid autopsies enable tumor evolution tracking and generation of preclinical models. JCO Precis Oncol. 2017;2017.
82. Wallace TA, Martin DN, Ambs S. Interactions among genes, tumor biology and the environment in cancer health disparities: examining the evidence on a national and global scale. Carcinogenesis. 2011;32:1107–1121. [PubMed: 21464040]
83. Yates LR, Campbell PJ. Evolution of the cancer genome. Nat Rev Genet. 2012;13:795–806. [PubMed: 23044827]

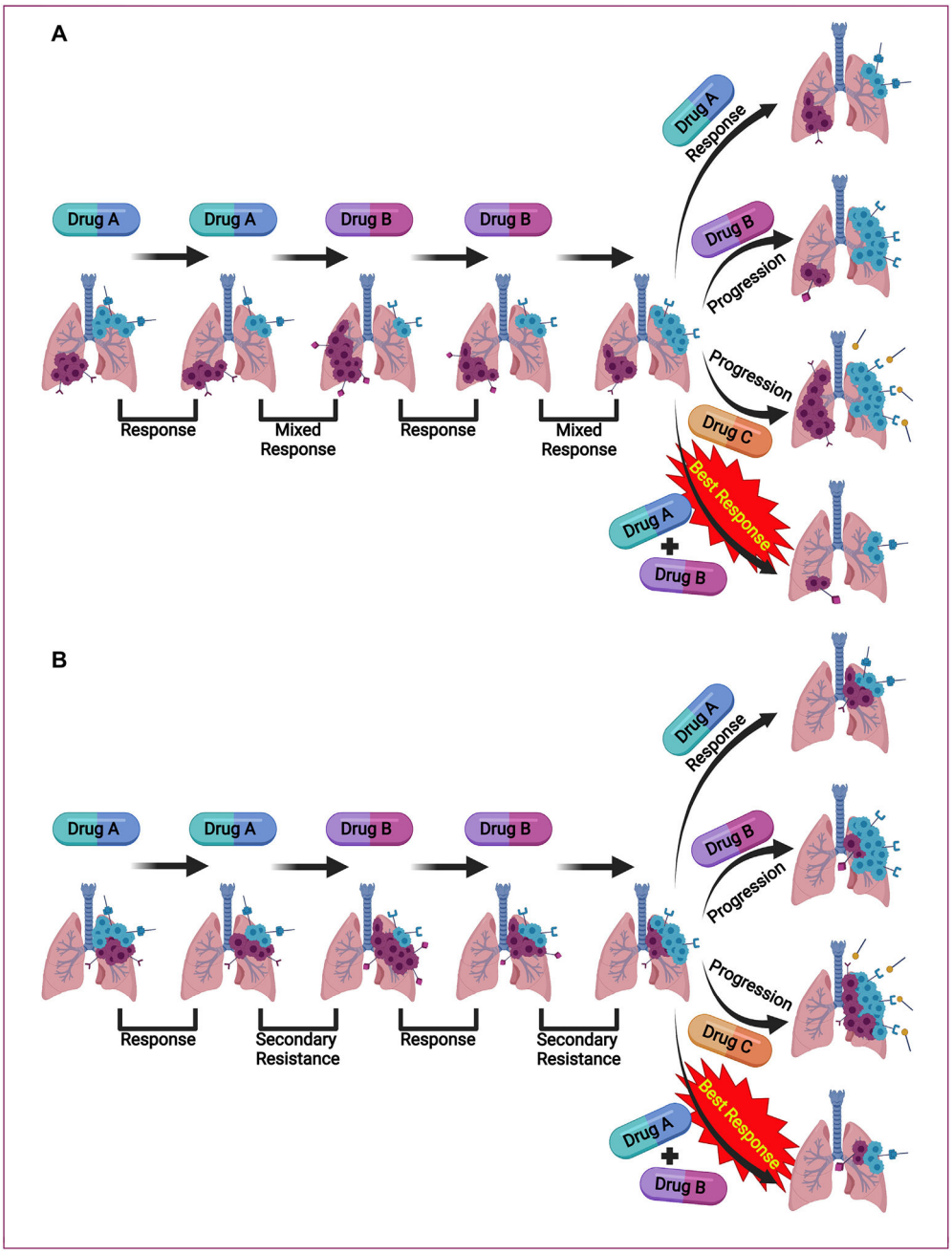

Figure 1.

(A) Mixed response in metastatic cancer reflecting different clones. Metastatic cancer harboring different clones within distinct tumor sites possibly reflects differing genomic drivers. When only one aberration is targeted with directed therapy such as ‘clone A’ with ‘drug A’, that tumor regresses, but ‘drug A’ has minimal to no effect on ‘clone B’ driven by a different aberration. Over time, a mixed response occurs when ‘clone B’ becomes larger, showing ‘progression’ even if clone A shows response to therapy. The same occurs when switching treatment to ‘drug B’ to target the progressing ‘clone B’ and stopping ‘drug A’; ‘clone B’ may show response to therapy, but ‘clone A’ now progresses. At this point

there are four potential next steps to management: (i) retreatment with ‘drug A’, which will likely yield a response in ‘clone A’; (ii) continue with ‘drug B’, which will likely lead to continued progression in ‘clone A’; (iii) switch to a new ‘drug C’, which, if it does not target either clone, will yield progression; or (iv) combine ‘drug A’ and ‘drug B’ to target both previously responsive genomic aberrations found in the different clones/metastatic sites, which will likely yield the best response. (B) Secondary resistance in heterogenous cancer clones within same mass. Heterogenous clones in the same tumor mass may reflect the same process uncovered by mixed responses. Because the clones coexist in the same tumor mass, a mixed response will not be seen. Rather the tumor mass will regress or grow depending on the dynamics of each of the clones and their responsiveness to specific therapies. Ultimately, however, the strategy for optimization of response recapitulates that for mixed responses as seen in (A).

Figure 2.

(A) Nine-headed cancer hydra. Battling the nine-headed cancer hydra with multiple modalities (e.g. fire torch and sword). (B) Injuring a head will not kill the nine-headed hydra. Furthermore, cutting off a head may result in two heads growing back (akin to the emergence of resistance mutations when a single mutation is targeted). (C) Slaying the nine-headed hydra requires severing all heads. Akin to targeting all important alterations in a cancer.

Table 1.

RECIST and iRECIST definition of progressive disease

	RECIST 1.1[66]	**iRECIST**[67]
Type of progressive disease	Progressive disease must be 20% increase over smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions	Unconfirmed progressive disease: ≥20% increase over smallest sum at baseline or on study and ≥5 mm increase or new lesions Confirmed progressive disease: additional new lesions or biopsy-proven progressive disease in the next imaging evaluation, carried out at 4–8 weeks after unconfirmed progression, or further increase in new lesion size from unconfirmed progressive disease
New lesions	Considered progressive disease	Considered unconfirmed progression, unless at next evaluation additional new lesions appear or an increase in size of new lesions is observed; the appearance of new lesions when none were previously observed can also establish progressive disease

Table 2.

Food and Drug Administration-approved combination targeted therapy regimens[a]

Drugs	Mechanisms of Action	Indication
Dabrafenib + trametinib	BRAF + MEK inhibition	• V600E anaplastic thyroid • Adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations • Unresectable stage IIIB or IV melanoma • Metastatic non-small-cell lung cancer with BRAF V600E mutation • Tissue agnostic
Vemurafenib + cobimetinib	BRAF + MEK inhibition	• BRAF V600 mutation-positive unresectable or metastatic melanoma
Encorafenib and binimetinib	BRAF + MEK inhibition	• Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation
Palbociclib + letrozole	CDK4/6 + aromatase inhibition	• ER-positive, HER2-negative advanced breast cancer
Palbociclib + fulvestrant	CDK4/6 + estrogen receptor inhibition	• HR-positive, HER2-negative advanced or metastatic breast cancer in women with disease progression following endocrine therapy
Abemaciclib + aromatase inhibitor	CDK4/6 + aromatase inhibition	• Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer
Abemaciclib + fulvestrant	CDK4/6 + estrogen receptor inhibition	• HR-positive, HER2-Slistanegative advanced or metastatic breast cancer with disease progression following endocrine therapy
Ribociclib + aromatase inhibitor	CDK4/6 + aromatase inhibition	• Pre/perimenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer
Ramucirumab + erlotinib	VEGF + EGFR inhibition	• First-line treatment of metastatic non-small-cell lung cancer with EGFR exon 19 deletions or exon 21 (L858R) mutations
Encorafenib + cetuximab	BRAF + EGFR inhibition	• Metastatic colorectal cancer with a BRAF V600E mutation
Alpelisib + fulvestrant	PI3K + estrogen receptor inhibition	• Postmenopausal women, and men, with HR-positive, HER2-negative, PIK3CA-mutated, advanced, or metastatic breast cancer
Lenvatinib + everolimus	VEGF + mTOR inhibition	• Renal cell cancer

CDK, cyclin-dependent kinase; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; HR, hormone receptor; MEK, mitogen-activated extra-cellular signal-regulated kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; VEGF, vascular endothelial growth factor.

[a]Verified via the US FDA Oncology (Cancer)/Hematologic Malignancies Approval Notifications website (https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications).