Tumor heterogeneity: a central foe in the war on cancer

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A major challenge to effective cancer treatment is the astounding level of heterogeneity that tumors display on many different fronts. Here, we discuss how a deeper appreciation of this heterogeneity and its impact is driving research efforts to better understand and tackle it and a radical rethink of treatment paradigms.

A complex and dynamic disease

The nonuniformity of cancer has long been appreciated, reflected most visibly in the variation of response to the same treatment across patients with the same type of tumor (*inter*-tumor heterogeneity). The extent of tumor heterogeneity is being fully realized only now, with the advent of next-generation sequencing technologies. Even within the same tumor, there can be significant heterogeneity from cell to cell (*intra*-tumor heterogeneity), yielding substantial complexity in cancer.

Heterogeneity reveals itself on many different levels. Histologically speaking, tumors are composed of a nonhomogenous mass of cells that vary in type and number. In terms of their molecular make-up, there is substantial variation in the types of molecular alterations observed, all the way down to the single cell level. In even more abstract terms, beyond the cancer itself, the microenvironment in which it resides can be highly heterogeneous, composed of a plethora of different supportive and tumor-infiltrating normal cells.

Heterogeneity can manifest spatially, reflecting differences in the composition of the primary tumor and tumors at secondary sites or across regions of the same tumor mass and temporally, at different time points across a tumor's natural history. Evocative of the second law of thermodynamics, cancers generally become more diverse and complex over time.[1-3]

A tale of 2 models

It is widely accepted that the transformation of a normal cell into a malignant one occurs with the acquisition of certain "hallmark" abilities, but there are myriad ways in which these can be attained. Two key models can be used to explain how tumors develop – the clonal evolution model and the cancer stem cell (CSC) model (Figure 1).

The clonal evolution model

As cells divide, they randomly acquire mutations as a result of DNA damage. The clonal evolution model posits that cancer develops as the result of a multistep accumulation of a series of "driver" mutations that confer a promalignant advantage to the cell and ultimately fuel a cancerous hallmark.

This evolution can occur in a linear fashion, whereby the emergence of a new driver mutation conveys such a potent evolutionary advantage that it outcompetes all previous clones. There is limited evidence for linear evolution in most advanced human cancers; instead, they are thought to evolve predominantly through a process of branching evolution, in which multiple clones can diverge in parallel from a common ancestor through the acquisition of different driver mutations. This results in common clonal mutations that form the trunk of the cancer's evolutionary tree and are shared by all cells and subclonal mutations, which make up the branches and differ from cell to cell.

More recently, several other mechanisms of clonal evolution have been proposed, including neutral evolution, a type of branching evolution in which there are no selective pressures and evolution occurs by random mutations occurring over time that lead to genetic drift, and punctuated evolution, in which there are short evolutionary bursts of hypermutation.[4,5]

The CSC model

This model posits that the ability to form and sustain a cancer is restricted to a single cell type – the cancer stem cells – which have the unique capacity for self-renewal and differentiation. Although the forces of evolution are still involved in this model, they act on a hierarchy of cells, with stem cells sitting at the top. A tumor is derived from a single stem cell that has acquired a mutation, and the heterogeneity observed results both from the differentiation and the accumulation of mutations in CSCs.

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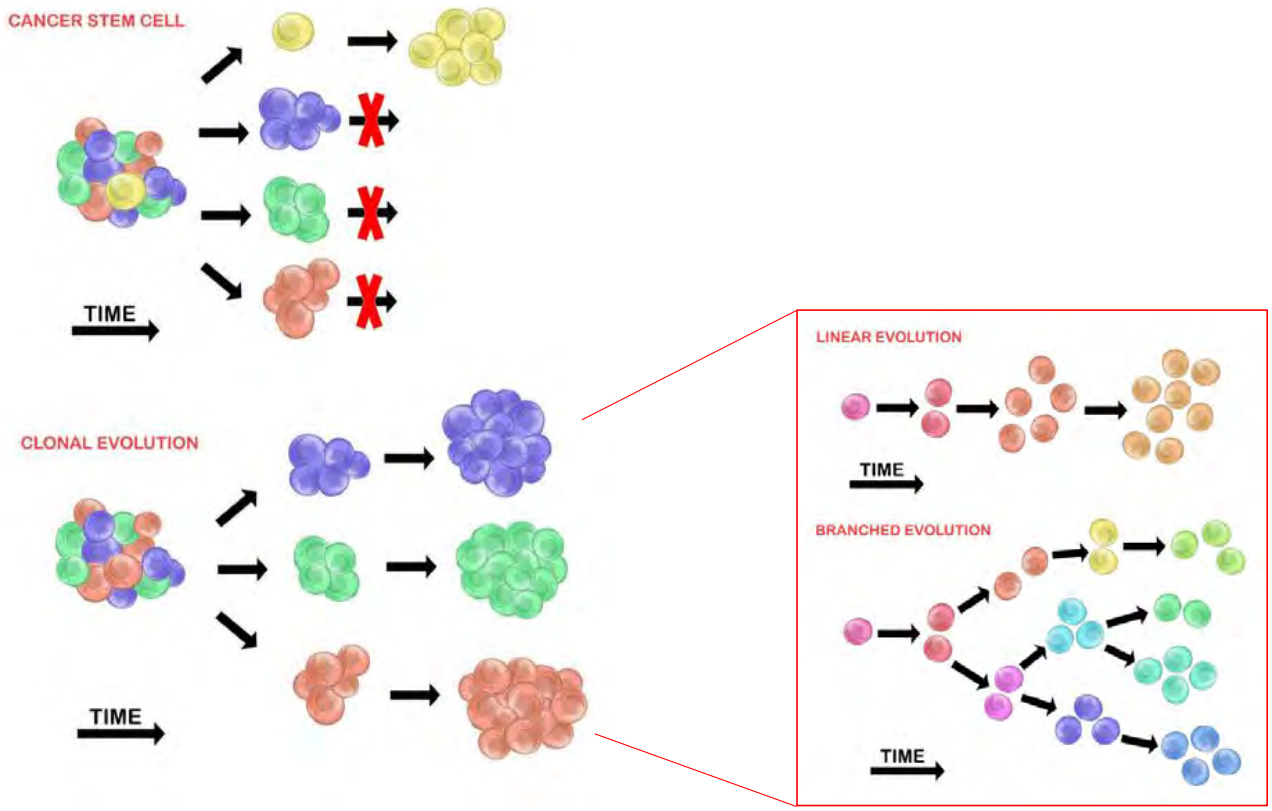

FIGURE 1 Evolution of heterogeneity over time. There are 2 prevailing models of tumor development that have implications for how heterogeneity evolves over time: the cancer stem cell model and the clonal evolution model, which are not mutually exclusive. The former posits that only a select few cancer cells, the cancer stem cells, have the potential to form new tumor cells and it is variability within these cells that gives rise to the heterogeneity observed in the tumors to which they give rise. In the clonal evolution model, tumor cells arise from a single mutated cell and acquire additional varied mutations as they progress. This can occur in a linear fashion, whereby the cells successively acquire mutations that confer a growth or survival advantage, or through a branched mechanism, giving rise to multiple genetically diverse subclonal populations. Available at https://en.wikipedia.org/wiki/Tumour_heterogeneity. Last update February 27, 2014. Accessed May 1, 2018. Reproduced under a Creative Commons Attribution ShareAlike License.

Accumulated experimental evidence suggests that these models are not mutually exclusive and that they can all contribute to heterogeneity in varied amounts across different tumor types. What is clear is that heterogeneity and evolution are intricately intertwined in cancer development.[1,2,6]

An unstable genome

Heterogeneity and evolution are fueled by genomic alterations and the genome instability that they foster. This genome instability can range from single base pair substitutions to a doubling of the entire genome and results from both exposure to exogenous mutagens (eg, chemicals and ultraviolet radiation) and genomic alterations that have an impact on important cellular processes (eg, DNA repair or replication).

Among the most common causes of genome instability are mutations in the DNA mismatch repair pathway proteins or in the proofreading polymerase enzymes. Genome instability is often associated with unique mutational signatures – characteristic combinations of mutations that arose as the result of the specific biological processes underlying them.[7]

Genome-wide analyses have begun to reveal these mutational signatures across the spectrum of human cancers. The Wellcome Sanger Institute's Catalogue of Somatic Mutations in Cancer (COSMIC) database has generated a set of 30 mutational signatures based on analysis of almost 11,000 exomes and more than 1,000 whole genomes spanning 40 different cancer types, some of which have been linked with specific mutagenic processes, such as tobacco, UV radiation, and DNA repair deficiency (Table 1).[8]

One potential downside to genome instability for cancer cells is that it can lead to massive deleterious effects that overwhelm the genome and lead to cell death. A potential way to overcome this is for the changes to be restricted to a small portion of the genome and there is evidence for this in the discovery of patterns of localized hypermutation (kataegis) described in breast cancer genomes and in several

TABLE 1 COSMIC mutational signatures in cancer[a]

Process	Associated signatures	Cancer types	Description
Age-related mutagenesis	Signature 1	All cancer types, most samples	■ Associated with small numbers of small insertions and deletions, resulting from spontaneous deamination of 5-methylcytosine
	Signature 5	All cancer types, most samples	■ Associated with a predominance of T>C substitutions in the ApTpN trinucleotide context with transcriptional strand bias, thought to result from loss of the *FHIT* gene
Homologous recombination deficiency	Signature 3	Breast, ovarian, and pancreatic cancers	Associated with an increased number of large insertions and deletions with microhomology at the breakpoints. Related to a failure of DNA double-strand break repair by homologous recombination (eg, *BRCA1/2* mutations)
APOBEC enzymes	Signature 2	22 cancer types, most common in cervical and bladder cancers, in at least 10% of samples	■ Enriched for C>T and C>G substitutions, commonly associated with the phenomenon of local hypermutation known as kataegis, thought to arise from cytidine deaminase activity of the AID/APOBEC enzyme family.
	Signature 13	Same as Signature 2	■ As above, but associated with mainly C>G mutations
DNA mismatch repair deficiency	Signature 6	■ 17 cancer types, most common in colorectal and uterine cancers	Associated with high numbers of small insertions and deletions at mono/polynucleotide repeats and microsatellite instability, related to defective DNA mismatch repair
	Signature 15	■ Stomach cancers and a single small cell lung carcinoma	
	Signature 20	■ Stomach and breast cancers	
	Signature 26	■ Breast, cervical, stomach, and uterine cancers	
DNA proofreading	Signature 10	6 cancer types, most common in uterine and colorectal cancers	Associated with huge numbers of mutations, thought to result from altered activity of the error-prone polymerase POLE
Base excision repair	Signature 18	Colorectal cancer[b]	Associated with enrichment of transversion mutations (G:C>T:A), related to defective *MUTYH* gene and base excision repair deficiency
UV radiation	Signature 7	Skin, head and neck, and oral squamous cancers	Associated with large numbers of CC>TT dinucleotide mutations at dipyrimidines, related to UV light exposure
Alkylating cytotoxic drugs	Signature 11	Melanoma and glioblastoma	Associated with a strong transcriptional strand bias for C>T substitutions, related to treatment with alkylating agents
Tobacco	Signature 4	Head and neck, liver, and esophageal cancers; lung adenocarcinoma; lung squamous cell carcinoma; small cell lung carcinoma	■ Associated with transcriptional strand bias for C>A mutations, related to exposure to tobacco carcinogens
	Signature 29	Gingivo-buccal oral squamous cell carcinoma	■ Associated with transcriptional strand bias for C>A mutations and CC>AA dinucleotide substitutions, related to exposure to chewing tobacco
Immunoglobulin gene hypermutation	Signature 9	Chronic lymphocytic leukemia and malignant B-cell lymphoma	Associated with enrichment of T>G transversions, related to the error-prone polymerase η. Observed predominantly in cancers with immunoglobulin gene hypermutation

[a]References: Wellcome Sanger Institute. Signatures of mutational processes in human cancer. https://cancer.sanger.ac.uk/cosmic/signatures. Update/publication date not available. Accessed May 1, 2018. Volinia S, et al. The ubiquitous 'cancer mutational signature' 5 occurs specifically in cancers with deleted *FHIT* alleles. Oncotarget. 2017;8(60):102199-102211. Pilati C, et al. Mutational signature analysis identifies MUTYH deficiency in colorectal cancers and adrenocortical carcinomas. J Pathol. 2017;242:10-15. [b]Signature 18 has been observed in other cancer types, but it has not yet been linked to base excision repair in those cases.

TABLE 2 Targeting DNA repair pathways

Drug	Manufacturer	Mechanism of action	Most advanced clinical setting (clinicaltrials.gov identifier)
Olaparib (Lynparza)	AstraZeneca	PARP inhibitor	*FDA approved* *BRCA*-mutated ovarian cancer (2014) Maintenance therapy ovarian cancer (2017) *BRCA*-mutated metastatic breast cancer (2018) *Phase 3* *BRCA*-mutated pancreatic cancer (POLO; NCT02184195)
Niraparib (Zejula)	Tesaro	PARP inhibitor	*FDA approved* Maintenance therapy ovarian cancer *Phase 3* Maintenance therapy SCLC (NCT03516084) Maintenance therapy ovarian cancer (NCT02655016)
Rucaparib (Rubraca)	Pfizer	PARP inhibitor	*FDA approved* *BRCA*-mutated ovarian cancer (2016) Maintenance therapy ovarian cancer (2018) *Phase 3* *BRCA*-mutated ovarian cancer (ARIEL-4; NCT02855944) HRD-positive mCRPC (TRITON3; NCT02975934)
Veliparib	Abbott	PARP inhibitor	*Phase 3* In combination with temozolomide in GBM (NCT02152982)
Talazoparib	BioMarin	PARP inhibitor	*Phase 2* *BRCA*/PTEN/HRD-positive cancers (NCT02286687) *BRCA*-wildtype TNBC/solid tumors (NCT02401347) HRD-positive squamous cell lung cancer (NCT03377556) mCRPC (NCT03148795)
MSC2490484A	EMD-Serono	DNA-PK inhibitor	*Phase 1* In combination with RT in advanced cancers (NCT02516813)
CC-115	Celgene	DNA-PK inhibitor	*Phase 1* In combination with enzalutamide in mCRPC (NCT02833883)
AZD0156	AstraZeneca	ATM inhibitor	*Phase 1* In advanced cancer (AToM; NCT02588105)
VX-970	Vertex	ATR inhibitor	*Phase 2* Urothelial cancer (NCT02567409) Ovarian cancer (NCT02627443)
AZD6738	AstraZeneca	ATR inhibitor	*Phase 2* In combination with olaparib in SCLC (SUKSES-N2; NCT03428607) In combination with acalabrutinib in CLL (NCT03328273)
Prexasertib (LY2606368)	Eli Lilly	CHK1/2 inhibitor	*Phase 2* SCLC (NCT02735980) *BRCA*-mutated breast or ovarian cancer or CRPC (NCT02203513) Solid tumors with replicative stress or HRD (NCT02873975) Ovarian cancer (NCT03414047)
AZD1775	AstraZeneca	Wee1 kinase inhibitor	*Phase 2* SCLC (NCT02688907) In combination with cisplatin in breast cancer (NCT03012477) +/- cytarabine in AML or MDS (NCT02666950)
Nivolumab (Opdivo)	Bristol-Myers Squibb	Immune checkpoint inhibitor	*FDA approved* MSI-H or dMMR CRC (2017) *Phase 2* Prostate cancer with DNA repair defects (ImmunoProst; NCT03040791) Uterine cancer with dMMR/MSI-H (NCT03241745)
Pembrolizumab (Keytruda)	Merck	Immune checkpoint inhibitor	*FDA approved* MSI-H or dMMR cancers (2017) *Phase 2* mCRPC with DNA damage repair defects (NCT03248570)

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Drug	Manufacturer	Mechanism of action	Most advanced clinical setting (clinicaltrials.gov identifier)
Atezolizumab (Tecentriq)	Genentech	Immune checkpoint inhibitor	*Phase 3* dMMR CRC in combination with bevacizumab and chemotherapy (NCT02997228)
Durvalumab (Imfinzi)	AstraZeneca	Immune checkpoint inhibitor	*Phase 2* MSI-H or POLE-mutated mCRC (NCT03435107)

AML, acute myeloid leukemia; ATM, ataxia telangiectasia mutated protein; ATR, ataxia telangiectasia and rad3 related protein; BRCA, breast cancer susceptibility gene; CHK1/2, checkpoint kinase 1/2; CLL, chronic lymphocytic leukemia; CRC, colorectal cancer; dMMR, defective mismatch repair; GBM, glioblastoma; HRD, homologous recombination deficiency; MDS, myelodysplastic syndrome; MSI-H, microsatellite instability-high; PARP, poly(ADP)ribose polymerase; POLE, DNA polymerase epsilon; PTEN, phosphatase and tensin homolog; RT, radiation therapy; SCLC, small cell lung cancer

novel classes of chromosomal rearrangements described in other genome sequencing studies (eg, chromothripsis and chromoplexy).[9]

Fueling resistance

Arguably, heterogeneity presents one of the most significant barriers to effective cancer therapy, and this has become increasingly true in the era of personalized medicine in which targeted therapies take aim at specific molecular abnormalities.

It is vital that drugs target the truncal alterations that are present in all cancer cells to ensure that the entire cancer is eradicated. However, it is not always possible to target these alterations, for example, at the present time tumor suppressor proteins like p53 are not druggable.

Even when truncal alterations have been targeted successfully, such as epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) chromosomal rearrangements in non–small-cell lung cancer (NSCLC) and *BRAF* mutations in melanoma, the long-term efficacy of these drugs is almost invariably limited by the development of resistance.

Tumor heterogeneity and the clonal evolution it fuels are central drivers of resistance. Because tumors are dynamic and continue to evolve, anticancer treatments can act as a strong selective pressure and drive the emergence of drug-resistant subclones that allow the tumor to persist. In fact, study findings have revealed that small populations of resistant cells may be present before treatment. Thus, resistance may also occur as a result of the outgrowth of preexisting treatment-resistant cells that suddenly find that they acquire a survival advantage in the presence of a drug.[1,6]

Tackling heterogeneity

Despite extensive clinical documentation of the existence of heterogeneity and its underlying mechanisms across a range of tumor types, the development of novel clinical trial designs and therapeutic strategies that account for its effects have only recently begun to be explored.

For the most part, this was because of a lack of effective methods for evaluating intratumor heterogeneity. Multiregion biopsies, in which tissue derived from multiple different regions of a single tumor mass or from distinct cancerous lesions within the same patient, give a snapshot of tumor heterogeneity at a single point in time. The repeated longitudinal sampling required to gain a deeper appreciation of tumor heterogeneity over the course of tumor evolution is often not possible because of the morbidity associated with repeated surgical procedures.

Liquid biopsies, in which DNA sequencing can be performed on tumor components that are found circulating in the blood of cancer patients (including circulating tumor cells and cell-free circulating tumor DNA) have rapidly gained traction in the past several decades and offer an unprecedented opportunity for real-time assessment of evolving tumor heterogeneity.

They have proved to be highly sensitive and specific, with a high degree of concordance with tissue biopsy, they can identify both clonal and subclonal mutations, and they can detect resistance substantially earlier than radiographic imaging, which could permit earlier intervention.[10,11] The first liquid biopsy-based companion diagnostic test was approved by the US Food and Drug Administration in 2016, for the detection of *EGFR* mutations associated with NSCLC.

Yet, even liquid biopsy alone is not able to fully dissect the extent of tumor heterogeneity, especially because it is limited in its ability to assess spatial heterogeneity. Truly effective assessment of tumor heterogeneity is likely to require a combination of liquid biopsy, carefully selected tumor tissue biopsies, imaging diagnostics, and biomarkers.

The ongoing TRACERx (Tracking cancer evolution through therapy [Rx]) trials are evaluating a combination of approaches to follow tumor evolution across the course of treatment. The study in NSCLC began in 2014 with a target enrollment of 842 patients and will follow patients over 6 years. Preliminary data from the first 100 patients were recently published and demonstrated that increased intratumor heterogeneity correlated with increased risk of recurrence or death.[12]

If patients consent, the TRACERx trials also feed into the PEACE (Posthumous evaluation of advanced cancer

environment) trials, which are collecting postmortem biopsies to further evaluate tumor heterogeneity and evolution. TRACERx trials in several other cancer types are now also underway.

Cutting off the source

The main therapeutic strategies for overcoming tumor heterogeneity are focused on the mechanisms of resistance that it drives. It is becoming increasingly apparent that rationally designed combinations of drugs are likely to be required and might need to be administered early in the course of disease to prevent resistance.

However, according to mathematical modeling studies, combinations of at least 3 drugs may be necessary.[13] In many cases, this is unlikely to be feasible owing to the unavailability of drugs for certain targets and issues of toxicity, as well as the high cost.

An alternative strategy is to use immunotherapy, because a single treatment can target multiple neoantigens simultaneously. Although immunotherapy has proved to be a highly effective treatment paradigm in multiple tumor types, resistance still arises through varied mechanisms with tumor heterogeneity at their core.[14,15]

A promising avenue for drug development is to cut off the source of tumor heterogeneity – genomic instability and the mutagenic processes that foster it (Table 2). This is exemplified by the success of poly(ADP-ribose) polymerase (PARP) inhibitors in patients with breast cancer susceptibility (*BRCA1/2*) gene mutations.

Both germline and somatic mutations in the *BRCA1/2* genes are observed in 10% to 15% of patients with ovarian cancer and a substantial number of patients with other types of cancer, including breast, pancreatic, and prostate cancers.[16,17]

These genes play a central role in the homologous recombination (HR) pathway of DNA repair, which repairs double-strand breaks in DNA. PARP inhibitors target a different DNA repair pathway, base excision repair, which repairs single-strand breaks. The use of PARP inhibitors in patients with *BRCA1/2* mutations is designed to create irreparable damage to the DNA repair processes and drive an unsustainable level of genome instability that leads to cell death, whereas normal cells without HR deficiency can survive.[18]

A growing number of PARP inhibitors are now approved for use in the United States for the treatment of ovarian cancer. In January, olaparib became the first PARP inhibitor approved for patients with *BRCA1/2*-mutant breast cancer, based on data from the OlympiAD trial in which 302 patients were randomized to receive olaparib 300 mg twice daily or physician's choice of chemotherapy. Olaparib improved progression-free survival from 4.2 months to 7.0 months (hazard ratio, 0.58; $P = .0009$), and the most common adverse events included anemia, nausea, fatigue, and vomiting.[19]

Tumors with other defects in HR have also shown susceptibility to PARP inhibition, shifting interest toward identifying and treating these tumors as a group, independent of histology – about a quarter of all tumors display HR deficiency.[20] This novel strategy of targeting mutational processes across a range of tumor types has also been exploited in the development of immunotherapies.

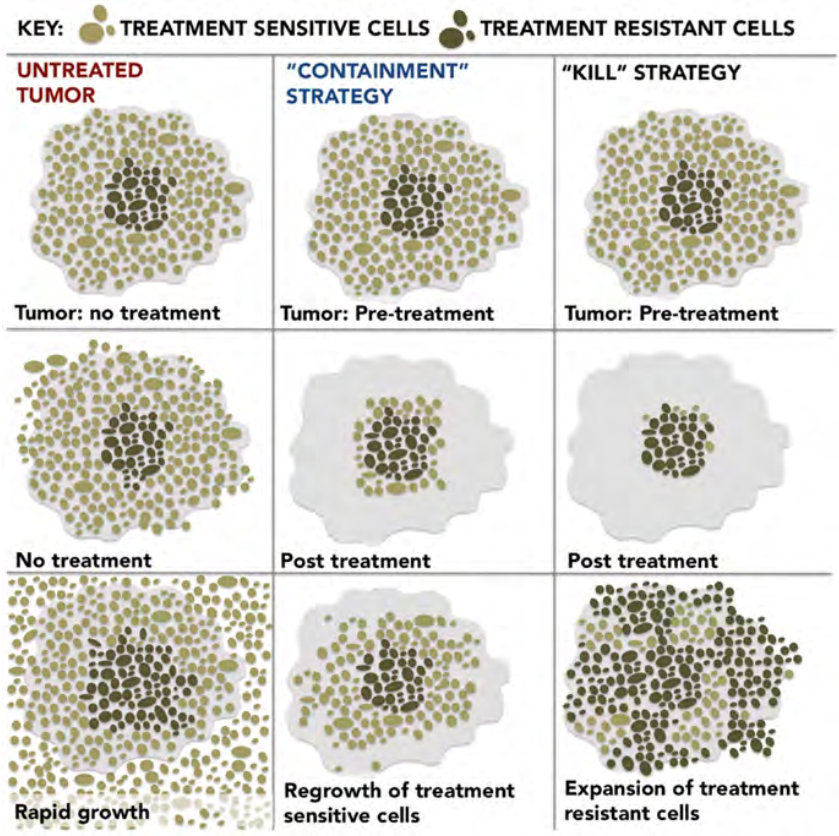

FIGURE 2 Adaptive therapy. Evidence suggests that a small population of resistant cells may exist before treatment, but the development of resistance is energetically costly and therefore treatment-sensitive cells predominate in an untreated tumor. Currently, the goal of anticancer therapy is to hit a tumor hard and fast and most clinical trials seek out the maximum tolerated dose ('kill' strategy). It is widely recognized that this can actually be counterproductive because the intense selective pressure and the elimination of their competition (the treatment-sensitive cells) drives the rapid emergence of treatment-resistant cells. Researchers are now testing out 'containment' strategies, which seek to keep the tumor under control by exploiting the high cost of resistance. Adaptive therapy is designed to use treatment holidays, intermittent dosing, and dose reductions, among other strategies, to this end. Oronsky B, et al. The war on cancer: a military perspective. Front Oncol. 2015;4:387. Reproduced under a Creative Commons Attribution License (CC BY).

Patients with defects in the mismatch repair (MMR) pathway and microsatellite instability (MSI) – multiple alterations in the length of microsatellite markers within the DNA – are more sensitive to immunotherapy, likely because they are predisposed to a high level of somatic mutations that can serve as neoantigens to provoke a strong anti-tumor immune response.

In 2017, 2 immune checkpoint inhibitors were approved for use in patients with MSI-high or defective MMR (dMMR) cancers. The indication for pembrolizumab (Keytruda) was independent of tumor histology, the first approval of its kind. It was based on the results of 5 clinical trials in which 149 patients with MSI-H or dMMR cancers were given pembrolizumab 200 mg every 3 weeks or 10 mg/kg every 2 weeks for a maximum of 24 months. The overall response rate was 39.6%, including 11 complete responses and 48 partial responses.[21]

A new paradigm

Treatment of a tumor is one of the major selective pressures

TABLE 3 Select ongoing clinical trials incorporating intratumor heterogeneity

Trial name/ identifier	Phase	Sponsor	Description
NCT02415621	NA	H Lee Moffitt Cancer Center and Research Institute	Adaptive (on and off scheduling) abiraterone therapy for metastatic CRPC; patients will be enrolled who achieve ≥50% decline in their PSA levels while on abiraterone and treatment will not be reinitiated until there is a ≥50% increase in PSA
NCT03511196	1	H Lee Moffitt Cancer Center and Research Institute	Intermittent ADT for stage IV castration-sensitive prostate cancer; PSA and testosterone level will be used to guide treatment
NCT03416153	2	University of Michigan Cancer Center	Individualized adaptive de-escalated radiotherapy for HPV-related oropharyngeal cancer; uses pre- and midtreatment imaging to guide de-escalation
NCT03122522	2	Memorial Sloan Kettering Cancer Center	Adaptive dosing of ipilimumab and nivolumab combination immunotherapy
NCT02771314	2	Hellenic Oncology Research Group	Liquid biopsy used as a tool to evaluate resistance to first and third generation EGFR TKIs in *EGFR*-mutant NSCLC; genetic evolution and biological characteristics of CTCs will be monitored over time after treatment
TRACERx NCT01888601	NA	University College London	Tracking non–small-cell cancer evolution through therapy; after tumors from diagnosis to relapse and tracking genetic evolution
TRACERx-TNBC NCT03077776	NA	UNICANCER	Tracking triple-negative breast cancer evolution through therapy; examining the relationship between intratumor heterogeneity and response to neoadjuvant chemotherapy
TRACERx-Renal NCT03226886	NA	Royal Marsden NHS Foundation Trust	Tracking renal cell carcinoma evolution through therapy
NCT02993536	NA	Abramson Cancer Center of the University of Pennsylvania	After the clonal evolution of B cells in high-risk CLL after idelalisib-rituximab treatment
NCT03059641	NA	GenePlus-Beijing Co Ltd	Therapeutic resistance and clonal evolution assessed with liquid biopsy of NSCLC patients in China
CHRONOS NCT03227926	2	Fondazione del Piemonte per l'Oncologia	Evaluating the safety and efficacy of rechallenge with panitumumab driven by Ras resistance dynamics in patients with metastatic CRC; using liquid biopsy to determine extended-Ras alterations
NCT0342529	1	John Wayne Cancer Institute	A longitudinal assessment of tumor evolution in patients with brain cancer following treatment with temozolomide + RT, ipilimumab monotherapy or ipilimumab + nivolumab combination therapy
DARWIN I NCT02183883			Deciphering afatinib response and resistance with intratumor heterogeneity; patients registered in the TRACERx study will receive afatinib
DARWIN II NCT02314481	2	University College London	Deciphering antitumor response and resistance with intratumor heterogeneity; evaluating the impact of intratumor heterogeneity on anti-PD-L1 therapy

ADT, androgen deprivation therapy; CLL, chronic lymphocytic leukemia; CTC, circulating tumor cells; EGFR, epidermal growth factor receptor; HPV, human papillomavirus; NSCLC, non-small cell lung cancer; RT, radiation therapy; PD-L1, programmed cell death ligand 1; PSA, prostate specific antigen

that shapes its evolution and recent evidence has emerged that these selective pressures can be highly dynamic. Study findings have shown that there is a cost associated with evolution of resistant subclones and, if the selective pressure of therapy is removed, that cost may become too high, such that resistant subclones are then outcompeted by drug-sensitive ones. There have been reports of reversal of drug resistance when drug treatment is interrupted.

The current treatment paradigm is to try to eliminate tumors by hitting them hard and fast with the maximum tolerated dose (MTD) of a drug. However, there is increasing appreciation that this may be inadvertently fostering more rapid disease progression because it selects for the emergence of resistant cells and eliminates all their competitors (Figure 2).

This is driving a potential paradigm shift, in which researchers are applying concepts from evolutionary biology and the control of invasive species to the treatment of cancer. Instead of completely eliminating a cancer, a strategy of adaptive therapy could be used to set up competition between different subclones and keep tumor growth in check by exploiting the high cost of resistance.[22]

Adaptive therapy involves the use of treatment holidays, intermittent dosing schedules or reduced drug doses, rather than using the MTD. Adaptive therapy was tested recently in mice with triple-negative and estrogen receptor-positive breast cancer. The standard maximum dose of chemotherapy was compared with adaptive therapy with either reduced doses or skipped doses as the tumor responded. Tumor growth initially decreased with all 3 treatment scenarios, but then regrew when chemotherapy was stopped or doses were skipped. However, adaptive therapy with lower doses resulted in long-term stabilization of the tumor where treatment was eventually able to be withdrawn.[23] Clinical trials of several different types of adaptive therapy strategies are ongoing (Table 3).

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