EDITORIAL

Innovative drugs bring continuous benefits to cancer patients

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Cancer, often referred to as the "emperor of all maladies", remains a persistent challenge for medical science and humanity. The complexity of cancer treatment presents an intricately woven biological spectrum encompassing various dimensions including genetics, epigenetics and the tumor microenvironment. The genetic heterogeneity and mutational burden of tumor cells necessitate considering the impact of multiple variations in drug interventions, while the cellular interactions, signaling pathway crosstalk, and molecular regulations within the tumor microenvironment pose profound challenges in selecting therapeutic strategies and evaluating treatment efficacy.[1] Recently, through a combination of cutting-edge research, technological advancements, and a profound understanding of the highly complex cancer biology, significant progresses have been achieved in the development of innovative anticancer drugs, which have redefined treatment protocols and patient experiences, and most importantly, extend survival periods and bring continuous benefits to individuals grappling with cancer.

In cancer therapy, the criteria for assessing treatment efficacy have transitioned from a singular focus on tumor inhibition rates to a heightened emphasis on enhancing the quality of life for patients. The remarkable

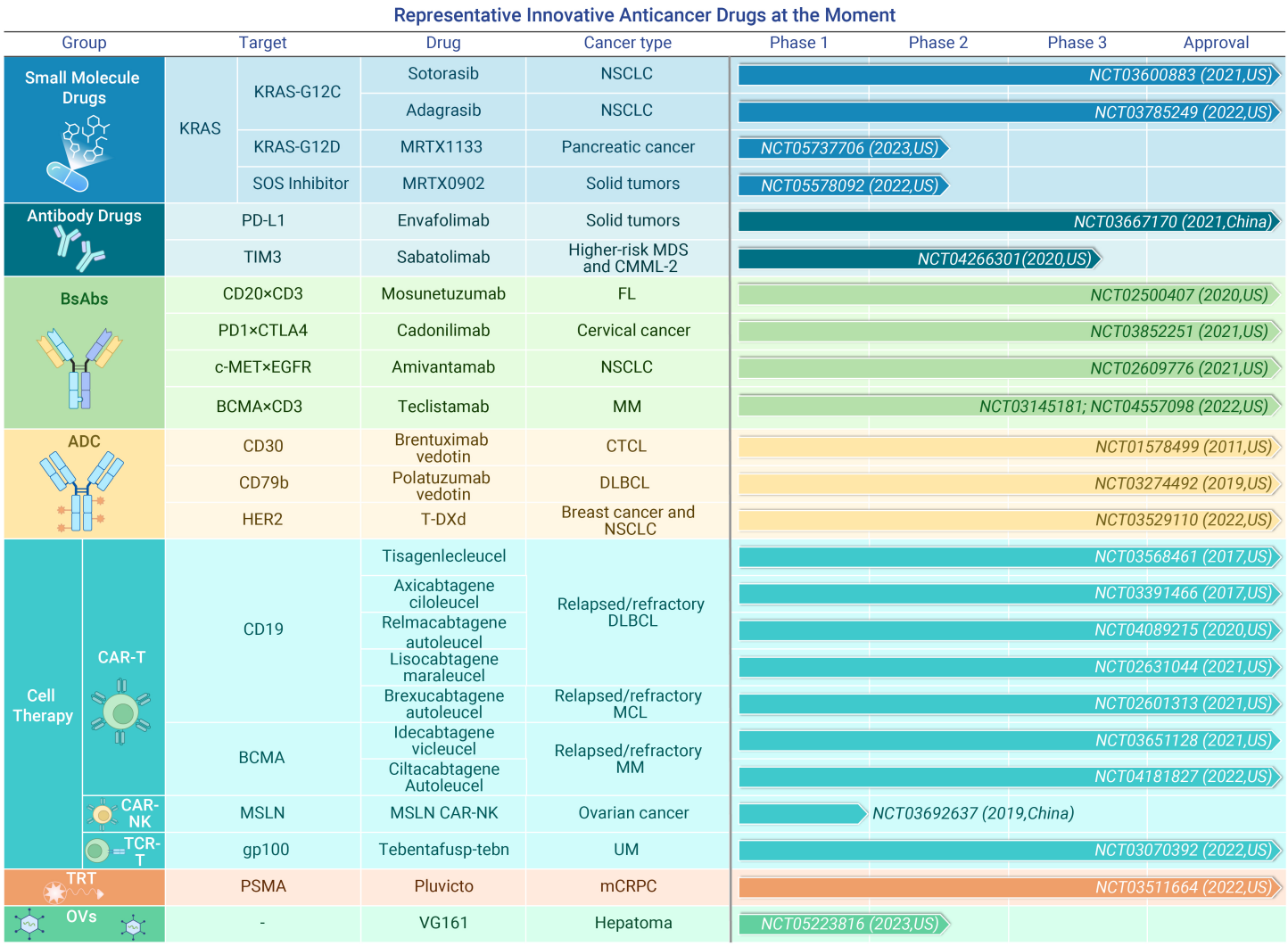

Figure 1. Representative innovative anticancer drugs at the moment The Gantt chart provides crucial information regarding targets, cancer types, and the progress of clinical trials for pivotal and innovative anti-cancer drugs.

advancements witnessed in the development of these pharmaceuticals not only underscore the promise of contemporary medicine but also stand as a beacon of hope for individuals contending with this formidable affliction. In the current landscape of anticancer therapeutics, a multitude of innovative drugs are developed rapidly. We posit that the key features defining such innovative pharmaceuticals encompass several critical aspects, including a novel mechanism of action (MOA), a distinct chemical structure, independent intellectual property rights, and, most importantly, a substantial improvement in therapeutic efficacy compared to previous treatments. Nevertheless, disparities in the progression of the cutting-edge anticancer drugs during clinical trials, making it challenging to provide a comprehensive longitudinal overview of their status, targets, applicable cancer types and overall progress for the broader public. To tackle this challenge, we present a concise Gantt chart (Figure 1) detailing essential information about target points, cancer

types, and the progress of clinical trials for pivotal innovative anti-cancer drugs. This visualization aims to assist a broader spectrum of precision medicine researchers in navigating the intricacies of this field.

Mutations in the KRAS gene are prevalent in nearly 90% of pancreatic cancers, 30-40% of colorectal cancers, and 15-20% of lung cancers (most commonly in NSCLC). Among these, mutations in codon 12 account for over 80% of cases and include G12C, G12D, G12S, and G12V mutations. Sotorasib, noteworthy for targeting an "undruggable" gene,[2] boasts a mPFS of 5.6 months, surpassing the 4.5 months achieved with Docetaxel for NSCLC patients with mutations. The second-generation drug Adagrasib, with superior efficacy and a longer half-life, rapidly obtained FDA approval. Simultaneously, in the realm of KRAS subtypes, drugs like MRTX1133, KRAS pathway collaborative agent SOS inhibitor MRTX0902 gains steadily prominence, with ongoing data evaluation.

Antibody-based drugs target and inhibit tumor growth through mechanisms such as ADCC, apoptosis induction, toxin conjugation, growth signal disruption, and angiogenesis inhibition. The PD-L1 antibody Envafolimab not only enhances patient adherence but also markedly improves the quality of life when juxtaposed with conventional PD-L1 monoclonal antibodies. This innovation opens up new avenues in cancer immunotherapy. The promising Sabatolimab, targeting TIM3, has received fast-track FDA approval for MDS treatment.[3] The rapid proliferation of BsAbs broadens their spectrum of targets. Currently, clinical trials are assessing their efficacy in combination with Azacitidine. Notable candidates in this category, such as Mosunetuzumab, Cadonilimab, Amivantamab, and Teclistamab, have shown a significant extension in patients' progression-free survival, providing further substantiation of their efficacy. These drugs hold considerable potential for future growth, offering hope to cancer patients who may have exhausted traditional treatment options.

ADC drugs combine monoclonal antibodies with potent cytotoxic drugs. In the field of ADC drugs, namely Brentuximab vedotin and Polatuzumab vedotin, have effectively addressed efficacy gaps in the treatment of CD30-positive Cutaneous T-cell lymphoma, Diffuse Large B-cell Lymphoma, and High-Grade B-cell Lymphoma. Consequently, they have rapidly gained prominence in the market. With a focus on targeting HER2, the highly acclaimed T-DXd has greatly benefited patients.[4] In the updated American Society of Clinical Oncology (ASCO) guidelines for the systemic treatment of HER2-positive advanced breast cancer (HER2+ABC), T-DXd has replaced T-DM1 as the new standard for second-line anti-HER2 therapy. Additionally, in the clinical pathway for anti-HER2 treatment in advanced HER2+ breast cancer, the guidelines suggest that patients who have received Trastuzumab±Pertuzumab as adjuvant therapy and experienced progression within 12 months can skip first-line THP treatment and opt for second-line T-DXd therapy directly. Furthermore, it is particularly noteworthy that T-DXd has demonstrated potent anti-tumor activity across various solid tumors exhibiting different levels of HER2 expression, including HER2-low breast cancer, HER2-positive gastric cancer, HER2-expressing colorectal cancer, and HER2-expressing or mutated NSCLC.

Cell therapy entails the infusion of engineered immune cells, such as CAR-T cells, CAR-NK cells, and TCR-T cells, designed to recognize and attack tumor cells. These modified immune cells harness the patient's immune system to target and destroy cancer cells.

CAR-T cell therapy has progressively made it a cornerstone in hematologic cancer treatment, particularly in lymphomas, acute lymphoblastic leukemia (ALL), and multiple myeloma (MM).[5] The primary targets of these therapies include CD19 (Tisagenlecleucel, Axicabtagene ciloleucel, Relmacabtagene autotolucel, Lisocabtagene maraleucel, Brexucabtagene autotolucel) and BCMA (Idecabtagene vicleucel, Ciltacabtagene autotolucel). Based on available clinical data, it is evident that these treatments hold significant promise and deliver substantial benefits to patients with hematological malignancies. The data in the figure underscore the highly promising results in hematologic cancers, demonstrating an overall improvement. The emergence of innovative drugs in this field holds the promise of extending the lifespan and improving the quality of life for hematologic cancer patients, signaling a hopeful future. Compared to CAR-T cell therapy, CAR-NK cell therapy demonstrates specific merits. CAR-NK therapy offers a higher level of safety, reducing the risk of Cytokine Release Syndrome (CRS). Furthermore, allogenic NK cells do not trigger Graft-Versus-Host Disease (GVHD), which is crucial for patients. Its safety has been confirmed in numerous clinical trials. In summary, it is a highly promising therapy and may become a game-changing treatment, but continuous efforts are still required to advance it further.

Meanwhile, TCR-T has made significant progress. The FDA has approved the first TCR-T therapy, Tebentafusp-Tebn, which is used to treat unresectable or metastatic uveal melanoma and is the first therapy to demonstrate a survival benefit in patients with this type of cancer, fills a critical gap in available treatment options.

Oncolytic viruses demonstrated significant antitumor efficacy across various tumor models. Following viral infection, oncolytic viruses can initiate tumor cells death. Subsequently, the presence of viral elements and tumor-associated antigens induces both innate and adaptive immunity, fostering antitumor immune responses. Consequently, distant lesions may regress even without direct exposure to the virus. Current clinical trials focus on melanoma and advanced glioblastoma. A novel immunotherapeutic oncolytic herpes simplex virus, VG161, which carries four genes, including IL12, IL15/15RA (comprising IL15 and the IL15 receptor alpha subunit), and a PD-L1 blocking peptide (PDL1B), received orphan drug designation from the FDA recently. Injected into tumor tissue, VG161 replicates within tumor cells, causing lysis and efficiently expressing the four immunostimulatory factors, harmonizing oncolytic activity with immune stimulation.

In summary, the amalgamation of cutting-edge research, technological advances, and a deep understanding of cancer biology is reshaping treatment modalities and enhancing the overall patient experience. First and foremost, these anticancer drugs demonstrate unequivocal merit by prolonging the survival of patients, providing them the opportunity to pursue life objectives. To elaborate further, these innovative drugs typically exhibit a heightened degree of therapeutic precision, thereby mitigating a range of adverse effects such as nausea, vomiting, and hair loss. This, in turn, significantly improves the overall comfort of patients' lives. Furthermore, the benefits conferred by these novel drugs extend beyond the confines of individual patients and encompass various facets of society and the healthcare system. The integration of medical resources not only benefits patients directly but also contributes to alleviating the broader healthcare burden. Targeted drugs, being effective with fewer side effects, not only reduce hospital admissions but also contribute to decreased medical expenses. Despite potential higher costs for specific ones, they often lead to overall lower long-term healthcare spending. Most significantly, in the forthcoming years, there is a growing anticipation for the emergence of new drugs that address previously unmet clinical needs. This holds the promises of a more judicious allocation of medical resources, an extension of human longevity, and a heightened level of scientific advancement.

REFERENCES

1. Hanahan, D., and Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. Cell **144**: 646–674. DOI: 10.1016/j.cell.2011.02.013.
2. Hong, D.S., Fakih, M.G., Strickler, J.H., et al. (2020). KRASG12C inhibition with sotorasib in advanced solid tumors. N. Engl. J. Med. **383**: 1207–1217. DOI: 10.1056/NEJMoa1917239.
3. Zeidan, A.M., Al-Kali, A., Borate, U., et al. (2021). Sabatolimab (MBG453) combination treatment regimens for patients (Pts) with higher-risk myelodysplastic syndromes (HR-MDS): the MDS studies in the stimulus immuno-myeloid clinical trial program. Blood **138 (Supplement 1)**: 4669. DOI: 10.1182/blood-2021-145626.
4. Tsurutani, J., Iwata, H., Krop, I., et al. (2020). Targeting HER2 with trastuzumab deruxtecan: a dose-expansion, phase I study in multiple advanced solid tumors. Cancer Discov. **10**: 688–701. DOI: 10.1158/2159-8290.CD-19-1014.
5. Nathan, P., Hassel, J.C., Rutkowski, P., et al. (2021). Overall survival benefit with tebentafusp in metastatic uveal melanoma. N. Engl. J. Med. **385**: 1196–1206. DOI: 10.1056/NEJMoa2103485.

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DECLARATION OF INTERESTS

The authors declare no competing interests.