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well as, genetic alterations have heralded the era of personalized (personalized or precision) cancer treatment. Molecular targeting agents with their improved tolerability and sustained responses compared to conventional cytotoxic chemotherapy have contributed to remarkable improvements in clinical outcomes. Dramatic phase 1 observations of antitumor activity of novel molecules in the relapsed or

# **Oncotherapeutics: A General Overview**

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**REVIEW ARTICLE** 

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## **1** | INTRODUCTION

• xperimental oncotherapeutics programs have been in place at major academic centres for • over four decades. The emergence of molecular targeting agents and the recent introduction of immuno-oncology drugs have expanded the scope and eligibility for first-in-human trials. Improved understanding of tumor biology coupled with the

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Abstract

Experimental oncotherapeutics programs have been in place at major academic centres for over four decades. The emergence of molecular targeting agents and the recent introduction of immuno-oncology drugs have expanded the scope and eligibility for first-in-human trials. Improved understanding of tumor biology coupled with the ability to screen for tumor associated targets, as well as, genetic alterations have heralded the era of personalized (personalized or precision) cancer treatment. Molecular targeting agents with their improved tolerability and sustained responses compared to conventional cytotoxic chemotherapy have contributed to remarkable improvements in clinical outcomes Dramatic phase 1 observations of anti-tumor activity of novel molecules in the relapsed or refractory setting have ofen led to their investigation as monotherapy or in combinatorial strategies early in the course of cancer treatment. Studies have thus evolved from the traditional role of dose and toxicity-fnding studies to innovative enrichment study designs which match patients with study agents, thus increasing the potential of clinical efcacy, even in the early dose escalation setting. Keywords: Oncotherapeutics, Oncology, Cancer, Pharmacist

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While chemotherapeutic agents still have an important role in oncology, the era of precision medicine is beginning to revolutionize treatment options and outcomes for cancer patients. The UABOCCC, Phase 1 Clinical Trials Program was formally established in 2015, in an effort to offer novel first-in- human therapeutic clinical trials to cancer patients in a onestop-shop setting. The program was initiated with 6 clinical trials and rose to 17 clinical trials by 2017. The study enrolled 60 patients in our first year and close to 100 by 2017. Tis single-centre, retrospective analysis was performed to assess clinical outcomes and the predictors of survival and efficacy in patients during the first two and a half years of the program. This program was unique in that all patients received targeted or immuno-oncology agents as the backbone of their <sup>1,2</sup>.

Cancer is the uncontrolled growth of abnormal cells in the body. Cancer develops when the body's normal control mechanism stops working. Old cells do not die and instead grow out of control, forming new, abnormal cells. These extra cells may form a mass of tissue, called a tumor. Some cancer , such as leukemia, do not form tumors.

### 2 | ONCOLOGY

Oncology is a study of cancer and its treatment in medical science. The branch of medicine dedicated

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**Corresponding Author:** Ms. Manaswi N 3rd Year PHARM D Department of Pharmacy Practice Sri Adichunchangiri College of Pharmacy to diagnosing, treating and researching cancer is known as oncology, while a physician who works in the field is called oncologist. Depending on the type, stage and of oncology has three main specialties medical, surgical and radiation and numerous subspecialties. location of a cancer, multiple oncology specialists may be involved in a patient's care. The field Cancer survival has improved due to three main components: improved prevention efforts to reduce exposure to risk factors (e.g., tobacco smoking and alcohol consumption), improved screening of several cancers (allowing for earlier diagnosis), and improvements in treatment.

Cancers are often managed through discussion on multi-disciplinary cancer conferences where medical oncologists, surgical oncologists, radiation oncologist, pathologists, radiologists, and organ specific oncologists meet to find the best possible management for an individual patient considering the physical, social, psychological, emotional, and financial status of the patient. It is very important for oncologists to keep updated with respect to the latest advancements in oncology, as changes in management of cancer are quite common.

Because a cancer diagnosis can cause distress and anxiety, clinicians may use a number of strategies such as SPIKES for delivering the bad news.

### 3 | HISTORY OF ONCOTHERPEUTICS

Personalized medicine (PM) is an integration of personal profiles of proteins or genes of healthcare at personalized level for strengthing and by aiding the emergent technologies "-omics," including, transcriptomics, genomics proteomics and pharmacogenomics<sup>13</sup>. Currently, for optimizing and selecting the cancer patient's therapeutic care, PM has exploited the systematic usage of genetic information that involve family history of patients and lifestyle in contrast to conventional cancer therapies<sup>14</sup>. National Institutes of Health (NIH) has defined personalized medicine as emerging medicine branch that uses genetic profile of individuals, for making decisions on disease diagnosis and treatment <sup>15</sup>. It targets the factors having positive effects on that disease to provide the timely, appropriate, and correct treatment to the right person 16. Cancer therapeutic drugs are not equally effective for all patients. Due to advance high-throughput genomics and proteomics tools available for cancer molecular mechanism understandings, it became easier to disclose the genes that are responsible for drug responses. PM is a revolution for healthcare regimen due to its ability to integrate genetic information, to increase the drug efficacy for treatment, and to introduce new healthcare business <sup>16</sup>. There is a huge variability across diseases, that is, 38-75% patients do not respond to a drug or treatment. In the case of cancer, average response rate of drug is minimum at 25%. In addition, adverse drug reaction is also a problem. In USA, 16% of the approved drugs have shown the disadvantageous drug reactions <sup>17</sup>. Due to the personalized medicine healthcare pattern, doctors or clinicians can make ideal selections to maximize the effectiveness of treatment, simultaneously adverse drug reactions risks can be avoided, and researchers can improve drug and medical device research process for enabling early detection of disease. Based on predictive biomarkers, molecular diagnostic tools provide valuable facts and figures of patients associated with genetically defined subgroups who would take advantage of specific therapy. For example, a 16-gene signature was used by a diagnostic device OncotypeDX® (Genomic Health, USA), to assess the recurrence risk in estrogen receptor positive breast cancer patients <sup>18-20</sup>. Likewise, MammaPrint<sup>®</sup> (Agendia, the Netherlands) practices on a 70-gene expression profile for assessment of distant metastasis risk in breast cancer patients of early stage <sup>21</sup>. In the case of lung cancer, based on recent modern genetic studies, epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), Cbl protooncogene (CBL), MET protooncogene, and receptor protein kinase (MET) are being used as targets for therapeutic purpose. Crizotinib has shown significant results in non-small cell lung cancer treatment by inhibiting ALK <sup>22</sup>. Personalized medicine is getting huge attention of researchers and clinicians for its remarkable potential and countless applications. The notable introduction of recent highthroughput tools combined with improved cancer molecular profile knowledge provides a stable plat-

form for novel molecular targets identification.

#### 4 | MANAGEMENT

FDA approval of ICIs has forever changed the landscape of cancer treatment for a number of diseases that, once metastatic, were considered incurable. Patients with metastatic melanoma, lung, and renal cell carcinoma, to name a few, have found renewed hope and active therapies that are prolonging life. Equally important in hematologic malignancies are the discovery and development of CAR T-cell (chimeric antigen-receptor T- cell) therapies. Currently, two different CAR T-cell therapies (tisagenlecleucel2 and axicabtageneciloleucel,3 both anti CD-19 agents) are approved for the treatment of select hematologic malignancies. Other interesting avenues of study in immunotherapy include vaccine and modified viral targets. While there have been a number of successful vaccine therapies in animal models, these unfortunately have not led to the same results in humans and we eagerly await the first true "cancer vaccine" in the prevention of cancer. Early cancer vaccine research was evaluated in patients with metastatic disease; however, for the large part research has been abandoned in this population because of poor clinical outcomes. The failure of cancer vaccines in the metastatic setting was largely because of the patient's immune systems being in a state of chronic inflammation, leading to T-cell exhaustion.<sup>4</sup> Newer and more promising research is exploring the use of vaccines in cancer recurrence after complete surgical resection. Modified viral targets are gaining momentum in cancer therapy as well. The first FDA approved therapy was talimogenelaherparepvec (T-VEC). T-VEC is a genetically engineered herpes virus (an oncolytic herpes virus) used to treat surgically unresectable melanoma.5,6

As mentioned previously, the first ICI approved for the treatment of metastatic melanoma was the anti-CTLA-4 inhibitor ipilimumab.1 Following the success of ipilimumab was the development of anti-PD-1/ PD-L1 inhibitors that led to FDA approval in multiple diseases,<sup>7</sup> With the success of singleagent ICI therapy came the introduction of dual combination ICI therapy in an attempt to improve

outcomes. The first approval for dual ICI therapy (ipilimumab/nivolumab) was for the treatment of metastatic melanoma in 2016,8Based on the success of ICI therapy in the metastatic setting, studies began investigating their use in the adjuvant setting. Early studies compared ipilimumab versus placebo (but at higher dosing [10 mg/kg]) in patients with highrisk (stage III) resected melanoma. The improvement seen in both relapse-free survival and overall survival led to the approval of this agent in the adjuvant setting in 2015.9 Two additional agents have been approved in the adjuvant setting for melanoma; nivolumab<sup>10</sup> and pembrolizumab,<sup>11</sup> However, with this success came the unfortunate consequences of increased autoimmune toxicity. Moving forward, researchers continue to work to find ways to safely harness the body's immune system to maximum efficacy and control the unpredictable and often severe irAEs that accompany treatment. In addition, researchers continue to look at combinations of different immune checkpoints in combination, as well as ICI agents in combination with chemotherapy and other targeted agents. New avenues of study also include identifying specific biomarkers to select who would be most likely to benefit from ICI therapy, as well as discovering mechanisms of resistance to immunotherapy.

One of the newest checkpoint inhibitors being studied is that of lymphocyte activation gene-3 (LAG-3) by a drug known as relatlimab. Relatlimab is an anti-LAG-3 antibody that works by inhibiting the protein LAG-3 on the surface of T cells, which results in "taking the brakes" off the immune system as other ICI agents have demonstrated,<sup>12</sup>Initial results from a phase 1/2 study of relatlimab in combination with nivolumab in patients with metastatic melanoma who had failed prior immunotherapy have shown promise in potentially overcoming resistance and allowing immunotherapy to continue.<sup>12</sup>In that study, seven of 61 evaluable patients had an objective response to the combination.<sup>12</sup>Additional studies are ongoing either as single agent or in combination with nivolumab in hematologic malignancies, glioblastoma, and renal, stomach, lung, and colon cancer.

While CAR T-cell therapy has had success in hematologic malignancies, it has not in solid tumors. However, this is a very active area of research, but is somewhat more difficult because, unlike checkpoint inhibitors, the targets for CAR T cell vary between malignancies with many not identified as of yet. Continued research in the vaccine and viral area continues, with multiple studies in breast, melanoma, and other solid tumors. The realization of the opportunities for the many uses of immunotherapy in the fight against cancer can be seen in the thousands of studies posted.

#### 5 | ROLE OF PHARMACIST IN ONCOLOGY

Oncology pharmacists are involved with the care of cancer patients at all phases of their treatment; from assessment and diagnosis, to treatment decisions, medication management, symptom management and supportive care, and finally with survivorship programs at the completion of their treatment. They work with other care providers to ensure a current and accurate medication list, select the most appropriate therapy, monitor the effects of medications prescribed, and manage the adverse effects that often accompany cancer treatment. As the care of cancer patients continues to be challenged with high cost therapies, medication shortages, regulatory requirements and dwindling reimbursement, the oncology pharmacist is heavily relied upon to provide support for the clinical team in an effort to improve overall cancer care and patient quality of life. Oncology pharmacists Are responsible for ensuring safety in the compounding and dispensing of chemotherapy, maintaining an adequate supply of medications, minimizing drug waste, minimizing unnecessary exposure to hazardous drugs, and managing cost and reimbursement for cancer drugs. With the advent of new technologies and assistance of support staff such as pharmacy technicians, these responsibilities are no longer the primary focus of a pharmacists' day Are viewed as the "cancer medication experts" who focus their time providing direct patient care, patient education, and actively participating in clinical decision making Work collaboratively with other health care professionals to develop institutional guidelines and make evidence-based decisions designed to improve patient care Participate on committees to improve the safety, efficacy, and quality of cancer care and are

#### ONCOTHERAPEUTICS: A GENERAL OVERVIEW

heavily relied upon to develop policies and implement programs to ensure the safety of staff and patients during the receipt, preparation, administration, and monitoring of anticancer agents Have training and expertise that places them in an optimal position to provide medication management services across the care continuum for most common patient complications pain management, nausea/vomiting, diarrhea, anemia, depression, fatigue, etc. Contribute to cancer research by leading clinical studies, reporting important observations from practice, and supporting investigational drug service programs<sup>23</sup>. They often provide information on how to take medications, potential drug interactions and tips on taking prescription medication on schedule.

They often provide information on how to take medications, potential drug interactions and tips on taking prescription medication on schedule. There are many kinds of pharmacists who work with people living with cancer during their treatment. You may be familiar with community pharmacists, who work in local pharmacies to fill your prescriptions. There are also pharmacists who work in hospitals, clinics and specialty pharmacies to provide you with the best care possible during your treatment.

### 6 | EARLY CLINICAL TRAILS.

Phase I trials represent the first introduction of a drug or combination of drugs into the clinical setting and seek to define the optimal or recommended phase II dose for further testing. In phase I trials, dose escalation is usually carried out until excess clinical toxicities ensue, thus defining the maximal tolerated dose (MTD). However, the era of targeted therapies is challenging the utility of such simple dose-escalation paradigms. The relationship between toxicity and activity may be less linear than with conventional cytotoxics. In up to a third of phase I trials of molecularly targeted drugs, the MTD is not reached.<sup>29</sup>Therapeutic activity may be seen at the low-dose levels used in the early stages of clinical trials with molecular therapeutics (as may also be observed with low doses of conventional cytotoxic

drugs)<sup>25</sup> Moreover, although regressions have been observed because of induction of apoptosis by some molecularly targeted agents, in other cases, the predominant effect at the cellular level may be cytostatsis, leading to disease stabilization that can be prolonged. Thus, in the setting of single agent phase I/II trials, drug activity does not always translate to typical response parameters according to the Response Evaluation Criteria in Solid Tumors (RECIST), underscoring the importance of incorporating measures of antitumor effect other than changes in tumor size into early clinical trials.<sup>26</sup>Pharmacodynamic (PD) biomarkers, which assess the effect a drug has on the body, can provide a useful indicator of drug activity, including both proximal effects on the molecular target and also effects on more distal downstream events. Such PD biomarkers allow the demonstration of proof of concept for intended target modulation and achievement of the desired biologic effects. Especially when coupled with pharmacokinetic (PK) measurements of drug exposure, PD end points can help us to understand better the dose-response relationship and provide a rational basis for dose and schedule selection.<sup>27-28</sup> Increasingly, the incorporation of mechanism-based biomarker end points into phase I/II clinical trials is improving our ability to make early "go-no go" decisions.<sup>29</sup> Efficiency of the drug development process can be enhanced by optimizing patient selection, demonstrating treatment effects earlier, eg, target modulation or cellular and tissue effects, and establishing sciencebased surrogate end points that correlate with response and survival.<sup>29-30</sup> With improved methods of tumor evaluation, including on invasive functional imaging<sup>31</sup> and analysis of circulating tumor cells (CTCs),<sup>32</sup> biomarker-driven early phase trials not only promise to accelerate the drug development process but also importantly provide a unique opportunity to interrogate human disease biology in the patient and gain mechanistic insights into targeted molecular cancer therapeutics. The success of this new biomarker-driven approach demands close collaboration between academia, industry, and regulatory agencies.

#### 7 | NEWER DEVELOPMENT IN ONCOLOGY

New approaches to tame the immune system in the fight against cancer are getting us closer to a future where cancer becomes a curable disease. Personalized vaccines, cell therapy, gene editing and microbiome treatments are four technologies that will change the way cancer is treated. Curing cancer is certainly one of the big challenges of the 21st century. Our knowledge of cancer has greatly improved in the last two decades. This has revealed the huge variability that can be found between not only different types of cancer, but also between patients with the same type of cancer. It seems increasingly evident that there won't be a single 'cure'. Rather, each patient will be treated accordingly to their specific needs. But for personalized medicine to become a reality, we need a range of therapies wide enough to cover the whole spectrum of cancer. In recent years, there has been a surge of new technologies aiming to help the immune system identify and attack tumors, a field known as immuno-oncology. These technologies could make a big difference in the way we treat cancer, taking us closer to being able to 'cure' this disease

# 8 | FUTURE DIRECTIONS IN ONCOTHERAPEUTICS

The advancements in the field of cancer therapies have transitioned their way from surgical therapies and radiotherapies to chemotherapy. Further, advancements in chemotherapy have made it possible to realize the potential of immune therapies. Also, with the ongoing research and translation into clinical trials, new oncology therapeutic drugs are being constantly envisaged to deliver best in care therapies. These novel targeted therapies are increasingly being looked up to for cancer specific treatment, and a number of immune therapies have also been approved by FDA in the past few years for treatment of renal cell carcinoma and melanoma of the lung, to name a few. With the public–private partnerships, comprehensive cancer care center are being established to extend best in care therapies and treatments to cancer. These promising approaches present a way ahead in onco therapy for the treatment of carcinomas for which we still do not have a potential cure.

#### List of Abbreviations-

1.FDA: Food and drug administration.

2.ICIS: Independent commodity intelligence services.

3.T-VEC:Talimogene laherparepvec.

4.CTLA4:Cytotoxic T-lymphocyte-associated protein 4.

5.PD-L1:Programmed death-ligand 1

6.LAG-3:Lymphocyte-activation gene 3

7.PM: Personalized medicine.

8.NIM: National Institutes of Health.

9.EGFR: Epidermal growth factor receptor.

10.ALK: Anaplastic lymphoma kinase.

11.MET: Metabolic equivalent.

12.MTD: Maximum tolerated dose.

13.RECIST: Response evaluation criteria in solid tumors.

14.PD: Pharmacodynamic.

15.PK:pharmacokinetic

16.CTC<sub>s</sub>:Circulating tumor cells.

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