FROM CONCEPT TO THE CLINICS: DEVELOPMENT OF CANCER THERAPEUTICS

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1 INTRODUCTION

Development of a therapeutic agent is a long and laborious process commencing with the discovery of a "druggable target" underlying the pathology of a disease. This finding is then exploited to identify molecules/compounds that can activate/antagonize this target. Rigorous testing for the specificity and potency of the identified agents then leads to the identification of a lead molecule/compound. The pharmacological formulation of the compound is then optimized for efficient and effective drug delivery. Initial laboratory testing is subsequently followed by detailed animal studies confirming its in vivo absorption, distribution, metabolism, elimination, efficacy, and toxicology. Following these initial laboratory observations, the drug then undergoes thorough pharmacological testing to evaluate its pharmacokinetic and pharmacodynamic properties. During this time, it may return back to the laboratory for additional modifications to modulate its half-life, solubility, bioavailability and the like. The modified agent then goes through rigorous preclinical development in good manufacturing practice (GMP)-certified laboratories, followed by studies geared to demonstrate its bioequivalency and efficacy relative to the initial molecule. The candidate agent is then carefully tested for toxicity in appropriate animal models in multiple species to define a dose that can be safely administered to human patients without adverse effects. After the successful completion of all these preclinical studies, the developer of the experimental drug typically completes an IND (investigational new drug) application to be approved for testing in human patients. After obtaining IND approval, the drug is then tested for safety and efficacy in clinical trials. Phase I clinical trials are typically dose escalation studies meant to evaluate the safety, adverse events, and maximum tolerated dose in human patients. Agents that appear to be reasonably safe then progress to phase II and eventually phase III studies to evaluate their efficacy prior to government approval and marketing. In this chapter we will discuss three recently approved agents that have been through this process and are now being tested in combination with other therapies and one experimental agent that is actively engaged in the developmental process.

2 BEVACIZUMAB (AVASTIN)

Bevacizumab is a humanized antivascular endothelial growth factor (VEGF) monoclonal antibody that, in combination with chemotherapy, was the first anti-angiogenic agent approved by the Food and Drug Administration (FDA) as first-line treatment for metastatic colorectal cancer. In this section we will describe the discovery of VEGF, its function and role played

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