Drug Resistance Updates 30 (2017) 48–62

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

Drug-biomarker co-development in oncology – 20 years and counting

Julianne D. Twomey, Nina N. Brahme, Baolin Zhang*

Office of Biotechnology Products, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD 20993, United States

ARTICLE INFO

Article history:
Received 28 November 2016
Received in revised form 10 February 2017
Accepted 17 February 2017

Keywords:
Targeted cancer therapy
Predictive biomarker
Companion diagnostics
Co-development
Tumor heterogeneity

ABSTRACT

Predictive biomarkers for oncology are necessary to accurately identify patients who will benefit from anticancer treatment. Recently approved oncology drugs target discrete molecular aberrations or pathways in tumor cells and consequently are active on a subset of patient population, yet clinical studies have shown that not all biomarker-positive patients respond. The advancement of predictive biomarkers needs to detect novel and evolving drug resistance mechanisms, not only to guide the selection of patient subsets for specific treatments, but to identify new therapeutic targets. Going beyond the "one marker, one drug" model to incorporate genomics, transcriptomics, and receptor status assessments during biomarker-drug co-development can aid in the successful application of molecular marker-based cancer therapy. This review provides the latest update of biomarker-based cancer therapeutics approved by the US Food and Drug Administration. We provide case studies of therapeutics selectively targeting HER2, EGFR, or PD-1/PD-L1 signaling pathways. We also discuss the challenges and promising future directions in the co-development of targeted cancer therapeutics and paired predictive biomarkers.

1. Introduction

The acquisition of tumor resistance to chemotherapies is observed in virtually all cases, significantly limits their utility, and remains a substantial challenge to the clinical management of advanced cancers. Multidrug resistance can be intrinsic or acquired during treatment, arising from genetic mutations, tumor microenvironment pH changes, activation of survival signaling pathways, increased drug efflux through the ABC transporter proteins, or the selection and emergence of an inherently resistant subpopulation of tumor cells (Dlugosz and Janecka, 2016; Livney and Assaraf, 2013; Rosa et al., 2016; Tuy et al., 2016; Wijdeven et al., 2016).

To improve cancer treatment outcomes, there is rapidly growing interest for the development of molecularly targeted therapeutics that block or stimulate specific signaling pathways of tumor cells. Over the past two decades, more than 80 molecularly-targeted oncology drugs have been approved by the US Food and Drug Administration (FDA) for treating various human malignancies (Table 1). These targeted therapies include small molecules and monoclonal antibodies aimed to block specific pathways driving carcinogenesis and tumor growth. They have diverse mechanisms of action: inducing programmed cell death (apoptosis) of cancer cells, blocking specific enzymes and growth factor receptors involved in cancer cell proliferation, or modifying the function of proteins that regulate gene expression and other cellular functions. Signaling components of human epidermal growth factor receptor 2 (HER2), epithelial growth factor receptor (EGFR), and programmed death receptor-1 (PD-1) are among these therapeutic targets that have led to successful development of molecular marker-driven cancer therapy (Fig. 1). By acting on specific oncogenic proteins, rather than interfering with all rapidly dividing cells, these targeted therapies hold promise for improved patient outcomes.

Due to the vast heterogeneity that exists in tumors, both between and within patients (Kalikaki et al., 2008; Wu et al., 2010), therapeutic targets are most likely present in some but not all tumor cells. As such, predictive biomarkers are needed to help identify

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; AKT, protein kinase B; ATP, adenosine triphosphate; cfDNA, circulating free DNA; CISH, chromogenic in-situ hybridization; CTC, circulating tumor cells; EGFR, epithelial growth factor receptor; EMT, epithelial to mesenchymal transition; ER, estrogen receptor; FDA, food and drug administration; FISH, fluorescent in-situ hybridization; GDP, guanosine diphosphate; GTP, guanosine triphosphate; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IVD, in vitro companion diagnostic device; KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; MAPK, mitogen-activated protein kinase; mCRC, metastatic colorectal cancer; miRNA, micro RNAs; NSCLC, non-small cell lung cancer; ORR, objective response rates; OS, overall survival; PD-1, programmed death receptor-1; PD-L1, programmed death receptor- ligand 1; PFS, progression free survival; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PR, progesterone receptor; PTEN, phosphatase and tensin homolog; PTM, post translational modifications; T-DM1, ado-trastuzumab emtansine; TKI, tyrosine kinase inhibitors.

* Corresponding author at: Food and Drug Administration, 10903 New Hampshire Avenue; Bldg. 52, Room 2128, Silver Spring, MD 20993, United States.
E-mail address: Baolin.Zhang@fda.hhs.gov (B. Zhang).

http://dx.doi.org/10.1016/j.drup.2017.02.002

Table 1
Targeted therapeutics based on cancer type with its associated therapeutic target and predictive biomarker. Predictive biomarkers are based on the therapeutics' indications for use. Companion diagnostic requirement indicated. Table modified from Targeted Cancer Therapies, NCI (http://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet) and List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm).

Cancer Type	Product/Year of Approval		Therapeutic Target	Predictive Biomarker	Req. IVD
Adenocarcinoma of the stomach or gastroesophageal junction:	Trastuzumab (Herceptin®) [Genentech]	10/20/2010	HER2	HER2+	Yes
	Ramucirumab (Cyramza®) [Eli Lilly and Co]	04/21/2014	VEGFR2		
Basal cell carcinoma:	Vismodegib (Erivedge®) [Genentech]	01/30/2012	Smoothened		
	Sonidegib (Odomzo®) [Novartis Pharms]	07/24/2015	Smoothened		
Bladder cancer:	Atezolizumab (Tecentriq™) [Genentech]	05/18/2016	PD-L1		
Brain cancer:	Bevacizumab (Avastin®) [Genentech]	05/05/2009	VEGF		
	Everolimus (Afinitor®) [Novartis]	10/29/2010	FKBP-12	ESR1+, HER2-	
Breast cancer:	Everolimus (Afinitor®) [Novartis]	07/20/2012	FKBP-12	ESR1+, HER2-	
	Tamoxifen (Nolvadex) [AstraZeneca]	12/30/1977	Estrogen Receptors	ESR1+, PGR+	
	Toremifene (Fareston®) [Prostrakan Inc]	05/29/1997	Estrogen Receptors		
	Trastuzumab (Herceptin®) [Genentech]	09/25/1998	HER2	HER2+	Yes
	Fulvestrant (Faslodex®) [AstraZeneca]	04/25/2002	Estrogen Receptors	ESR1+, PGR+, HER2-	
	Anastrozole (Arimidex®) [AstraZeneca]	12/27/1995	Aromatase Inhibitor	ESR1+, PGR+	
	Exemestane (Aromasin®) [Pharmacia and Upjohn]	10/21/1999	Aromatase Inhibitor	ESR1+, PGR+	
	Lapatinib (Tykerb®) [Novartis Pharms Corp]	03/13/2007	Tyrosine Kinase Domain (HER2, EGFR)	HER2+	
	Letrozole (Femara®) [Novartis Pharms]	07/25/1997	Aromatase Inhibitor	ESR1+, PGR+	
	Pertuzumab (Perjeta®) [Genentech]	06/08/2012	HER2	HER2+	Yes
	Ado-trastuzumab emtansine (Kadcyla®) [Genentech]	02/22/2013	HER2	HER2+	Yes
	Palbociclib (Ibrance®) [Pfizer Inc]	02/03/2015	CDK4, CDK6	ESR1+, PGR+, HER2-	
Cervical cancer:	Bevacizumab (Avastin®) [Genentech]	08/14/2014	VEGF		
Colorectal cancer:	Cetuximab (Erbitux®) [Imclone]	02/12/2004	EGFR	EGFR+, K-Ras WT	Yes
	Panitumumab (Vectibix®) [Amgen]	09/27/2006	EGFR	EGFR+, K-Ras WT	Yes
	Bevacizumab (Avastin®) [Genentech]	02/26/2004	VEGF		
	Ziv-aflibercept (Zaltrap®) [Sanofi Aventis US]	08/03/2012	VEGF-A, VEGF-B, PlGF		
	Regorafenib (Stivarga®) [Bayer Healthcare]	09/27/2012	RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-α, PDGFR-β, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, $BRAF^{V600E}$, SAPK2, PTK5, Abl		
	Ramucirumab (Cyramza®) [Eli Lilly and Co]	04/24/2015	VEGFR2		
Dermatofibrosarcoma protuberans:	Imatinib mesylate (Gleevec®) [Novartis]	10/19/2006	BCR-ABL tyrosine kinase, PDGF-RTKs, SCF, c-kit,	Ph+, PDGFR rearrangements, D816V c-Kit mutation, FIP1L1-PDGFRα fusion kinase, Kit (CD117)+,	
Endocrine/neuroendocrine tumors:	Lanreotide acetate (Somatuline® Depot) [Ipsen Pharma]	08/30/2007	SSTR2, SSTR5		
Head and neck cancer:	Cetuximab (Erbitux®) [Imclone]	03/01/2006	EGFR	EGFR+, K-Ras WT	
	Pembrolizumab (Keytruda®) [Merck Sharp Dohme]	08/05/2016	PD-1		
Gastrointestinal stromal tumor:	Imatinib mesylate (Gleevec®) [Novartis]	04/18/2003	BCR-ABL tyrosine kinase, PDGF-RTKs, SCF, c-kit,	Ph+, PDGFR rearrangements, D816V c-Kit mutation, FIP1L1-PDGFRα fusion kinase, Kit (CD117)+,	Yes
	Sunitinib (Sutent®) [CPPI CV]	01/26/2006	PDGFR-α, PDGFR-β, VEGFR1, VEGFR2, VEGFR3, Kit, FLT3, CSF-1R, RET		
	Regorafenib (Stivarga®) [Bayer Healthcare]	05/29/2013	RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-α, PDGFR-β, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, $BRAF^{V600E}$, SAPK2, PTK5, Abl		