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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

EDITORIAL

How often do highly promising cancer biology discoveries translate into effective treatments?

INTRODUCTION

The rate and speed with which cancer biology discoveries translate into clinical practice have importance for oncologists, researchers, and policy makers. A prior study found that among 101 science articles claiming a highly promising result for clinical translation, only 19 of 101 (18.8%) interventions had positive randomized trials, whereas five had been licensed for clinical use with a median follow-up of 12 years.[1]

This analysis, however, spanned all disciplines, and, to our knowledge, no study has investigated how frequently 'highly promising' cancer discoveries lead to actionable clinical treatments in cancer medicine.

METHODS

Highly promising discoveries

On 23 July 2019, we searched PubMed for articles published between 1999 and 2009 that include the search term 'cancer' in the title or abstract along with 'highly promising', 'groundbreaking', 'landmark', or 'breakthrough'. We included all original publications describing therapies or preventive treatments while excluding early detection and nontherapeutic studies. We only considered studies that remained in the experimental stage including *in vitro* and *in vivo* cellular models, animal models, or nonrandomized human trials. We also considered reviews and commentaries of experimental phase research. Randomized controlled trials and meta-analyses were excluded.

Eventual adoption

For each 'highly promising' strategy, we performed a mixed methods search to identify clinical success by the date of 3 June 2020. First, we compared the target and/or compounds against all FDA-approved therapies in cancer medicine. Second, we discussed with a practicing hematologist—oncologist (VP) to see if the doctor had exposure to products related to the claim. Third, we performed Google searches, using keywords, including, but not limited to, drug, target, strategy, method, reagent, company, and/or chemical name. This allowed us to build a set of adopted therapies.

Statistical analysis

Kaplan—Meier curves were constructed for the time to approval or adoption. Descriptive statistics were performed. This study of published research data did not involve personal medical records and does not constitute human subject research.

RESULTS

Our search identified 88 eligible articles (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2020.10.484). These 88 articles represent 70 distinct claims of which 12/70 (17.1%) have been adopted into clinical practice and 58/70 (82.9%) have failed clinical efficacy to date.

With a median follow-up of 15 years, 17 (19.3%) therapies had been adopted into clinical practice, whereas 71 (80.7%) therapies have failed to demonstrate clinical efficacy to date. Among studies where industry funding could be assessed ($n = 70$), those with funding were more likely to be clinically adopted 5/11 (45.5%) than those that did not report industry funding 6/59 (10.2%; $P = 0.0032$).

For adopted therapies (Table 1), we determined the time from the claim until adoption (Figure 1), with a mean time to adoption of 4.9 years, median of 4.4 years, and maximum of 12.1 years.

For each FDA-approved drug, we determined the clinical endpoint utilized for approval. Of these treatments, 12/17 (70.6%) had a surrogate endpoint as the primary outcome measure, with 8/17 (47.1%) demonstrating an overall survival benefit or 8/88 (9.1%) overall. These claims represent 12 distinct approvals (therapy/indication combinations) of which 9/12 (75%) were approved based on surrogate endpoints as the primary outcomes with six based on progression-free survival and one each based on durable response rate, duration of locoregional control, or the development of precancerous changes. Of these 12 distinct approvals, 5 (41.7%) had demonstrated overall survival benefits, with a mean of 6.0 months and a median of 2.8 months.

DISCUSSION

Less than 20% (19.3%) of cancer science discoveries touted as breakthrough, landmark, groundbreaking, or highly promising translated into clinical therapy or practice with a median follow-up of 15 years.

Among clinically adopted treatments in our analysis, most were approved based on surrogate endpoints and only 9.1% found a survival benefit. Among the eight therapies with an OS benefit, the median benefit provided was 2.8 months.

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Table 1. Therapies that have been FDA approved or adopted for off-label use

First author	Journal	Impact	Ind. funding	Therapy	Class	Cancer claim	Approved drug	Cancer approval	App. date	Time to App. (years)	Primary EP	OS (months)
Joensuu[2]	Med Klin (Munich). 2002	0.32	Excluded	Imatinib	Tyrosine kinase inhibitor	GI stromal tumor	Imatinib	GI stromal tumor	31 January 2002	0.0	PFS	0
Peifer[3]	Biochem J. 2009	1.66	Yes	PDK1, PI3K, Akt, S6K, and mTOR inhibitors	Kinase inhibitors	Breast cancer	Everolimus	Breast cancer	30 March 2009	0.2	PFS	0
Ebert[4]	Zentralbl Gynakol. 2006	0.00	Excluded	HPV vaccine	HPV vaccine	Cervical	Gardisila	Cervical[a]	8 June 2006	0.3	CIN II/III	0
Te Velde[5]	Exp Mol Pathol. 2003	1.03	No	Antiangiogenic therapy	Antiangiogenic therapy	Cancer	Bevacizumab	Colon cancer	26 February 2004	0.4	OS	4.7, 2.2, 1.4
No author[6]	Health News. 2005	0.00	Excluded	Gardisil	HPV vaccine	Cervical	Gardisil[a]	Cervical[a]	8 June 2006	0.7	CIN II/III	0
Semiglazov[7]	Vopr Onkol. 2001	0.01	Excluded	Fulvestrant	Antiestrogen	Breast cancer	Fulvestrant	Breast cancer	25 April 2002	1.3	PFS	0
Raben[8]	Expert Rev Anticancer Ther. 2002	0.81	No	Cetuximab + radiation	Anti-EGFR + radiation	Head/neck cancer	Cetuximab[b]	Head/neck cancer[b]	12 February 2004	1.5	DLRC	19.7
Harari[9]	Semin Radiat Oncol. 2001	1.63	Excluded	Anti-EGFR + radiation	Anti-EGFR + radiation	Cancer	Cetuximab[b]	Head/neck cancer[b]	12 February 2004	2.4	DLRC	19.7
Scheithauer[10]	Colorectal Dis. 2003	0.88	No	Oxaliplatin	Chemotherapeutic	Upper GI	Oxaliplatin	Upper GI	20 March 2008	4.4	PFS	0
Santiago-Schwarz[11]	Rheum Dis Clin North Am. 2004	1.22	No	Dendritic cell-based therapy	Dendritic cell therapy	Cancer	Sipuleucel-T[c]	Prostate[c]	29 April 2010	6.2	OS	4.1
Drew[12]	Ann N Y Acad Sci. 2008	1.75	No	PARP inhibitors	PARP inhibitors	BRCA+ Breast/Ovarian	Olaparib	BRCA+ breast/ovarian	19 December 2014	6.3	PFS	0, 0, 2, 0
Grégoire[13]	Bull Cancer. 2007	0.18	Excluded	Immunotherapy	Immunotherapy	Mesothelioma	Bevacizumab	Mesothelioma	6 August 2013	6.6	OS	2.7
Irvine[14]	Nat Biotechnol. 2000	8.20	Yes	Dendritic cell-based immunization	Dendritic cell therapy	Cancer	Sipuleucel-T[c]	Prostate[c]	29 April 2010	9.4	OS	4.1
Walensky[15]	Cell Death Differ. 2006	3.80	Yes	BCL-2 antibody	BCL-2 antibody	Cancer	Venetoclax	Cancer	11 April 2016	9.7	PFS	0
Liu[16]	Mol Ther. 2005	2.78	No	Oncolytic virotherapy	Oncolytic virotherapy	Cancer	T-vec[d]	Melanoma[d]	26 October 2015	10.6	DRR	0
Lund-Johansen[17]	Tidsskr Nor Laegeforen. 1999	0.05	Yes	Dendritic cell-based therapy	Dendritic cell therapy	Cancer	Sipuleucel-T	Prostate	29 April 2010	10.8	OS	4.1
Lundstrom[18]	Technol Cancer Res Treat. 2003	0.69	Yes	Viral/nonviral vectors	Viral/nonviral vectors	Cancer	T-vec[d]	Melanoma[d]	26 October 2015	12.1	DRR	0

Presented data include author name, journal, impact factor, and whether they reported industry funding. Additionally, the claim was evaluated to determine the therapy, therapy class, and cancer referenced in the claim, as well as the drug, indication, approval date, time to approval, primary endpoint, and overall survival of therapy approved.

App., approval; CIN, cervical intraepithelial neoplasia; DCRR, duration of locoregional control; DRR, durable response rate; EGFR, epidermal growth factor receptor; EP, endpoint; GI, gastrointestinal; HPV, human papillomavirus; Ind., Industry; OS, overall survival; PARP, poly-ADP ribose; PFS, progression-free survival.

[a-d] Cells with the same superscript letter represent the same drug—indication combination.

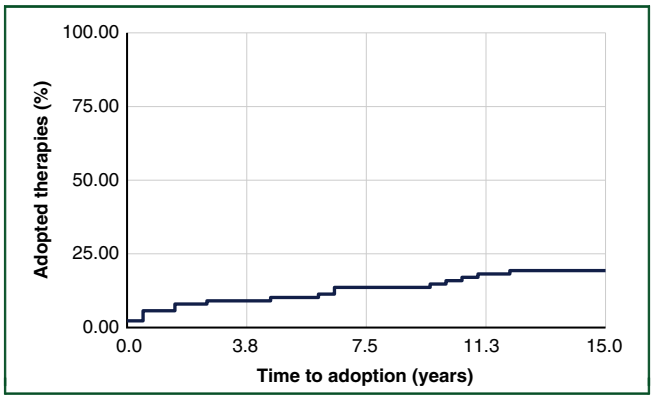

Figure 1. Kaplan–Meier curve demonstrating the time in years from claim until adoption as determined by initial FDA approval (either primary or accelerated) or publication of phase III trial used as the basis for clinical use.

Our results suggest that claims of major discovery are associated only with modest rates of ultimate clinical success.

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