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Follow the Money: Reporting Public Contributions and Incentives on Research and Development Programs for Agenzia Italiana Del Farmaco (AIFA; Italian Medicines Agency)

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Background

- In Italy, the price of medicinal products which are reimbursed by the National Health System (NHS) is negotiated between the marketing authorization holder (MAH) and the Italian Medicines Agency, AIFA.
- The seventy-second World Health Assembly (WHA) held in May 2019 has urged member states to work collaboratively in improving the reporting of information by pharmaceutical companies on registered health products, (including reports on sales revenues, prices, units sold, marketing costs, subsidies and incentives) through the resolution on “Improving the transparency of markets for medicines, vaccines, and other health products”. [1]
- On 24 July 2020, following the seventy-second WHA, AIFA published the new criteria and procedures for the negotiation of the price of medicinal products and related reimbursement status, which was previously approved by the Ministry of Health and the Ministry of Economy and Finance on 2 August 2019 (New Pricing and Reimbursement Decree).[1]
- Italy is the first country to add the requirement for pharmaceutical companies to disclose data about public contributions, subsidies, and incentives received for the research and development of the medicines during drug pricing and reimbursement negotiations with AIFA.
- The key features of the Pricing and Reimbursement Decree includes mandatory requirements on the disclosure of public contributions to research and development (R&D), patent transparency, and the provision of annual reports regarding sales data, revenues, and marketing expenses. [1]

Objective

- To identify sources of publicly available information regarding public contributions and incentives for research and development, using products treating acute myeloid leukemia, multiple myeloma, non-Hodgkin lymphoma, and primary myelofibrosis as examples.

Methods

Public funding research database identification

- We conducted extensive research to identify databases that had a structured public repository on contributions and incentives granted by bodies governed by public law (**Table 1**). Relevant databases and online archives were searched for the research and development programs of drugs, specifically for the following countries or regions:
  - EU-5 countries (Italy, France, Germany, Spain, and the UK), EU, Ex-EU (US and Canada)

Table 1: Publicly funded research databases

Region	Database	Number of Total Records	Link to Source
Italy	Consiglio Nazionale delle Ricerche (CNR)	Over 42,800	Link
	AIFA	Not available	Link
	Governo italiano	Not available	Link
	Ministero della Salute (MOH)	Not available	Link
European Commission	Community Research and Development Information Service (CORDIS)	131,682	Link
United Kingdom	UK Research and Innovation (UKRI)	117,859	Link
France	L'Agence nationale de la recherche (ANR)	Over 30,000	Link
	scanR	108,440	Link
Spain	Ministry for Science and Innovation (MCIN)	Not available	Link
	IIb Sant Pau	Not available	Link
	Carlos III Health Institute (ISCIII)	Not available	Link
Germany	Deutsche Forschungsgemeinschaft (DFG)	Over 31,000 (in 2019)	Link
United States	RePORT	Not available	Link
Canada	Grants and Contribution Dataset	Over 42,800	Link

Literature search

- A list of search terms was developed using various terms for disease area, drug classes, manufacturer/sponsor names, and names/registration numbers of pivotal trials.
- Predefined search terms were used across all identified databases in May 2021 to identify relevant records with information related to funding, research grants, or any contributions pertaining to acute myeloid leukemia, multiple myeloma, non-Hodgkin lymphoma, and primary myelofibrosis
- Boolean operators (“AND”, “OR”) were used where possible. Records were exported and relevant funding sources were identified. For databases that did not support use of Boolean operators, additional search terms were used to identify relevant records following export of all available data.
- Database searches were supplemented by searching the US (http://clinicaltrials.gov) and EU (https://www.clinicaltrialsregister.eu/) clinical trial registries to identify sponsors of relevant clinical trials that may have received or provided public funding.
- Finally, targeted online searches were conducted to identify relevant news articles, prominent publications, pivotal trials, and press releases (e.g., from government bodies, pharmaceutical companies) to capture potential records which were not included in the main search.
- Searches were recorded only if information pertaining to public contributions, grants, subsidies, tax rebates as well as other forms of sponsorship were reported for products used to treat acute myeloid leukemia, multiple myeloma, non-Hodgkin lymphoma, and primary myelofibrosis.

Methods (continued)

Data extraction and quality check

- Data extraction of included records was performed by an investigator and verified for accuracy and completeness by a lead senior researcher. Data was stored and managed in a Microsoft Excel workbook. Quality control procedures were undertaken during data extraction to verify the accuracy and completeness of each collected data point. For each of the included records, the following information was extracted in a tabular format as per AIFA's requirements for EU and non-EU institutions, subject to data availability.
  - **For Italy and EU institutions:** Brief description of the nature of contributions and incentives (e.g., money transfers, support of various kinds), disburser and geographical origin, identification of the contribution (e.g., name/number of funding program), precise indication or at least an accurate estimate of their economic value, and any exclusive or shared intellectual property rights or profit-sharing schemes with Italy and/or other EU institutions.
  - **For Ex-EU institutions**: Brief description of the nature of contributions and incentives (e.g., money transfers, support of various kinds) and disburser (e.g., NIH-USA) and geographical origin.

Results

Summary of findings

- Information related to the nature of contributions, geographical origin and disburser was available; however, information pertaining to contributions or profit-sharing schemes were not uniformly found (**Table 2**). Information pertaining to intellectual property rights was not available.
- Information was most available from the US, particularly for studies funded by governmental agencies. Italy had some funding information, while other EU countries and the United Kingdom reported projects but not source or amount of funding.

Table 2: Summary of select publicly available information on contributions

Origin	Disbursing Subject	Nature of Contribution/Incentive	Amount	Source of Information
Acute Myeloid Leukemia				
UK	University of Birmingham	Non-commercial sponsor: University of Birmingham Monetary/Material Support for the clinical trial of a demethylation agent was provided by Leuka UK; Anthony Nolan UK; NHS Blood & Transplant UK; Celgene International II Sàrl Switzerland	NA	Clinicaltrialsregister.eu (Link)
US	NIH	NIH grant/contract (P30CA093373) for a demethylation agent	NA	Clinicaltrials.gov (Link)
	Dr. Reville (supported by grants from the NIH)	Funding for research article [Dr. Reville is supported by grants from the NIH, US (NIH grants T32CA009666)] for Maintenance Therapies in AML	NA	Peer-reviewed article identified through online searching (Link)
Multiple Myeloma				
Italy/Spain	Instituto de Salud Carlos III, Spanish Ministry of Health, Fondo Europeo de Desarrollo Regional (FEDER), and AGAUR; Generalitat de Catalunya	Funding for research article [Instituto de Salud Carlos III, Spanish Ministry of Health (FIS PI19/00669), FEDER, and 2017SGR00792 (AGAUR; Generalitat de Catalunya)] for CAR T-cell therapies	NA	MOH Italy; Source of information is peer-reviewed article identified through online searching (Link)
Germany	DFG (German Research Foundation)	Research grant for Anti-BCMA therapies	NA	DFG database (Link)
Belgium	Research Fund (FWO) Flanders (Belgium), Baillet-Latour Fund, Belgian Foundation against Cancer (Stichting tegen Kanker), Foundation Horlait-Dapsens, Shanghai Rising-Star Program; and Methusalem Fund from the University of Antwerp, from the Kaushik Bhansali Fund, and from Gilead Sciences and Janssen Pharmaceuticals	Funding for research article [FWO Flanders (Belgium), Baillet-Latour Fund, Belgian Foundation against Cancer (Stichting tegen Kanker), Foundation Horlait-Dapsens, and by the Shanghai Rising-Star Program; and Methusalem Fund from the University of Antwerp, from the Kaushik Bhansali Fund, and from Gilead Sciences and Janssen Pharmaceuticals] for BCMA CAR-T therapies	NA	Peer-reviewed article identified through online searching (Link)
US	NIH	NIH funding to National Cancer Institute (NCI) for Anti-BCMA CAR T-cell therapies	$150,681 (2012) $126,171 (2013) $450,431 (2014)	NIH RePORT (Link) NIH RePORT (Link) NIH RePORT (Link)
	NIH	NIH funding to NCI for Anti-BCMA CAR T-cell therapies	$252,827 (2015) $367,151 (2016) $472,700 (2017) $673,197 (2018) $877,892 (2019) $1,251,559 (2020)	NIH RePORT (Link) NIH RePORT (Link) NIH RePORT (Link) NIH RePORT (Link) NIH RePORT (Link) NIH RePORT (Link)
	NIH	NIH funding to Fred Hutchinson Cancer Research Center for BCMA CAR T-cells	$796,412 (2018) $775,192 (2019) $861,992 (2020) $859,480 (2021)	NIH RePORT (Link) NIH RePORT (Link) NIH RePORT (Link) NIH RePORT (Link)
	Wesley family	Donation by Wesley family for CAR T-cell therapies	$10 million (2021)	News article (Link)
	Thermo Fisher Scientific Inc.	Donation by Thermo Fisher Scientific Inc. to the Leukemia & Lymphoma Society	NA	News article (Link)
Non-Hodgkin Lymphoma				
Italy	Ministero della Salute (MOH)	MOH Italy: Parliament had allocated funds for a research project related CAR T-cell therapies	€60 million (2019)	News article (Link)
US	Wesley family	Donation by Wesley family for CAR T-cell therapies	$10 million (2021)	News article (Link)
Primary Myelofibrosis				
Italy	AIL	AIL provided grants for a research article on oncogenetic mutations in MPNs and disease-modifying effects of JAK2 inhibitors.	NA	Journal article (Link)
US	NCI	NCI funding to University of Iowa for research on targeting JAK2 kinase in lymphoma.	$291,843 (2012) $10,064 (2012) $271,040 (2013) $274,658 (2014) $270,847 (2015) $274,574 (2016)	NIH RePORT (Link) NIH RePORT (Link) NIH RePORT (Link) NIH RePORT (Link) NIH RePORT (Link) NIH RePORT (Link)
	NHLBI	NHLBI funding to Cincinnati Children's Hospital Medical Center for research on mechanisms of drug resistance in MPNs treated with JAK2 inhibitors.	$182,070 (2013) $224,910 (2014)	NIH RePORT (Link) NIH RePORT (Link)
	Medicxi Ventures (Private investment company)	Medcxi provided Series A financing support to Impact Biomedicines toward development of a JAK2 inhibitor.	$22.5 million (2017)	News article (Link)
	Oberland Capital (Private investment company)	Financing with Oberland Capital to advance the development, global supply chain build-out, and future commercialization of a JAK2 inhibitor.	$90 million (2017)	News article (Link)
	Charlie McDermott (President and Chief Business Officer at Impact Biomedicines, Inc.)	Mr. McDermott raised more than $110 million in venture and non-dilutive royalty financing to fully fund the development and commercialization of a JAK2 inhibitor.	$110 million (2020)	News article (Link)

Abbreviations: AGAUR = Agència de Gestió d’Ajuts Universitaris i de Recerca, AIL = Associazione Italiana Leucemie, AML = Acute myeloid leukemia, BCMA = B cell maturation antigen, CAR = Chimeric antigen receptor, DFG = Deutsche Forschungsgemeinschaft, FDA = Food and Drug Administration, FEDER = Fondo Europeo de Desarrollo Regional, FWO = Research Fund - Flanders, IPR = Intellectual Property Rights, MF = Myelofibrosis, MM = Multiple Myeloma, MOH = Ministero della Salute, MPN = Myeloproliferative Neoplasms, NA = Not Available, NCI = National Cancer Institute, NHLBI = National Heart, Lung, and Blood Institute, NHS = National Health System, NIH = National Institutes of Health, UK = United Kingdom, US = United States

Conclusions

- While difficult and time-consuming, it is possible to identify and provide sources of publicly available information regarding public contributions and incentives for research and development intended for reimbursement dossiers submitted in Italy.
- There seems to be a pattern of more transparency with respect to the funding amount provided by the US compared to other countries.
- This work would benefit from being updated and replicated in other therapeutic areas to identify any temporal or disease-specific differences in such reporting.

References

1. Agenzia Italiana del Farmaco (AIFA). Pricing and Reimbursement Decree. 2019. www.gazzetta ufficio.it/eli/id/2020/07/24/20A03810/sg. [Accessed May 2021].

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