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PCN265: Timeline of authorization and reimbursement for oncology drugs in Italy (Jan 2013-Dec 2015)

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Introduction

New oncology drugs in Europe are assessed under a centralized procedure by the European Medicines Agency (EMA); however, even if an European marketing authorization has been granted, this does not imply that the product will be available to patients everywhere in the EU immediately. A recent report presented by Karl Broich, president of the German Federal Institute for Drugs and Medical Devices, in occasion of the HMA meeting (Heads of Medicines Agencies) in Rotterdam (June 2016) highlighted the comparison between the average times to access to drugs in the US, in the European Union Five (France, Germany, Italy, Spain, UK) and in the rest of Europe. According to the presented data referring to year 2014, Italy ranked 18 (out of 22 countries) in average time from regulatory approval to market access (14.5 months). However, when considering average time for market authorization and for final decisions on price, Italy is the country with the lowest average time amongst the EU5 (Sources: AIFA Official website; IMS Health Report "Pricing & Market Access Outlook" 2015/2016 Edition). A number of steps have been taken to improve time to market through legislation, the most important of which is the creation of a new class (named "Cnn" where 'C' stands for 'not reimbursed' and 'nn' stands for 'not negotiated'), which grants MA (Marketing Authorization) within 60 days after EMA approval, even before price negotiation begins. Class "Cnn" has been introduced by the legislative decree nr. 158/2012, so-called Balduzzi Decree, converted by law nr. 189/2012.

Objectives

The main purpose of this analysis was to quantify, for each single step of the approval process, the time between the validation date of EMA centralized procedure and the first purchase of a product by at least one Italian health care structure, the number of CHMP approved products available on the Italian market and the impact of the Balduzzi Decree (introduction of the Cnn class), for oncology drugs.

Methods

The patient access time to new oncology drugs was analyzed considering the time elapsed along each step from the European context to the availability of the medicine at the regional level. The evaluated panel of oncology products has been defined considering brand name drugs approved by EMA between January 2013 and December 2015 authorized for the treatment of oncology diseases, excluding generics. We considered just the first application, excluding all possible further dossiers of the same product for any extension of therapeutic indication or other different procedures. Data were obtained by EMA website (EPAR), by a systematic review of all the reports of each AIFA CTS and CPR meeting, by the analysis of the official administrative acts of marketing authorization published on the Italian Official Journal (Gazzetta Ufficiale). The date of the first purchase has been considered the first day of the first handling month (data provided by IMS Health).

Our analysis has some methodological limits. Not all the information are public and available: 1) considering the EMA time we don't have the detail about the "clock stop" days (generally connected to additional request of technical documentation); 2) when the product is in Cnn, the Company is allowed to start the commercialization just communicating the price, but this information is not public, therefore we weren't able to estimate the patient access time for 9 drug commercialized in Cnn class. With reference to the handling data (data expressed in months), we considered the first day of the handling month as registered by IMS Health.

The steps detailed in our analysis are expressed in days, as follows: EU Time: difference between the date of EU Commission Decision and the application date; Submission Period Time*: difference between AIFA "CTS openness" and Commission Decision; AIFA assessment and HTA Time: difference between "CTS openness" and "CPR closure"; AIFA administrative and GU Time: difference between "CPR closure" and publication on the Italian Official Journal (Gazzetta Ufficiale); Best Regional time: difference between publication on the Gazzetta Ufficiale and the date of the first purchase of the product by at least one of the public care health structure (first day of the month); Last Regional Time: difference between publication on the Gazzetta Ufficiale and the date of the first purchase of the product by the last Italian region (first day of the month, considering data available).

Table 1: list of oncology products approved by EMA between January 2013 and December 2015, date of EC Decision (ECD); days between ECD and AIFA CTS openness, AIFA Time and date of publication on the Italian Official Journal (GU)

Product	Active substance	Date ECD	Submission Period Time	GU Cnn	AIFA Assessment and HTA Time	GU H/C
Blincyto	blinatumomab	23/11/15	-12	NA	NA	NA
Bosulif	bosutinib	27/03/13	224	12/07/13	202	16/09/14
Cometriq	cabozantinib	21/03/14	80	11/07/14	C Class	04/05/16
Cotellic	cobimetinib	20/11/15	108	NA	112	01/10/16
Cyramza	ramucirumab	19/12/14	-59	27/03/15	217	13/10/15
Erivedge	vismodegib	12/07/13	117	04/03/14	385	09/04/15
Farydak	panobinostat	28/08/15	NA	23/08/16	NA	NA
Gazyvaro	obinutuzumab	23/07/14	-2	14/10/14	NA	03/01/15
Giotrif	afatinib	25/09/13	110	27/12/13	162	09/12/14
Iclusig	ponatinib	01/07/13	128	NA	327	10/12/14
Imbruvica	ibrutinib	21/10/14	50	19/02/15	294	21/12/15
Imlygic	talimogene	16/12/15	NA	NA	NA	NA
Imnovid	pomalidomide	05/08/13	93	04/02/14	NA	09/10/14
Kadcyla	trastuzumab	15/11/13	17	18/03/14	85	26/09/14
Keytruda	pembrolizumab	17/07/15	59	29/10/15	199	10/05/16
Kyprolis	carfilzomib	19/11/15	-8	NA	230	03/10/16
Lenvima	lenvatinib	28/05/15	46	NA	261	10/06/16
Lynparza	olaparib	16/12/14	62	27/03/15	345	26/04/16
Mekinist	trametinib	30/06/14	560	14/10/14	190	NA
Neofordex	dexamethasone	16/03/16	NA	20/07/16	NA	NA
Odomzo	sonidegib	14/08/15	NA	NA	NA	NA
Oncaspar	pegarspargase	14/01/16	242	NA	NA	NA
Opdivo	nivolumab	19/06/15	24	14/10/15	197	24/03/16
Portrazza	necitumumab	15/02/16	NA	NA	NA	NA
Spectrila	asparaginase	14/01/16	NA	11/04/16	NA	NA
Stivarga	regorafenib	26/08/13	224	06/12/13	NA	30/07/14
Sylvant	siltuximab	22/05/14	18	29/08/14	688	28/07/16
Tafinlar	dabrafenib	26/08/13	72	06/12/13	230	21/10/14
Unituxin	dinutuximab	14/08/15	NA	16/11/15	NA	NA
Vargatef	nintedanib	21/11/14	150	NA	NA	NA
Xofigo	radium Ra223	13/11/13	145	21/02/14	175	27/05/15
Xtandi	enzalutamide	21/06/13	164	30/10/13	239	10/12/14
Zydelig	idelalisib	18/09/14	83	02/01/15	167	27/08/15
Zykadia	ceritinib	06/05/15	217	NA	NA	NA
Mean			**108**		**248**	

Table 2: number of products available in the Italian regions by July 2016

Italian Regions	No of available products (out of 9 commercialized in Cnn or C class)	No of available products (out of 8 which completed the P&R process)
Abruzzo	9	7
Basilicata	7	6
Calabria	8	6
Campania	8	8
Emilia Romagna	5	5
Friuli Venezia Giulia	6	6
Lazio	9	7
Liguria	9	5
Lombardia	9	7
Marche	9	7
Molise	6	1
P.A. Bolzano	8	6
P.A. Trento	7	4
Piemonte	9	6
Puglia	9	7
Sardegna	7	6
Sicilia	9	7
Toscana	9	7
Umbria	9	5
Valle d'Aosta	9	6
Veneto	8	7

Table 3: timing (days) of different steps in patient access for oncology products in Italy

Time	Mean Days	Mean Months	No of products
EU Time	441	14,7	34
Submission Period Time	108	3,6	27
AIFA assessment and HTA Time	248	8,3	19
AIFA administrative and GU Time	114	3,8	18
Best Regional Time	29	1,0	8
Last Regional Time*	293	9,8	8

* the Last Regional Time is underestimated, considering that -in July 2016- only 4 of the marketed oncology drug were available in all te 21 Italia Regions

Results

In the time elapsed between January 2013 and December 2015, EMA granted 34 Positive Opinions for branded oncology products (Table 1), 14 of them with an orphan drug designation.
As of July 2016 17/34 products are commercially available (8 completed the national assessment and 9 marketed through the Cnn class). The remaining products: 7 are still waiting for P&R Dossier submission to AIFA, 4 are under AIFA evaluation, 1 just completed AIFA P&R process (waiting for the publication on the Gazzetta Ufficiale), 4 are waiting for the inclusion into regional formularies and 1 is still in Cnn (from Oct 2014).

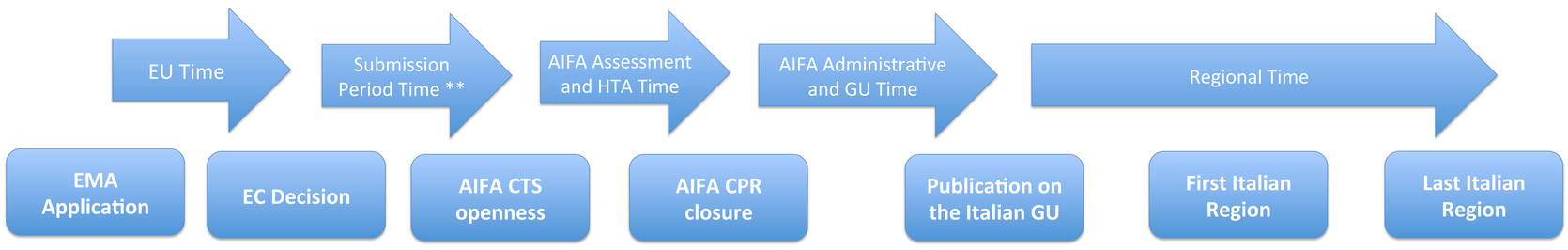
The mean time of EMA evaluation for the considered panel of medicines was 441 days (including "clock-stop" days not attribuible to the Agency), AIFA assessment and HTA evaluation required a lower time of a mean of 248 days (median 217 days, considering the high procedures' variability i.e. when an agreement on price between AIFA and the pharmaceutical company is difficult to be reached). Interestingly, the mean AIFA evaluation time descreased significatively: from 264 days for products submitted to AIFA assessment in 2013-2014 to 219 days for products evaluated in 2015-2016 (median from 224 days in 2013-2014 to 215 days in 2015-2016). Unexpectedly the mean AIFA assessment and HTA Time for orphan drugs was superior to the access time for non-orphan products (345 vs 197 days). This could be partially explained by the long negotiation process for a single drug, which has taken 688 days. The authorization of products reimbursed with a Registry (13) was associated with a mean shortening of the timing of approval (232 vs 298 days for products not subjected to a Registry). AIFA administrative and GU time required further 114 days.

Focusing on the regional access, both timing and number of drugs available for patients are widely different from region to region, and this is mainly due to organizational factors, such as the use of regional/local/hospital formularies periodically updated by regional commissions. Mean Best Regional Time (defined as the average number of days from AIFA market authorization as published in the GU and the first purchase date in the first Italian region) is 29 days. Last Regional Time (number of days between GU and the first purchase in the last region for which data are available on July 2016) is 293 days. This last data is underestimated, considering that not all products are available in all the Italian regions (see Table 2). Out of the 9 products commercialized in C or Cnn class (not reimbursed), an average of 8 are available on the Italian regions and out of the 8 commercialized after AIFA price and reimbursement achievement, an average of 6. On average, 10 Italian regions started to treat patients with drugs in C or Cnn class, before the price and reimbursement process conclusion (with a wide variability among the products, range 1-18). Italian regions made disposable a mean of 4 products classified in C/Cnn (with a range from 2 to 8); the regions with the higher number of products commercialized in C/Cnn (Puglia and Lombardia) are also the regions where time to access is the shortest for most of the drugs under evaluation.

Conclusions

The current analysis showed that the drug assessment process before patient access is complex, multifaceted and time consuming. The greater proportion of time is required by EMA for the official assessment about safety, efficacy and clinical value of the product. After EMA approval, thanks to the introduction of the Cnn class, drugs have become immediately available to the hospitals, awaiting price negotiation. By our analysis, AIFA requires an average of 248 days for its scientific and HTA evaluations, but this time is decreased significatively in the last years. A positive impact is attributable to the monitoring registries and the related MEAs, which grant a balance between a rapid access to market and appropriateness. The regional situation is widely variable: patient access was not simultaneously achieved for all oncology products in each Italian region and, in some cases, drugs are not yet available, ever after years from the approval.

Further research and monitoring are needed to examine which factor most affects the time to patient access and to assess causal relationships between drug characteristics and time to market.



*The Submission Time Period includes the time attributable to both pharmaceutical companies for P&R Dossier submission and administrative workloads, which may delay the "CTS openness"

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