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ORIGINAL RESEARCH

Skip pattern approach toward the early access of innovative anticancer drugs

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Background: With the rapid development of innovative anticancer treatments, the optimization of tools able to accelerate the access of new drugs to the market by the regulatory authority is a major issue. The aim of the project was to propose a reliable methodological pathway for the assessment of clinical value of new therapeutic innovative options, to objectively identify drugs which deserve early access (EA) priority for solid and possibly in other cancer scenarios, such as the hematological ones.

Materials and methods: After a comprehensive review of the European Public Assessment Report of 21 drugs, to which innovation had previously been attributed by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA), an expert panel formulated an algorithm for the balanced use of three parameters: Unmet Medical Need (UMN) according to AIFA criteria, Added Benefit (AB) according to the European Society for Medical Oncology's Magnitude of Clinical Benefit Scale (ESMO-MCBS) criteria and Quality of Evidence (QE) assessed by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) method. By sequentially combining the above indicators, a final priority status (i.e. EA or not) was obtained using the skip pattern approach (SPA).

Results: By applying the SPA to the non-curative setting in solid cancers, the EA status was obtained by 5 out of 14 investigated drugs (36%); by enhancing the role of some categories of the UMN, additional 4 drugs, for a total of 9 (64%), reached the EA status: 2 and 3 drugs were excluded for not achieving an adequate score according to AB and QE criteria, respectively. For hematology cancer, only the UMN criteria were found to be adequate.

Conclusions: The use of this model may represent a reliable tool for assessment available to the various stakeholders involved in the EA process and may help regulatory agencies in a more comprehensive and objective definition of new treatments' value in these contexts. Its generalizability in other national contexts needs further evaluation.

Key words: early access priority, innovative anticancer treatments, unmet medical need, added benefit, quality of evidence

INTRODUCTION

Anticancer treatment options have rapidly increased in the past 20 years, with the introduction of targeted agents and immunotherapy in different cancer types. The optimization of the diagnostic pathway and the subsequent enrichment of the therapeutic *armamentarium* translate into survival improvement, accompanied by a rise in costs.[1] Innovative drugs' clinical use, following European Medicines Agency's

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(EMA) Committee for Medicinal Products for Human Use (CHMP) approval, has been a subject of debate for a long time.[2] The Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) is the regulatory authority responsible for drug registration and access, working on behalf of the government for pharmaceutical expense monitoring and warranting a national consistency of the pharmaceutical system in agreement with regions. In this context, innovative drugs usually enter into a regulatory, bureaucratic and organizational 'gray area' until their real accessibility in all regions is granted. The time interval from the CHMP approval to the drug's accessibility can sometimes reach up to 2 years, subtracting potentially improving or, more rarely, 'game changing' therapeutic options from a quick and extended clinical use, until the price and reimbursement negotiations between the marketing authorization holder and AIFA are completed.

Equal access to cancer care is one of the main goals for different stakeholders, though several challenges have been identified at each step of the process, from clinical trials to regulatory approval, up to national and regional pricing and reimbursement.[3] A key challenge is represented by a reliable assessment of the clinical value and the cost-effectiveness of new therapeutic options, compared with the standard available care. Study design, efficacy and activity endpoints as well as patients' follow-up or patient-reported outcomes should be collected during trials to support the level of evidence, which should also be considered in the drug development and approval path.

As far as solid tumors are concerned, the main scientific societies have proposed some tools to establish the clinical benefit of anticancer drugs, based on the added therapeutic value of each drug compared with control options in different settings.[4,5] Particularly, the European Society for Medical Oncology's Magnitude of Clinical Benefit Scale (ESMO-MCBS)[4,5] was developed in 2015 and applied to each new drug or intervention approved by the EMA. This scale was applied both in curative and non-curative settings of most solid tumors and drugs with higher scores were considered for inclusion in ESMO guidelines.[4] As regards the hematological area, a recent publication by Kiesewetter et al.[6] describes a collaborative project between ESMO and the European Society of Hematology for the validation of ESMO-MCBS criteria in hematological malignancies. In 2017, AIFA identified the criteria for classification of innovative drugs focusing on therapeutic need, added therapeutic value and quality of evidence.[7-10] While previous experience in other European countries explored the relationship between the added therapeutic value and price definition of anticancer drugs for solid tumors,[11] no evidence is available on reproducible multi-parameter integrated criteria for early access (EA) priority classification of anticancer drugs both for solid and hematological tumors. Moreover, homogeneous criteria for the evaluation of clinical benefit are still not available for both solid oncology and hematology: the first being firmly anchored to the ESMO criteria, and the second currently lacking a similar methodological tool.

Starting from these premises, two Italian workshops involving a multidisciplinary expert panel addressed these issues. Specifically, the aim was to bring balanced and shared proposals to the attention of regulatory institutions, from a clinical, regulatory and health-economic point of view. In particular, the second workshop, held on 28-29 June 2018 in Villa Braida (Veneto) produced a preliminary publication,[12] which raised the interest of some members of the AIFA Commission. The interest was focused not only on the specific EA area, but also on some in-depth analysis of the issues related to pharmaceutical innovation and its measurement, in case the current criteria will be revised in the future. Accordingly, a new project was set up to carry out a retrospective review of eligibility profiles for an EA ideal use of all the drugs that AIFA had considered innovative (and therefore authorized for clinical use and reimbursed through an '*ad hoc* innovation fund') from March 2017 to September 2019.

The aim of the present paper is to propose simple and clear criteria, based on three parameters [unmet medical need (UMN), added benefit (AB) and quality of evidence (QE)], that, properly combined, could make the process of eligibility assessment as objective and reproducible as possible. The algorithm here proposed has been firstly applied in the non-curative solid oncology setting in order to evaluate its ability in defining the eligibility of innovative oncological cancer drugs for EA in Italy. This setting could be viewed as a template model to be adapted to both alternative scenarios, such as the hematological tumors, as well as in other European countries.

MATERIALS AND METHODS

Study design

The retrospective evaluation was carried out between July 2019 and May 2020 through the implementation of a working group. The latter consisted of nine medical oncologists (AA, ABi, CCa, MD, AI, RL, GP, DS, MV), four hematologists (CCr, GG, FL, GS) and one pharmacist (ABo) who evaluated the drugs/indications considered. In addition, two methodologists (GA, Gianluigi Casadei) and seven senior experts (PC, FdB, SG, MM, FP, AR, GR), who provided major contribution to the design of the study and supervised the data analysis and discussion, were involved. Thirty-one indications (Table 1) were selected referring to 21 drugs, to which the status of innovation had previously been attributed by AIFA: 22 indications were defined innovative according to the 2017 criteria[13] (9 concerned onco-hematology and 13 solid cancer) and 9 according to previously defined criteria (4 concerned onco-hematology and 5 the oncology of solid tumors).

Data described in the European Public Assessment Report (EPAR) were taken as reference for each specific indication.[14,15] Studies subsequent to the EPAR publication have not been evaluated, in order to line up with the knowledge available at the time of approval by the European agency (EMA).

Table 1. List of the considered indications

Indications	Setting	RS-1	RS-2
Indications defined innovative according to the 2017 criteria			
01—Alectinib NSCLC ALK+ 1L	Solid cancer	ABo, GP	MD, DS
02—Daratumumab—MM 2 + L	Onco-hematology	GG	CCr
05—Pembrolizumab—NSCLC TPS50 1L	Solid cancer	ABo, GP	AA
06—^{177}Lu oxodotreotide—GEPNET	Solid cancer	AI	ABo, GP
10—Dinutuximab—neuroblastoma	Solid cancer	RL	ABi
11—Midostaurin—AML FLT3+	Onco-hematology	FL, AR	GS
12—Atezolizumab NSCLC 2L	Solid cancer	ABo, GP	AA
13—Durvalumab NSCLC	Solid cancer	ABo, GP	FP, CCa
14—Tisagenlecleucel—RR LLA	Onco-hematology	GG	GR
15—Daunorubicin—Cytarabine—AML 1L	Onco-hematology	FL, AR	GS
16—Alectinib NSCLC ALK 2L	Solid cancer	ABo, GP	MD, DS
17—Avelumab—MCC	Solid cancer	FP, CCa	MM, MV
18—Inotuzumab ozogamicin—ALL 2L	Onco-hematology	FL	AR
20—Palbociclib—mBC HR+ HER2−	Solid cancer	AI	FP, CCa
21—Ibrutinib—CLL 1L	Onco-hematology	FL, AR	GS
22—Ribociclib—mBC HR+ HER2−	Solid cancer	FP, CCa	MD, DS
23—Nivolumab—RR cHL	Onco-hematology	GG	CCr
24—Lenalidomide—MM ASCT	Onco-hematology	GG	CCr
25—Regorafenib—HCC 2 + L	Solid cancer	FP, CCa	MD, DS
27—Niraparib—rOCplatino _responsivi	Solid cancer	FP, CCa	MD, DS
28—Pembrolizumab—RR cHL	Onco-hematology	GG	CCr
29—Pembrolizumab—Urothelial	Solid cancer	AI	MM, MV
Indications defined innovative before the 2017 criteria			
03a—Ibrutinib—RR MCL_CL	Onco-hematology	GG	GS
03b—Ibrutinib—WM	Onco-hematology	GG	GS
04a—Pembrolizumab—Melanoma advanced	Solid cancer	ABo, GP	MD, DS
04b—Pembrolizumab—NSCLC TPS1 2L	Solid cancer	ABo, GP	MD, DS
07—Nivolumab—Melanoma advanced	Solid cancer	FP, CCa	MD, DS
08—Nivolumab—NSCLC 2L	Solid cancer	ABo, GP	FP, CCa
09—Nivolumab—RCC 2L	Solid cancer	FP, CCa	DS
19—Blinatumomab—RR LLA Ph−	Onco-hematology	FL, AR	GS
26—Venetoclax—CLL 17p-TP53 2L	Onco-hematology	FL, AR	CCr

ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ASCT, allogeneic/autogeneic stem-cell transplantation; cHL, classical Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia; FLT3, FMS-like tyrosine kinase receptor-3; GEPNET, gastroenteropancreatic neuroendocrine tumor; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer; MCC, metastatic Merkel cell carcinoma; MM, multiple myeloma; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; rOC, relapsed ovarian cancer; RR, relapsed/refractory; RS, review sections; TPS, tumor proportion score; WM: Waldenstrom macroglobulinemia.

Oncologists or hematologists evaluated in two independent review sections, the EPAR documentation or individual articles (when available) and expressed their judgment through an *ad hoc* designed case report form. In case of disagreement, a consensus value was achieved by collegial discussion also including the senior experts. A dedicated database was created using Microsoft Office Access 2007 (Microsoft Corporation, Redmond, WA).

Data generation and analysis

The process, applied to solid and hematological cancer indications, relied on the evaluation of the following three measurements: UMN, AB and QE. Table 2 reports the scales and relative categories for the three considered parameters. As regards the UMN, a five-point scale according to the 2017 AIFA criteria was adopted.[8,10,13] Details about the scale are reported in Galeone et al.[8] The AB evaluation was carried out according to the version 1.1 (v1.1) of the ESMO-MCBS criteria.[5,16] Finally, for the QE parameter, the AIFA assessments for all indications considered innovative since 2017 were adopted. In addition, for indications considered innovative before 2017, QE was evaluated according to the GReFO (Regional Group of Oncological Drugs) of the Emilia Romagna region, based on the Grades of Recommendation Assessment, Development and Evaluation (GRADE) method.[8,17,18] According to this scale, the quality of evidence can be scored as High (i.e. further research is very unlikely to change our confidence in the estimate of effect), Moderate (i.e. further research is likely to have an important impact on our confidence in the estimate of effect and

Table 2. Scales considered for the three parameters

Unmet medical need[8]
High
Important
Moderate
Scarce
Absent
Added benefit[5,16]
High (5)
Important (4)
Moderate (3)
Scarce (2)
Absent (1)
Quality of evidence[8,17]
High
Moderate
Low
Very Low

may change the estimate), Low (i.e. further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) and Very Low (i.e. any estimate of effect is very uncertain).[17] In case of disagreement, a consensus value for each of the above parameters was reached by joint examination.

A simulation analysis was carried out by jointly considering the above three parameters in order to generate a priority score. Briefly, in this analysis, each *i*-th measurement ($i = 1, \ldots, 3$, where 1 = UMN, 2 = AB and 3 = QE) defines a decision level and each *j*-th category ($j = 1, \ldots, J$) of each measurement a decision rule (i.e. stop or pass). The process starts with the assignment of each considered measurement to a decision level and then proceeds with the definition of the decision rule for each measurement. The final output of this Skip Pattern Approach (SPA) consists of a priority status (i.e. EA or not) obtained by sequentially combining the considered measurement.

RESULTS

Solid oncology setting

Original skip pattern approach. Figure 1 shows the general scheme of the proposed SPA. Briefly, the UMN was the first-level measurement used to discriminate drugs needing further evaluation or not. Drugs with a 'Scarce' or 'Absent' score were immediately stopped, whereas those judged with at least a 'Moderate' score were further evaluated according to the AB. At this second level—where the AB was evaluated—drugs with a 'Moderate' UMN moved to the third level only if a 'High' score for the AB was achieved; else they were stopped. In the 'High/Important' arm of the UMN, only drugs with a 'Scarce/Absent' AB were stopped. At the third level—where the QE was evaluated—drugs were considered valid for 'EA' if a 'High' or 'High/Moderate' score was obtained.

According to the developed SPA, Table 3 reports the priority status (i.e. EA or not) for each of the 14 considered drugs, with 5 drugs out of 14 (36%, 95% confidence interval: 13% to 65%) in EA. Interestingly, no drugs were excluded at the first level (UMN), whereas five and four drugs were excluded at the second (AB) and third levels (QE), respectively.

Updated skip pattern approach. To enhance the role of some relevant categories of the AB and QE in the SPA, an updated algorithm was implemented by collapsing (i) for the AB, the 'Important' and the 'High' categories in the 'Moderate' UMN arm and (ii) for QE, the 'Moderate' category with the 'High' ones (Figure 2). In this case, at the second level—where the AB was evaluated—drugs with a 'Moderate' UMN moved to the third level also if an 'Important' score for the AB was achieved; else they were stopped. Similarly, at the third level—where the QE was evaluated—drugs were considered valid for 'EA' if a 'High' or 'Moderate' score was obtained in each flow arm. According to this updated SPA, four additional drugs moved to the EA status, for a total of nine drugs (64%; 95% confidence interval: 35% to 87%) (Table 4).

Hematological setting

Similar to the solid cancer setting, the working group carried out a thorough analysis of the abovementioned parameters. As regards the UMN, the criteria adopted by AIFA were

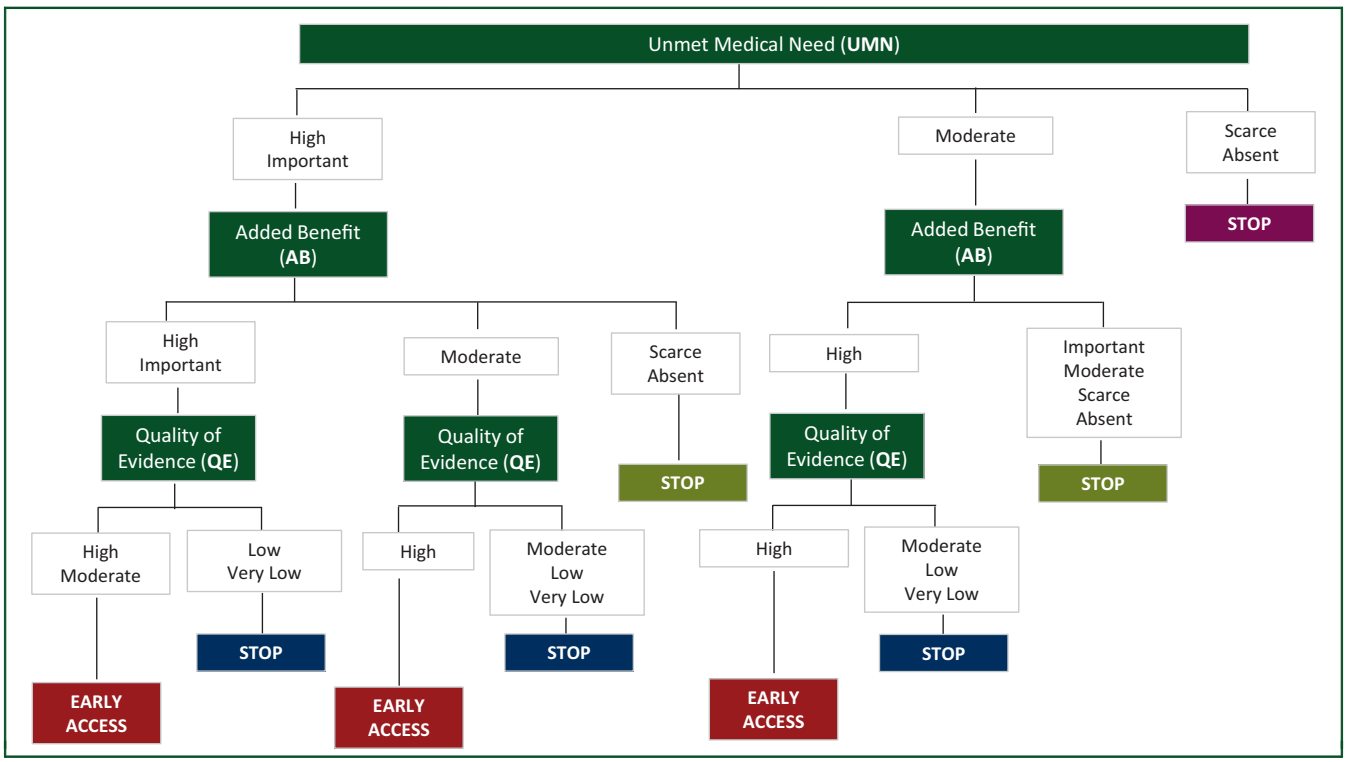

Figure 1. General scheme of the skip pattern approach.
Colored cells indicates the priority status and the exclusion level according to the general scheme of the skip pattern approach.

Table 3. Evaluation of the 14 indications according to the SPA

Indication	UMN	AB	QE	Outcome
01—Alectinib NSCLC ALK+ 1L	Moderate	Important	Moderate	STOP
05—Pembrolizumab—NSCLC TPS50 1L	Moderate	Important	High	STOP
06—177Lu oxodotreotide—GEPNET	Important	Moderate	Low	STOP
10—Dinutuximab—Neuroblastoma	High	High	Moderate	EARLY ACCESS
12—Atezolizumab NSCLC 2L	Important	High	High	EARLY ACCESS
13—Durvalumab NSCLC	Important	Important	Moderate	EARLY ACCESS
16—Alectinib NSCLC ALK 2L	Moderate	Important	Moderate	STOP
17—Avelumab—MCC (setting naive)	Important	Moderate	Very Low	STOP
17—Avelumab—MCC (setting refrattario)	Important	Moderate	Low	STOP
20—Palbociclib—mBC HR+ HER2−	Moderate	Moderate	Moderate	STOP
22—Ribociclib—mBC HR+ HER2−	Moderate	Moderate	Moderate	STOP
25—Regorafenib—HCC 2+L	High	Moderate	High	EARLY ACCESS
27—Niraparib—rOC platino _responsivi	Important	Moderate	Moderate	STOP
29—Pembrolizumab—Urothelial	Important	Moderate	High	EARLY ACCESS

Colored cells indicates the priority status and the exclusion level according to the general scheme of the skip pattern approach (see Figure 1).
AB, added benefit; ALK, anaplastic lymphoma kinase; GEPNET, gastroenteropancreatic neuroendocrine tumor; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer; MCC, metastatic Merkel cell carcinoma; NSCLC, non-small-cell lung cancer; QE, quality of evidence; rOC, relapsed ovarian cancer; SPA, skip pattern approach; TPS, tumor proportion score; UMN, unmet medical need.

found to be adequate. On the other hand, as far as the AB is concerned, the use of the ESMO-MCBS v1.1 scale[5,6] was considered not applicable in most indications, because it does not take into account the specific and particular aspects of hematological diseases. Moreover, as regards the assessment of the QE, the low number of randomized clinical trials (RCTs) strongly affects the evaluation of quality of evidence. In fact, >60% of analyzed studies were non-RCT, compared with the 27% in the solid oncology setting.

DISCUSSION

Constant and growing innovation in diagnostic and therapeutic pathways in oncology has rapidly raised the critical issue of a timely and extended access to new interventions able to improve survival and quality of life of cancer patients. Considering high disparities across European countries,[19] the EMA established the PRIME (PRIority MEdicine) scheme for the optimization of regulatory tools, in order to prioritize innovative medicines addressing an unmet medical need and bringing a major potential therapeutic advantage to patients.[20]

In Italy, as in other European countries, different regulatory tools for EA to innovative drugs are available, even though a comprehensive evaluation process of the new drug which takes into consideration the added value (compared with available options) and the place in therapy

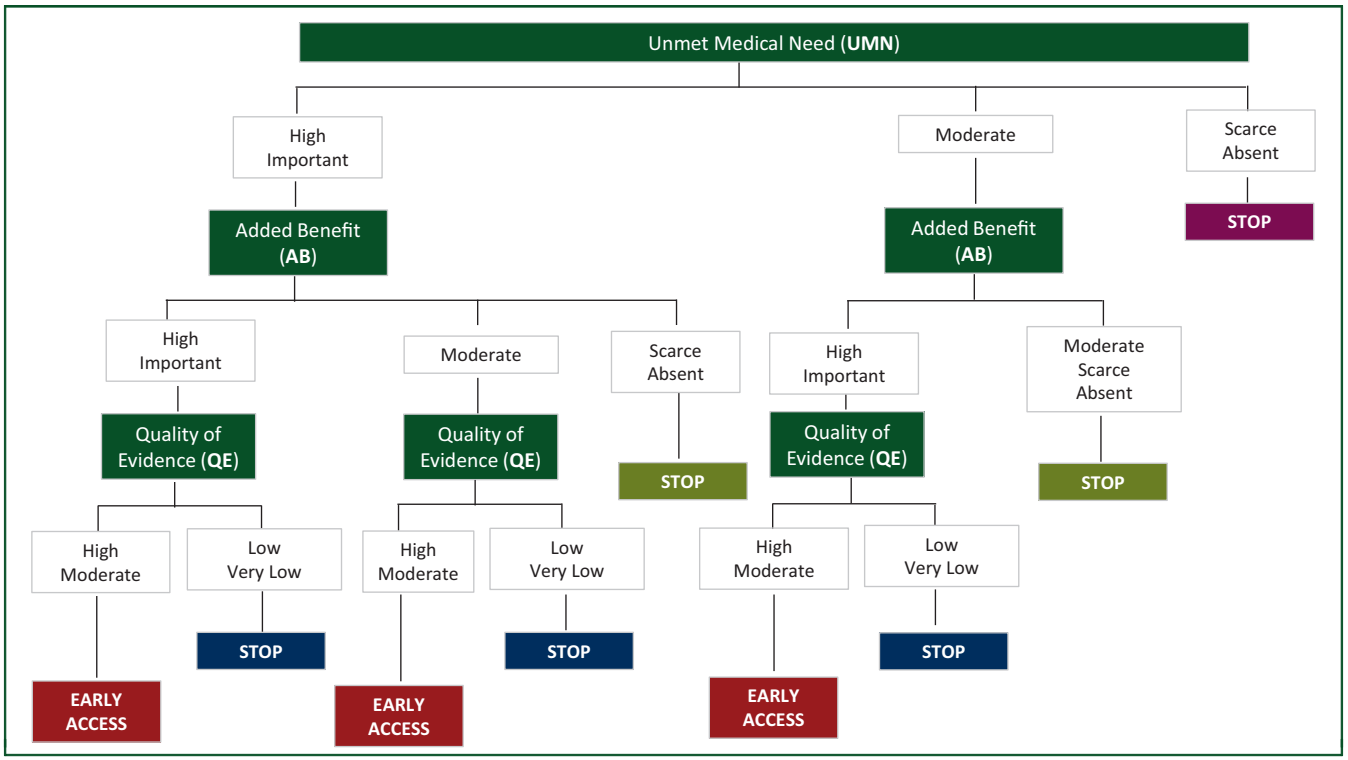

Figure 2. General scheme of the updated skip pattern approach.
Colored cells indicates the priority status and the exclusion level according to the updated scheme of the skip pattern approach.

Table 4. Evaluation of the 14 indications according to the updated SPA

Indication	UMN	AB	QE	Output
01—Alectinib NSCLC ALK+ 1L	**Moderate**	**Important**	**Moderate**	**EARLY ACCESS**
05—Pembrolizumab—NSCLC TPS50 1L	**Moderate**	**Important**	**High**	**EARLY ACCESS**
06—177Lu oxodotreotide—GEPNET	Important	Moderate	Low	STOP
10—Dinutuximab—Neuroblastoma	High	High	Moderate	EARLY ACCESS
12—Atezolizumab NSCLC 2L	Important	High	High	EARLY ACCESS
13—Durvalumab NSCLC	Important	Important	Moderate	EARLY ACCESS
16—Alectinib NSCLC ALK 2L	**Moderate**	**Important**	**Moderate**	**EARLY ACCESS**
17—Avelumab—MCC (setting naive)	Important	Moderate	Very Low	STOP
17—Avelumab—MCC (setting refrattario)	Important	Moderate	Low	STOP
20—Palbociclib—mBC HR+ HER2−	Moderate	Moderate	Moderate	STOP
22—Ribociclib—mBC HR+ HER2−	Moderate	Moderate	Moderate	STOP
25—Regorafenib—HCC 2 + L	High	Moderate	High	EARLY ACCESS
27—Niraparib—rOC platino _responsivi	**Important**	**Moderate**	**Moderate**	**EARLY ACCESS**
29—Pembrolizumab—Urothelial	Important	Moderate	High	EARLY ACCESS

The drugs moved to the early access status according to the updated SPA are given in bold. Colored cells indicates the priority status and the exclusion level according to the updated scheme of the skip pattern approach (see Figure 2).
AB, added benefit; ALK, anaplastic lymphoma kinase; GEPNET, gastroenteropancreatic neuroendocrine tumor; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer; MCC, metastatic Merkel cell carcinoma; NSCLC, non-small-cell lung cancer; QE, quality of evidence; rOC, relapsed ovarian cancer; SPA, skip pattern approach; TPS, tumor proportion score; UMN, unmet medical need.

in different settings is still lacking. A French experience[6] reported the absence of correlation between the price of new cancer drugs and their added therapeutic benefit, as assessed by the French High Authority of Health Scale and the ESMO-MCBS for drugs introduced in France between 2004 and 2017.

To our knowledge, this is the first effort proposing a reliable integrated algorithm for the classification of innovative drugs suitable for EA. Specifically, we simulated the process of assessment of the EA status for 14 indications in solid neoplasms by considering, as pivotal measurements, the UMN, AB and QE.

Some intriguing cues were derived from our results, warranting further discussion. Firstly, no drugs were excluded at the first level of the developed SPA algorithm, which was set as the UMN. We evaluated all the drugs and indications in the non-curative setting of solid tumors, and the reported UMN was always found to be moderate to high. Indeed, in this setting, we lack therapeutic options or, more often, there is only an availability of treatment options with no or limited impact on relevant outcome endpoints and/or with an unfavorable safety profile. An example is represented by the second-line treatment of metastatic non-oncogene-addicted non-small-cell lung cancer (NSCLC), where the immune programmed cell death protein 1/programmed death-ligand 1 (PD-L1) checkpoint inhibitors nivolumab, pembrolizumab and atezolizumab were assessed. The standard of care in this setting before the advent of immunotherapy was the chemotherapeutic agent docetaxel, showing modest survival outcomes and a poor safety profile, thus underlining the important clinical need in this setting.[21-24]

The second and third levels of the SPA algorithm resulted in the exclusion of five and four drugs for the AB and QE, respectively, for a total of nine drugs. When the weight of some decision levels of these two measurements was enhanced in the updated SPA, four more indications moved to the EA. These findings further highlight the importance of a multidimensional evaluation of each new drug, in terms of endpoints reached, safety, quality of life, its setting and the scientific evidence supporting each treatment choice. Prospective studies should be carried out to eventually assess the SPA's applicability, including the choice of the decision level for the AB and QE parameters in solid cancer.

In this context, where a moderate clinical need is shown, as in the first line setting of metastatic NSCLC, the clinical value of a drug, such as pembrolizumab[25,26] in case of high PD-L1 expression, may make the difference in the path to EA, especially in case of high-quality evidence. Indeed, the clinical value of this drug within the specific setting has been graded as important, considering the primary endpoint of the pivotal phase III RCT, which was set as progression-free survival (PFS), as far as its added benefit to the available standard of care, safety and quality of life is concerned.[27]

Moreover, a moderate quality of evidence should not preclude the EA of a drug in some contexts, especially when an important clinical need and a moderate clinical value are reported, as in platinum-sensitive relapsed ovarian cancer patients receiving maintenance niraparib.[28]

One of the critical issues leading to a moderate quality of evidence is the availability of alternative drugs with the same mechanisms of action and the same indication, which makes the control arm not adequate. This is particularly true for small tyrosine kinase inhibitors, such as poly(ADP-ribose) polymerase inhibitors in ovarian cancer or anaplastic lymphoma kinase inhibitors in NSCLC, where the quality of evidence supporting a 'next in class' may be affected. In general, the central role of the clinical need would deserve a discussion with regulatory agencies (e.g. AIFA) and the technical—scientific committee about the role of the new therapeutic alternatives, because they could be affected in terms of innovation and EA.

For the hematological area, it was not possible to apply the SPA approach due to difficulties in assessing AB and QE. As regards the AB, the difficulties were mainly related to the

behavior of hematological malignancies, the survival outcomes and relative metrics used in hematology and the existence of single-arm trials only. Hematological diseases include rapidly fatal but also curable tumors, such as acute leukemia and chronic forms characterized by very long survival time, although still definable as incurable (such as chronic lymphocytic leukemia). In some hematological diseases, treatments have curative intent and generate survival curves with plateaus, where the evaluation of the AB on survival may be carried out more efficiently using alternative parameters (like the restricted mean survival time).[29] In addition, the endpoints used in hematology are sometimes different from those commonly used in solid oncology. For example, in some diseases and/or for some 'precision drugs' with a specific immunological or molecular target, response is assessed in terms of measurable residual disease negativity. Accordingly, the introduction of proper predictive metrics could be of help in evaluating such setting. With regard to QE, the rarity of many diseases may explain a difficulty in performing RCT and consequently in providing a suitable QE assessment.

Despite the abovementioned limitations, during the working group discussions, the potential role of the SPA approach emerged even in the hematological setting. To this end, the AIFA assessments of UMN could be integrated with the AB assessment using a validated ESMO-MCBS version developed for hematological malignancies, such as that recently suggested by ESMO and the European Hematology Association.[6]

We believe that the strength of our study concerns the scales adopted for the three considered measurements; indeed, both ESMO and AIFA metrics are validated tools already used by clinicians and regulators in different contexts of drug development process. A further strength of our experience consists in the availability of measurements reached after a consensus discussion, in case of a judgment disagreement. This supports the need for establishing a multidisciplinary expert panel, which leads, in our case, to a validation of the EA in 60% of the assessed indications. Regarding the study limitations, these are mainly related to the retrospective review of the analysis, which should be prospectively validated. Moreover, the developed SPA does not cover other regulatory aspects such as those related to the subsequent negotiation—reimbursement process, based on parameters which are difficult to put under control and homogenize. However, it could be viewed as a pilot experience in developing a structured approach for the decision-making process granting an EA to innovative anticancer drugs. Study design, efficacy and activity endpoints as well as patients' follow-up or patient-reported outcomes should be collected during trials to support the level of evidence, which should also be considered in the drug development and approval path. Finally, it should be considered, as published recently,[30] that methodological aspects related to trial design and statistical analysis can affect the trial's interpretation and conclusions. Such methodological aspects should be taken into account during the appraisal process of innovative drugs.

In conclusion, this model represents a step toward a consensus between several stakeholders involved in the EA process. Coherently, the considered setting can be viewed as a template model to be opportunely evaluated to both alternative scenarios, such as the hematological tumors, as well as in other European countries to eventually assess its generalizability. In the near future, as regulatory agencies and scientific committee will be called to assess new drugs with longer survival outcomes, surrogate endpoints such as PFS in solid tumors and minimal residual disease should be opportunely considered within the regulatory framework of innovative drugs.

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