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ORIGINAL RESEARCH

Oncology Products in the European Union: An Analysis of Regulatory Approvals with a CHMP Oral Explanation

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Abstract

Background The oral explanation (OE) is a critical event during new marketing authorisation procedures in the European Union (EU). The primary objective of the present study was to investigate how many procedures, having an OE in front of the Committee for Medicinal Products for Human Use (CHMP), resulted in a regulatory approval for oncology products.

Methods Procedures for new marketing authorisation applications (MAAs) and Type II variations (new indication) for oncology products with at least one OE (with or without a Scientific Advisory Group (SAG) meeting) and for which the outcome took place between 31 January 2016 to 31 January 2020 were included in the analysis. Publicly available agendas/meeting minutes and assessment reports were used to obtain information on the products.

Results An OE occurred in about 20% of procedures ($n = 28/150$) for oncology products during the review period. The majority of procedures having an OE (61%), with or without any SAG meeting, led to MAA/Type II variation approval in the Centralised Procedure. It was also observed that in 41% of the cases a successful outcome was contingent upon willingness of the applicant to restrict the indication.

Conclusion A majority of oncology procedures that had an OE resulted in a positive outcome suggesting that such agency interaction is an important opportunity for the applicant to have a last chance to resolve any outstanding issues at the final stage of the procedure.

Keywords Oral explanation · Oncology · Drug approval · CHMP · Scientific Advisory Group

Introduction

A new oncology product can only be marketed in the EU after the European Commission grants a marketing authorisation. This authorisation is based on the favourable opinion from EMA's CHMP following a rigorous scientific evaluation. However, following the scientific evaluation a new product may also be refused by CHMP. This happens in the event any outstanding issues remain with major objections raised by CHMP, that are not resolved during the final stage of the procedure for a new marketing authorisation application (MAA), or a variation to an existing marketing authorisation to extend the indication (Type II variation). In order to resolve these issues, an OE may be requested by the CHMP or even by the applicant and can be held more than once during the same procedure. Therefore, an OE is regarded as an ultimate opportunity for applicants to explain their position and present their arguments to the CHMP in case there are still major objections. It is important that applicants preparing for an OE bear in mind that only clarification of the aspects relating to the outstanding issues is allowed [1–3].

At any stage during MAA or Type II variation application review, the CHMP can request the involvement of a Scientific Advisory Group (SAG), composed of independent European experts, where the applicant may be given the opportunity to present data supporting the application and addressing the specific questions addressed by the CHMP to the SAG [4]. This consultation can also be triggered by the applicant in case of a re-examination procedure. SAG provides a non-binding advice to CHMP on specific scientific matters but does not address the benefit-risk balance which is under the CHMP remit. The Inter-Committee SAG for Oncology (hereinafter referred to as

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the SAG-O) is the group dealing with oncology aspects. CHMP will ultimately adopt a final opinion and a summary of the SAG written answers will be published in the European public assessment report (EPAR) [5].

The applicant also has the option to apply for a re-examination procedure after a CHMP Opinion has been adopted for a MAA or Type II variation application within 15 days of receipt of the opinion (after which, if the applicant does not appeal, the opinion shall be considered as final).

An overview of the human medicines regulatory approval process depicting the different phases from pre-submission (with Scientific Advice (SA)) up to marketing authorisation granted by the European Commission is provided in Fig. 1.

After the initial Marketing Authorisation is granted, the applicant can extend the authorised indication(s) by submitting a major variation of Type II for a new or modified therapeutic indication for which a "90-day timetable" applies.

In summary, an OE is an important event during procedures for a MAA or Type II variation application to extend the indication. Extensive preparation is required by the applicant and the regulators for this meeting with CHMP as it may well be the key moment in the approval process. Considering the importance of OEs for the availability of new oncology treatments, the objectives of the present study were aiming to investigate how many procedures having an OE resulted in a regulatory approval for oncology products in the EU and to understand the factors associated with a positive or negative outcome.

Methods

Procedures for new MAAs and Type II variations to an existing marketing authorisation to extend the indication for oncology products with at least one OE, and a final outcome taking place in a period of 4 years (31 January 2016 to 31 January 2020) in which many new oncology products were assessed and approved, were included in the analysis.

Procedures of interest were identified using publicly available CHMP agendas/meeting minutes where outcome of the oral explanation is explicitly given. A positive outcome was defined as a positive opinion by the CHMP. A negative outcome was defined as a negative opinion by the CHMP or withdrawal of the application by the applicant prior to CHMP opinion.

The publicly available EPARs of the initial MAA or Type II variation to extend the indication on the EMA website were used to obtain public information of the selected oncology procedures and their final outcome. In case of withdrawal by the applicant after the first stage of the assessment, the publicly available withdrawal assessment report was consulted. From the EPARs, general information was extracted (type of product, active substance, and therapeutic indication (proposed and approved), key milestones (OE, SAG-O, re-examination procedure, CHMP opinion, CHMP opinion date or withdrawal date)).

The EPARs were also used to confirm if a CHMP SA had been given during any of the MAA/Type II procedures, but compliance with the given SA was not assessed, and to identify whether divergent opinions were

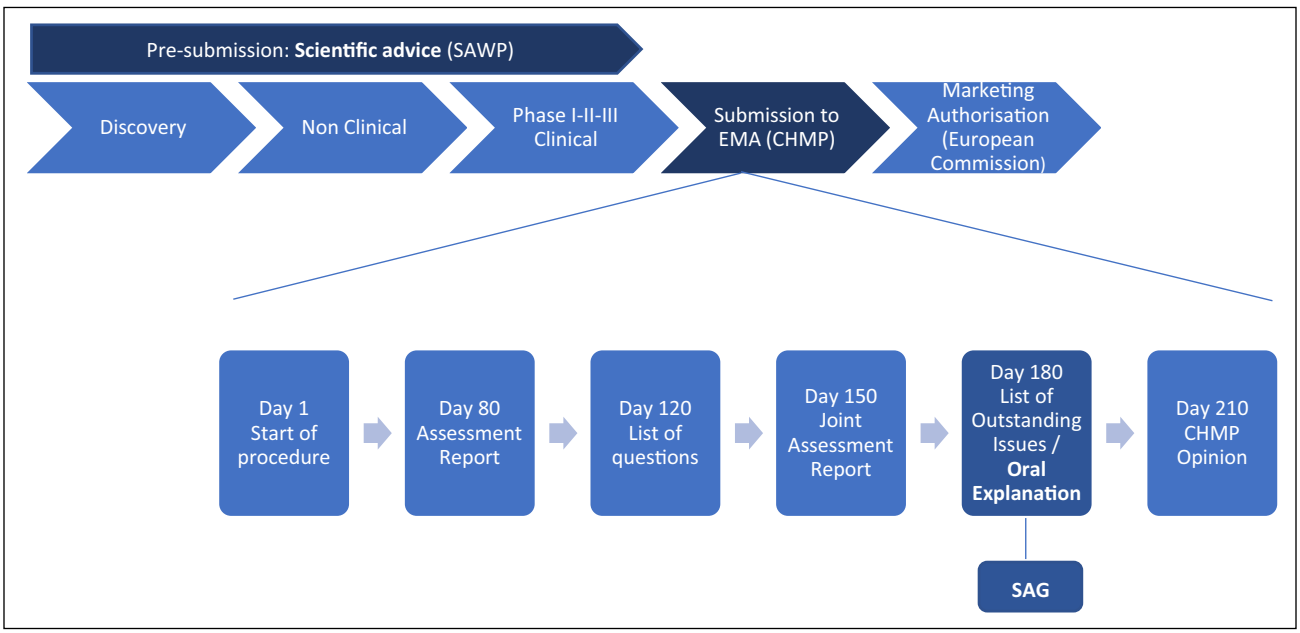

Fig. 1 Overview of the human medicines regulatory approval process

Table 1 List of oncology products by mechanism of action

Mechanism of action	Product
Immune checkpoint inhibitors	Nivolumab—pembrolizumab—cemiplimab—atezolizumab—durvalumab
Tyrosine kinase inhibitors	Gilteritinib—neratinib—lorlatinib—larotrectinib—quizartinib
Other types of inhibitors	Vosaroxin (topoisomerase II inhibitor) Etirinotecan pegol (topoisomerase inhibitor) Enasidenib (IDH2 inhibitor) Rucaparib (PARP inhibitor) Abemaciclib (cyclin-dependant kinase (CDK) inhibitor)
Monoclonal antibodies (mABs)	Human IgG1 monoclonal antibody specific for human interleukin-1 Alpha trastuzumab (mAB biosimilar) Blinatumomab (mAB, bi-specific T-cell engager) Polatuzumab vedotin (antibody–drug conjugate)
Other	Padeliporfin (vascular-acting photosensitizer) Plitidepsin (dehydrodidemnin B) Doxorubicin hydrochloride (anthracycline antibiotic biosimilar)

expressed by CHMP members when a positive opinion was ultimately adopted. Data entry was checked by a second person and corrected in case of a data entry error.

Results

For the period from 31 January 2016 up to 31 January 2020, an average overall number of 150 oncology procedures had a final review outcome by EMA based on the summaries of opinions that EMA has posted on approvals, negative opinions, withdrawals for initial MAAs and for the extensions of indications. An OE occurred in about 20% of procedures ($n = 28/150$) for oncology products during the review period. These 28 procedures selected for the analysis included a total of 22 products with different mechanisms of action. The products can be divided into 5 main categories as shown in Table 1.

These 22 products, assessed in 28 procedures, could be divided into 19 new MAAs and 9 Type II variations, which had at least one OE, with or without any SAG-O meeting, as detailed in Supporting Information Table S1.

In total, 44 meetings were held for these selected oncology products, consisting of 32 OE and 12 SAG-O meetings. Analysing the distribution of these meetings over this 4-year period (Fig. 2), there was a high number of OE/SAG-O meetings seen in 2017, 2018, 2019 and overall, a more limited number of SAG-O consultations compared to OE meetings.

Procedures with a Positive Outcome

Out of the 28 procedures, the majority, **61%** ($n = 17/28$), resulted in a positive opinion for **12 MAA** (atezolizumab, durvalumab, cemiplimab, gilteritinib, larotrectinib, lorlatinib, neratinib, trastuzumab, polatuzumab vedotin, abemaciclib, rucaparib, padeliporfin) and **5 Type II** (nivolumab in 2L Non-Small Cell Lung Carcinoma (NSCLC), melanoma, Renal Cell Carcinoma (RCC)), pembrolizumab in 2L Head and Neck Squamous Cell Carcinoma (HNSCC), blinatumomab in leukaemia).

Although a positive opinion was adopted for these 17 procedures, only half of the procedures ended with a unanimous vote by CHMP namely for **5 MAA** (durvalumab, cemiplimab, abemaciclib, gliterinib, larotrectinib) and **3 Type II** (nivolumab CheckMate-057 (NSCLC), pembrolizumab KEYNOTE-040 (2L HNSCC), blinatumomab (leukaemia)), while the other half of these positive procedures concluded with divergent opinions expressed by some CHMP members divided as **7 MAA** (atezolizumab, rucaparib, padeliporfin, trastuzumab, lorlatinib, neratinib, polatuzumab vedotin) and **2 Type II** (nivolumab CheckMate-067 in melanoma and CheckMate-214 in RCC).

Furthermore, it should be noted that among those procedures with a positive outcome, **41%** ($n = 7/17$) were approved with a restricted indication (5 MAA and 2 Type II) as summarised in Table 2.

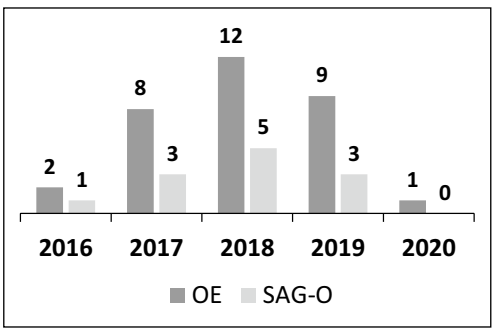

Fig. 2 OE and SAG-O meetings between 31 January 2016 up and 31 January 2020

Table 2 MAA/Type II procedures resulting in a restricted indication

	Proposed indication	Restricted indication (revisions in bold)
Product (indication)/MAA		
Padeliporfin (prostate)	Tookad is indicated for the treatment of low-risk localised prostate cancer. Tookad is indicated in adult males	Tookad is indicated **as monotherapy** for adult patients **with previously untreated, unilateral, low-risk,** adenocarcinoma of the prostate **with a life expectancy ≥ 10 years and:** **- Clinical stage T1c or T2a,** **- Gleason Score ≤ 6, based on high-resolution biopsy strategies,** **- PSA ≤ 10 ng/mL,** **- 3 positive cancer cores with a maximum cancer core length of 5 mm in any one core or 1 -2 positive cancer cores with ≥ 50% cancer involvement in any one core or a PSA density ≥ 0.15 ng/mL/cm3.**
Abemaciclib (breast)	Treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer: -in combination with an aromatase inhibitor as initial endocrine-based therapy -in combination with fulvestrant as initial endocrine-based therapy, or following endocrine therapy -as monotherapy following disease progression after endocrine therapy and one or two chemotherapy regimens in the metastatic setting	*Approval granted for combination only, monotherapy indication was withdrawn by the applicant:* Verzenios is indicated for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy
Rucaparib (ovarian)	Rubraca is indicated as monotherapy in the treatment of advanced ovarian cancer in adult patients with deleterious BRCA mutated tumours, inclusive of both germline BRCA and somatic BRCA mutations, and who have been treated with two or more prior lines of chemotherapy	Rubraca is indicated as monotherapy treatment of adult patients **with platinum-sensitive, relapsed or progressive**, BRCA mutated (germline and/or somatic), **high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer**, who have been treated with two or more prior lines of **platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy**
Durvalumab (locally advanced NSCLC)	Imfinzi as monotherapy is indicated for the treatment of adults with locally advanced, unresectable non small cell lung cancer (NSCLC) whose disease has not progressed following platinum based chemoradiation therapy	Imfinzi as monotherapy is indicated for the treatment of locally advanced, unresectable non small cell lung cancer (NSCLC) in adults **whose tumours express PD-L1 on ≥ 1% of tumour cells** and whose disease has not progressed following platinum based chemoradiation therapy
Neratinib (breast)	Nerlynx as a single agent is indicated for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy	Nerlynx is indicated for the extended adjuvant treatment of adult patients with early stage hormone receptor positive HER2-overexpressed/amplified breast cancer and **who are less than one year from the completion of** prior adjuvant trastuzumab based therapy
Product (indication)/Type II		
Blinatumomab (leukaemia)	Treatment of adults with minimal residual disease (MRD) positive B cell precursor acute lymphoblastic leukaemia (ALL) for BLINCYTO	Treatment of adults with **Philadelphia chromosome-negative CD19** positive B precursor ALL **in first or second complete remission** with minimal residual disease (MRD) **greater than or equal to 0.1%** for BLINCYTO monotherapy
Pembrolizumab (2L HNSCC)	KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy	KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) **in adults whose tumours express PD-L1 with a ≥ 50% TPS** and progressing on or after platinum-containing chemotherapy **(see section 5.1)**

BRCA BReast CAncer gene, *HER2* human epidermal growth factor receptor 2, *TPS* tumour proportion score

Procedures with a Negative Outcome

Out of the 28 procedures, **39%** ($n=11/28$) resulted in a negative outcome (i.e. withdrawal or refusal) including **7 MAA** (quizartinib, mAB for IL-1α, vosaroxin, etirinotecan pegol, enasidenib, plitidepsin, doxorubicin HCL) and **4 Type II** (nivolumab in gastric cancer and 1L NSCLC, pembrolizumab in 1L NSCLC and oesophageal cancer). The main reasons for a negative outcome for these procedures were reviewed and have been summarised in Table 3.

Re-examination Procedure

Furthermore, a re-examination was requested in half of the procedures where a negative opinion was initially adopted by CHMP ($n=7/14$). This resulted in a negative outcome for **4 MAA** (57%) namely etirinotecan pegol, mAB for IL-1α, plitidepsin and doxorubicin HCL and a positive outcome for **2 Type II** and **1 MAA** (43%) namely blinatumomab (leukaemia), nivolumab (1L RCC) and neratinib.

SAG-O Consultation

As indicated earlier, CHMP can request involvement of the SAG-O and consultation can also be triggered by the applicant in case of re-examination procedure. For the 28 procedures with at least one OE, SAG-O was also consulted in **45%** of procedures ($n=12/28$). Among those 12 procedures: **66%** resulted in a positive outcome ($n=8/12$–5 MAA/3 Type II) and **34%** resulted in a negative outcome ($n=4/12$–4 MAA) as summarised in Fig. 3 below.

The final CHMP outcome was fully aligned with SAG-O advice in these 12 procedures. Notably, all 3 Type II variations that had an OE and a SAG-O meeting ended positively and 3 out of the 4 MAAs with a positive outcome were conditional MAs based on less comprehensive data than normally required, which means that the applicant should be able to provide the comprehensive clinical data in the future.

Impact of SA Consultation

Finally, among the 28 identified procedures with an OE, the proportion of the MAA/Type II that had received SA was **79%**. Obtaining a SA was mainly pursued for new MAA compared to Type II (18 vs 4) and interestingly may be associated with a slightly better outcome (63% vs 50%) as shown in Fig. 4 below.

Discussion

It was decided to retrospectively evaluate 19 MAA and 9 Type II variations (28 procedures) for oncology treatments which had at least one OE and which final outcome took place between 31 January 2016 up to 31 January 2020 with the aim of better understanding how many procedures having an OE, with or without any SAG-O meeting, resulted in a regulatory approval for oncology products in the EU. In addition, another objective was to evaluate if obtaining a Scientific Advice by the CHMP impacted the MAA/Type II outcome for those procedures having at least one OE.

The results of this analysis suggest that the majority of procedures having an OE, with or without any SAG-O meeting, led to MAA/Type II variation approvals in the Centralised Procedure. The MAA/Type II approval rate of close to 61% for the studied oncology products is a good indicator that this type of agency interaction is an important opportunity for the applicant to have a last chance to defend their position and provide clarifications in front of the CHMP, and to resolve any outstanding major objections at the final stage of the procedure. Other research suggests that larger companies may have more opportunities to experience such meetings at high stake than SMEs and may be better positioned by having more resources to prepare for these highly demanding meetings and engage with external experts to increase their chance for a positive outcome and patient access to new treatments [6]. Interestingly, it is noted that for nearly half of the procedures which concluded positively, there was no unanimous vote with 2 to 8 CHMP members expressing divergent opinions.

In addition, it was also observed that a successful outcome may be contingent upon willingness of the applicant to restrict the indication. As no additional data can be presented by the applicant during an OE, labelling can be considered as a key driver for a successful outcome. This suggests that the applicants should be prepared for potential labelling scenarios to be ready at the time of the OE meeting, especially noting the rate of successful procedures which led to a restricted indication (41%).

It has also been found that the final CHMP outcome was fully aligned with SAG-O advice when requested for some procedures and SAG-O consultation during re-examination procedure could sometimes reverse the initially adopted CHMP negative opinion. It is assumed that SAG-O involvement would be generally expected if there is a new mode of action or innovative treatment for a specific indication.

Table 3 Reasons for negative outcome (negative CHMP Opinion or withdrawal)

Main Reason	Product/Procedure Type	EPAR conclusions
Unfavourable Benefit/Risk		
Benefit/Risk not demonstrated in subgroup analyses	Vosaroxin—MAA	Lack of strong external and internal replication of the subgroup finding in the context of a (negative) single pivotal trial with inconsistent results within this age-defined subgroup not pre-specified for confirmatory testing. Lack of efficacy and increased toxicity in the sub-subgroup of patients ≥ 60 years with late relapse
	Etirinotecan pegol—MAA	Efficacy claims were based on subgroup analysis from a single pivotal trial which failed to convincingly demonstrate efficacy
	Nivolumab[a]—Type II ONO-4538–12 (Gastric cancer)	Single-arm trial. Benefit/Risk in non-Asian patients was not demonstrated which prevented CHMP to conclude on a positive outcome for EU
	Pembrolizumab—Type II KEYNOTE-181 (2L oesophageal squamous cell carcinoma in patients whose tumours express CPS ≥ 10)	Benefit-Risk was not demonstrated in exploratory subgroup analyses without any statistically significant OS benefit
Single arm trial (efficacy not established)	Enasidenib—MAA	Not possible to conclude that clinical benefit has been established based on the evidence presented. Results from single arm trial in a very heterogeneous population are not considered outstanding in relation to available therapies. Due to the limitations of comparisons to external controls, OS results remain descriptive and non-inferential
	Quizartinib—MAA	Single pivotal trial was borderline positive on the primary endpoint, overall survival. Results of the primary endpoint are not supported by established effects on the secondary endpoint event free survival and the exploratory endpoints related to complete remission. Consequently, efficacy has not been established
	Pembrolizumab—Type II KEYNOTE-021G (1L NSCLC)	Uncertainties were seen with efficacy and safety data for pembrolizumab combination with chemotherapy in KEYNOTE-021-G (small randomized Phase 2 study). KEYNOTE-189 Phase 3 Interim Analyses data results were awaited to confirm benefit-risk profile of the combination
Modest benefit and substantial toxicity	Plitidepsin—MAA	Results from the primary analysis showed no statistically significant difference in terms of OS and not a clinically meaningful difference in PFS although being statistically significant Use of plitidepsin in combination with DXM is associated with substantial toxicity (high proportion of patients with treatment-related severe and life-threatening adverse events). The benefits observed cannot be considered to outweigh the observed risks
GCP issues	Nivolumab (in combination with ipilimumab)—Type II CheckMate-227 (1L NSCLC)	Validity of the data was called into question due to some GCP inspection findings with extensive protocol amendments that were conducted
CMC deficiencies		
	Human IgG1 monoclonal antibody specific for human interleukin-1 alpha—MAA	A control strategy that would ensure consistent manufacture of a product with characteristics that are equivalent to the product used in pivotal clinical studies has not yet been provided

Table 3 (continued)

Main Reason	Product/Procedure Type	EPAR conclusions
Similarity not demonstrated (Biosimilar)		
	Doxorubicin hydrochloride—MAA	Similarity in terms of efficacy and safety between Doxolipad and Caelyx, a liposomal formulation of doxorubicin hydrochloride, was not sufficiently established

CHMP Committee for Medicinal Products for Human Use, *CRC* colorectal cancer, *DXM* dexamethasone, *EPAR* European Public Assessment Report, *GCP* Good Clinical Practice, *HCC* Hepatocellular Carcinoma, *MAA* Marketing Authorisation Application, *MSI-H* Microsatellite Instability-High, *OS* Overall Survival, *PFS* Progression-Free Survival

[a]Nivolumab had two more withdrawals/procedures with a negative outcome that did not have any OE, namely in HCC (CheckMate-040) and MSI-H CRC (CheckMate-142) indications, both were single arm trials

When comparing the outcome for MAAs and Type II respectively, the analysis showed that a higher number of OEs was reported for MAAs (19 vs 9), which makes sense as this is the first procedure for a product with a potentially new mechanism of action. In addition, slightly more procedures for MAA ended positively compared to those for Type II [$n = 12/19$ (63%) vs $n = 5/9$ (55%)]. Here it is important to note that for a new MAA a conditional approval is a valid option, whereas this is not an option for Type II, which might raise the bar to be successful for this type of procedure. However, Post-Authorisation Measures may still be requested for Type II variations.

Although based on a limited number of products and compliance with SA could not be assessed, the MAA/Type II success rate (63%) of procedures that received a SA when compared to procedures that did not receive any SA (50%), suggests that companies who intend to use the Centralised Procedure would benefit from engaging in a dialogue with EMA regarding their development programme via the SA procedure. This is in line with previous researches which show that complying with SA increases the chances of receiving marketing authorisation but it does not guarantee it [7, 8].

A limitation of the analysis was that the selection of the 28 procedures which had at least one OE was based on the review of agenda/minutes of the CHMP meetings and EPARs published by the EMA, which may not accurately reflect the total number of OE/SAG-O meetings that were actually held during this 4-year period. These data are therefore dependent on the information summarised and published by the EMA. In addition, because the numbers are low, it is challenging to do statistical assessments with any confidence; as such, this analysis is only considered as descriptive.

Conclusion

In conclusion, this descriptive analysis indicates that an OE is an important agency meeting for applicants which in the majority of cases may have helped to overcome major objections, resulting in a regulatory approval for oncology products in the EU. The successful outcome for those procedures may be contingent upon willingness to restrict the indication. In addition, obtaining SA by the CHMP early in development and at major transition points is recommended to increase MAA/Type II success rate.

Further research is needed to confirm the current conclusion, considering future procedures in which oncology procedures with an OE are available. In addition, a comparative analysis with other therapeutic areas evaluating how often procedures with this type of meeting led to an approval could be performed. It is important that continuous research

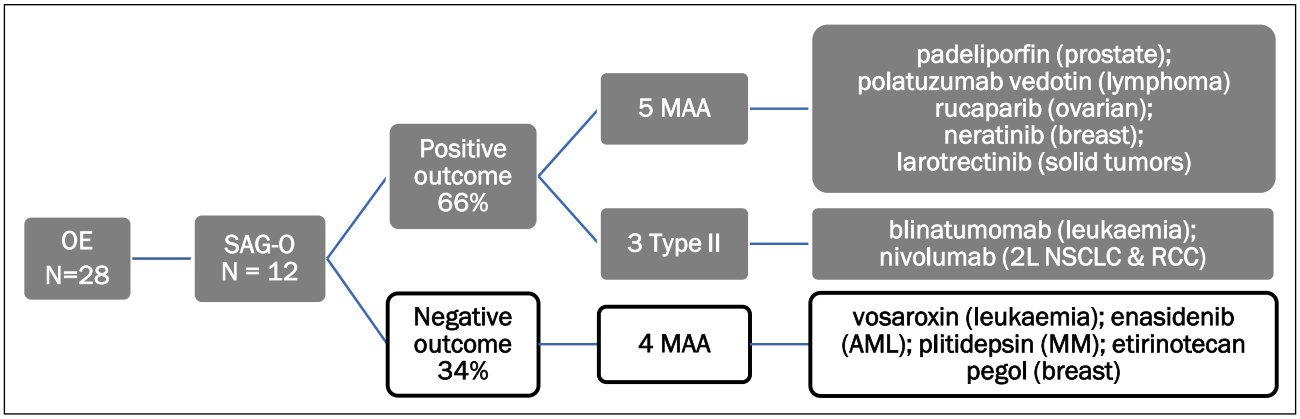

Fig. 3 MAA/Type II procedures with SAG-O consultation

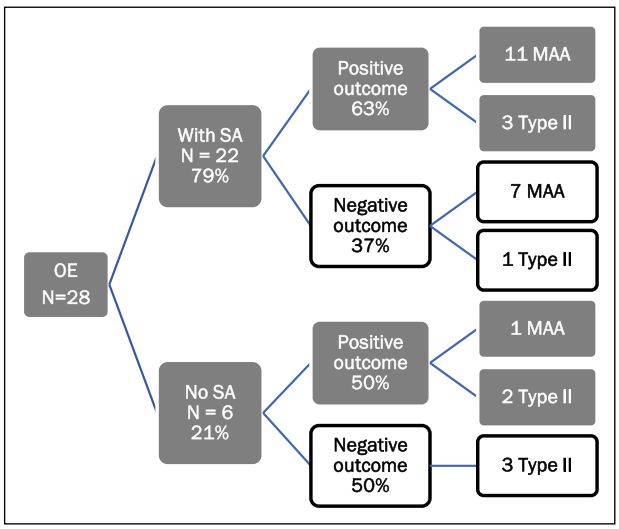

Fig. 4 Outcome of MAA/Type II procedures with or without any SA

efforts are pursued in this area of importance to better understand the impact of the different measures offered by the regulatory system in the EU.

Author Contributions

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Declarations

Conflict of interest

There are no competing interests to declare.

Supplementary Information

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