Post-authorisation Safety and Efficacy studies

Cancer Medicines Forum - 20th December 2022

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Agenda

1. **Regulatory background on imposed post-authorisation safety and efficacy studies**
2. **How to address treatment optimisation through the life cycle of the medicine evaluation?**

Approval of cancer medicines

Principles: no further development changes (formulation, dose, posology)

However, in the context of the obligation of the MAHs to take due account of technical and scientific progress in accordance with Article 16 (1) of Regulation (EC) no 726/2004

A benefit-risk decision based on the applicant's data

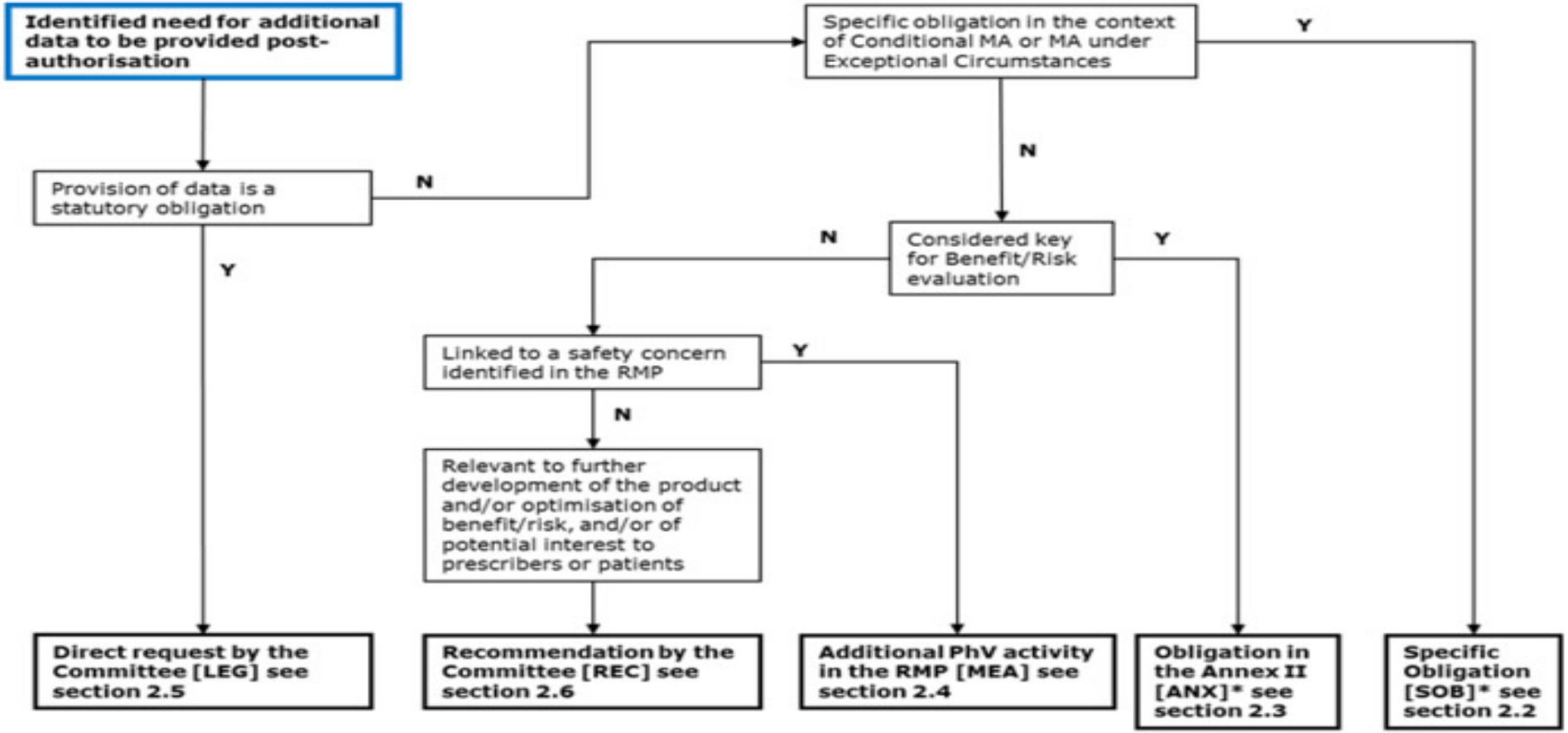
Chapter 2

Supervision and penalties

Article 16

1. After a marketing authorisation has been granted in accordance with this Regulation, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in points (d) and (h) of Article 8(3) of Directive 2001/83/EC, take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods. He shall apply for approval of corresponding variations in accordance with this Regulation.

Fig.: Schematic overview of decision tree for the classification of PAMs



* plus potentially also additional PhV activity in the RMP [MEA] if linked to a safety concern identified in the RMP

Imposition of post-authorisation safety and efficacy studies

- Additional evidence needed for aspects key to B/R
- Potential changes to PI

Full MAA

Annex II:

PAES delegated act:

a) surrogate endpoints
b) combination
c) sub populations
d) long term efficacy
e) real –life conditions (vaccines)
f) change of standard of care
g) new scientific factors

PASS

Annual re assessment

Exceptional circumstances

Specific obligations

- Comprehensive data cannot be provided based on rarity
- Based on scientific grounds
- Ethics
  - B/R positive
  - Comprehensive data will never be provided

Need for annual renewal

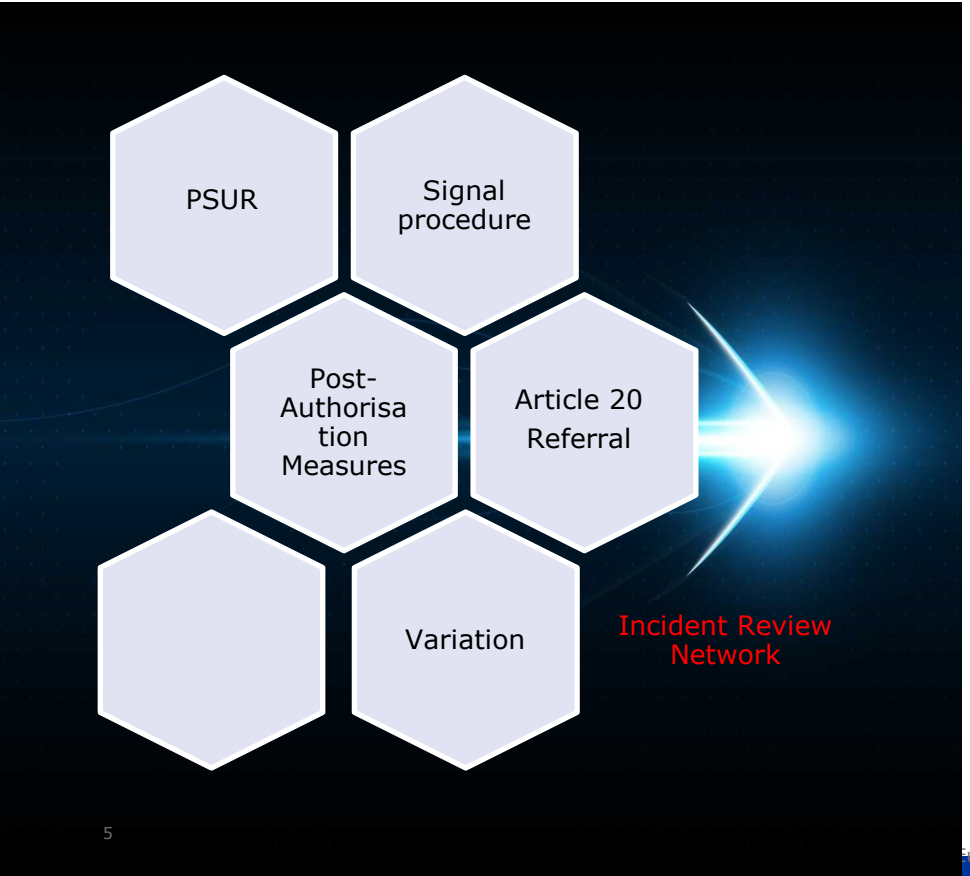
Conditional MA

Specific Obligations

- Seriously debilitating / life threatening diseases
- Emergency
- Orphans
  - B/R positive
  - Comprehensive data will be provided
  - Unmet medical need
  - Public health benefit outweighs the risks

In order to confirm the long-term efficacy and safety of <product> in<indication>, the MAH should conduct and submit the results of study <X> <according to an agreed protocol>

Regulatory tools to take regulatory action post-marketing



2. Objectives of the incident management plan

Throughout the lifecycle of a medicinal product various types of events can occur or new information can arise which could have a serious impact on public health. In order to ensure the most appropriate management of such events or new information whilst also aiming for an efficient operation of the EU Regulatory Network in this field, the objectives of the EU Regulatory Network Incident Management Plan are:

- To continuously monitor such events and new information (hereafter called "incidents"), to review their public health impact, and to take the necessary routine measures to remedy the situation. This activity is referred to in this document as proactive incident management, the main aim being to prevent an incident developing into a crisis.
- To request further analysis under the form of the Preliminary Risk Analysis when routine measures are not considered sufficient to address the incident. This PRA is requested by the Incident Review Network from the relevant party and constitutes the basis of the decision on whether or not a crisis management phase should be triggered.
- To undertake in case of a confirmed crisis the initiatives necessary to manage and control the situation, whereby urgent and coordinated action within the EU Regulatory Network is necessary. This activity is referred to in this document as reactive incident management and is led by the EU Executive Task Force and EU Operational Task Force.

Examples of regulatory actions taken – Keytruda and Tecentriq

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 June 2018
EMA/364553/2018

EMA restricts use of Keytruda and Tecentriq in bladder cancer

Data show lower survival in some patients with low levels of cancer protein PD-L1

Early data from two clinical trials[1] show reduced survival with Keytruda (pembrolizumab) and Tecentriq (atezolizumab) when used as first-line treatments for urothelial cancer (cancer of the bladder and urinary tract) in patients with low levels of a protein called PD-L1. The data indicate that Keytruda and Tecentriq may not work as well as chemotherapy medicines in this group of patients.

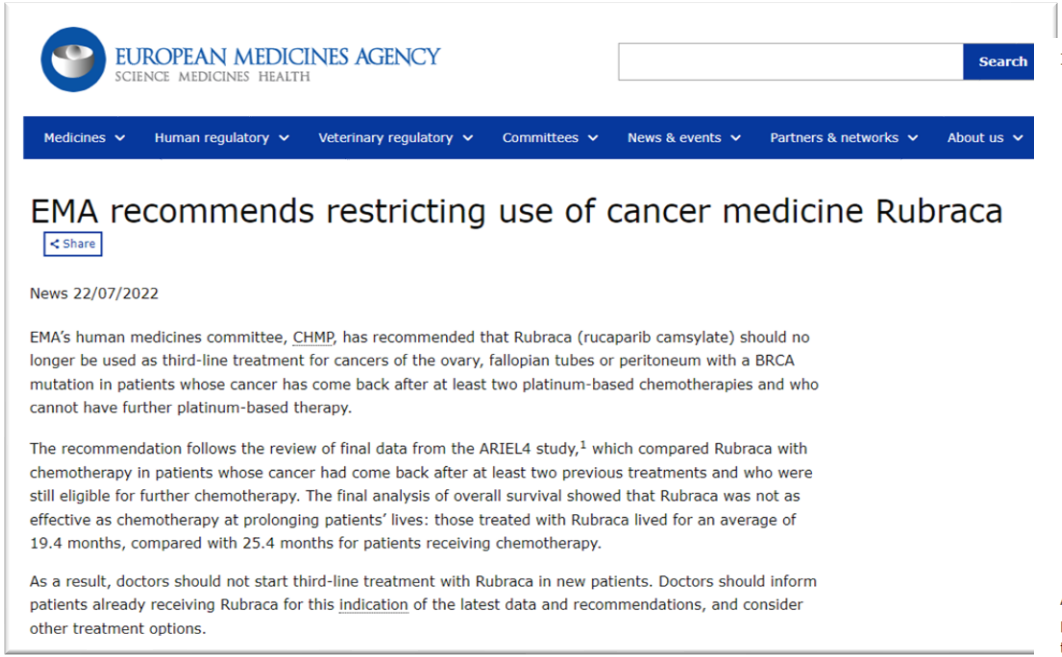
As a result, the European Medicines Agency (EMA) has recommended restricting the use of these medicines as first line-treatments for urothelial cancer.

Keytruda and Tecentriq should now only be used for first-line treatment of urothelial cancer in patients with high levels of PD-L1 (see full indications below)

Information for healthcare professionals

- Preliminary data from Keynote-361 and IMvigor130 show a reduced survival with Keytruda and Tecentriq compared with chemotherapy in patients with locally advanced or metastatic urothelial cancer who have not received prior therapy and whose tumours have low expressions of PD-L1.
- Based on the data from the trials, which are still ongoing, the urothelial cancer indications for Keytruda and Tecentriq are being revised as follows:

Examples of regulatory actions taken - Rubraca



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EMA recommends restricting use of cancer medicine Rubraca

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News 22/07/2022

EMA's human medicines committee, CHMP, has recommended that Rubraca (rucaparib camsylate) should no longer be used as third-line treatment for cancers of the ovary, fallopian tubes or peritoneum with a BRCA mutation in patients whose cancer has come back after at least two platinum-based chemotherapies and who cannot have further platinum-based therapy.

The recommendation follows the review of final data from the ARIEL4 study,[1] which compared Rubraca with chemotherapy in patients whose cancer had come back after at least two previous treatments and who were still eligible for further chemotherapy. The final analysis of overall survival showed that Rubraca was not as effective as chemotherapy at prolonging patients' lives: those treated with Rubraca lived for an average of 19.4 months, compared with 25.4 months for patients receiving chemotherapy.

As a result, doctors should not start third-line treatment with Rubraca in new patients. Doctors should inform patients already receiving Rubraca for this indication of the latest data and recommendations, and consider other treatment options.

Information for healthcare professionals

- EMA has recommended that Rubraca should no longer be authorised as monotherapy for the treatment of 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.
- The recommendation follows the final analysis of data from a phase 3 study, ARIEL4, comparing Rubraca with chemotherapy in patients with relapsed, BRCA-mutated, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer.
- A difference in favour of Rubraca was observed for the primary endpoint of progression free survival by investigator (invPFS) (7.4 months for the Rubraca group compared with 5.7 months for the chemotherapy group (hazard ratio (HR)=0.665 (95% CI: 0.516, 0.858); p=0.0017)).
- However, overall survival with Rubraca was lower than that with chemotherapy (19.4 months versus 25.4 months, respectively, with a HR of 1.31 (95% CI: 1.00, 1.73); p=0.0507).
- The CHMP therefore concluded that the benefit of Rubraca, when used in the above-mentioned indication, had not been confirmed and that treatment may be associated with an increased risk of death. Ongoing treatment in this setting should be reconsidered and patients should be informed of the latest data and recommendations.
- This recommendation does not affect the use of Rubraca as maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

A direct healthcare professional communication (DHPC) will be sent in due course to healthcare professionals prescribing, dispensing or administering the medicine. The DHPC will also be published on a dedicated page on the EMA website.

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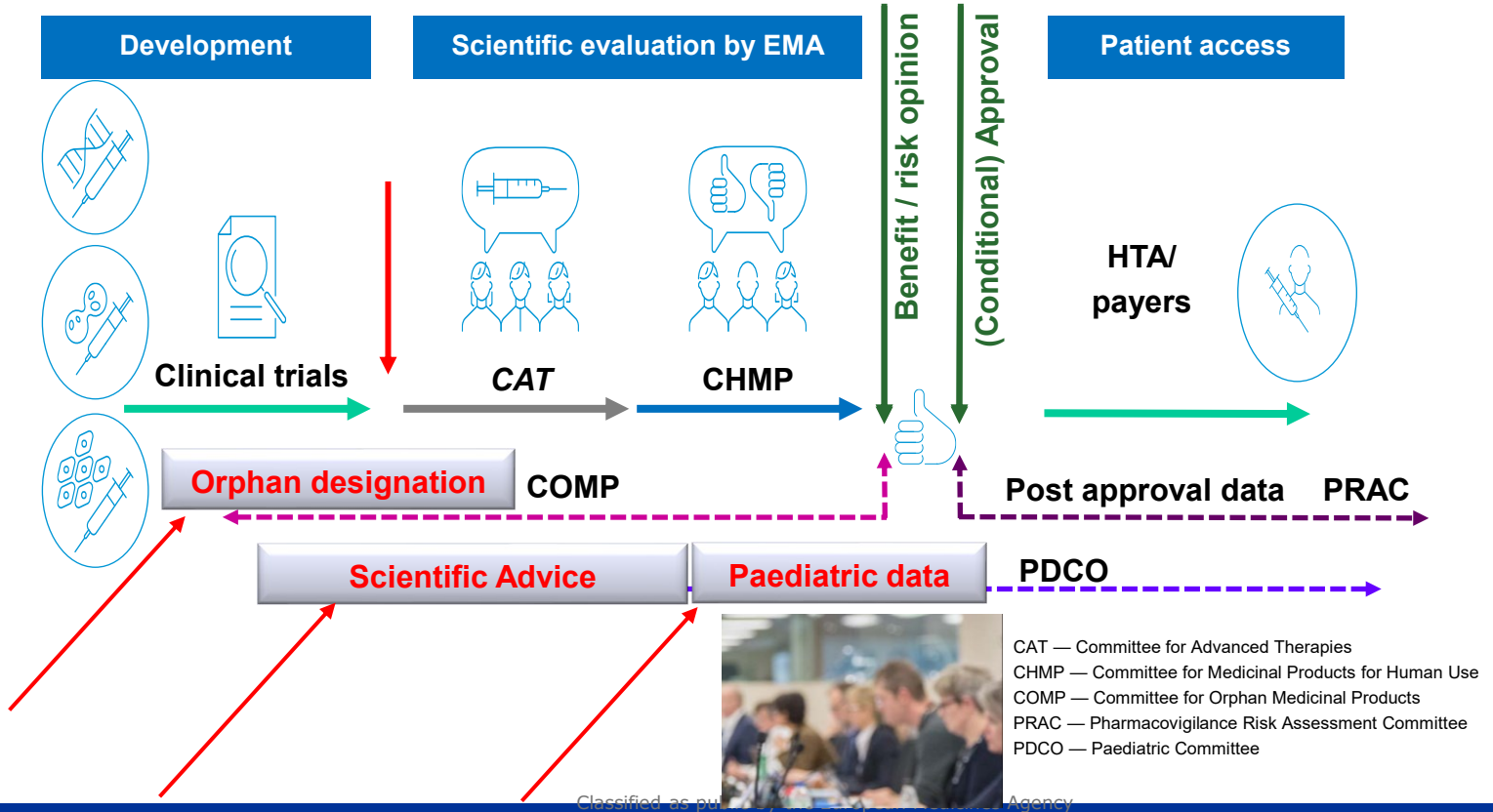
Start at the development phase



CAT — Committee for Advanced Therapies
CHMP — Committee for Medicinal Products for Human Use
COMP — Committee for Orphan Medicinal Products
PRAC — Pharmacovigilance Risk Assessment Committee
PDCO — Paediatric Committee

Significant benefit for orphan medicines

Clinically relevant advantage based on improved efficacy:

- Evidence of clinical improved effect
- Efficacy in combination
- Meaningful and clinically relevant changes that allow the product to be used in a wider patient population or previously excluded sub-groups

Improved safety:
Complementary safety profile, less serious or severe or frequent ADRs

Major contribution to patient care:

- Ease of use: such as formulation/administration route, dosing schedule
- Availability, shortage of supply/ improved availability, from EU authorisation

Significant Benefit

Discussion on study design in Scientific Advice

How scientific advice works

EMA gives scientific advice by **responding to specific questions** posed by the medicine developer on the development of a particular medicine.

The developer of a medicine presents the way it plans to develop its medicine and identifies questions and possible solutions. EMA then gives advice on the developer's proposals.

Scientific advice is prospective in nature. EMA **does not pre-evaluate** the results of the studies and in no way concludes on whether the benefits of the medicine outweigh the risks.

Scientific advice from EMA is not legally binding on EMA or on the medicine developer with regard to any future marketing authorisation applications for the medicine concerned.

- What is the target indication?
- What is the MoA? What are the expected side effects?
- What are the treatment options for this indication?
- Which study design to use (RCT?), duration of the study?
- Is the dose investigated optimal?
- Patients included reflected of the target patients population? Paediatric patients?
- ….

- Will the generated data allow for a comprehensive B/R discussion?

Thank you for your attention

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