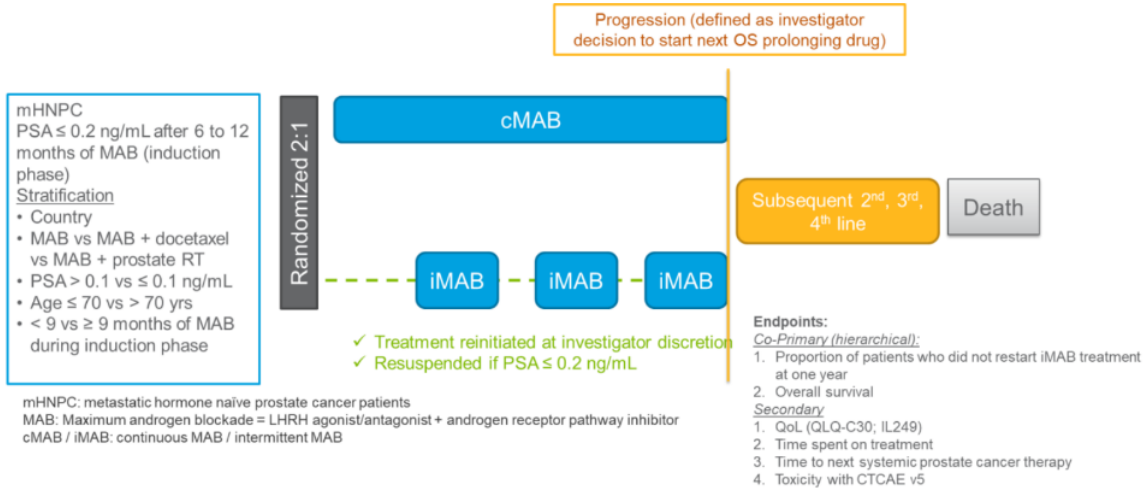
EORTC
European Organisation for Research and Treatment of Cancer

Low-intervention clinical trials

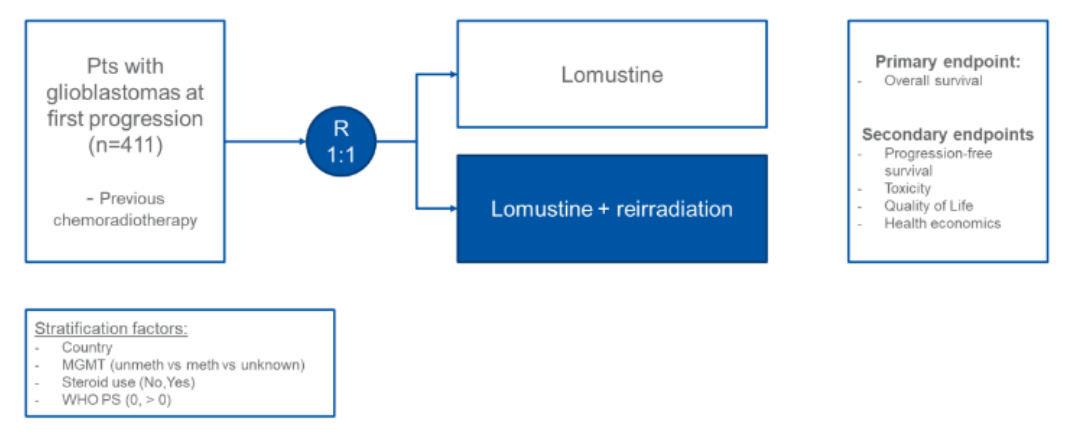
Two examples: EORTC 2238-GUCG (DE-ESCALATE) and EORTC 2227-BTG (LEGATO)

Trial designs

EORTC 2238-GUCG (DE-ESCALATE)



EORTC 2227-BTG (LEGATO)



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Low-intervention CT classification

EORTC 2238-GUCG (DE-ESCALATE)

Sponsor's rationale:

- All drugs are authorized in at least one country, if not all.
- They are all being used as per their marketing authorization. The combination treatment of ADT and ARpI (MAB) is approved by the European Medicine Agency and recommended by guidelines for our target population.
- Patients entering this study have already been on this combination treatment for 6 to 12 months, and they will either continue it as is or will be prescribed a "treatment holiday" in the form of temporarily interrupting their treatment. This is possible by the monitoring of PSA levels, which are used as an indicator of cancer status (controlled or growing). This interruption approach is already applied in daily practice and supported by studies when ADT is administered without intensification of an ARpI. Presently to manage toxicities, clinicians will apply an ad hoc approach based on patient desire and their "gut feeling".
- There are no extra tests or required imaging as we allow patient management to follow the standard of care and only collect data. It is standard to monitor PSA and testosterone levels in these patients as an early signal of cancer resurgence. The burden on patients is limited to completing questionnaires, which can also be done over the phone or from home rather than during a clinic visit.

Outcome: low-intervention CT classification **not accepted** and withdrawal of the CT.

EORTC 2227-BTG (LEGATO)

Sponsor's rationale:

- The investigational medicinal product (lomustine) is authorised in at least one of the Member States participating in this trial.
- The investigational medicinal product is used in accordance with the terms of its marketing authorisation - lomustine is authorized for use in primary brain tumours. The dosage varies by country (e.g., France recommends 130 mg/m2, Austria 100-130 mg/m2 whereas Germany mentions 70-100 mg/m2 which corresponds to recommendations when given as part of combination therapy in other member states). Consequently, this trial's recommended lomustine use is based on the guidelines developed by a task force selected by the Guideline Committee of the European Association of Neuro-Oncology (EANO)
- There are no additional diagnostic or monitoring procedures posing additional risk or burden to the safety of the subjects compared to normal clinical practice in any of the Member States participating. This study was developed to be pragmatic: it adheres to guidelines for the use of lomustine; the extra safety monitoring usually associated with clinical trials with lomustine is not mandatory but left up to investigators' clinical judgement ("if clinically indicated"); and re-irradiation is already being offered to patients in an ad hoc manner in some centres participating in the study

Outcome: low-intervention CT classification **accepted.**

Key messages

- The CTR focuses on “new Drugs” but does not consider other types of protocols such as studies aiming to optimise existing strategies in the best interest of patients with an improved QoL and aiming to decrease toxicities.

- In our example, the DE-ESCALATE protocol aims at addressing a schedule de-escalation. It addresses a patient / disease-oriented question, not a drug question. The end-points are relevant for patients, not to the drugs. It has been developed as a pragmatic clinical trial, adopting approaches which are consensual in the academic settings.

    - Whereas not considered as LICT by the CTR assessors, it would fall under “category A” in Switzerland and under the “New notification Scheme” in the United Kingdom.

- EORTC is concerned of not having at least the possibility to use the LICT status but is fundamentally willing to alert EU on the risk to create an environment which is not “patient centric” and enable frameworks which only allow limited types of protocol while excluding those addressing over-utilisation of therapeutic interventions.

Suggestions/needs and other challenges

- Address appraisal controversies between MS: how to grow a collegial, consistent approach of different types of trials across assessors
  - DE-ESCALATE: new application to be started, disproportionate consequences impacting on patients
- Consolidate and Structure RFIs: up to 120 RFIs on LEGATO ! Role of the RMS?
- Concerns of longer timelines while the pressure increases on all stakeholders
- As of today, our observations are: increased pressure, additional complexity and longer timelines.
- **How can we build from the current regulation(s), and the work of ACT EU, a Europe that welcomes efficiently early and late clinical research, commercial and non-commercial trials, drug centred and patient centred research?**

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