Oncology and Hematology Development

Development of Complex Treatment Strategies: What is the Clinical Question of Interest ?

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Thanks to a lot of work from/with M. Akacha, F. Bretz, A.Buchbinder, R.Capdeville, E.Degtyarev, B.DiDomenico, A.Maniero, K.Sen, M.Voi, J.Weber, N.Yateman

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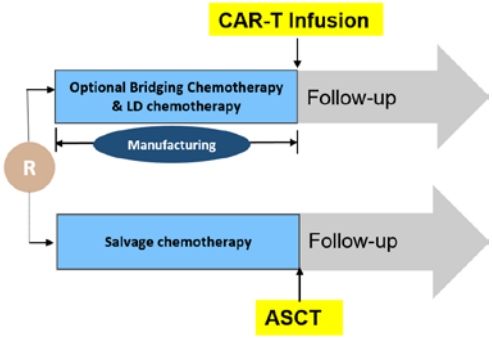
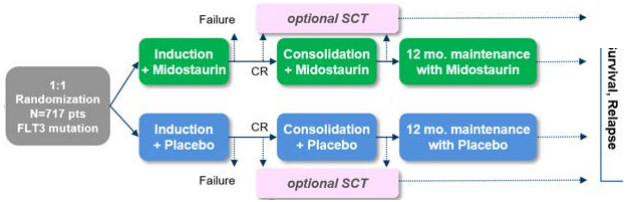
ICHE9(R1): first estimand attribute, «the treatment condition of interest»

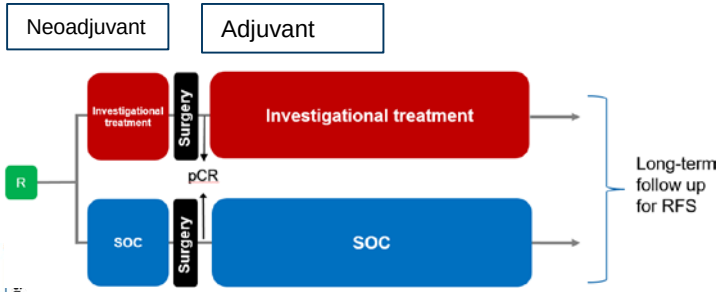
- New attribute in final version (vs. consultation draft):
  - « the treatment condition of interest » and
  - « the alternative treatment condition to which comparison will be made »
  - « might consist of an overall regimen involving a complex sequence of interventions »
  - “Treatment Policy” strategy: « the intercurrent event is considered to be part of the treatments being compared »
- This presentation :
  - From internal discussions on estimands, to identify clinical questions of interest vs. definition of the treatment attribute in several Oncology and Hematology development settings
  - Reflects the ongoing and evolving thinking of the authors from Novartis
  - Calls for a broader reflection on the evidence needed to optimally study, register and prescribe treatment strategies

Examples of treatment strategies in oncology and hematology

- Treatment strategy is defined by the intent to treat with a sequence of interventions including investigational treatment
  - Treatment strategy defines personalized treatment journeys
  - Sequence of interventions may depend on intermediate assessment of outcomes/multiple intermediate steps
  - Some patients may not receive some interventions in the intended sequence







CAR-T=Chimeric Antigen Receptor T cells, R=randomization, LD=Lymphodepleting, ASCT=Autologous Stell Cell Transplant, CR=Complete Response, SOC=Standard of Care, pCR=pathological complete response, RFS=relapse-free survival,

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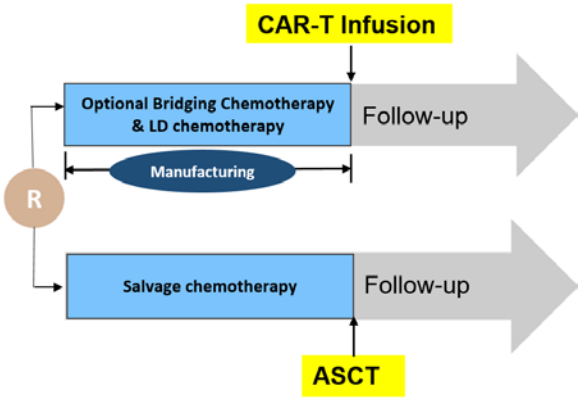
Question of interest: Effect of the whole treatment strategy ?

- Efficacy and safety of the treatment strategy as a whole, in several disease settings:
  - A particularly relevant question of interest for physicians and patients at time of prescription decision
  - Ideally should be reflected in the label
  - May appear as not aligned with the FDA's more specific focus on the Experimental Drug
- Assessing effect of whole sequence of interventions as primary goal of development plan
  - May deeply determine the corresponding development plan
  - May not always enable to assess meaningfully the contribution of each component
  - Raises issues of
    - efficiency and feasibility of development plans
    - necessary and sufficient scientific evidence for different stakeholders

Development planning considerations

- Assessing the **whole sequence** of interventions **within one trial** can provide data for the label of a treatment strategy
  - Efficacy and safety profile of the **overall sequence** cannot be assessed in **separate clinical trials** each designed to evaluate effect of **individual components** of the treatment strategy
  - For example: assessing maintenance vs. induction/consolidation separately: such separate trials address different questions
- Assessing **individual components** of the treatment strategy in **one confirmatory fully powered trial** may not represent an efficient path of drug development
  - **re-randomization** at each step of treatment strategy needed to ensure confirmatory evidence for each individual component in the sequence
  - a study with multiple randomizations may take too long to complete, e.g., in rare diseases or settings of very acute medical need
- What is the necessary and sufficient evidence to support the label of a treatment strategy ?
  - It is unclear under which circumstances such re-randomization steps are warranted
  - Consideration of the disease, drug mode of action, scientific and available clinical data, ...

CAR-T cells: Comparing two treatment strategies



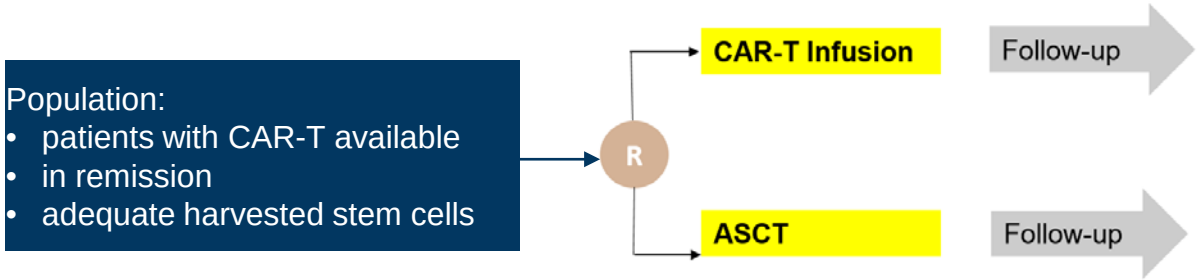
CAR-T treatment strategy: intent to treat with optional bridging chemotherapy and lymphodepleting chemotherapy followed by a single CAR-T infusion, regardless of tumor response to bridging chemotherapy

SOC treatment strategy: intent to treat with 2-3 cycles of salvage chemotherapy followed by ASCT only for patients in remission; 2nd salvage chemotherapy is administered with intent to transplant if patient is not in complete remission after 1st salvage chemotherapy

- **Main clinical question of interest:** Treatment effect of CAR-T treatment strategy relative to SOC treatment strategy in patients with relapsed/refractory cancer after first line therapy
- **Clinical rationale:** Comparing treatment strategies including all paths in the patient journeys corresponds to clinical practice, where not all patients will receive all components of the treatment strategy
  - some patients may never receive CAR-T infusion for example because of patient's condition or reasons related to manufacturing
  - some patients may never receive ASCT for example because of inability to achieve response, clinical deterioration and/or inability to harvest enough stem cells

CAR-T=Chimeric Antigen Receptor T cells, SOC=Standard of Care, R=randomization, LD=Lymphodepleting, ASCT=Autologous Stell Cell Transplant

CAR-T cells : comparing individual components of treatment strategies



- Study comparing individual components CAR-T vs ASCT (and not CAR-T vs SOC treatment strategies) possible, but appears irrelevant for most patients
- Only an artificial subset of r/r cancer patients who fulfill all 3 criteria are eligible
  - have CAR-T product available
  - are in remission after salvage chemotherapy and
  - have adequate harvested stem cells to undergo ASCT

CAR-T=Chimeric Antigen Receptor T cells, SOC=Standard of Care, R=randomization, LD=Lymphodepleting, ASCT=Autologous Stell Cell Transplant, r/r=relapsed / refractory

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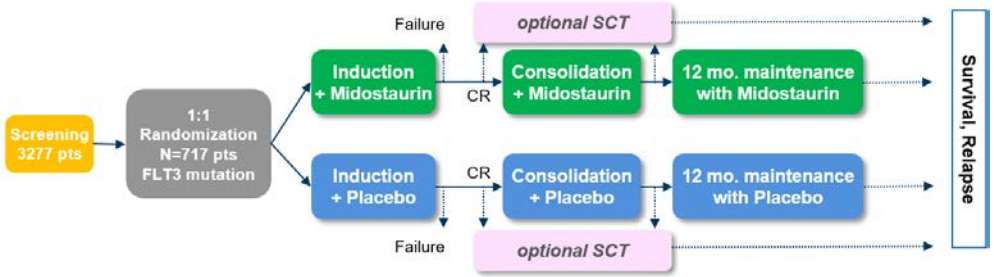
Comparing treatment strategies Rydapt in Acute Myelogenous Leukemia



Which question are we asking?

Contrasting initial protocol objective with approved drug labels

- **Protocol objective**: To determine if the addition of midostaurin to **induction, consolidation, and maintenance** therapy improves overall survival in mutant AML
- **SmPC indication:**
  - In combination with **induction and consolidation**, and for patients in complete response followed by single agent **maintenance** therapy
- **USPI indication:**
  - In combination with **induction and consolidation**

- Managing AML patients involves a treatment strategy including a sequence of decision points and treatment modalities
- Despite a detailed description of objectives and treatment in the protocol, there was insufficient alignment of the underlying question of interest
  - The protocol's trial objective did not clearly outline the impact of SCT, a component of the treatment strategy with a potential major impact on benefit and risk
  - Despite its explicit inclusion in the study objective, the maintenance phase was not included consistently in approved labels although it was part of the studied treatment strategy (accepted by EMA, not accepted by FDA)

SCT= Stell Cell Transplant, CR=Complete Response

RYDAPT: differences in interpretation between EMA and FDA

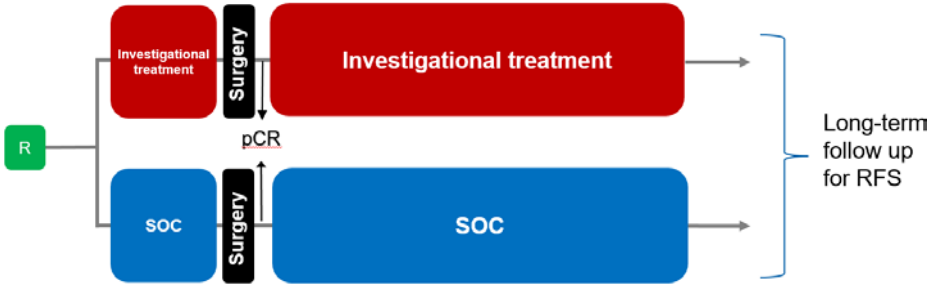
- EMA's rationale to include maintenance in label:

  "*Therefore, the available data did not allow a firm conclusion regarding the added value of the continuation therapy. However, there is a clear scientific rationale for maintenance therapy in FLT3-mutated AML, which has a high relapse rate partly attributed to FLT3 clones. Furthermore, the efficacy has been demonstrated only when a maintenance phase is applied. In addition, the safety profile is favourable. For these reasons, the proposed indication which includes a post-remission maintenance phase is considered acceptable*."

- SmPC indication consistent with efficacy and safety results describing the effect of the whole treatment strategy
  - Safety section includes additionally results in the maintenance phase only
- USPI indication inconsistent with OS and EFS results in «Clinical studies» section describing the treatment effect after induction, consolidation and maintenance treatment with Rydapt
  - includes statement «There was no re-randomization at the start of post-consolidation therapy» - re-randomization was not required to address the protocol objective
  - Safety section includes results of the whole treatment strategy including maintenance

OS=Overall Survival, EFS=Event Free Survival

Neoadjuvant/Adjuvant: Comparing treatment strategies



Investigational treatment strategy: investigational treatment administered as neoadjuvant therapy, followed by surgery, followed by investigational treatment administered as adjuvant therapy

SOC treatment strategy: neoadjuvant SOC therapy followed by surgical excision of the tumor followed by adjuvant SOC therapy

- **Main clinical question of interest:** What is the effect of the investigational treatment strategy relative to SOC treatment strategy in patients with resectable tumors?
- **Clinical rationale:** Comparing treatment strategies includes all paths in the patient journeys, which corresponds to clinical practice, where not all patients will receive all components of the strategy
  - some patients may discontinue neoadjuvant treatment and/or progress before starting adjuvant therapy, thus jeopardizing their ability to receive adjuvant treatment

pCR=pathological complete response, R=randomization, SOC=Standard of Care, RFS=relapse-free survival

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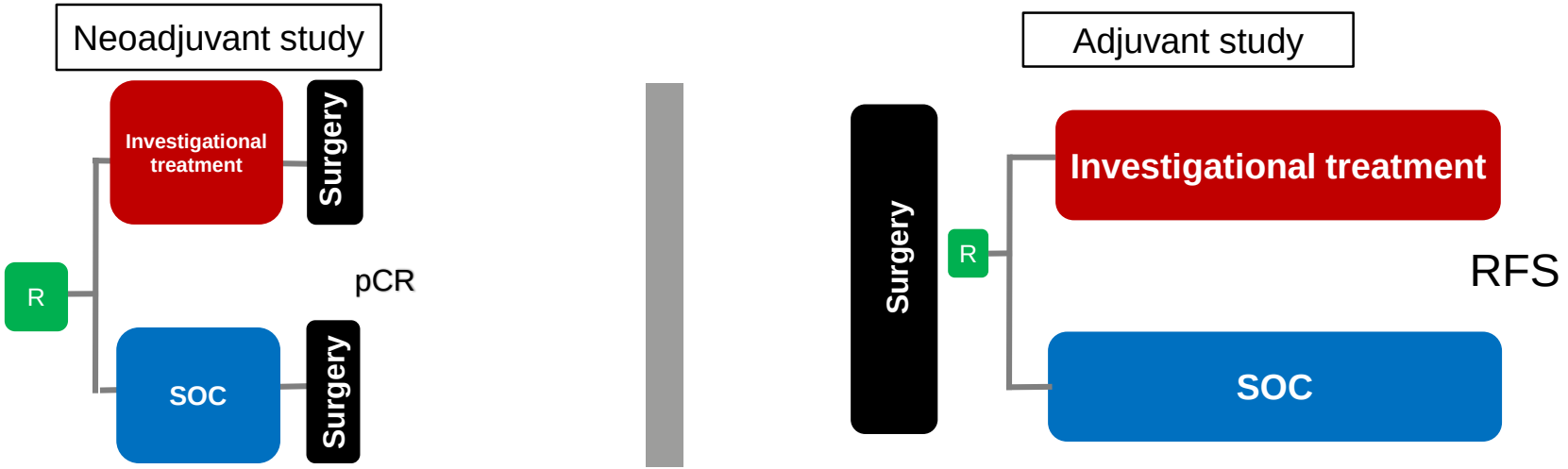
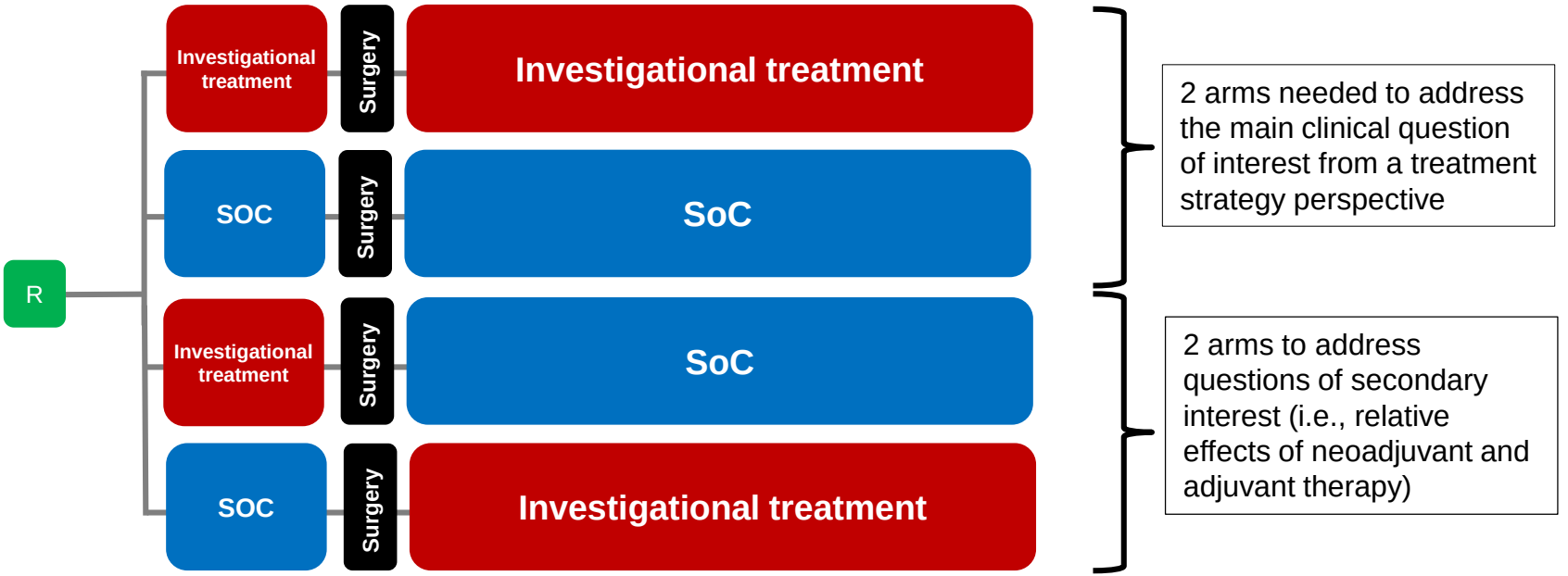
Neoadjuvant/Adjuvant: Two separate studies approach #1



Study designs assessing the relative contribution of the neoadjuvant and adjuvant parts of the investigational strategy are possible, but do not address the main clinical question of interest from a treatment strategy perspective

pCR=pathological complete response, R=randomization, SOC=Standard of Care, RFS=relapse-free survival

Neoadjuvant/Adjuvant: 2x2 factorial design approach #2



- Trial design requiring considerably more patients and adding significantly to the development time, which may not be ultimately viable

R=randomization, SOC=Standard of Care

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Conclusions

- Evolving treatment landscape, in particular in Oncology and Hematology
  - Multiple treatment modalities
  - Innovative diagnostics and disease monitoring tools
  - More and more individualized therapies, i.e. patient journeys
- More and more treatment strategies to be investigated
  - Guidance to treating physicians and patients
  - Guidance to sponsors and drug developers
- Opening the discussion on
  - Question of interest for treatment strategies, for different stakeholders
  - Relevant and efficient development plans and study designs
  - Labeling implications

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Some questions

- In which settings are the efficacy and safety of the **treatment strategy** (as opposed to the investigational agent) the primary question of relevance to physicians and patients ?
- Under what circumstances should benefit-risk assessment of the treatment strategy be the **primary goal** of a development plan?
- What are the relevant factors influencing how much information is needed on the **individual components** of a treatment strategy for approval?
  - question of interest related to individual components? E.g.
    - effect of a new drug as maintenance in responders after induction and consolidation **with the same drug** (randomized vs new drug as induction and consolidation followed by placebo)
    - effect of a new drug as maintenance in responders after **any** induction/consolidation therapy (randomized vs placebo)
  - plausibility of biological rationale (e.g. to maintain inhibition)
  - availability of efficacy and safety data for this individual component in other indications
  - high unmet need
  - rarity and severity of disease
- What are efficient **development plan and design** options to address those needs ?
- How might the **label** describe efficacy and safety of the entire treatment strategy (possibly in addition to that of individual components) ?

Thank you

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