CDDF Annual Conference 2024

CDDF Cancer Drug Development Forum

CHALLENGES IN DEVELOPING NOVEL-(NOVEL) COMBINATIONS

Regulatory Perspective

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Changing paradigms to accelerate oncology drug development

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Combinations with targeted or immunotherapy in oncology

Rationale for combination of IMPs

- Combinations could improve treatment outcomes and result in superior therapeutic effects, especially when a **synergistic anticancer activity** is achieved
- The combinational approach can overcome **clonal heterogeneity**
- Could reduce the emergence of **drug resistance**

➢**Identifying which combinations are appropriate and in which subpopulations are among the most difficult questions**

Challenges for development of combinations

- **Tolerability**
- **Contribution of components (CoC)**
- **Targeted or Immunotherapies:**

  (Novel IMP- Novel predictive ? biomarke

Tolerability

- **The conventional maximum tolerated dose (MTD) based dose-finding paradigm is not suitable for the development of targeted or immunotherapy agents**
  - **The dose–response relationship has not been established for the majority of the anticancer agents**
  - **The combinations could be poorly tolerable, reflected by the high discontinuation and dose reduction rates**
- **Dose optimization (for the combination) in early phases is essential**

Information from Preclinic and Phase I
Optimal biological dose (OBD)?
→
Phase II dose optimization (RCT)
Information on exposure-response
→
Phase III dose selection

Contribution of Components (CoC)

- Requirement for demonstrating the contribution of each agent to the activity of the combination
  - (Early Development Considerations for Innovative Combination Products (FDA)/ Guideline on the evaluation of anticancer medicinal products in man (EMA))

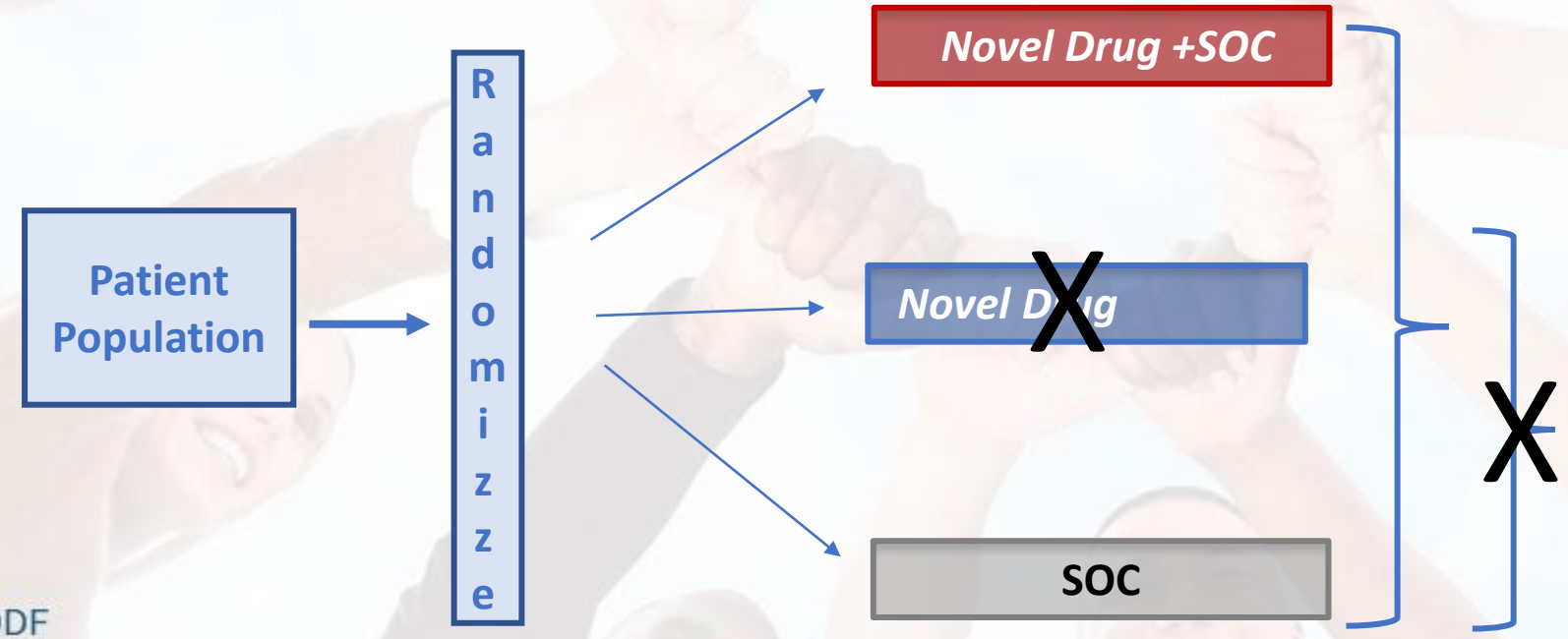
- Depends on the level of enhanced activity expected with the combination vs individual monotherapy components

- Different scenarios are foreseeable:
  - **Scenario A**: If the experimental agent (A) is added to an established regimen (B)
  - **Scenario B:** If both combination partners demonstrate anti-tumour activity individually
  - **Scenario C**: If one or both combination partners have no or minimal anti-tumour activity per se as monotherapy

Contribution of Components (CoC)/ Scenario A

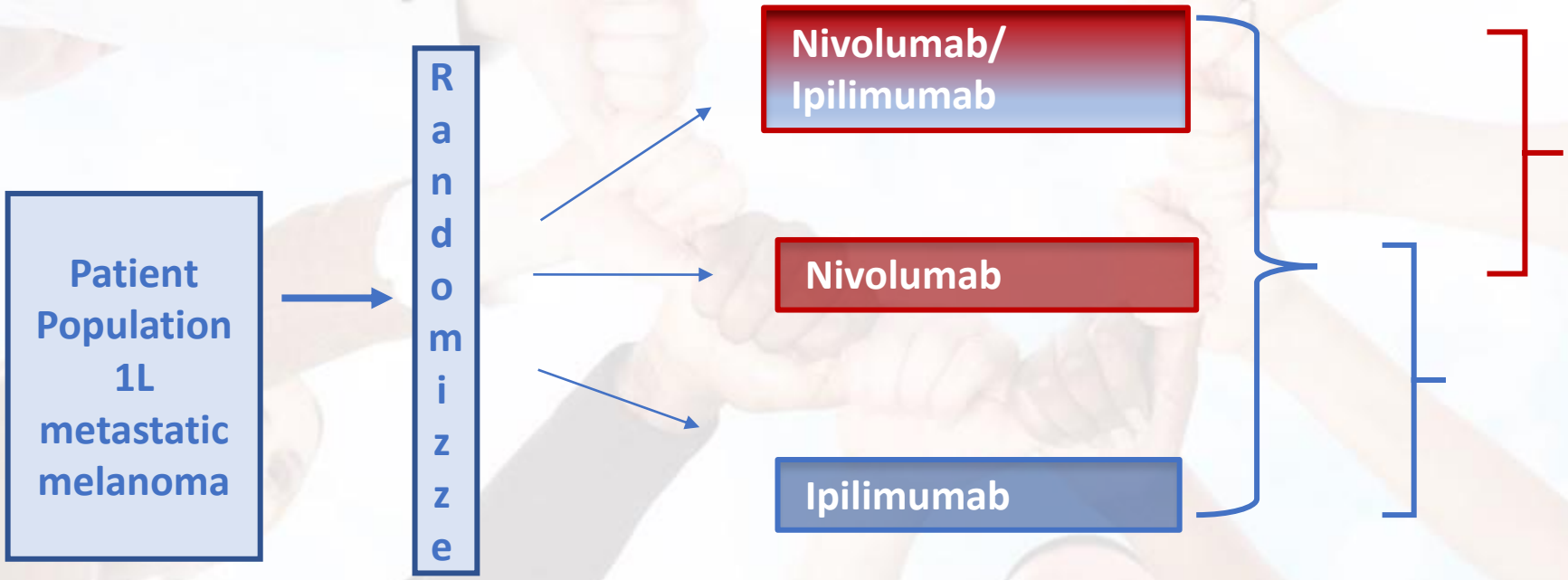
Experimental agent (A) is added to an established regimen (B)

- Superiority of AB vs. B should be demonstrated.
- A discussion is expected based on available data as regards treatment effect of A
- Often, this type of studies does not include an A alone third arm (should be justified..)

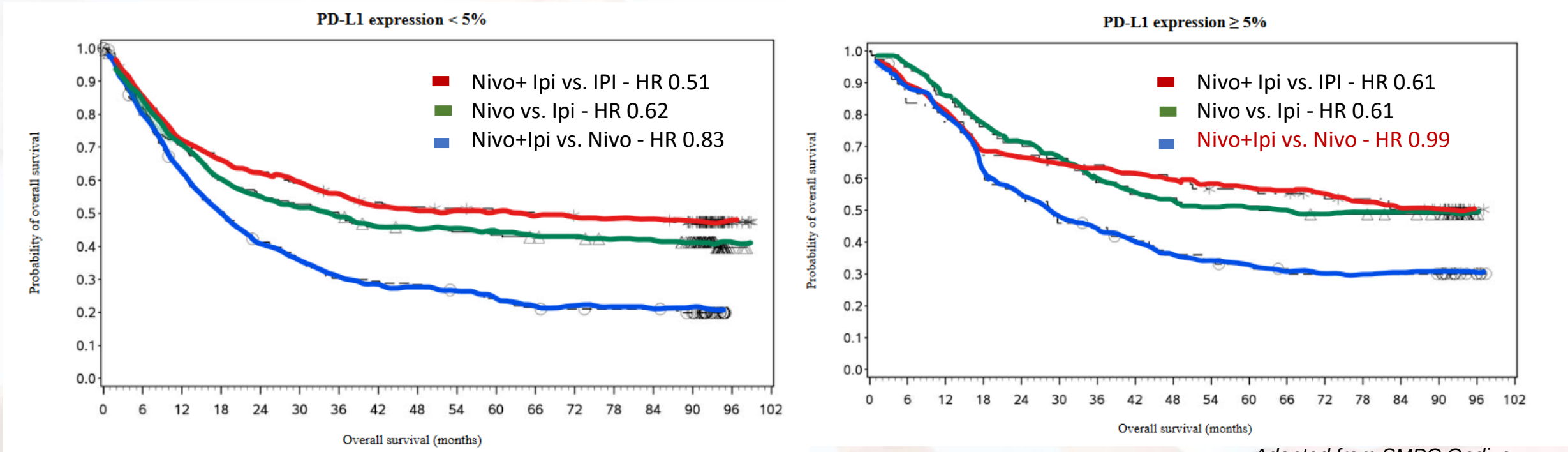


Contribution of Components (CoC)/Scenario A

- CheckMate 067 phase III study in 1L unresectable or advanced melanoma



Contribution of Components (CoC)/Scenario A

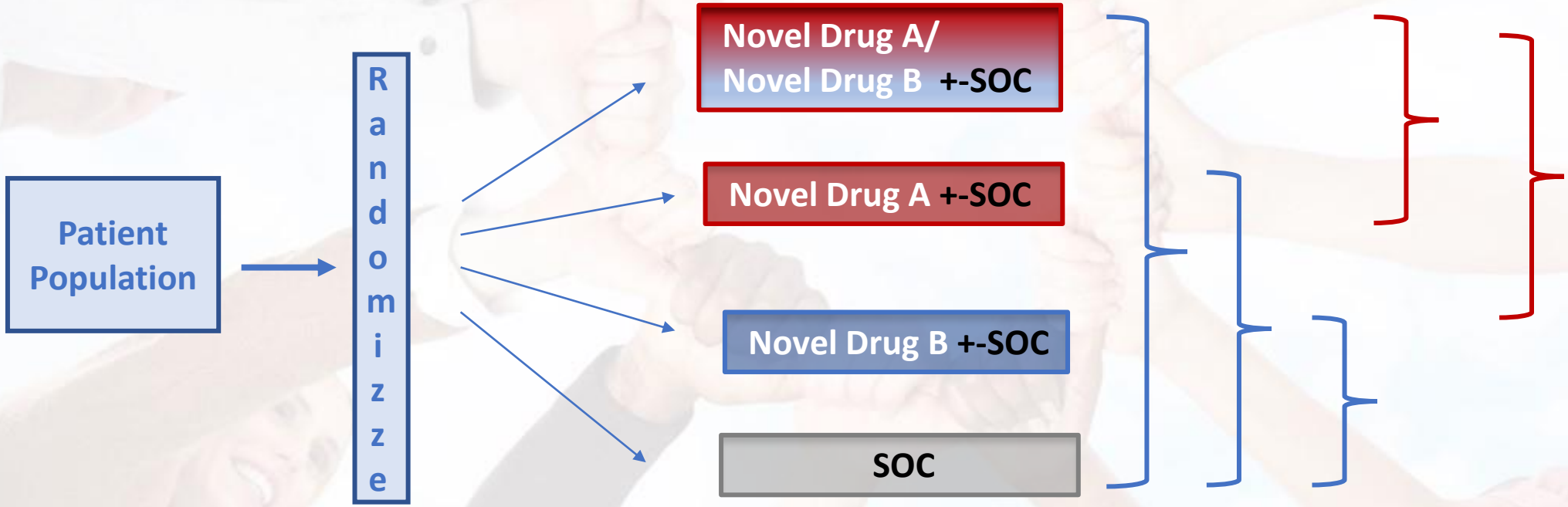


Adapted from SMPC Opdivo

B/R negative for the PD-L1 positive patients – Subgroup analysis essential

Contribution of Components (CoC)/Scenario B

both combination partners demonstrate anti-tumour activity individually

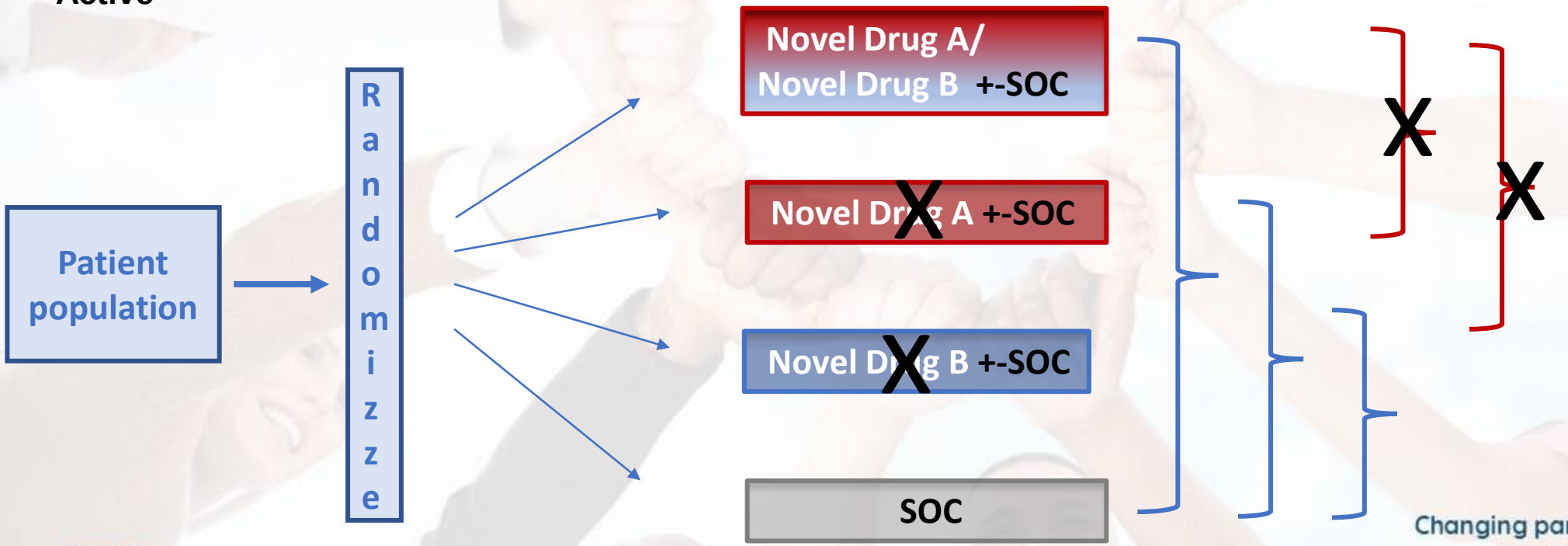


➡ **Data could be generated in Phase 2 trial/ smaller arms or early futility utility analysis possible**

Contribution of Components (CoC)/ **Scenario C**

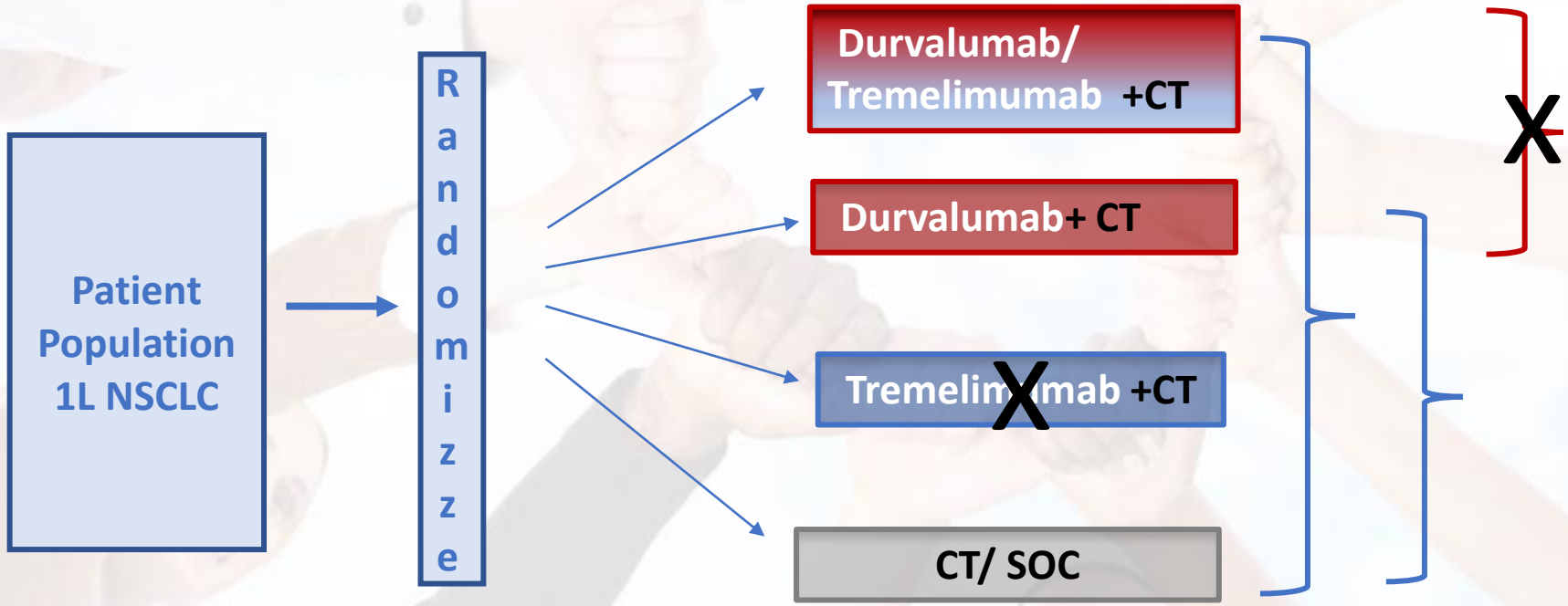
one or both partners have no or minimal anti-tumour activity per se

- **External -/ Preclinical-/ Phase 1-2 -Data to support that Novel Drug A or B Monotherapy is not or minimally Active**

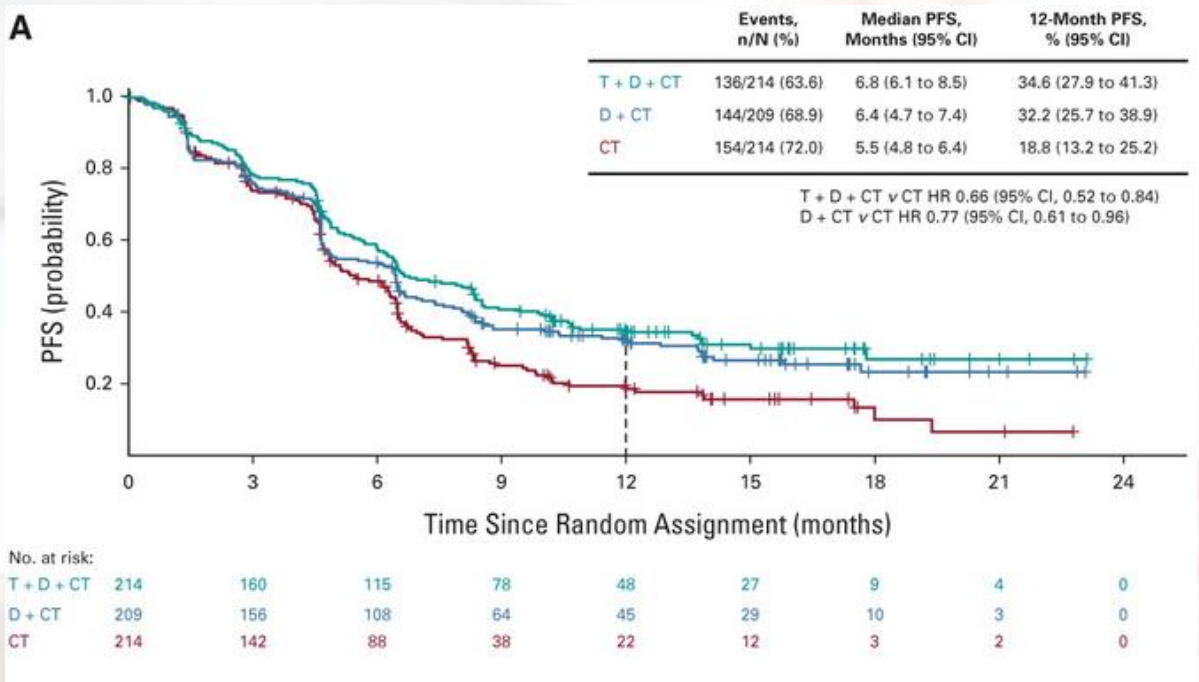


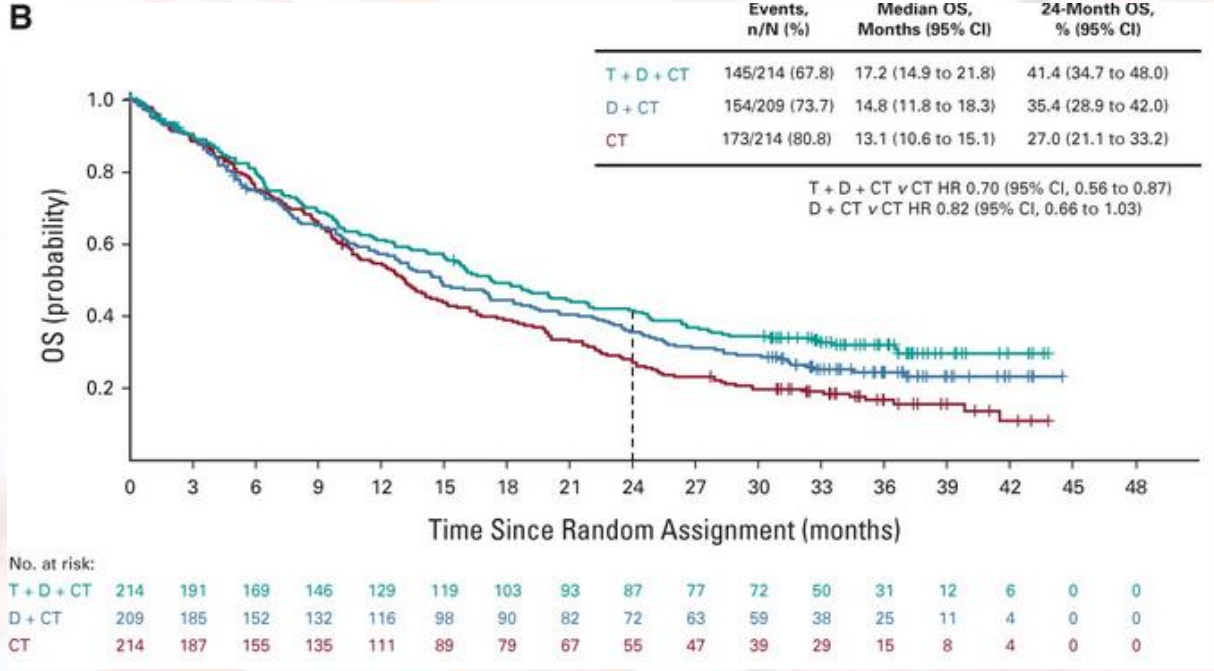
Contribution of Components (CoC)/Scenario C

- **Study POSEIDON: phase III study in 1L NSCLC**
  - **External/ Preclinical Data: Tremelimumab Monotherapy not sufficiently active ;Durvalumab +CT included**



Contribution of Components (CoC)/Scenario C



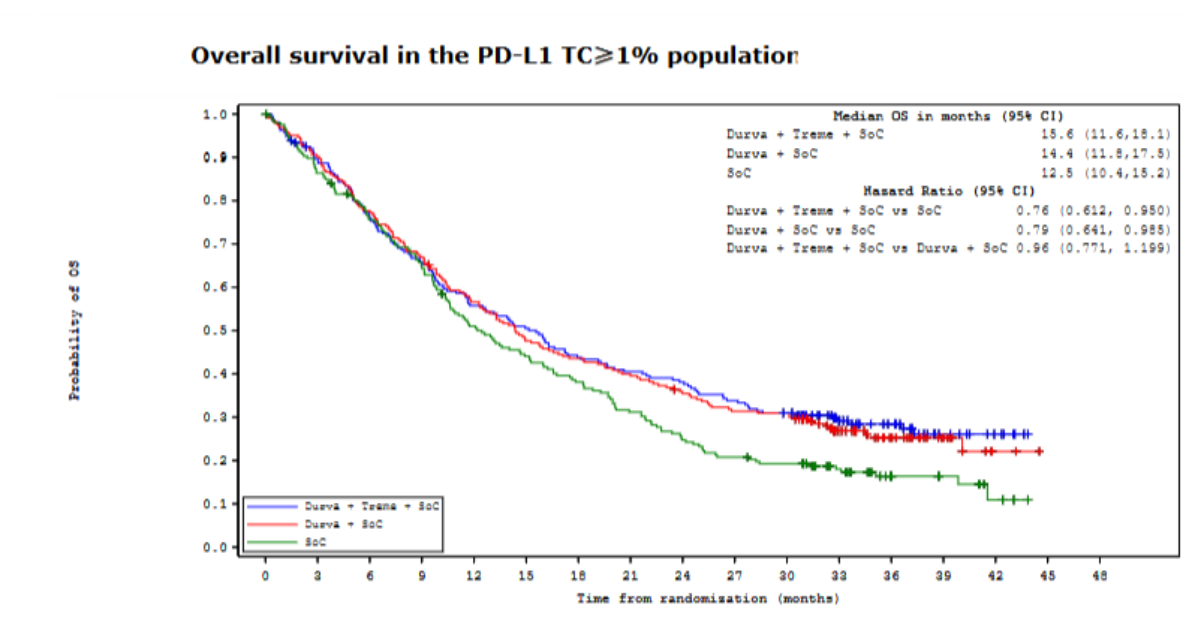


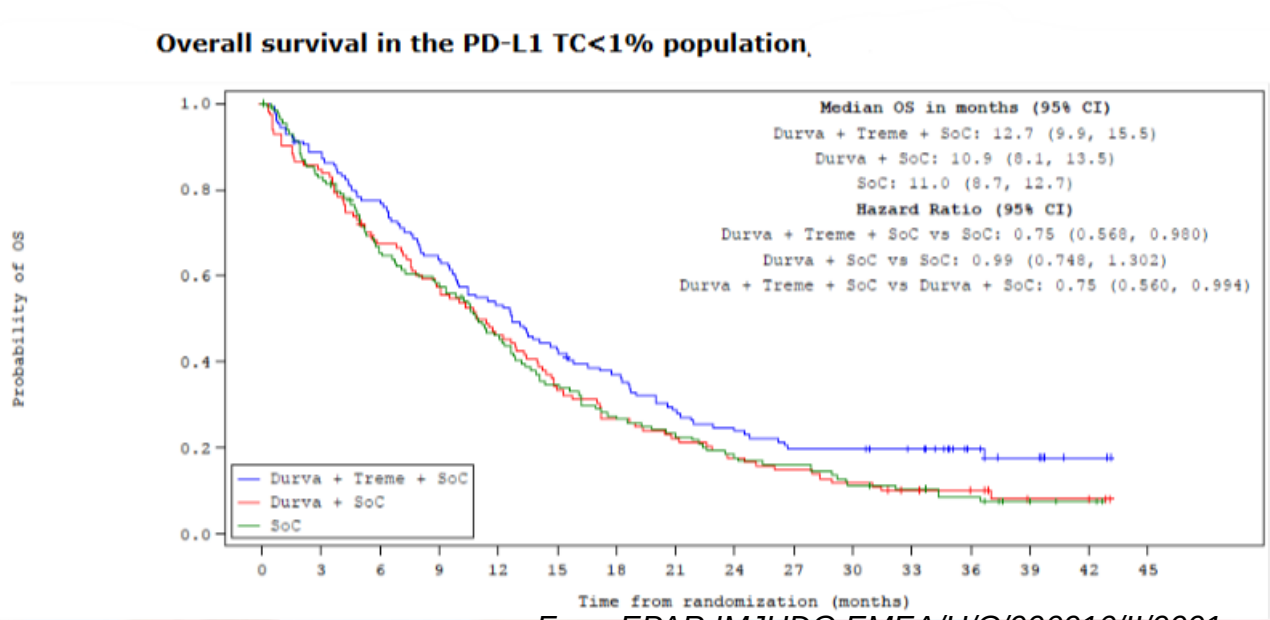
From Johnson et al. JCO, Nov 2023

D + CT significantly improved PFS and T + D + CT significantly improved OS and PFS versus CT.

Contribution of Components (CoC)/Scenario C

- Subgroup analysis/predictive biomarker





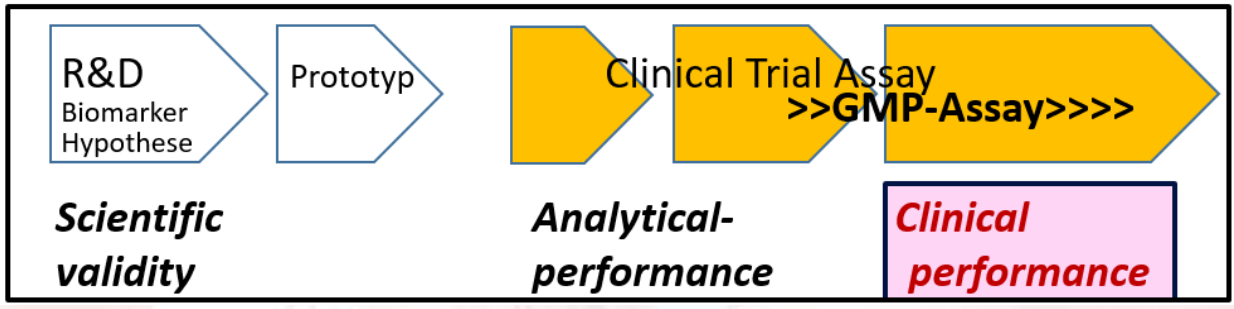
From EPAR IMJUDO EMEA/H/C/006016/II/0001

- **The inclusion of the D + CT arm allowed approximate assessment of the contribution of tremelimumab**
- **No formal comparison of both arms**

Novel IMP-Novel biomarker

- Early evaluation of the predictive value of the target/biomarker

  - Biomarker assay (analytically fully validated)/ prototype before FIM
  - Pivotal study: confirmatory prospective randomized controlled trial
  - Stratification (if applicable for different cut-offs)
  - Prespecified cut-offs
  - Adequate tumor material / central assessment
  - Biomarker assessment for all study patients



Novel/ Novel Combinations

- Combination therapies are rationale, but challenging
- Randomized trials (large!) to demonstrate contribution of components important; however, monotherapy arms may be omitted in case of evidence for limited activity (as monotherapy)
- **Careful dose-selection und evaluation of efficacy in relevant biomarker subgroups essential to optimize B/R balance of combination treatment**

Relevant guidance/publications

- **Guideline on the clinical evaluation of anticancer medicinal products** EMA/CHMP/205/95 Rev.6 (draft) Revision section 5 Biomarkers
- **FDA Guidance Codevelopment** of Two or More New Investigational Drugs for Use in Combination
- **Questions & Answers** on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR)

Thank you for your attention!

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