QUESITO CLINICO 2:

Nelle pazienti con carcinoma mammario HR-positivo/HER2-negativo operato, è opportuno considerare terapia adiuvante con Abemaciclib?

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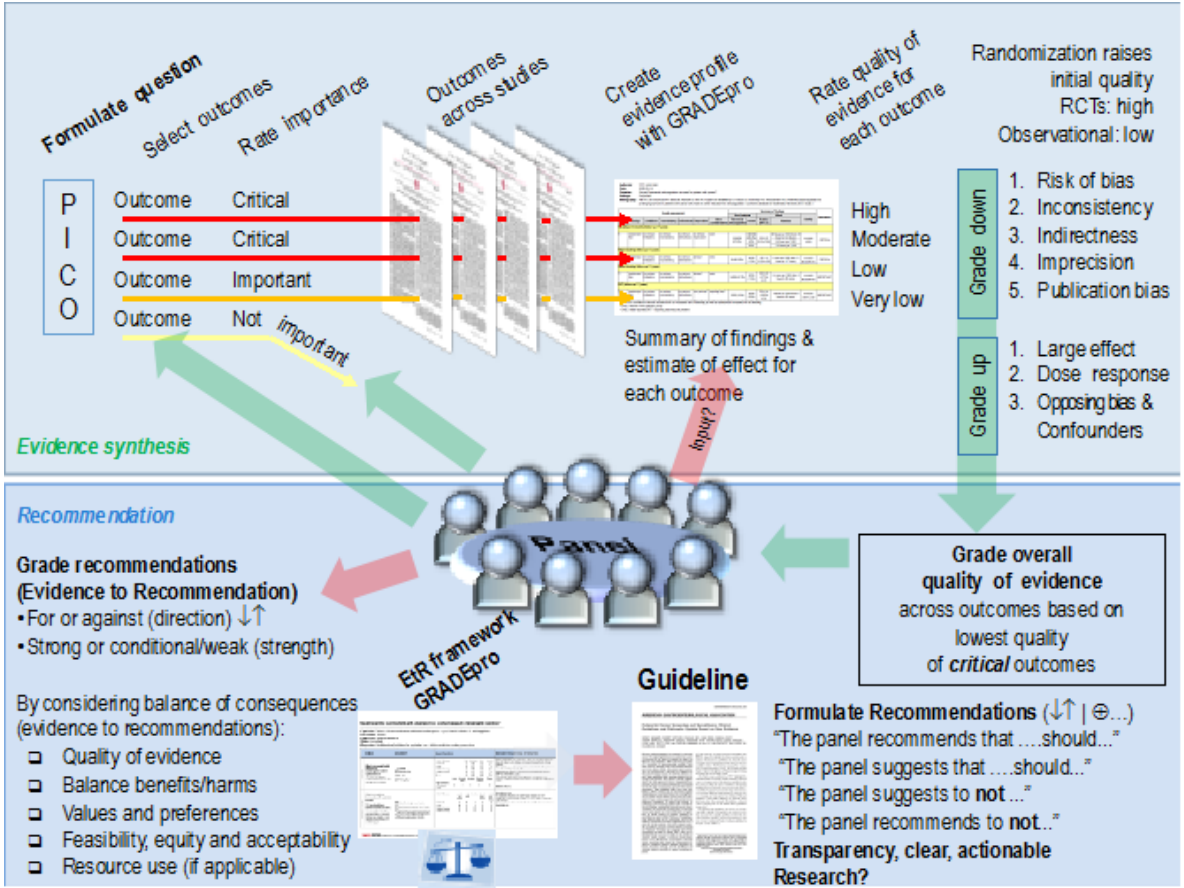
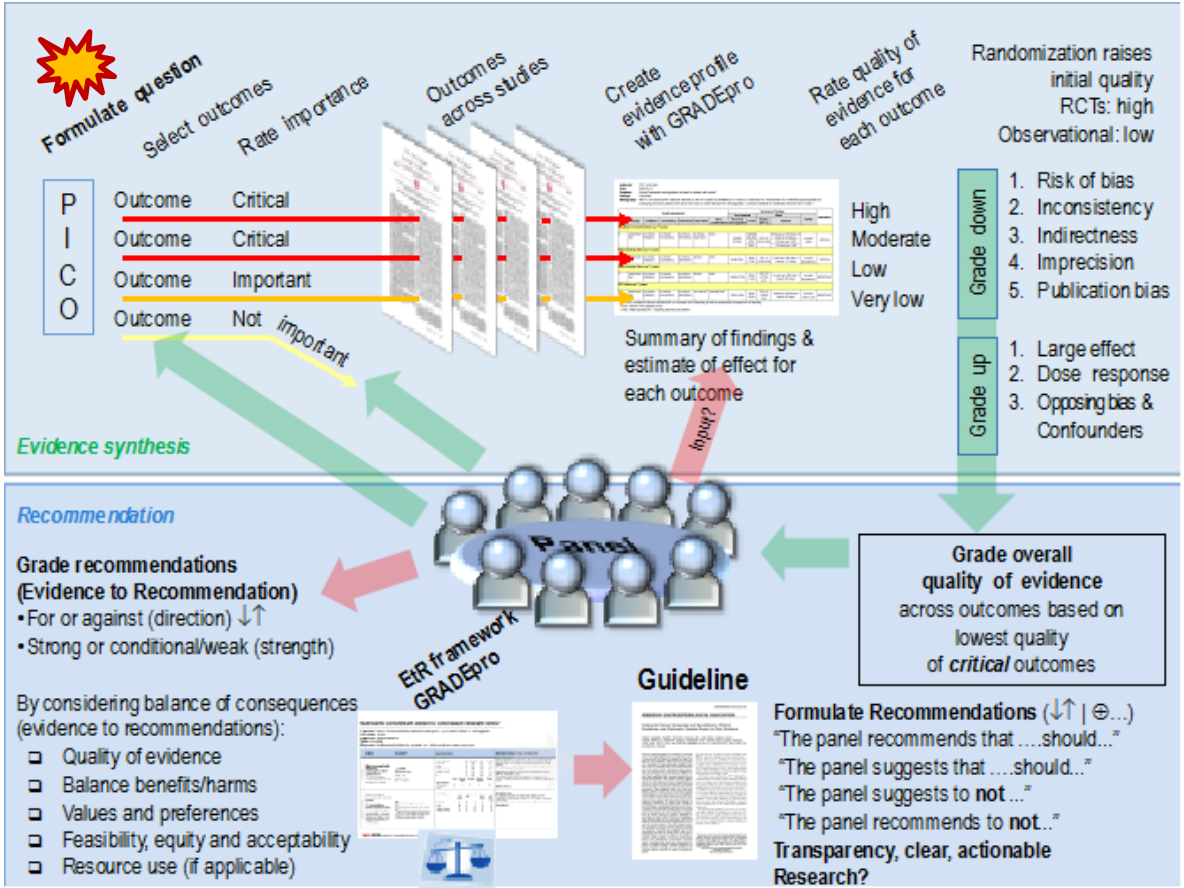
GRADE methodology



GRADE methodology



Clinical question

Abemaciclib + endocrine therapy compared to endocrine therapy alone for the Adjuvant Treatment of HR+/HER2-, Node-Positive, High-Risk, Early Breast Cancer

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O HARM and BENEFIT

→ voted by the panelists

Outcome selection

BENEFIT

Overall Survival

Invasive-Disease-free Survival

(ipsilateral invasive BC recurrence, local/regional invasive BC recurrence, diatnt recurrence, death from any cause, contralateral invasive BC, secondy primary)

Distant relapse-free Survival

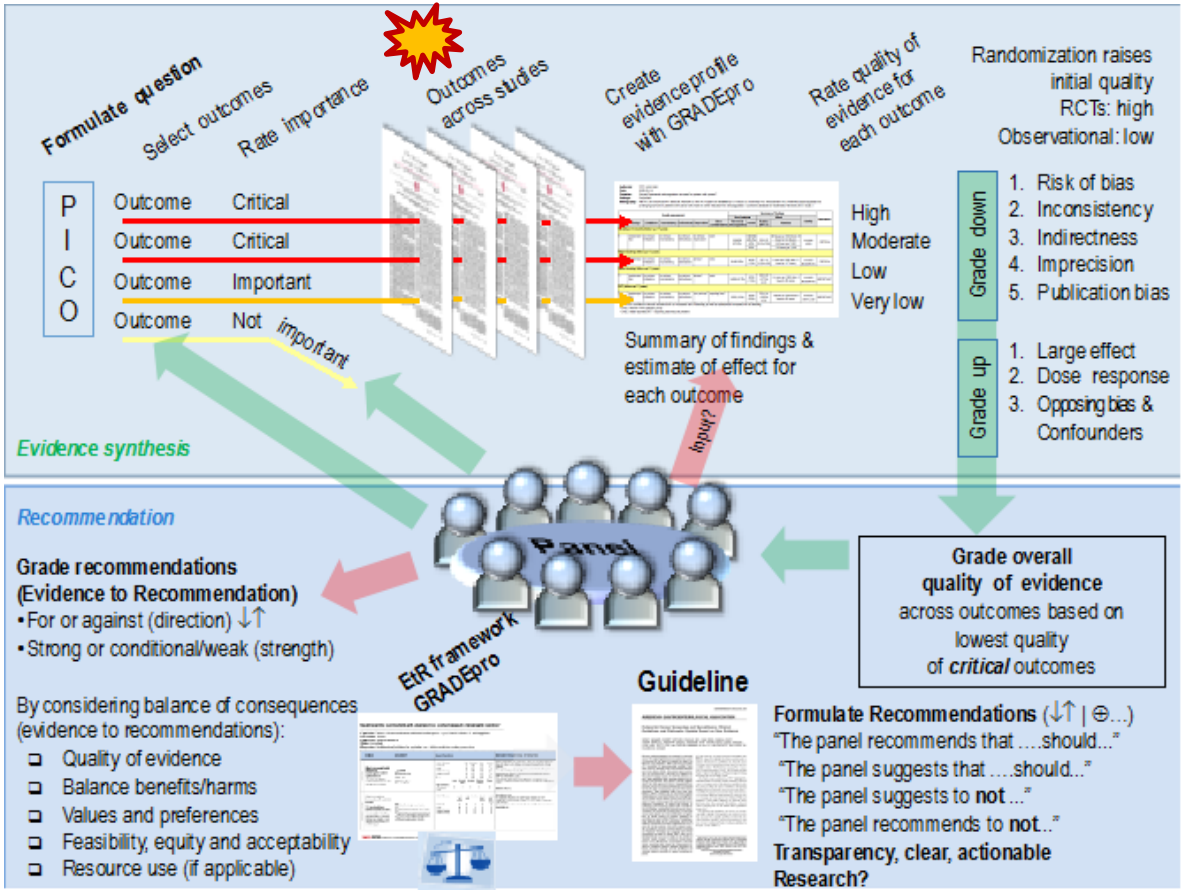
(distant recurrence or death from any cause)

HARM

Any grade adverse event

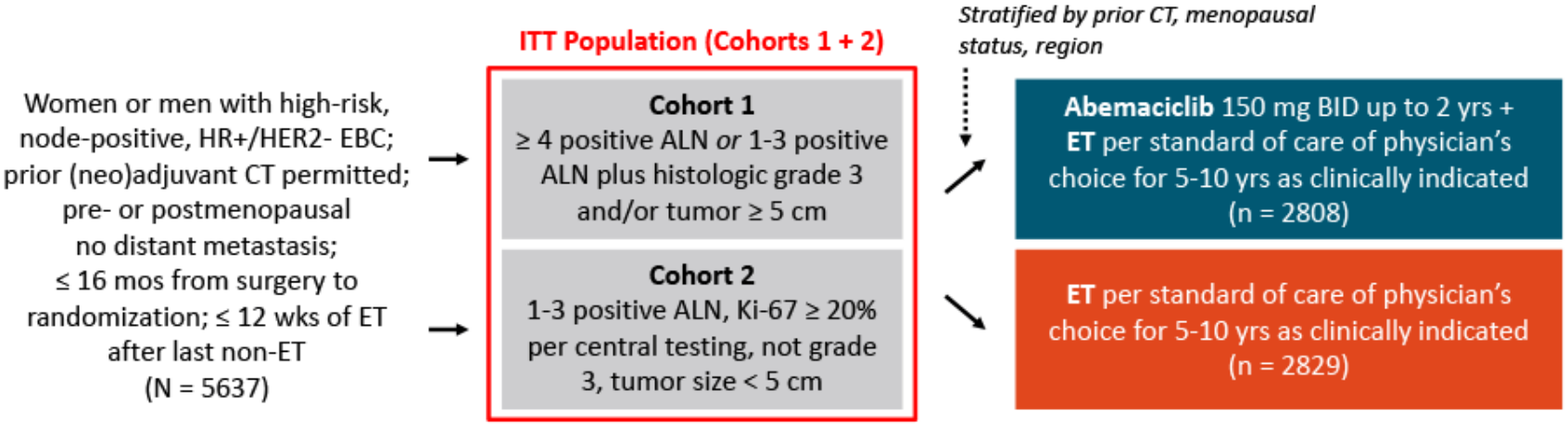
Grade≥3 adverse events

GRADE methodology



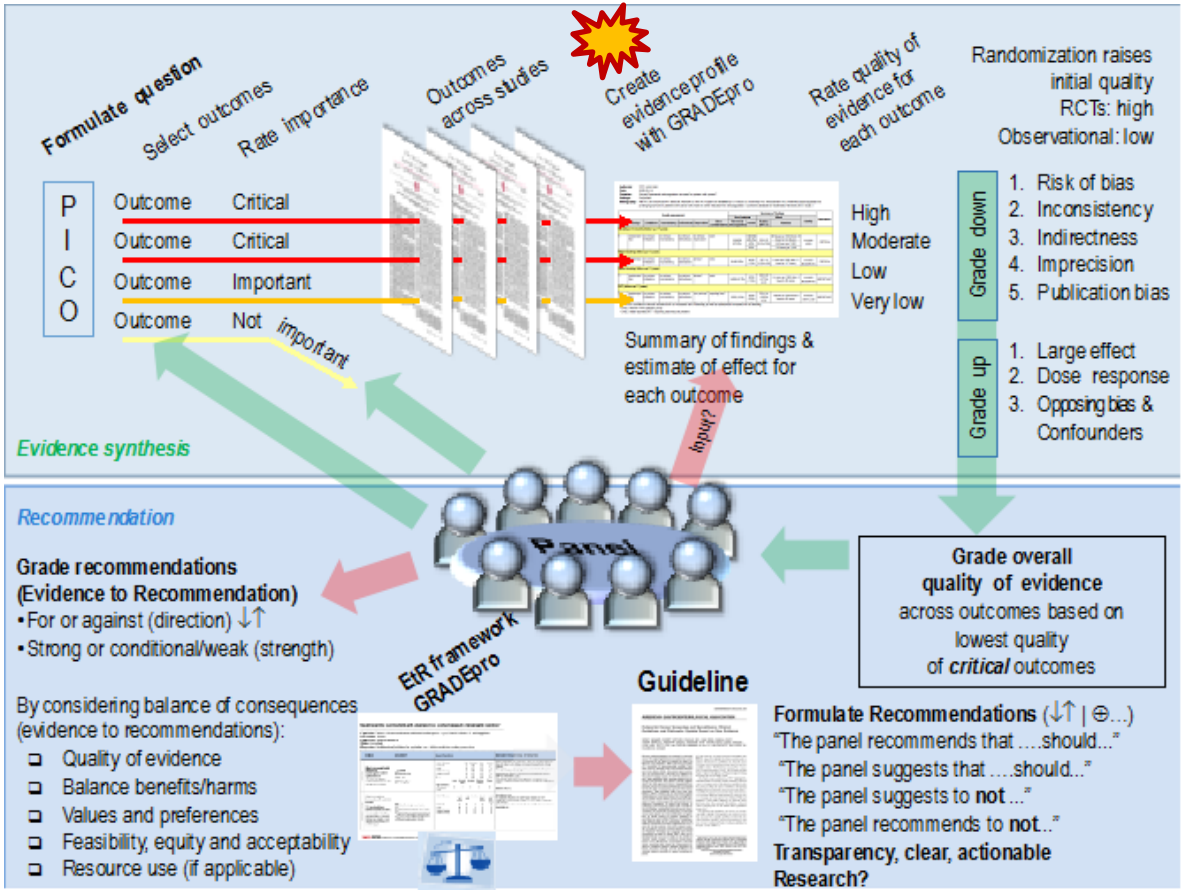
Systematic review

1 randomized phase III clinical trial = Monarch-E



- Primary endpoint: iDFS
  - Planned for after ~ 390 iDFS events (~ 85% power, assumed iDFS HR of 0.73, cumulative 2-sided $\alpha = 0.05$)
  - Current primary outcome efficacy analysis occurred after 395 iDFS events in ITT population
- Key secondary endpoints: iDFS in Ki-67 high (≥ 20%) population, distant RFS, OS, safety, PRO, PK

GRADE methodology



Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	abemaciclib + endocrine therapy	endocrine therapy alone	Relative (95% CI)	Absolute (95% CI)		
OS												
-	-	-	-	-	-	-	-	-	-	-	-	
iDFS												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	2808 participants	2829 participants	**HR 0.70** (0.59 to 0.82) [first occurrence of ipsilateral invasive breast tumor recurrence, local/regional invasive breast cancer recurrence, distant recurrence, death attributable to any cause, contralateral invasive breast cancer, or second primary nonbreast invasive cancer]	**118 more per 1.000** (from 63 more to 181 more)	⨁⨁⨁◯ Moderate	
							-	16.6%		**118 more per 1.000** (from 63 more to 181 more)		
D-RFS												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	2808 participants	2829 participants	**HR 0.69** (0.57 to 0.83) [distant recurrence or death from any cause]	**117 more per 1.000** (from 55 more to 186 more)	⨁⨁⨁◯ Moderate	
							-	13.9%		**117 more per 1.000** (from 55 more to 186 more)		

Detection bias and performance bias

Detection bias and performance bias

Evidence Profile

Any grade AEs

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	abemaciclib + endocrine therapy	endocrine therapy alone	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	not serious	none	2731/2791 (97.9%)	2410/2800 (86.1%)	**RR 1.14** (1.12 to 1.16)	**120 more per 1.000** (from 103 more to 138 more)	⨁⨁⨁◯ Moderate	

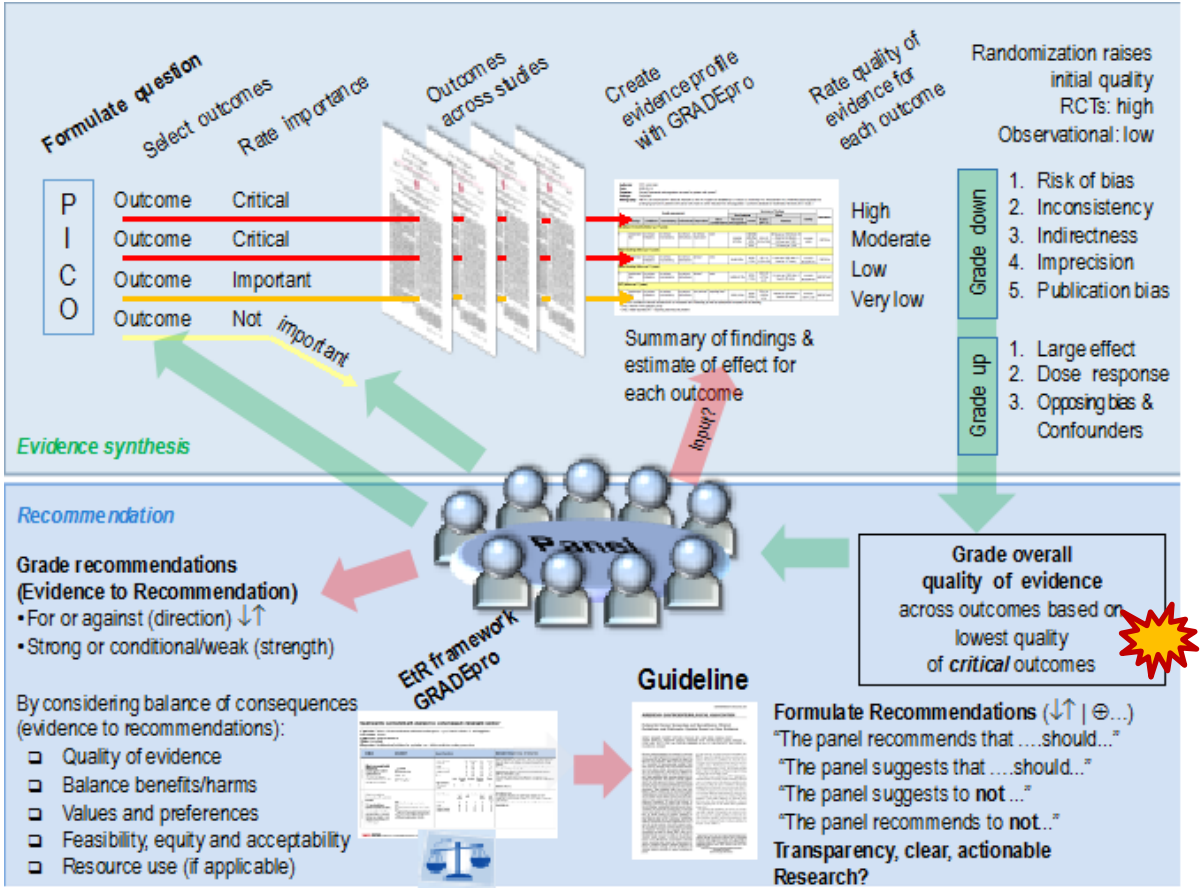
Detection bias and performance bias

Grade≥3 AEs

1	randomised trials	serious[a]	not serious	not serious	not serious	none	1270/2791 (45.5%)	354/2800 (12.6%)	**RR 3.60** (3.24 to 4.00)	**329 more per 1.000** (from 283 more to 379 more)	⨁⨁⨁◯ Moderate	

Detection bias and performance bias

GRADE methodology



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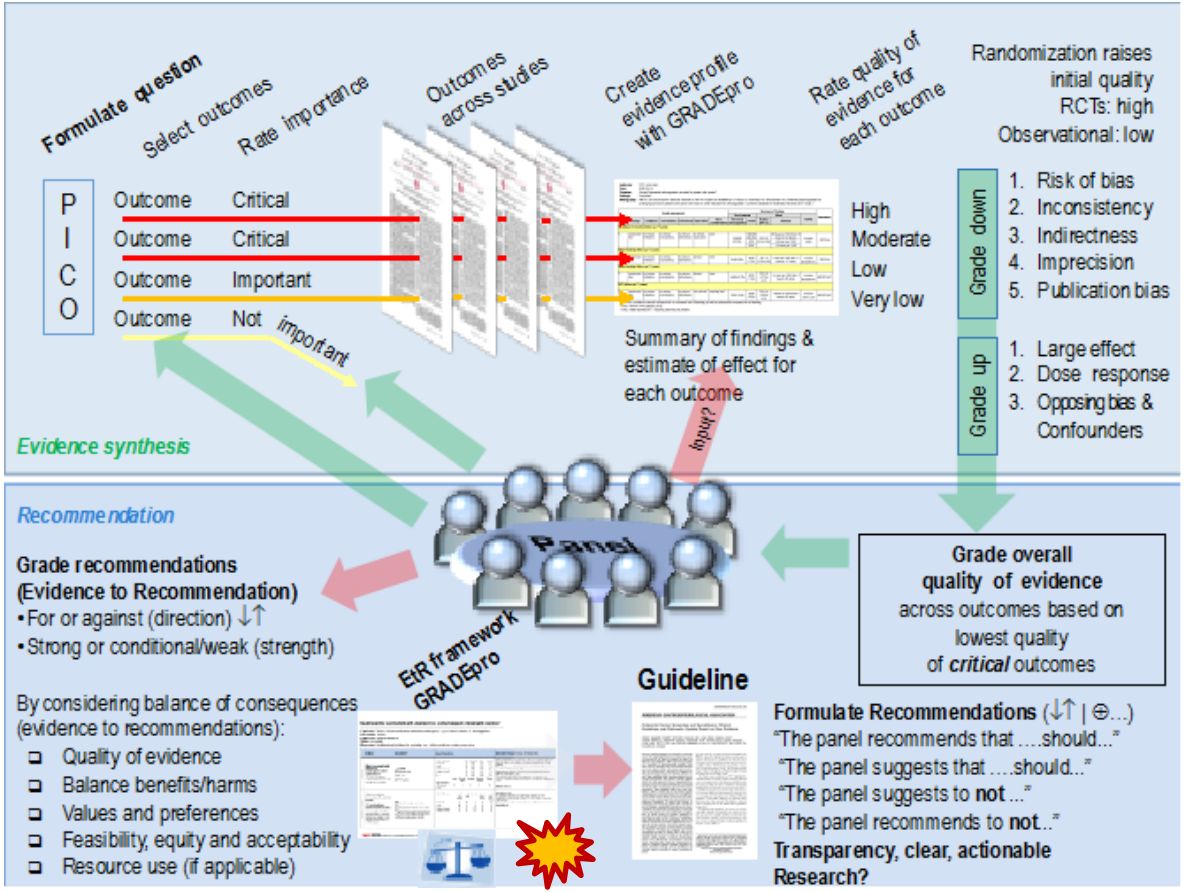

EdT

Problem: Is the problem a priority?
Desirable Effects: How substantial are the desirable anticipated effects?
Undesirable Effects: How substantial are the undesirable anticipated effects?
Values: Is there important uncertainty about or variability in how much people value the main outcomes?
Certainty of evidence: What is the overall certainty of the evidence of effects?
Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?
Equity: What would be the impact on health equity?
Acceptability: Is the intervention acceptable to key stakeholders?
Feasibility: Is the intervention feasible to implement?

Considerations to be kept in mind when producing the EtD

1) **Possibile issues of indirectness:** how to integrate Monarch-E trial results in a contemporary scenario of availability of multigene tests?

2) **Possible equity issue:** omission of DA in case of SLB+ may result in tumor «under-staging», thus possible resulting in missing a subgroup of patients who may represent potential target for abemaciclib

3) **The population to which the clinical question is addressed encompassess also subgroup for which alternative options are currently available:**

   - gBRCA mut: adjuvant Olaparib for high-risk patients
   - Althougn post-neoadj capecitabine is generally considered only in TNBC, CREATE-X trial reported a benefit in the ITT population, also including HR+/HER2- BC

Discussion: many things in the fire

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Any grade AEs

Abemaciclib + endocrine therapy likely increases any adverse event.

Grade≥3 AEs

Abemaciclib + endocrine therapy likely results in a large increase in 3/4 grade any adverse event.

Evidence Profile

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Abemaciclib + endocrine therapy likely increases D-RFS