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Learnings from the first JCA procedures – statistical assessor's perspective

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JCA of Tovorafenib

Indication:

Ojemda is indicated as monotherapy for the treatment of patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies

- Assessor and co-assessor: National Centre for Pharmacoeconomics (NCPE), Ireland and Institute for Quality and Efficiency in Healthcare (IQWiG), Germany
- First completed JCA, published 9th June 2026 ☺

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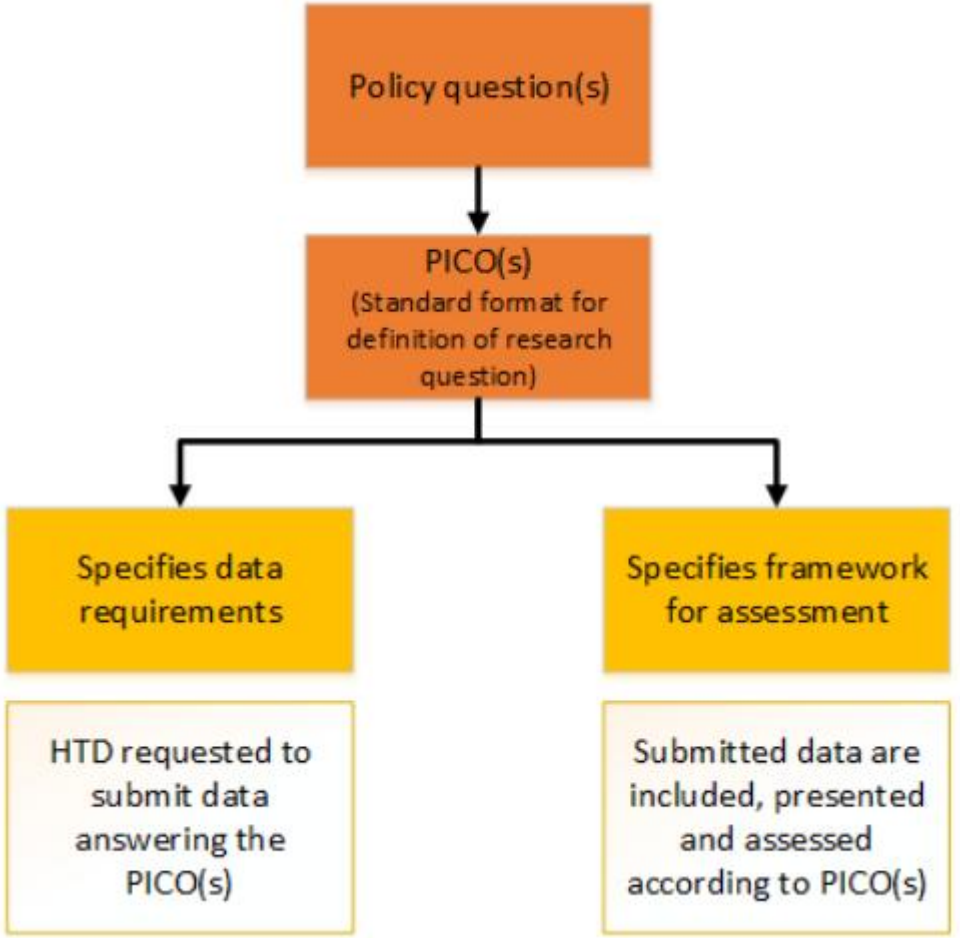
Reminder - JCA Scoping

- Questions of **comparative** effectiveness in PICO framework: population, intervention, comparator, outcome(s)
- HTA Regulation: JCA Scope should reflect Member States' (MS) evidence needs
- Generally requires identifying those comparators which represent current clinical practice across EU MS
- Consolidation into smallest number of PICOs that addresses MS evidence needs – not straightforward!



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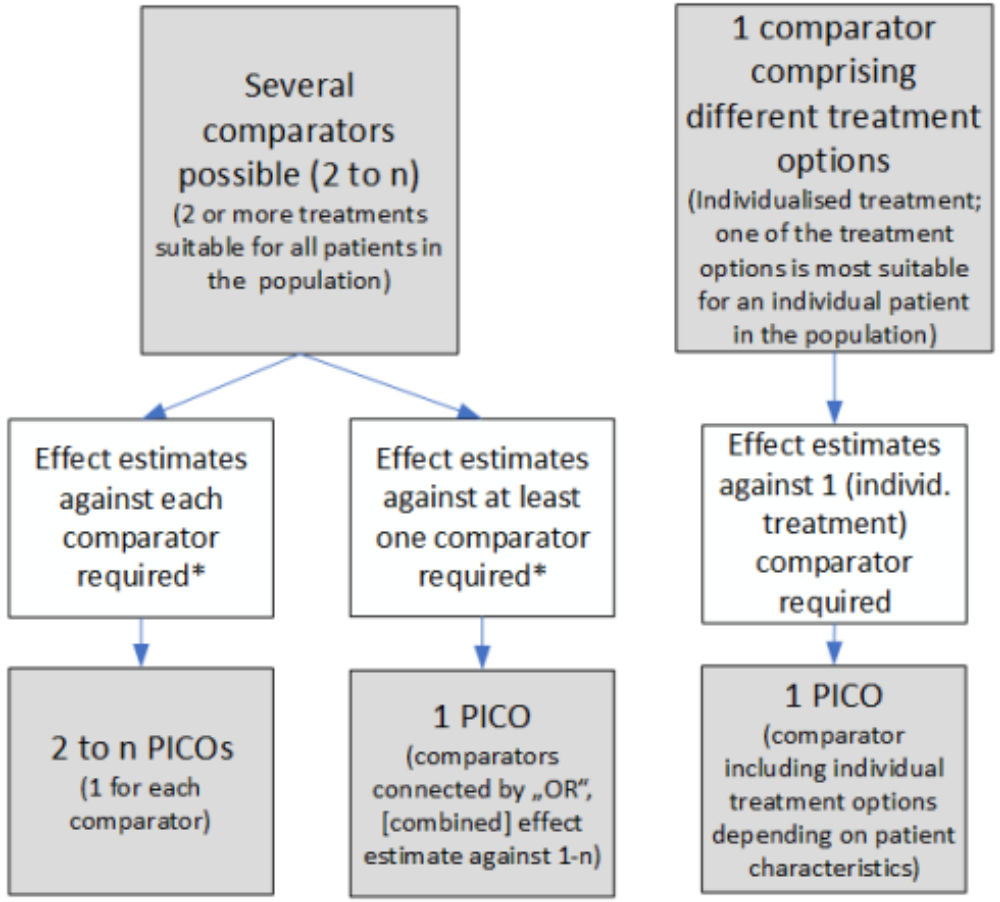
How do different PICOs arise?

- Relevant comparators include
  - dabrafenib+trametinib (V600E only)
  - various chemotherapies….
- May differ across MS depending on availability or clinical practice
- Multiple relevant treatment options handled differently when defining PICOs
  - Full population or subpopulation?
  - Equivalent or not?
  - Combined versus separate effect estimates required, e.g., “individualised treatment.”



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Population 1 *(full claimed indication)*: Patients 6 months of age and older with paediatric LGG harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have received one or more prior systemic therapies				**Population 2: *(subpopulation)* BRAF V600E mutation in patients > 1 year**		**Population 3 *(subpopulation)*: BRAF fusion, rearrangement, or V600 [non-E] mutation**	
Individualised treatment	Individualised treatment	Unique comparator	Unique comparator	Unique comparator	Individualised treatment	Unique comparator	Individualised treatment
vinblastine	vinblastine		vinblastine		vinblastine		vinblastine
carboplatin + vincristine	carboplatin + vincristine	carboplatin + vincristine			carboplatin + vincristine		carboplatin + vincristine
TPCV	TPCV						
dabrafenib + trametinib	dabrafenib + trametinib			dabrafenib + trametinib			
everolimus							
bevacizumab + chemo							
						trametinib	

Possible evidence scenarios for JCA

(1) Evidence need not be "exact match" to PICO for inclusion in JCA

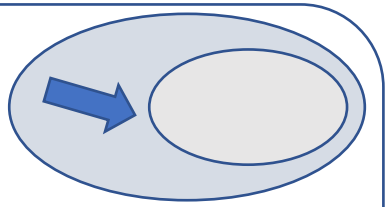
(2) Possible for same study to address multiple PICOs

Existing comparative studies

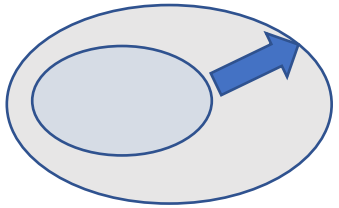
RCT

Prospective external control

Re-analysis of existing PICO



Subgroup



Extrapolation

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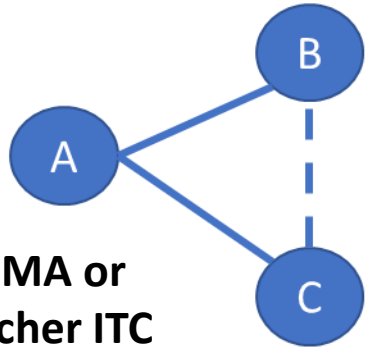
New indirect comparisons



NMA or Bucher ITC

Unanchored ITC

Evidence gap

+ adequate justification that no comparison is possible!

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Tovorafenib JCA scope: outcomes

- Safety outcomes
- OS
- PFS
- ORR
- Composite of complete response, partial response, or stable disease lasting a minimum of (i) 6 and (ii) 12 months
- Symptoms of the disease
- HRQoL, generic and disease-specific
- Symptomatic disease control
- General and cognitive fatigue
- Duration of response*
- Time-to-response*
- Best overall response*

Aside: surrogate outcomes requested by MS

* arm-based data requested but no relative effect estimate required

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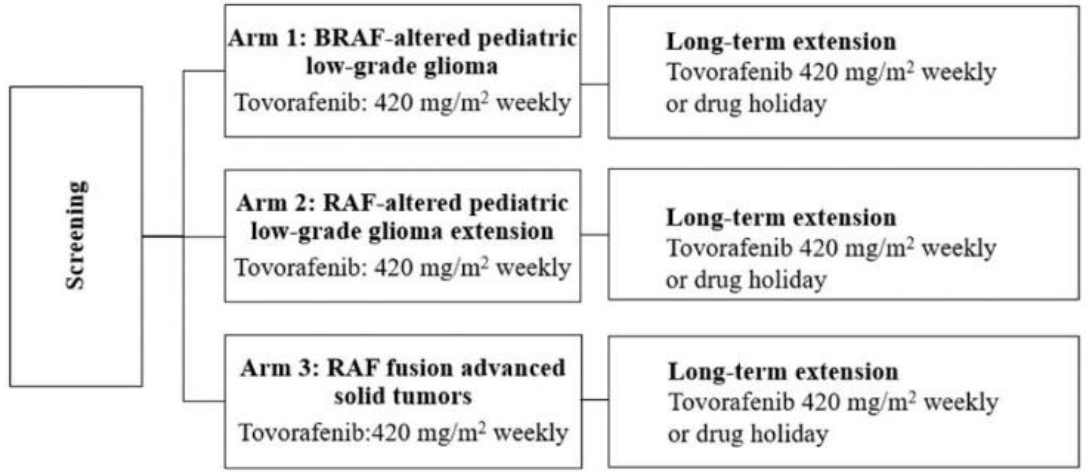
Clinical trial(s) of tovorafenib

- FIREFLY-1 trial
  - Single-intervention, non-comparative
  - N=77 (efficacy), N=137 (safety)
  - Primary endpoint ORR
- Non-comparative studies cannot
  - provide evidence of relative effectiveness
  - isolate effect of treatment on outcomes such as quality-of-life, symptoms, progression-free survival etc.
- Indirect comparison(s) required for JCA
- Non-comparative data submitted for consideration at national level

Figure 1. Study design schema for FIREFLY-1



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Comparative evidence submitted by PICO

Population 1: full claimed indication	Population 2: BRAF V600E mutation in patients > 1 year	Population 3: BRAF V600E mutation in patients > 1 year
4 PICOs	2 PICOs	2 PICOs
• No comparative evidence for any PICO	• Unanchored MAIC versus dabrafenib+trametinib only • Outcomes: ORR, PFS, Safety	• Unanchored MAIC versus trametinib monotherapy only • Outcome: ORR
Feasibility assessment for ITC versus a basket of comparators from RWD reported	(Most) analysis results included in JCA	Analysis results not included in JCA

Evidence gaps typically justified by lack of suitable comparator data, following systematic search of literature, study registries etc.

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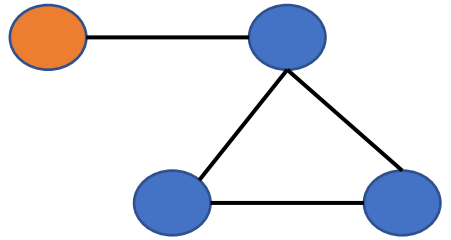
ITCs and dossier completeness?

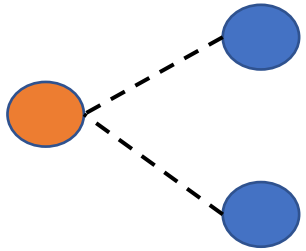
- Regulation requires that submitted dossier be complete w.r.t. evidence to inform PICOs
- "Completeness" likely requires any ITC
  - **already conducted** by the HTD, or published
  - Informed by **published data,** e.g. NMA of RCTs
- **De-novo ITCs** requiring **patient-level comparator data** may not be feasible during dossier preparation
  - does not necessarily imply incompleteness
- Implications of JCA evidence needs for study design?

Integration of RCT in connected network:



Typically feasible

New un-anchored ITC(s)



Much more challenging if not planned in advance!

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Inclusion of non-randomised evidence in JCA

Unanchored MAIC for PICO 5

- Assessed in detail and results included in the JCA
- Uncertainties described in the report
- Decision on “acceptability” made at MS level

Unanchored MAIC for PICO 7

- Not included in JCA
- insufficient information on comparator group for assessment (abstract only)

Intervention	Tovorafenib		Dabrafenib + trametinib		Indirect comparison method	Tovorafenib vs. dabrafenib + trametinib	
Study	FIREFLY-1		Bouffet 2023				
Data-cut	2 year		NR				
Outcome	Events (sample size)	Rate (%) [95%-CI]	Events (sample size)	Rate (%) [95%-CI]		ESS (FIRE-FLY-1)	OR[a]/RR[b] [95%-CI] p-value[c]
OS							
Relative effectiveness results not available							
PFS *These results are associated with a number of major uncertainties. The effect estimates presented here should not necessarily be interpreted as causal effects of treatment.*							
6-month PFS rate[d] by RANO-LGG criteria, IRC-assessment	NR (12)[e]	94 [85, 100]	NR (36)	86 [75, 98]	MAIC base case: adjusted for age, prior surgery, prior radiotherapy, Karnofsky/Lansky score, gender	5.81	RR: 1.09 [0.92; 1.30] –
12-month PFS rate[d] by RANO-LGG criteria, IRC-assessment	NR (12)[e]	76 [52, 100]	NR (36)	83 [71, 96]		5.81	RR: 0.92 [0.61, 1.38] –

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Living Q&A document informed by ongoing JCAs

- Individualised treatment
- Confounder identification
- Data-cuts
- Subgroup analysis
- …..

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Thank you for listening

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