
Conditional marketing authorization and testing strategy on a single pivotal trial – A call for consistency

**Under which conditions
is the Regulator open to base conditional approval on conditional results?**

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Testing approaches



Traditionally

1. ORR/PFS Primary, OS Key Secondary: Fixed sequence testing

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|------|---|
| Pros | <ul style="list-style-type: none">• Possible early declaration of positive study |
| Cons | <ul style="list-style-type: none">• If ORR/PFS negative: OS missed de facto• Risk on OS integrity & quality of follow up• Clinical hierarchy of endpoints not respected |

2. ORR/PFS & OS Dual Primary: (Weighted) Bonferroni / Bonferroni-Holm

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|------|---|
| Pros | <ul style="list-style-type: none">• Possible early declaration of positive study, yet stronger emphasis on OS |
| Cons | <ul style="list-style-type: none">• Sample size $\nearrow$ or power $\searrow$ from multiplicity control• If ORR/PFS positive:
Risk on OS integrity & quality of follow up |

Recent (Regulator) Proposal

3. ORR/PFS & OS Co-Primary: Both endpoints need to be positive

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|------|---|
| Pros | <ul style="list-style-type: none">• For regulator: guarantee sponsor's commitment to OS integrity and quality of follow up• Higher level of evidence : both endpoints need to be positive |
| Cons | <ul style="list-style-type: none">• Sample size $\nearrow$ to maintain overall study power (e.g., both endpoints powered at 95% under independence)• If ORR/PFS negative: study is negative even if OS positive !!! (clinical/scientific relevance ?)• Clinical hierarchy not reflected in testing strategy• Conditional approval at the IA on study not yet positive ? |

Liu X, Thomas NH, Asikanius E, Pothet C, Großhennig A, Koch A. A statistical concept for conditional marketing authorisation based on the intermediate and final outcomes of a single confirmatory randomised clinical trial. Pharm Stat. 2026;25(2):e70078

Call for Consistency...



Testing approach

4. OS Primary, ORR/PFS Key Secondary: Fixed sequence testing

Pros	• Fully aligned endpoint clinical and testing hierarchy with regulatory decision making: conditional positive result → conditional approval • Guarantee sponsor's commitment to OS integrity and quality of follow up • Sample size & power optimized • Study positive only on hard clinical endpoint OS, Interim analysis to inform separate regulatory process not impacting the scientific objective of the study
Cons	• Results on ORR/PFS only conditional on final (future) OS results (= > concept of conditional approval !) • Conditional approval on conditionally positive key secondary endpoint ? (Same issue as with previous approach: approval on study not yet positive)

Under which conditions
is the Regulator open to base conditional approval on conditional results?