Evolving endpoints in cancer trials
EU Regulator's perspective

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Innovative oncology trial designs

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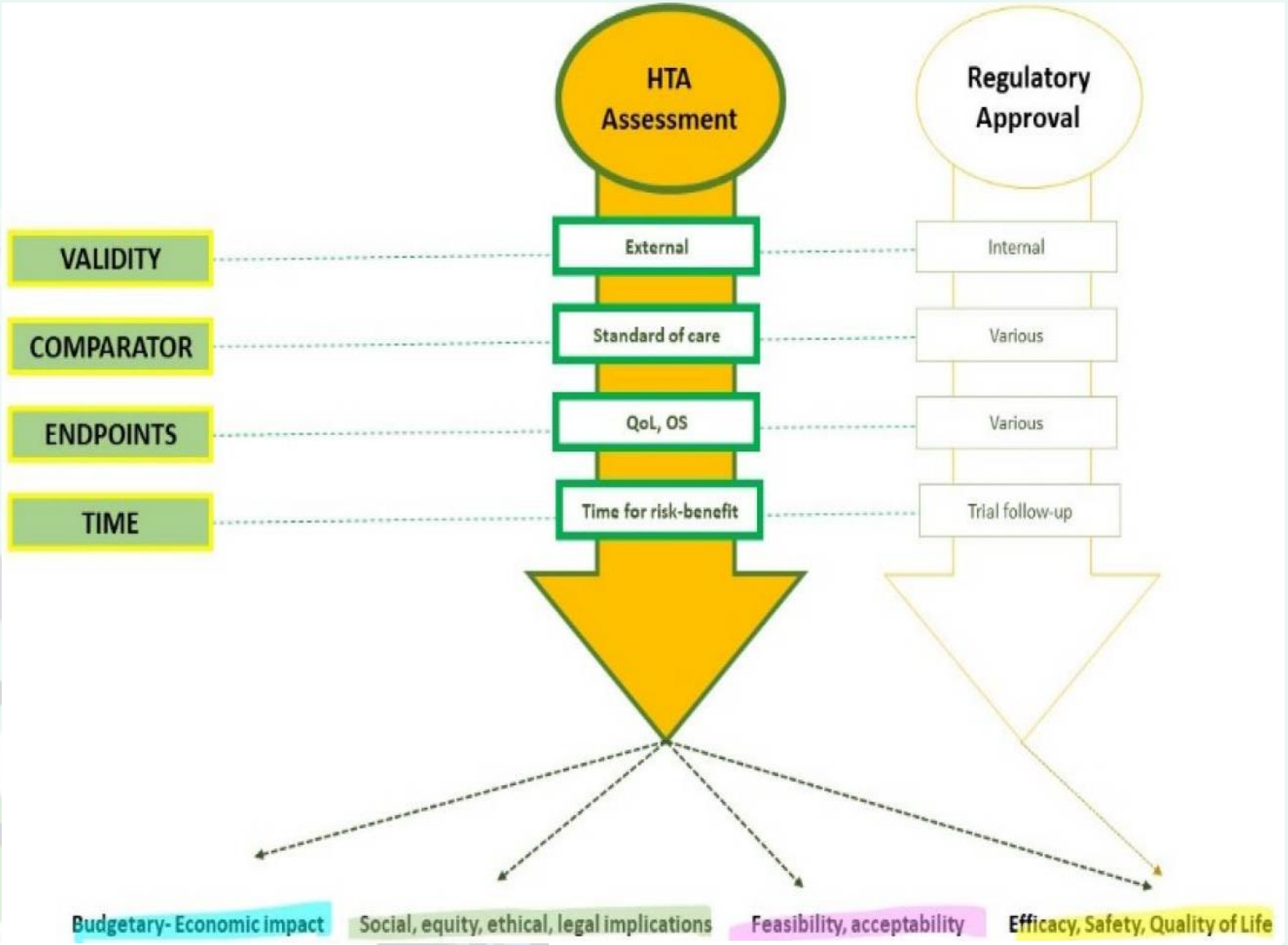
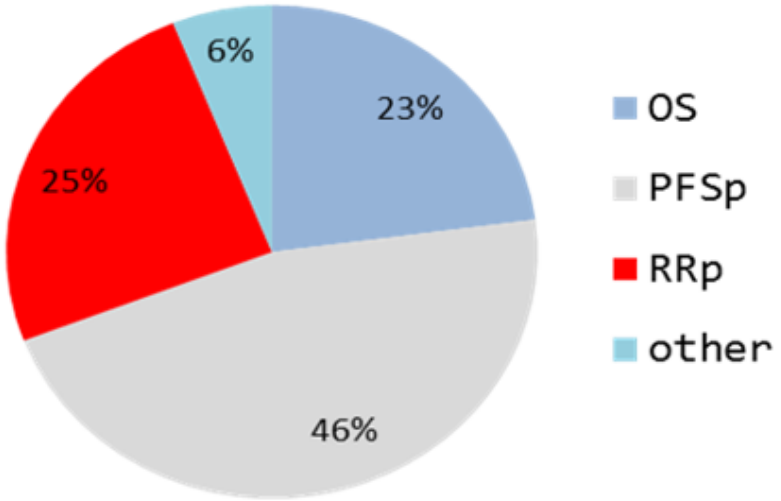
Regulatory approval

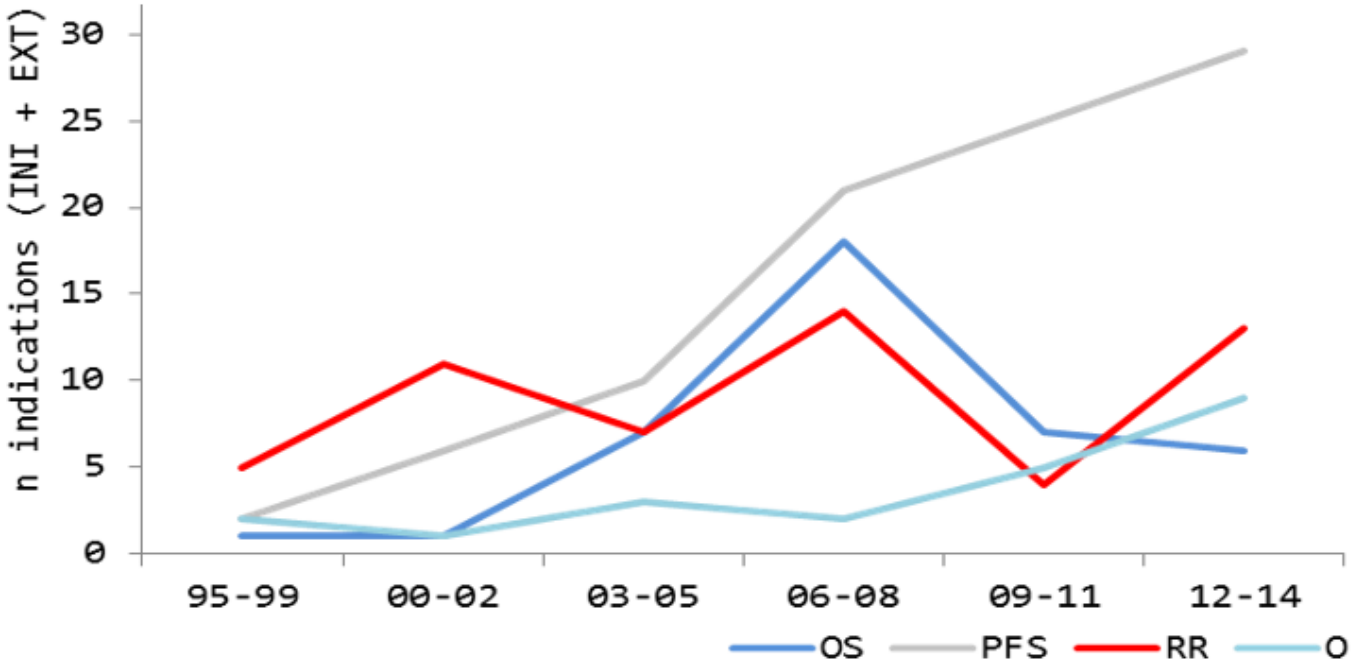
- Aims to establish if benefits > risks [Regulation (EC) No. 726/2004]
- New drugs not necessarily “superior” to those already on the market
- Patient perspective is central
  - No relative-effectiveness
  - No pricing or health-economic considerations



Trapani et al. Curr Oncol. 2022 Aug; 29(8): 5774–5791.

Primary endpoints for approval of cancer drugs, EMA experience up to 2016

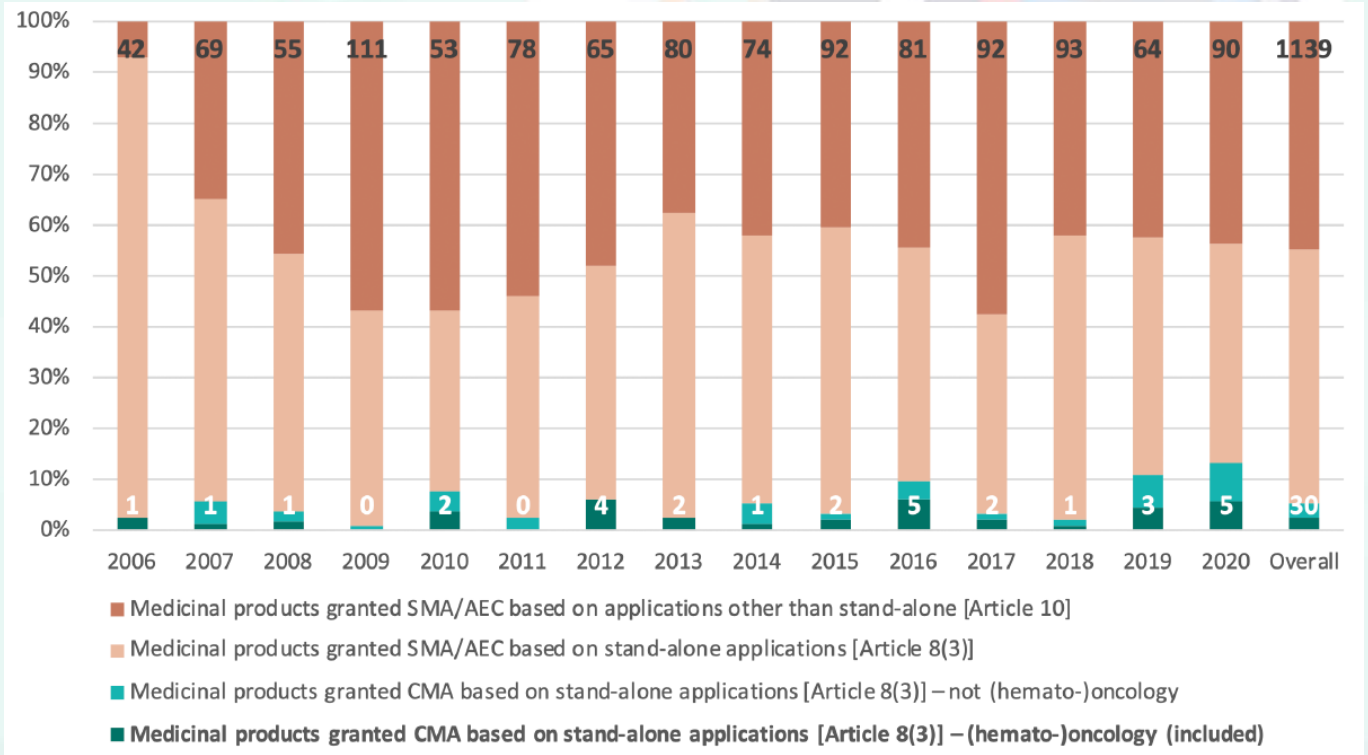




J. Martinalbo, ESMO 2016

What have we seen in the last few years?

Increased number of conditional marketing authorisations (CMA) based in single arm trials (SAT) with response-related endpoints as primary endpoint, particularly for targeted therapies intended for oncogene-addicted (biomarker+) diseases



Bloems et al, European CMA in a Rapidly Evolving Treatment Landscape: A Comprehensive Study of Anticancer Medicinal Products in 2006–2020. Clin Pharmacol Ther 2023 Jul;114(1):148-160

Current trends in decision-making

My interpretation from the anticancer guideline V6 on primary Eff endpoints:

Varies according to disease and setting/line of therapy, but in general:

- Metastatic setting: Improved OS in RCT against SOC is gold standard
  - PFS with sufficient maturity (avoid early IAs) and non-detrimental OS in RCTs acceptable in particular circumstances
  - ORR in SATs for specific populations may grant CMA, but eventual provision of comprehensive data (usually an RCT) must be agreed upfront
- Adjuvant setting: Sufficiently mature DFS and non-detrimental OS in RCTs
- Neoadjuvant setting: Sufficiently mature EFS and non-detrimental OS in RCTs
  - Pathologic response endpoints (PCR, MPR, etc.) not sufficiently validated across histologies

Scientific advice (SAWP) from the CHMP is recommended when deviations from the guideline are in consideration

What about newer surrogate endpoints?

- Early metabolic response in neoadjuvant trials
- ctDNA to monitor response in metastatic trials
- CCR12 in neoadjuvant approach to LARC

Too early to conclude on their validity as surrogate endpoints for regulatory decisions – time will tell

What about PCR/MPR in neoadjuvant NSCLC trials?

Opdivo II-117 EPAR (21.07.2023): pCR has not been validated as a surrogate endpoint of survival, but results on this endpoint provide information about treatment's antitumour activity and are considered supportive.