Background: The Breakthrough Therapy program was established in July 2012 to expedite drug development and approval in the US, although it is unclear if cancer drugs qualifying for this program are more effective or safer than non-breakthrough-designated drugs. The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) is a validated tool to assess the clinical benefit of cancer drugs. Here, we compare the magnitude of clinical benefit of clinical trials leading to FDA approval of breakthrough-designated and non-breakthrough-designated cancer drugs.

Methods: We searched the Drugs@FDA website to identify anticancer drugs for solid tumors approved by the FDA between July 2012 and December 2017. For each drug, we collected data on breakthrough therapy designation, pivotal trial design, efficacy, safety, and quality of life outcomes, and applied ESMO-MCBS v1.1 grades. Substantial benefit was defined as a grade of A or B for trials of curative intent and 4 or 5 for those of palliative intent. Trial characteristics and ESMO-MCBS grades were compared using Chi squared or Mann Whitney U tests.

Results: We identified 110 trials supporting the approval of 52 individual drugs for 96 indications. Of these indications, 49% received breakthrough designation. Compared
to non-breakthrough drugs, trials supporting breakthrough drugs had a smaller sample size (median 401 vs 604, \( P = .047 \)), were less likely to evaluate experimental cytotoxic chemotherapy or endocrine therapy than targeted therapy (0% vs 10%, \( P = .004 \)), and were less often randomized (60% vs 84%; \( P = .009 \)) or double-blind (15% vs 46%, \( P = .001 \)). A similar proportion of trials supporting breakthrough and non-breakthrough drugs approved for palliative intent showed substantial clinical benefit using ESMO-MCBS v1.1 (36% vs 29%; \( P = .45 \)). There were too few trials performed with curative intent (\( n = 10 \)) to perform statistical testing.

**Conclusions:** Compared to non-breakthrough drugs, trials of breakthrough drugs are smaller and more likely to be single-arm and not double-blinded. A similarly low proportion of breakthrough and non-breakthrough cancer drugs met the standard of substantial clinical benefit as applied in ESMO-MCBS v1.1.

**Legal entity responsible for the study:** Hospital de la Santa Creu i Sant Pau.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.