Global Perspectives on Clinical Cancer Research: A Comparison of Randomized Controlled Trial (RCT) Design and Outcomes Across High Income and Low-Middle Income Countries

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Background
Cancer clinical trials have become increasingly international in scope. There are limited data regarding trial variation based on the economic status of the country in which they are conducted. Here we describe trial characteristics, design, and results of all RCTs published globally during 2014-2017.

Methods
A structured literature search was designed using PUBMED to identify all RCTs evaluating anti-cancer therapies published during 2014-2017. Data captured included authorship, participants, study characteristics, design, and results. RCTs were classified based on the World Bank country-level economic classification of the first author [low-middle/upper-middle income countries (LMIC) and high-income countries (HIC)]. Among superiority RCTs that met the primary endpoint (i.e. statistically "positive"), we calculated the ESMO-MCBS to identify trials with substantial clinical benefit (MCBS scores 4/5 or A/B). Outcomes were compared with Chi Square or Fisher's Exact tests.

Results
The study cohort included 694 RCTs; 636 (92%) were led by HIC and 58 (8%) were led by LMIC. Compared to LMIC, RCTs in HICs were more likely to be funded by industry [73% vs 41%, $p<0.001$] and more likely to test novel systemic therapies [87% vs 78%, $p=0.027$]. LMIC studies were typically smaller (median N=220 vs N=474 participants, $p<0.001$) and more likely to meet their primary endpoints [66% vs 44%, $p=0.002$]. In "positive" superiority trials, the effect size was larger in LMICs compared to HICs (median HR 0.62 vs HR 0.84, $p<0.001$). The proportion of trials identifying treatments with substantial clinical benefit (ESMO MCBS 4/5/A/B) was 45% (LMIC) and 31% (HIC, $p=0.291$). Studies from LMIC were published in journals with lower impact factors (IF) (median IF 7 vs 21, $p<0.001$); a publication bias persisted when adjusted for whether a trial was positive or negative: median IF LMIC negative trial=5 vs HIC negative trial=18 ($p<0.001$); median IF LMIC positive trial=9 vs HIC positive trial= 26 ($p<0.001$).

Conclusions
Only a small minority of oncology RCTs are led by investigators in LMIC; these trials are less likely to be funded by industry and more likely to meet their primary endpoint. "Positive" RCTs from LMIC identify therapies with a substantially larger effect size than HIC. These data identify a substantial publication bias towards RCTs conducted in LMIC.