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Assessing Patient Risk, Benefit, and Outcomes in Drug Development: A Decade of Regorafenib Clinical Trials

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Background

Creating a novel chemotherapy is costly both in time and capital spent for drug manufacturers. To regenerate what they've spent, drug manufacturers may attempt to repurpose their medications for new indications via clinical trials. In order to fully understand the risk/benefits in comparison to a drug's efficacy a pooled analysis must be completed.

Methods

On May 25th, 2023, we searched Pubmed, Embase, Cochrane CENTRAL, and ClinicalTrials.gov for trials of regorafenib used to treat solid cancers. Eligible articles were adult clinical trials, used RECIST criteria, published in English, and involved solid tumors. Screening and data collection took place in a masked, duplicate manner. For each trial, we extracted trial characteristics, median progression-free survival (PFS) and overall survival (OS) in months, adverse event rates, and objective response rate. Studies were deemed positive, negative, or indeterminate based on their pre-specified endpoints and tolerability.

Results

Regorafenib was originally approved for colorectal cancer but has since been tested across 27 different cancers. Since approval, cumulative risk increased with 3,900 grade 3-5 adverse events being reported in 4,960 participants while the objective response remained low at 7.0% and a complete response of 0.2%. Comparatively, the change in PFS and OS for regorafenib's original indication was shown to be worse than other cancers. Colorectal cancer with the treatment of regorafenib showed positive outcomes around the time of FDA approval but have declined since.

Results

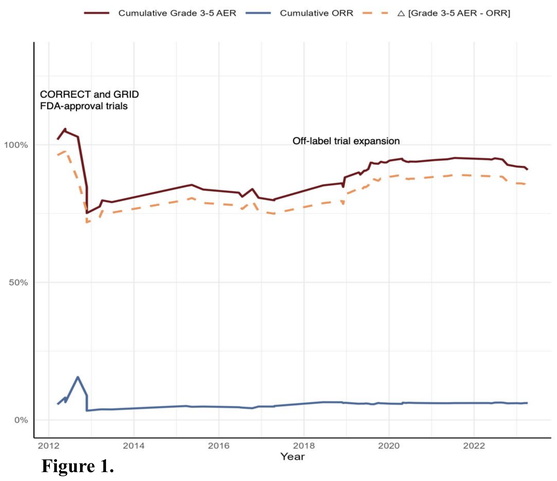

Figure 1.

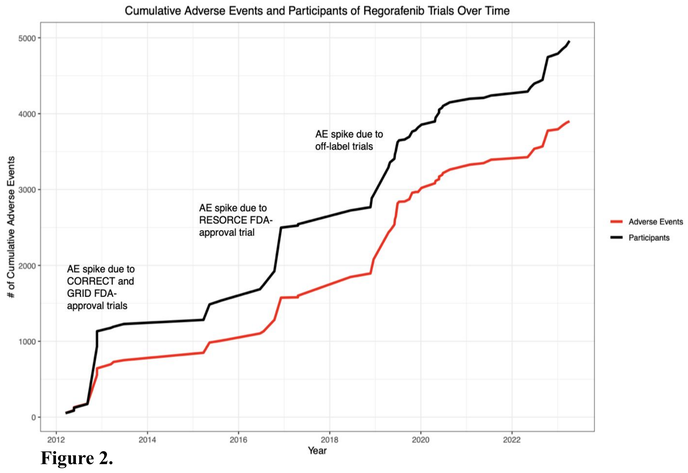

Figure 2.

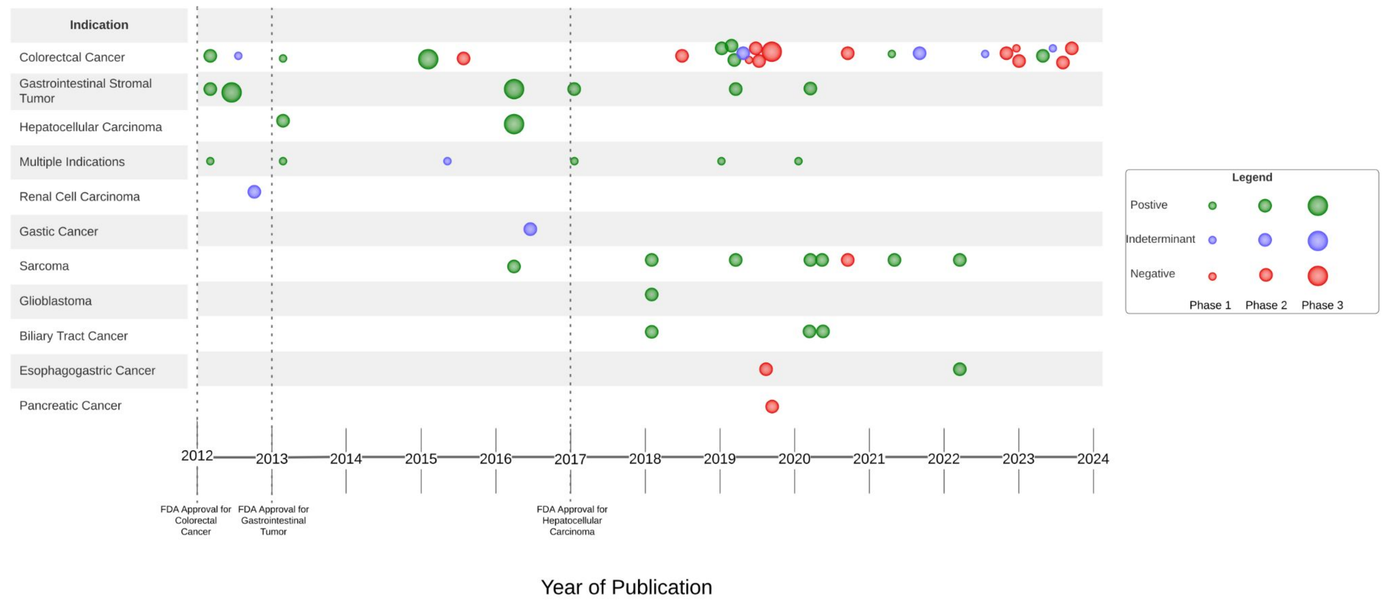

Figure 3.

Figure 1. AER for each trial vs. the cumulative ORR for each trial per year plotted over time. Δ[AER - ORR] is the absolute difference between the cumulative AER and ORR.
Figure 2. The cumulative number of patients vs. the cumulative number of adverse events over time.
Figure 3. AERO diagram for regorafenib clinical trials.

Conclusion

The persistently negative outcomes in cancer trials are concerning and raise important questions about its continued use with this patient population. Furthermore, given the adverse event profile we observed across clinical trials, physicians should carefully weigh the risk-to-benefit profile of regorafenib when considering this therapy.

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