

Breaking News



Patient Powered Real World Evidence

NOVEMBER 2021

This Breaking News issue showcases additional commentary on our September 2021 issue which, based on current studies, asserts the belief that placebos do not benefit patients with advanced disease. The article entitled "It's Time to Rethink Placebos in Advanced GIST", illustrates the effect of placebos in trials and appeals to stakeholders to begin discussing alternatives and changes in order to save lives by extending the time on treatment instead of using placebos in advanced trials. After all the evidence is considered, the question "Do placebos in clinical trials benefit patients with advanced GIST?" is posed and the author encourages discussion between primary stakeholders as the next step for this issue.

The commentary below was provided by a team of GIST experts from Instituto Alexander Fleming in Buenos Aires, Argentina. The original article is available at <https://indd.adobe.com/view/60d0a521-a763-4c5b-a011-ffc5318336ab>. We invite any commentary on our LRG Science articles. Submission guidelines are on the back page of this issue.

Commentary

It's Time to Rethink Placebos in Advanced GIST

By Dr. Federico Waisberg, Dr. Diego Enrico, Dr. Matías Chacón, Alexander Fleming Institute, Buenos Aires

A careful methodological assessment is critical at the moment of analyzing clinical trials. Usual characteristics of randomized studies in soft tissue sarcomas (STS) should be reevaluated in order to promote an earlier access to new drugs for our patients.

While a clinical trial design that includes patients with triple negative as well as Her2 positive breast cancer is unthinkable, it is frequent that the main conclusions for patients with key driven mutations for GIST are obtained after a multivariate analysis is performed. In this context, the "lumper vs splitter" discussion of the target population to assess developing drugs can be easily overcome by implementing master protocols that may bring rapid answers for infrequent populations.

Control arms are also a matter of debate. Undoubtedly, the best standard of care must be offered to patients that are not randomized to the experimental arm. Under these premises, placebos have been routinely used in settings without available beneficial treatments.

In a meta-analysis performed by our group¹, we obtained an overall incidence of 18% grade 3 - 4 adverse events in the subgroup of patients that received only placebo as an intervention for cancer in the adjuvant setting. This uncommon finding, in an otherwise healthy population, can be explained by suggestions and perceptions that may be generated after reading an extensive informed consent before initiating a clinical trial. Concomitantly, the regular visits that a patient needs to undergo during a clinical trial may lead to patient's overmedicalization and, in the long run, to a possible deterioration of quality of life.

For these reasons, it can be concluded that for some clinical trials placebos have no other role than harming patients. Observation should be a suitable control arm when spontaneous tumor regression or psychological adverse events are not being anticipated.

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The complexity of GISTs brings up the necessity of undertaking a collaborative effort to provide higher opportunities of receiving an effective drug for trial participants. It could be conceived that umbrella or platform trial designs may allow the initial evaluation of different developing drugs considering specific tumor subtypes.

After the proof of concept trials are concluded, efforts to promote randomized clinical trials against current effective drugs should be promoted in this infrequent tumor model. Hierarchical statistical analysis evaluating both non-inferiority and superiority hypothesis may also allow the reduction of the necessary number of clinical trials to submit a new drug for regulatory approval.

In a similar approach, the European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors (ESMART) trial

platform bases the decision of enrolling a patient in a clinical trial in a multidisciplinary tumor board². The study design comprehends a phase I with dose-escalation. If the target efficacy endpoint is met, a phase II-III expansion is conducted with continuous evaluation of enrollment on the basis of efficacy.

In conclusion, we can avoid placebos by considering that 1) there are not clear reports of spontaneous regression in GISTs, 2) there are not relevant psychological effects in drugs that are currently being tested in this tumor model, 3) we count with at least five possible effective control arms, such as imatinib, sunitinib, regorafenib, ripretinib and avapritinib, and 4) the implementation of modern designs in clinical trials allows an earlier access to drugs in development. Collaborative efforts to promote the creation of master protocols will spare patients from receiving these 'not-so' inert substances.

References

1. Chacón M, Enrico D, Burton J, et al. Incidence of Placebo Adverse Events in Randomized Clinical Trials of Targeted and Immunotherapy Cancer Drugs in the Adjuvant Setting. A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2018;1(8):e185617
2. Hont A, Bollard C. Using Molecular Stratification for Smart Combination Therapies. *Journal of Clinical Oncology* 2021; DOI: 10.1200/JCO.21.01804



Interested in Submitting an Article to LRG Science?

LRG Science is based on a foundation of Real World Evidence and Real World Data collected from: The LRG GIST Patient Registry, Global Surveillance Team, and our collaborative efforts such as the Pediatric & SDH-Deficient GIST Consortium.

We welcome content from other sources of Real World Evidence, and invite submissions of articles, editorials, case studies or breaking news for future issues, most especially, although not limited to gastrointestinal stromal tumor, SDH-deficiency and sarcoma.

To inquire about authoring an LRG SCIENCE article, providing commentary on an article, or to subscribe to our LRG SCIENCE mailing list, please contact Mary Garland, Director of Communications, at mgarland@liferaftgroup.org.



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