Cholangiocarcinoma Foundation®

Crossover Design Paper
6.29.2023 Final Content

Title:

"Cross-over arms in oncology clinical trials: An important consideration for patients"

Authors/Contributors:

- Wendy Selig, WSCollaborative
- Stacie Lindsey, CCF
- Melinda Bachini, CCF
- Rachna Shroff, Arizona

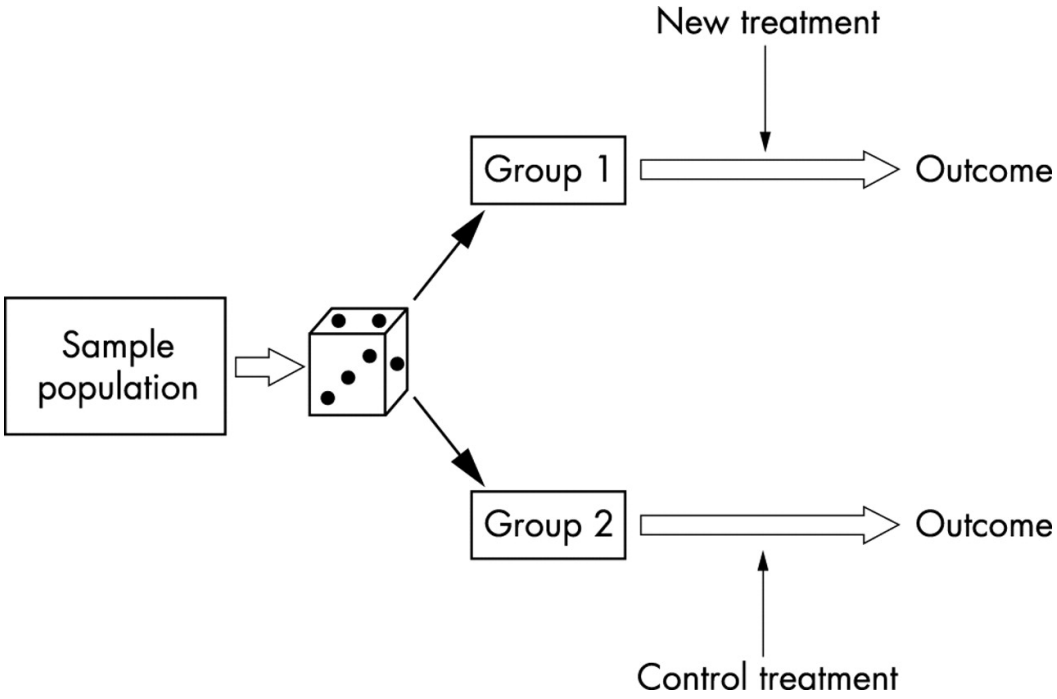
I. Abstract/Summary

Patients with cancer types for which there are few effective therapy options often see participation in clinical trials as their best option. The gold standard for cancer clinical trials designed for regulatory review and ultimate approval of new treatments is a randomized study comparing the novel therapy to current standard of care. However, in tumor types for which there is no standard of care or current standards of care are generally ineffective, the need for strict adherence to the gold standard must be tempered by an effort to provide acceptable options for patients who enroll in studies, including the opportunity to eventually receive the experimental treatment in certain circumstances. While including "cross-over" in trials can complicate the statistical analysis and ability to draw conclusions about the study endpoints, such studies have been designed and conducted successfully, with the input of patient advocates.

This paper details key patient perspectives relating to clinical trial design, especially for tumor types in which there are few or no effective standard of care treatment options. We discuss the importance to patients of including opportunities for cross-over from a control arm within a trial to the investigational arm. This approach can minimize the risk to participants of being restricted through randomization to an ineffective control, afford more patients access to a promising novel therapy under study, and make enrollment in the study more attractive for patients. Here we describe patient perspectives on these issues and a recent example in a Cholangiocarcinoma indication where direct patient input on the study design led to inclusion of cross-over in a pivotal study. By presenting this example in which results from a study with cross-over option were ultimately used to secure regulatory approval in the US and several other jurisdictions, the authors seek to promote sponsors' use and regulators' acceptance of these types of patient-centric trial designs.

II. Introduction

The gold standard for cancer clinical trials designed for regulatory review and ultimate approval of new treatments is a randomized study comparing the novel therapy to current standard of care.[1] Randomized controlled clinical trials (RCTs) have been used as the foundation for oncology clinical development for decades, as researchers have sought to remove variables and minimize bias, thereby improving the reliability of study results. Traditional RCT designs ensure that patients have equal chance of being assigned to receive control (generally in oncology this implies current standard-of-care, or when none is available, placebo) as they have of receiving the experimental therapy. The two groups are followed to see if there are any differences in outcomes. Results and subsequent analysis of the trial are used to assess the effectiveness of the experimental therapy.[2] Where possible, to minimize bias, these trials are "blinded" or "double-blinded," meaning investigators and patients may be unaware of which treatment a patient is receiving.

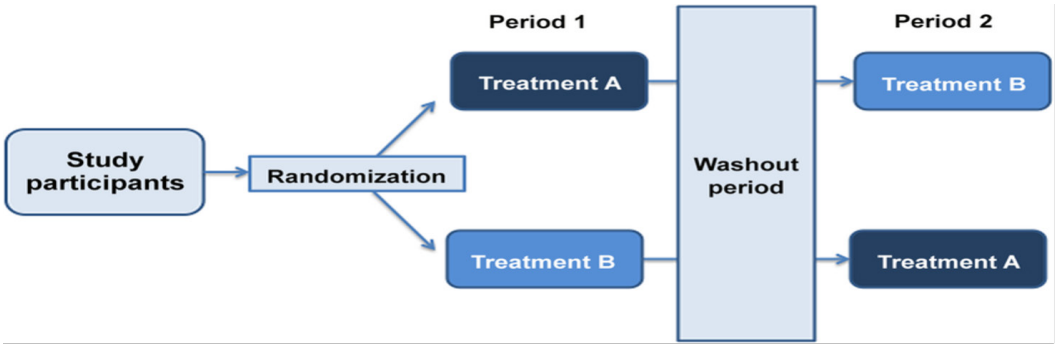


In cancer clinical trials, the use of placebo as control is relatively rare, but may be proposed in cases where there is no standard of care therapy, or the standard of care is highly toxic and generally viewed as ineffective. In these circumstances, the need for strict adherence to the RCT gold standard is often tempered by ethical concerns. One approach to providing acceptable options for patients who enroll in studies in these

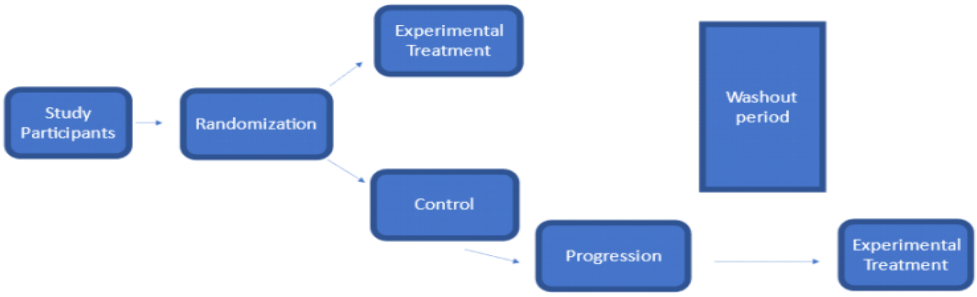
1 Booth CM, Cescon DW, Wang L, Tannock IF, Krzyzanowska MK. Evolution of the randomized controlled trial in oncology over three decades. J Clin Oncol. 2008 Nov 20;26(33):5458-64. doi: 10.1200/JCO.2008.16.5456. Epub 2008 Oct 27. PMID: 18955452; PMCID: PMC2651075.

2 Kendall, J. M. (2003). Designing a research project: Randomised Controlled Trials and their principles. Emergency Medicine Journal, 20(2), 164–168. https://doi.org/10.1136/emj.20.2.164

cases is known as a “cross-over” trial design.[3]



While typically used to evaluate efficacy of sequencing among two treatments, cross-over arms can also be incorporated into studies testing the efficacy of a single treatment by offering patients in the control group the opportunity to receive the experimental treatment upon disease progression.[4]



The limitations and benefits of allowing patients to “cross-over” within an efficacy trial (sometimes called a “cross-over allowance”) for a novel treatment (prior to reporting interim results or by without mandate from a trial’s data safety monitoring board (DSMB)) have been debated among the cancer research community. Including a “cross-over allowance” in trials can complicate the ability to draw conclusions about the study endpoints. For example, allowing cross-over may confound interpretation of overall survival among patients in the experimental arm.[5][6] However, it has also been argued

3 Illustration of the design and analysis of a randomized crossover trial. Retrieved April 30, 2023, from https://www.researchgate.net/figure/Illustration-of-the-design-and-analysis-of-a-randomized-crossover-trial_fig6_342719374

4 What is “treatment switching” in cancer clinical trials? Cancer.Net. (2019, September 26). Retrieved April 30, 2023, from https://www.cancer.net/blog/2019-09/what-treatment-switching-cancer-clinical-trials

5 Chen, E. Y., & Prasad, V. (2018). Crossover is not associated with faster trial accrual. Annals of Oncology, 29(3), 776–777. https://doi.org/10.1093/annonc/mdx793

6 Haslam A, Prasad V. When is crossover desirable in cancer drug trials and when is it problematic? Ann Oncol. 2018 May 1;29(5):1079-1081. doi: 10.1093/annonc/mdy116. PMID: 29648572; PMCID: PMC5961160

that failure to allow patients to cross-over from the control, especially in trials focused on rare tumor types with ineffective or no standard therapy options, will make the study unattractive for patients and difficult to enroll.

III. Incorporating Patient and Clinician Perspectives in Clinical Trial Designs

Sponsors of cancer clinical trials have many factors to consider in designing their efficacy studies for novel treatments, including ensuring that they can successfully enroll the numbers of patients needed to complete the trial. A bedrock ethical principle of clinical trial design is that the study must have equipoise, meaning that genuine uncertainty exists within the expert medical community prior to running the trial about whether any one arm in a study is superior to the others. In this way, randomization to any of the arms would be viewed as ethical and appropriate.[7]

Increasingly, clinical trials are seen by clinicians and patients as part of an active treatment plan, rather than a last resort. This is especially true in cancers for which there is no standard-of-care treatment, or the existing standard-of-care is ineffective. Patients view the opportunity to be treated with a novel therapy in a clinical trial as their best option, particularly when early data about a new agent for a hard-to-treat cancer are promising.[8] Patients in these circumstances are frequently uncomfortable with randomization, citing concerns about receiving placebo or ineffective standard-of-care therapy in a control arm rather than the investigational agent.[9]

Clinicians treating these patients also seek opportunities for them to access promising new therapies and are hesitant about recommending a clinical trial when there is a 50-50 chance the patient could receive an ineffective or placebo control instead of an investigational agent that appears to be active. While clinicians recognize and support the importance of research integrity and the need for randomized studies, they also have a commitment to clinical integrity and providing their individual patients with the best possible treatment options.

Reflecting these concerns, patients and patient advocacy organizations have urged trial sponsors and regulators to accept study designs that allow for more flexibility for participants to access the experimental treatment. These efforts have found traction in recent years with the advent of patient-focused drug development (PFDD). To accelerate development of promising cancer therapies and make their trials more attractive to patients for recruitment and retention, sponsors have turned to single-arm studies when enrolling a randomized trial would be especially challenging. Allowing for cross-over is an alternate approach if a randomized trial is deemed necessary.[10]

---

7 The question of clinical equipoise and patients' best interests. (2015). AMA Journal of Ethics, 17(12), 1108–1115. https://doi.org/10.1001/journalofethics.2015.17.12.ecas1-1512

8 Isbary, G., Staab, T. R., Amelung, V. E., Dintsios, C.-M., Iking-Konert, C., Nesurini, S. M., Walter, M., & Ruof, J. (2018). Effect of crossover in oncology clinical trials on evidence levels in early benefit assessment in Germany. Value in Health, 21(6), 698–706. https://doi.org/10.1016/j.jval.2017.09.010

9 Madsen, S. M., Holm, S., & Riis, P. (2007). Attitudes towards clinical research among cancer trial participants and non-participants: An interview study using a grounded theory approach. Journal of Medical Ethics, 33(4), 234–240. https://doi.org/10.1136/jme.2005.015255

10 Faulkner, S.D., Somers, F., Boudes, M. et al. Using Patient Perspectives to Inform Better Clinical Trial Design and Conduct: Current Trends and Future Directions. Pharm Med 37, 129–138 (2023). https://doi.org/10.1007/s40290-022-00458-4

IV. Statistical and Regulatory Considerations for Allowing Cross-Over

While sponsors have been willing to consider more flexible trial designs to accommodate patient concerns, allowing patients whose disease progresses while on the control arm of a clinical trial to cross-over to the experimental arm can make it more difficult to discern the impact of the intervention being studied. Implementing cross-over in a trial may confound the treatment differences between the randomized arms for long-term trial end points, such as overall survival. There are multiple analytical and statistical approaches for addressing this challenge,[11] [12] including various methods for dealing with "unblinding" of patients at progression, grouping patients among the trial cohorts to limit the impact of the cross-over and applying more advanced statistical methods to assessing the data. [13]

In the United States, the Food and Drug Administration (FDA) addressed some of these issues in its 2019 Guidance for Industry on blinding and use of placebo controls in cancer clinical trials. In this Guidance, FDA states that a patient whose disease progresses within a placebo-controlled RCT should be "unblinded" to allow the patient the opportunity to pursue additional treatment options.[14] FDA has previously noted the importance of documenting further anti-cancer therapy for patients who have been in trials, including those who have received experimental treatment through a cross-over opportunity.[15] To provide flexibility and options for patients, FDA has approved therapies based on data from these studies.[16] [17] The European Medicines Agency (EMA) has generally taken a more conservative approach, advising sponsors not to allow cross-over after disease progression unless there is confidence that the objectives of the trial can

11 Isbary, G., Staab, T. R., Amelung, V. E., Dintsios, C.-M., Iking-Konert, C., Nesurini, S. M., Walter, M., & Ruof, J. (2018). Effect of crossover in oncology clinical trials on evidence levels in early benefit assessment in Germany. Value in Health, 21(6), 698–706. https://doi.org/10.1016/j.jval.2017.09.010

12 Ishak, K.J., Proskorovsky, I., Korytowsky, B. et al. Methods for Adjusting for Bias Due to Crossover in Oncology Trials. PharmacoEconomics 32, 533–546 (2014). https://doi.org/10.1007/s40273-014-0145-y

13 Ishak, K. J., Caro, J. J., Drayson, M. T., Dimopoulos, M., Weber, D., Augustson, B., Child, J. A., Knight, R., Iqbal, G., Dunn, J., Shearer, A., & Morgan, G. (2011). Adjusting for patient crossover in clinical trials using external data: A case study of lenalidomide for advanced multiple myeloma. Value in Health, 14(5), 672–678. https://doi.org/10.1016/j.jval.2011.02.1182

14 Center for Drug Evaluation and Research. Placebos and blinding in randomized controlled cancer clinical trials. U.S. Food and Drug Administration. Retrieved April 30, 2023, from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/placebos-and-blinding-randomized-controlled-cancer-clinical-trials-drug-and-biological-products

15 Cancer Drug and Biological Products — Clinical Data in Marketing Applications Guidance for Industry - Food and Drug Administration. Retrieved April 30, 2023, from https://www.fda.gov/media/71270/download

16 Center for Drug Evaluation and Research. FDA approves ivosidenib for advanced or metastatic cholangiocarcinoma. U.S. Food and Drug Administration. Retrieved April 30, 2023, from https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ivosidenib-advanced-or-metastatic-cholangiocarcinoma#:~:text=On%20August%2025%2C%202021%2C%20the,by%20an%20FDA%2Dapproved%20test.

17 Study of AG-120 (Ivosidenib) vs. placebo in combination with azacitidine in participants with previously untreated acute myeloid leukemia with an IDH1 mutation - full text view. Study of AG-120 (Ivosidenib) vs. Placebo in Combination With Azacitidine in Participants With Previously Untreated Acute Myeloid Leukemia With an IDH1 Mutation - Full Text View - ClinicalTrials.gov. Retrieved April 30, 2023, from https://clinicaltrials.gov/ct2/show/NCT03173248

be met, and adequate conclusions can be drawn.[18] [19] [20] However, the current regulatory landscape is highly dynamic as global perspectives on the need for greater flexibility in clinical trial design are evolving.

V. Case Study: Cholangiocarcinoma and TIBSOVO® Clinical Development

The recent clinical development and regulatory approval of TIBSOVO® for IDH1-mutated Cholangiocarcinoma (bile duct cancer) patients offers a useful case study for the themes addressed in this paper, including the importance of offering flexible trial designs that adapt to patient input.

Background

TIBSOVO® (ivosidenib tablet) is an oral inhibitor of the mutated isocitrate dehydrogenase-I (IDH-1) enzyme first developed by Agios and eventually commercialized by Servier for treatment of Cholangiocarcinoma and AML. Cholangiocarcinoma (CCA), also known as bile duct cancer, is a rare and aggressive tumor with 5-year survival rates below 10%. There are approximately 10,000 cases of CCA per year diagnosed in the US. Globally, CCA is increasing globally, currently accounting for ~15% of all primary liver cancers and ~3% of gastrointestinal malignancies.[21]

CCA is generally diagnosed when it has reached an advanced state. Until recently, surgery and chemotherapy were the only standard treatments offered to CCA patients, providing little to no benefit for most and leaving no standard options for patients who progress and need a later line of treatment.

Not only is CCA a rare cancer, but there are also rare sub-populations of CCA patients who have known biomarkers that suggest opportunities for targeted treatments. In the case of IDH-1, it is estimated that approximately 15% of CCA patients harbor an IDH mutation.[22]

Cholangiocarcinoma Patient Advocacy

Since its founding in 2006, the Cholangiocarcinoma Foundation (CCF) has been focused on its mission of finding a cure and improving the quality of life for those affected by CCA. CCF is the primary hub for patients, caregivers, loved ones, researchers, clinicians, and companies to collaborate in advancing better outcomes for patients. Through CCF's extensive community engagement activities, the needs and priorities of

18 Guideline on the Evaluation of Anticancer Medicinal Products in Man rev 5. Retrieved April 30, 2023, from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf

19 Appendix 1 to the Guideline on the Evaluation of Anticancer Medicinal Products in Man rev 5. Retrieved April 30, 2023, from https://www.ema.europa.eu/en/documents/scientific-guideline/appendix-1-guideline-evaluation-anticancer-medicinal-products-man-methodological-consideration-using_en.pdf

20 Question and answer on adjustment for cross-over in estimating effects in oncology trials. EMA. December 2018. Retrieved May 11, 2023, from https://www.ema.europa.eu/en/adjustment-cross-over-estimating-effects-oncology-trials-scientific-guideline

21 Banales, J.M., Marin, J.J.G., Lamarca, A. et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol 17, 557–588 (2020). https://doi.org/10.1038/s41575-020-0310-z

22 Rizzo A, Ricci AD, Brandi G. IDH inhibitors in advanced cholangiocarcinoma: Another arrow in the quiver? Cancer Treat Res Commun. 2021;27:100356. doi: 10.1016/j.ctarc.2021.100356. Epub 2021 Mar 24. PMID: 33799004.

people dealing with CCA are identified and communicated to all stakeholders to help shape research and development of better treatments and an eventual cure. CCF is proactive in partnering with sponsors of research studies and works to ensure that all CCA patients have treatment options that include access to relevant clinical trials.

Adapting to Clinician and Patient Input in the ClarIDHy Trial Design

While there was a placebo control in the ClarIDHy trial, the final design included a more favorable randomization scheme (2:1 between the investigational agent and the control) and the opportunity for patients to cross-over from the control arm to the experimental arm upon progression. These design flexibilities providing additional options for participants to receive AG-120 (now known as TIBSOVO®) reflected significant clinician and patient input coordinated by CCF over several years.

Initially, Agios was focused on designing a traditional, randomized pivotal study with placebo control, reflecting the belief that this would be necessary to reach an overall survival endpoint (traditional gold standard for phase 3 trials) and ensure sufficient power for successful regulatory review. In addition, given the lack of an acceptable standard-of-care for previously treated CCA patients, and specifically IDH-1 mutated patients, the company saw a need for a placebo control arm to serve as a consistent comparator to its investigational therapy (AG-120).

At an early meeting between Agios clinical development officials, members of the CCF scientific and medical leadership, and patient advocates, concerns were raised about a randomized trial using placebo control for this patient population. As additional information emerged about the potential impact of AG-120 from earlier phase 1 studies, Agios and members of the CCA community discussed options to make the trial design more desirable for patients and clinicians. These options included a randomization scheme that would allow more patients to access the investigational drug and a cross-over option for patients who progress on the control arm. While such design features create a less clear picture for overall survival analysis, clinicians saw an opportunity to evaluate a totality of evidence from the study, including various clinically meaningful secondary outcomes.

Ultimately, the phase 3 ClarIDHy trial (NCT03173248) had a primary endpoint of progression free survival (PFS) and a secondary endpoint of overall survival (OS), included flexible design features that would permit more patients access to study drug. These features included a 2:1 randomization between the experimental arm and the placebo control and permitted patients who progressed on the control arm to cross-over and receive AG-120. Additionally, patients in the experimental arm whose disease was deemed to have progressed based on their scans but were still seen to be receiving clinical benefit by their doctor could remain on the drug.

The ClarIDHy trial launched in February 2017 with its first patient and completed its enrollment of 187 patients in early 2019, a relatively short period for full accrual, especially in a rare cancer type. Advocates cite the flexible trial design, and specifically the permitted cross-over option, as a major factor in speeding trial enrollment.

The outcome of the ClarIDHy trial was positive, demonstrating a statistically significant

improvement in PFS compared with placebo.[23] [24] Based on the results of the study, Agios submitted its new drug application (NDA) to the FDA in February 2021, and, in August 2021 TIBSOVO® was approved for patients with previously treated, locally advanced or metastatic IDH-1 mutated CCA. On May 10, 2023 after having received a positive opinion from its Committee for Medicinal Products for Human Use (CHMP), the European Commission granted a marketing authorization for TIBSOVO® for treatment of previously treated IDH-1 mutated CCA patients.

VI. Voices of Patients

The CCA patient community was highly active in communicating about the design features of the ClarIDHy study. Through online discussion boards, a Facebook Group, and in-person meetings convened by CCF, patients shared their concerns about placebo controls and their strong interest in having access to the experimental drug through the trial.

Comments made by patients through these forums included:

- "With the trial my only concern was what happens if it is the placebo?"
- "Placebo should never be used with cancer. It just allows the cancer to grow."
- "Confirmed – received the placebo. Two months of them just letting it [the cancer] grow."
- "All trials must be deemed ethical, and this seems to be so unethical."
- "They are playing with people's lives!""
- "I believe a placebo in a trial is ancient and cruel."

Overall, it is clear from this experience that CCA patients were willing to "vote with their feet," when it came to the flexibility within the ClarIDHy study design. Patient accrual to this trial occurred in less than 2 years, marking a much speedier recruitment effort than is often the case for rare cancer types and small patient subsets. While the literature suggests that this may not always be the case,[25] it is important to consider that patients and their clinicians in disease settings where there is no effective standard of care option, are more likely to consider a clinical trial if their chances of receiving the experimental agent are greater than 50%.

---

23 Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, Cleary JM, Catenacci DV, Borad MJ, Bridgewater J, Harris WP, Murphy AG, Oh DY, Whisenant J, Lowery MA, Goyal L, Shroff RT, El-Khoueiry AB, Fan B, Wu B, Chamberlain CX, Jiang L, Gliser C, Pandya SS, Valle JW, Zhu AX. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2020 Jun;21(6):796-807. doi: 10.1016/S1470-2045(20)30157-1. Epub 2020 May 13. Erratum in: Lancet Oncol. 2020 Oct;21(10):e462. PMID: 32416072; PMCID: PMC7523268.

24 Zhu AX, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, Cleary JM, Catenacci DVT, Borad MJ, Bridgewater JA, Harris WP, Murphy AG, Oh DY, Whisenant JR, Lowery MA, Goyal L, Shroff RT, El-Khoueiry AB, Chamberlain CX, Aguado-Fraile E, Choe S, Wu B, Liu H, Gliser C, Pandya SS, Valle JW, Abou-Alfa GK. Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With IDH1 Mutation: The Phase 3 Randomized Clinical ClarIDHy Trial. JAMA Oncol. 2021 Nov 1;7(11):1669-1677. doi: 10.1001/jamaoncol.2021.3836. PMID: 34554208; PMCID: PMC8461552.

25 Chen, E. Y., & Prasad, V. (2018). Crossover is not associated with faster trial accrual. Annals of Oncology, 29(3), 776–777. https://doi.org/10.1093/annonc/mdx793

VII. Conclusion

The randomized clinical trial remains a crucial bedrock of clinical research, providing the opportunity to compare impact on overall survival for new therapies against the standard of care. In cases where there is no clear standard of care, or the prevailing standard of care is generally ineffective, patients and their clinicians are increasingly seeking flexibility within trial designs to increase their opportunity to receive the experimental agent. This is especially important when early data indicates the experimental therapy is active and shows real potential to provide clinical benefit. Regulators and sponsors are showing increased willingness to consider flexible trial designs (including weighted randomization with fewer patients in a control arm, and opportunities to allow patients to cross-over from the control arm to the experimental arm). In recent months additional trials with these features have been launched by various sponsors. This evolution in approach to clinical trials reflects passionate input from patients and patient advocates, as clinical trials become a central aspect of an individual's treatment plan. With breathtaking advances in our knowledge of cancer and its mechanisms, continuing progress in developing more effective treatments depends on the willingness of the drug development ecosystem to push its boundaries toward more nimble and innovative clinical trial designs.

VIII. Acknowledgements

The authors gratefully acknowledge all who contributed to this paper, including many members of the CCA community. We are grateful to the CCF team and the leadership of the AMMF for their input and support. We are deeply thankful for the courage and perseverance of the patients who participated in the ClarIDHy trial, their caregivers and loved ones. We also thank the dedicated researchers and scientists who worked tirelessly to bring this new therapy for CCA patients to fruition, both the investigators who ran the trials and the company officials who believed in the program. We also thank the officials at FDA who worked with the sponsor to design a more flexible trial and positively reviewed the results for approval.

This paper was developed with funding support from Servier and in-kind support from the Cholangiocarcinoma Foundation.

IX. Resources

- When is crossover desirable in cancer drug trials and when is it problematic? Annals of Oncology https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5961160/
- Trends in the crossover of patients in phase III oncology clinical trials in the USA ecancer Medical Science https://ecancer.org/en/journal/article/1142-trends-in-the-crossover-of-patients-in-phase-iii-oncology-clinical-trials-in-the-usa
- What Is "Treatment Switching" in Cancer Clinical Trials? Cancer.Net https://www.cancer.net/blog/2019-09/what-treatment-switching-cancer-clinical-trials
- Adjusting for Patient Crossover in Clinical Trials Using External Data: A Case Study of Lenalidomide for Advanced Multiple Myeloma Value in Health https://www.sciencedirect.com/science/article/pii/S1098301511014161
- Which Treatment Is Better? Ascertaining Patient Preferences with Crossover Randomized Controlled Trials Journal of Pain & Symptom Management https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4359650/
- Crossover trials: what are they and what are their advantages and limitations? https://s4be.cochrane.org/blog/2020/09/07/crossover-trials-what-are-they-and-what-are-their-advantages-and-limitations/
- Crossover in oncology clinical trials JCO https://ascopubs.org/doi/10.1200/jco.2015.33.15_suppl.e15592
- The Question of Clinical Equipoise and Patients' Best Interests AMA Journal of Ethics https://journalofethics.ama-assn.org/article/question-clinical-equipoise-and-patients-best-interests/2015-12
- Clinical equipoise: Why still the gold standard for randomized clinical trials? Clinical Ethics https://journals.sagepub.com/doi/10.1177/14777509221121107
- Ibrutinib CLL Trial: Where Is the Equipoise? ASCO Post https://ascopost.com/issues/may-1-2013/ibrutinib-cll-trial-where-is-the-equipoise.aspx
- Barriers to Patient Enrollment in Therapeutic Clinical Trials for Cancer: A Landscape Report ACSCAN https://www.fightcancer.org/sites/default/files/National%20Documents/Clinical-Trials-Landscape-Report.pdf
- Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With IDH1 Mutation: The Phase 3 Randomized Clinical ClarIDHy Trial JAMA Oncology https://jamanetwork.com/journals/jamaoncology/fullarticle/2784216
- Evolution of the Randomized Controlled Trial in Oncology Over Three Decades JCO https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2651075/
- Designing a research project: randomised controlled trials and their principles BMJ Journal https://emj.bmj.com/content/20/2/164
- Ethical, Scientific, and Regulatory Perspectives Regarding the Use of Placebos in Cancer Clinical Trials JCO https://old-prod.asco.org/sites/new-www.asco.org/files/content-files/advocacy-and-policy/documents/2008-ASCO-Statement-Ethical-Scientific-Regulatory-Perspectives-Regarding-Use-Placebos-Cancer-Clinical-Trials.pdf DOI: 10.1200/JCO.2007.13.5335
- Sibbald B, Roberts C. Understanding controlled trials Crossover trials. https://pubmed.ncbi.nlm.nih.gov/9614025/

- Crossover is not associated with faster trial accrual Annals of Oncology https://www.annalsofoncology.org/article/S0923-7534(19)35504-8/fulltext
- Using Patient Perspectives to Inform Better Clinical Trial Design and Conduct: Current Trends and Future Directions Pharmaceutical Medicine https://link.springer.com/article/10.1007/s40290-022-00458-4
- Attitudes towards clinical research among cancer trial participants and non-participants: an interview study using a Grounded Theory approach BMJ Journal of Medical Ethics https://jme.bmj.com/content/33/4/234
- Placebos and Blinding in Randomized Controlled Cancer Clinical Trials for Drug and Biological Products Guidance for Industry FDA https://www.fda.gov/media/130326/download
- Effect of Crossover in Oncology Clinical Trials on Evidence Levels in Early Benefit Assessment in Germany Value in Heath https://www.sciencedirect.com/science/article/pii/S1098301517335210
- Methods for Adjusting for Bias Due to Crossover in Oncology Trials PharmacoEconomics https://link.springer.com/article/10.1007/s40273-014-0145-y
- Guideline on the evaluation of anticancer medicinal products in man EMA https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-4_en.pdf
- Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man EMA https://www.ema.europa.eu/en/documents/scientific-guideline/appendix-1-guideline-evaluation-anticancer-medicinal-products-man-methodological-consideration-using_en.pdf
- Question and answer on adjustment for cross-over in estimating effects in oncology trials. EMA. December 2018. Retrieved May 11, 2023, from https://www.ema.europa.eu/en/adjustment-cross-over-estimating-effects-oncology-trials-scientific-guideline
- Cancer Drug and Biological Products — Clinical Data in Marketing Applications FDA https://www.fda.gov/media/71270/download
- Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nature Reviews. https://www.nature.com/articles/s41575-020-0310-z
- IDH inhibitors in advanced cholangiocarcinoma: Another arrow in the quiver? Cancer Treat Res Commun. 2021 https://pubmed.ncbi.nlm.nih.gov/33799004/
- Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2020 https://pubmed.ncbi.nlm.nih.gov/32416072/
- Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With IDH1 Mutation: The Phase 3 Randomized Clinical ClarIDHy Trial. JAMA Oncol. 2021 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8461552/