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Letter

Sustained cancer clinical trial activity in a French hospital during the first wave of the COVID-19 pandemic

Arnaud Bayle,[1,2,3,*] Capucine Baldini,[1] Patricia Martin-Romano,[1] Jean-Marie Michot,[1] Stéphane Champiat,[1] Rastilav Bahleda,[1] Anas Gazzah,[1] Aurélien Marabelle,[1] Loic Verlingue,[1] Arthur Geraud,[1] Daphné Morel,[1] Stefan Michiels,[3,4] Antoine Hollebecque,[1] Laurence Albiges,[5] Benjamin Besse,[2,5] Jean-Charles Soria,[1,2] Christophe Massard,[1,2] Fabrice Barlesi,[5,6] and Sophie Postel-Vinay[1,7,*]

[1]Drug Development Department (DITEP) Gustave Roussy–Cancer Campus, Villejuif, France
[2]Université Paris Saclay, Université Paris-Sud, Faculté de Médicine, Le Kremlin Bicêtre, Paris, France
[3]Oncostat U1018, Inserm, Paris-Saclay University, Labeled Ligue Contre le Cancer, Villejuif, France
[4]Biostatistics and Epidemiology Office, Gustave Roussy, Villejuif Cedex, France
[5]Department of Medical Oncology, Gustave Roussy, Villejuif, France
[6]Aix Marseille University, CNRS, INSERM, CRCM, Marseille, France
[7]ATIP-Avenir, U981 INSERM, Villejuif, France
*Correspondence: arnaud.bayle@gustaveroussy.fr (A.B.), sophie.postel-vinay@gustaveroussy.fr (S.P.-V.)
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The COVID-19 pandemic has had a major impact on patient care (Schmidt et al., 2020). In oncology, it especially challenged the rigorous conduct of clinical trials, notably by delaying site initiation visits, patient enrollment, treatment administration, trial-associated procedures, and data monitoring. Importantly, limiting access to oncology clinical trials means not offering all possible innovative treatment options to patients and may be detrimental.

The US Food and Drug Administration (https://www.fda.gov/media/136238/download) and the European Medicines Agency (https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf) have issued guidelines for the management of clinical trials during the COVID-19 pandemic. Neither guideline is specific to oncology, and both primarily focus on patient safety, with recommendations being oriented toward limiting enrollment, trial opening, or allowing delays in trial conduct. Almost no consideration is made regarding a potential loss of chance for oncology patients. More recently, American Society of Clinical Oncology has issued guidelines on how to preserve clinical research in oncology, highlighting that maintaining open studies is a priority (Pennell et al., 2021).

Data on the COVID-19 impact on oncology clinical trials are still scarce (Waterhouse et al., 2020; Unger et al., 2020; Xue et al., 2020; Zon et al., 2020). Here, we report quantitative data on the conduct of clinical trials during the first wave of the COVID-19 pandemic at Gustave Roussy (Albiges et al., 2020), one of the largest European comprehensive cancer centers, where more than 3,000 patients (approximately 25% of all patients) are continuously involved in clinical trials.

In this retrospective single-center study, we collected clinical-trial-specific items (including patient-related or trial management-related items) between March and June 2020, i.e., the first pandemic wave, including the first severe lockdown (March 17–May 11). We subsequently compared them to those of the same period in 2019.

At the first lockdown implementation, 84 phase I and 210 phase II/III trials were open for recruitment at Gustave Roussy (Figure S1A). During the first pandemic wave, 21 (25%) phase I and 20 (9%) phase II/III trials were temporarily halted, following a unilateral sponsor decision in virtually all cases. Halted trials were mostly industry-sponsored studies (40/41, 97.5%), intravenous drugs (24/41, 59%), and immunotherapy (23/41, 56%). Despite this, and despite the fact that approximately 15% of the phase I physicians were continuously unavailable because they volunteered for assisting in the COVID-19-specific unit open to face the crisis, all important metrics of the early phase trial activity remained similar to those of 2019, including the number of patients referred for inclusion (599 in 2020 versus 620 in 2019), inclusion consultations (215 versus 247), patients starting treatment (130 versus 130), Internal Review Board (IRB) submissions (14 versus 16), and site initiation visits (11 versus 15), respectively. Although a temporary slowdown in activity was observed at the lockdown initiation, measures that were promptly and pro-actively implemented allowed us to rapidly compensate for this, with a subsequent increase in patient inclusions (Figure S1B).

The impact of the first lockdown was more marked on phase II/III trials—supporting the idea that phase I trials are essential in patient care who have no other therapeutic options—with 152 patient inclusions in 2020 (versus 346 in 2019), 125 randomizations (versus 278), 43 IRB submissions (versus 50), and 34 site initiation visits (versus 40). However, in parallel, 475 patients were included in three "COVID and cancer"-dedicated clinical trials, and in five studies initiated to explore the biological consequences of COVID-19 in patients with cancer, and/or to assess its impact on their safety (NCT04331808; NCT04333914).

Among the 443 patients treated in phase I trials between March and June 2020, 198 COVID-19 PCRs were performed internally, and five (2.5%) were positive. One patient was sent back home with self-isolation recommendations, three were hospitalized, and one required transfer to intensive care for a COVID-19-unrelated reason. Among the 2,851 patients treated in late phase trials, 628 COVID-19 PCRs were performed internally, and 15 (2.4%) were positive. Only one patient with community-based COVID-19 died after transfer to intensive care.

Despite no global initiative like the FDA's decentralized clinical trials approach at the EU level, multiple novel measures were implemented in order to ensure a rigorous and continuous conduct of open trials. For instance, in phase I studies (which request the most thorough trial conduct and are the most consuming of time, staff, and resources), treatment was shipped home for 35 patients, for 140 monitoring was performed remotely (versus none before), and 587 consultations occurred over the phone (versus 377 during the same period in 2019, a 56% increase).

These data show that, thanks to internal measures that were rapidly implemented, the clinical trial activity was preserved during the first pandemic peak, which results from a proactive institutional choice, in accordance with our previously proposed guidelines (Postel-Vinay et al., 2020). Importantly, to our knowledge, none of the patients included in a trial were infected with SARS-CoV-2 due to a trial-related procedure. Similar measures were rapidly implemented during the second wave, allowing maintenance of all clinical trials open and to limit the impact on early and late-phase trials (222 patient inclusions versus 208 in 2019). Now that COVID-19 is becoming a ''chronic'' risk despite vaccination policies, and as pandemic recurrences are expected, it is critically important to evaluate the long-term impact of such measures and to identify which ones should now be systematically prospectively implemented. We can indeed anticipate that some measures will remain short-termed and will no longer be relevant outside a crisis context, while others (e.g., remote monitoring) do represent long-term innovations that will durably transform (and improve) clinical trials and patient care. In line with this idea, guidelines for COVID-19 vaccination of patients enrolled in oncology clinical trials have recently been issued (Desai et al., 2021; Yap et al., 2021).

In conclusion, cancer clinical trials can be maintained despite challenges brought by COVID-19. Sharing experiences and retrospectively evaluating the impact on patients' safety and cancer-related outcomes will be critical to durably improve the conduct of clinical trials and, most importantly, anticipate at best challenges brought by future similar crises in order to always provide optimal care to patients with cancer.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2021.06.010.

DECLARATION OF INTERESTS

As part of the Drug Development Department (DITEP), A.B., C.B., P.M.-R., J.-M.M., S.C., R.B., A. Gazzah, A.M., L.V., A. Geraud, A.H., C.M., and S.P.-V. report the following: Principal/sub-Investigator of Clinical Trials for Abbvie, Adaptimmune, Adlai Nortye USA Inc., Aduro Biotech, Agios Pharmaceuticals, Amgen, Argen-X Bvba, Astex Pharmaceuticals, Astra Zeneca Ab, Aveo, Basilea Pharmaceutica International Ltd., Bayer Healthcare Ag, Bbb Technologies Bv, Beigene, BicycleTx Ltd, Blueprint Medicines, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Ca, Celgene Corporation, Chugai Pharmaceutical Co, Clovis Oncology, Cullinan-Apollo, Curevac, Daiichi Sankyo, Debiopharm, Eisai, Eisai Limited, Eli Lilly, Exelixis, Faron Pharmaceuticals Ltd., Forma Tharapeutics, Gamamabs, Genentech, Glaxosmithkline, H3 Biomedicine, Hoffmann La Roche Ag, Imcheck Therapeutics, Innate Pharma, Institut De Recherche Pierre Fabre, Iris Servier, Iteos Belgium SA, Janssen Cilag, Janssen Research Foundation, Kura Oncology, Kyowa Kirin Pharm. Dev, Lilly France, Loxo Oncology, Lytix Biopharma As, Medimmune, Menarini Ricerche, Merck Sharp & Dohme Chibret, Merrimack Pharmaceuticals, Merus, Millennium Pharmaceuticals, Molecular Partners Ag, Nanobiotix, Nektar Therapeutics, Novartis Pharma, Octimet Oncology Nv, Oncoethix, Oncopeptides, Orion Pharma, Ose Pharma, Pfizer, Pharma Mar, Pierre Fabre, Medicament, Roche, Sanofi Aventis, Seattle Genetics, Sotio A.S, Syros Pharmaceuticals, Taiho Pharma, Tesaro, Turning Point Therapeutics, and Xencor; research grants from Astrazeneca, BMS, Boehringer Ingelheim, GSK, INCA, Janssen Cilag, Merck, Novartis, Pfizer, Roche, and Sanofi; and non-financial support (drug supplied) from Astrazeneca, Bayer, BMS, Boringher Ingelheim, GSK, Medimmune, Merck, NH TherAGuiX, Pfizer, and Roche. J.-M.M. reports other support from Astra-Zeneca, Bristol-Myers Squibb, Boehringer–Ingelheim, Eli Lilly Oncology, β. Hoffmann–La Roche Ltd, Merck, MSD, Pfizer, Regeneron, outside this work. Over the last 5 years, A.M. has been a Principal Investigator of Clinical Trials from the following companies: Roche/Genentech, BMS, Merck (MSD), Pfizer, Lytix pharma, Eisai, Astra Zeneca/Medimmune, Tesaro, Chugai, OSE immunotherapeutics, SOTIO, Molecular Partners, IMCheck, Pierre Fabre, and Adlai Nortye. A.M. has been a Member of Clinical Trial Steering Committees for NCT02528357 (GSK), NCT03334617 (AZ) and a Member of Data Safety and Monitoring Board: NCT02423863 (Sponsor: Oncovir), NCT03818685 (Sponsor: Centre Léon Bérard). A.M. has been a compensated member of the following Scientific Advisory Boards: Merck Serono, eTheRNA, Lytix pharma, Kyowa Kirin Pharma, Novartis, BMS, Symphogen, Genmab, Amgen, Biothera, Nektar, Tesaro/GSK, Oncosec, Pfizer, Seattle Genetics, Astra Zeneca/Medimmune, Servier, Gritstone, Molecular Partners, Bayer, Partner Therapeutics, Sanofi, Pierre Fabre, RedX pharma, OSE Immunotherapeutics, Medicxi, HiFiBio, IMCheck, MSD, iTeos, Innate Pharma, Shattuck Labs, Medincell, Tessa Therapeutics, and Deka Biosciences. A.M. has provided compensated Teaching/Speaker activities for Roche/Genentech, BMS, Merck (MSD), Merck Serono, Astra Zeneca/Medimmune, Amgen, Sanofi, and Servier. A.M. has provided compensated Scientific & Medical Consulting for Roche, Pierre Fabre, Onxeo, EISAI, Bayer, Genticel, Rigontec, Daichii Sankyo, Imaxio, Sanofi/BioNTech, Molecular Partners, Pillar Partners, BPI, Faron, and Applied Materials. 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