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Letter to the Editor

Conducting phase 1 cancer clinical trials during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–related disease pandemic

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Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–related disease (COVID-19) has spread worldwide, we need to share insights and advice on how to continue providing optimal cancer care during the pandemic. Northern Italy has been significantly affected by the outbreak, requiring immediate emergency measures to contain the spread [1]. In such a challenging scenario demanding major efforts for the entire health system, measures were also required to address the medical needs of patients with cancer. Indeed, they are subject to high mortality [2], representing about 20% of the COVID-19-related deaths in Italy [3] and suggesting the need for special precautions during the pursuit of oncological treatment.

While various degrees of flexibility can be acceptable for standard cancer treatments, it is far more difficult to reconcile phase I (ph1) strict protocol prescriptions with rapidly evolving scenarios, when the priority is both to ensure patients' safety and maintain a high scientific rigour.

The ph1 study represents the cornerstone of drug development, linking the preclinical and the clinical

stage of pharmacotherapy science. Such trials are intended to offer tangible therapeutic options, undressing from their original nature of remote lands in patients at the poorest prognosis [4]. However, ph1 studies are often demanding in term of procedures and multiple access to the health institutions, and facilitations should be discussed with the sponsors, now more than ever. In this framework, on March 2020, a Food and Drug Administration guidance on conduct of clinical trials of medical products during the COVID-19 pandemic has been released [5].

Our ph1 study Department at European Institute of Oncology in Milan is currently conducting 43 clinical trials in parallel with 150 patients on active treatment. As of March 30, 11,151 people have died from COVID-19 in Italy and 6818 in the Lombardia region where we practice. Our area was the epicentre of the outbreak with 41,161 positive patients, 11,815 hospitalised and 1330 in intensive care unit.

As committed to quality drug development, our ph1 study Department has been asked to make decisions during the COVID-19 pandemic, by balancing benefits and harms.

We immediately discussed with sponsors case by case focussing on the potential impact on the safety of trial participants and modifying study logistics accordingly. Study decisions included those regarding continuing

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trial recruitment (reducing patient accrual), continuing treatment for patients already enrolled (drug delivery at home) and the need to change patient monitoring during the trial (limited access to hospital due to general lockdown). In all cases, we guaranteed that trial participants have been kept informed of changes to the study and monitoring plans that could impact them.

Ensuring the safety of trial participants and health-care staff was of paramount importance for us. We provided clinic staff with additional training on symptom recognition, screening procedures and use of personal protective equipment. A phone contact the day before the visit was carried out to limit hospital access for patients with clear COVID-19 symptoms. Ph1 study facility access excluded vendors, minimal ancillary services, all visitors and medical monitors and auditors. We established triage checkpoint outside the facility, clinic or office, with social distancing of at least six feet apart to screen patients and visitors for COVID-19 symptoms and fever before they enter. We converted any current open infusion suite to semi-private space with at least six feet distance between patients and/or use available curtains as a barrier between patients. We moved to a virtual platform all multidisciplinary discussions.

When safety measures have been fully implemented, we dealt with logistic issues. One of the most effective measures aiming to contain the pandemic spread is social isolation, including quarantine of entire areas and travel bans [6]. These norms can pose significant challenges to patients residing far from the study centre, demanding the implementation of flexibility in performing the experimental clinical procedures. Therefore, a set of solutions have been discussed with the sponsors. Overall, optional trial procedures (e.g. biopsies) have been withdrawn. Biochemical and radiological assessments, with the permission of the sponsors, have been performed in the accredited closest facility to the patients. We locally and centrally revised all scans to guarantee the high quality of data. In our experience, scheduled visits at clinical sites have been significantly impacted for patients outside our region. For certain investigational products, such as those distributed for self-administration, we agreed with the sponsors alternative safe delivery methods. For other investigational products normally administered in a healthcare setting (intravenous or subcutaneous treatments), we guaranteed on time administration for all local patients and we delayed, within the window of treatment, for patients with difficulties in accessing the facility. We implemented telemedicine for more intense safety active monitoring of patients [7].

As a result of facing the COVID-19 pandemic, we generated a huge amount of protocol deviations, and in parallel many protocol amendments have been submitted to the ethical committee for approval. In the last 4 weeks, we have negotiated 72 ‘COVID19-related’ protocol deviations with the sponsors, of which about two-

thirds concerned the execution of examinations and imaging procedures and one-third the delay or shipment of planned treatments. For all of the deviations from the protocol rules, the safety of patients was the priority – minimising the avoidable risk of COVID-19.

Our experience suggests that pursuing the conduction of ph1 study during the pandemic is potentially feasible, if punctually dictated by safety and scientific rigour. The central dogma of any decision is to align with the global, national and local standards for social containment, as non-negotiable. The implementation of alternative processes should be consistent with the protocol to the largest possible extent, and sponsors and clinical investigators should document the reasons for any contingency measures disposed. Sponsors and clinical investigators should document how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted.

Developing a patient-centred set of safe recommendations to maintain the quality research in the pandemic is thus a priority in oncology care – whenever possible – in a framework of close cooperation between all the stakeholders involved.

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