Reply to 'Fasting in oncology: a word of caution'

Alessio Nencioni, Irene Caffa, Salvatore Cortellino and Valter D. Longo

We would like to thank Caccialanza and colleagues for their thoughtful letter on our recent Opinion article (*Nat. Rev. Cancer* **18**, 707–719 (2018))[1]. We fully agree with these authors (Fasting in oncology: a word of caution. *Nat. Rev. Cancer* https://doi.org/10.1038/s41568-018-0098-0 (2019))[2] that until larger clinical studies confirm the efficacy of fasting and fasting-mimicking diets (FMDs) in cancer therapy, these dietary regimens should only be applied as part of clinical trials. We also agree that, even though the published studies of these approaches failed to highlight severe side effects[3–6], issues of malnutrition and of sarcopenia were only partially addressed in these studies. With this in mind, and considering guidelines on nutrition in patients with cancer[7], one key end point of a clinical study of a FMD in patients with cancer that we are currently performing[8] is to monitor how FMD cycles combined with light muscular exercise affect the patient's body composition (manuscript in preparation). In our Opinion article[1], we explicitly recommended that "periodic anorexia and nutritional status assessments using gold-standard approaches should be an integral part of studies of fasting and/or FMDs in cancer and that any ensuing nutritional impairment in patients undergoing fasting and/or FMDs should be corrected". Also, we specified that "frail or malnourished patients or patients at risk of malnutrition should not be enrolled in clinical studies of fasting or FMDs".

However, we feel that there is a need to assess malnutrition and sarcopenia together with therapy-mediated anticancer effects to determine which trade-offs are acceptable and which are not. Dietitians and oncologists are often focusing on different end points and operate in 'information silos'. This approach should be replaced by a more comprehensive, integrated and clinical evidence-based nutrition and drug therapy strategy focusing on the overall therapeutic index. Notably, accepting trade-offs is an inherent part of cancer treatment as anticancer therapies can have severe and even life-threatening side effects. For example, chemotherapy-mediated immunosuppressive and cardiotoxic adverse effects have been carefully assessed and, owing to the lack of viable alternatives, considered acceptable for many patients with cancer. Thus, the goal will be to identify nutritional interventions that minimize malnourishment and sarcopenia but maximize progression-free and overall survival of patients with cancer. Considering all clinical trials on fasting or FMDs in patients with cancer so far, at least 200 patients have undergone multiple cycles of fasting or FMDs in combination with cancer treatment and there is no evidence of severe adverse events in terms of malnutrition or of weight loss. Still, should the FMD be found to promote sarcopenia or excessive weight loss in certain patients, these effects will have to be weighed against the extent to which the FMD influences cancer progression and/or adverse events of the standard therapy. Therefore, our statement, "We propose that the combination of FMDs with chemotherapy, immunotherapy or other treatments, represents a potentially promising strategy to increase treatment efficacy, prevent resistance acquisition and reduce side effects", is appropriate. Considering this strategy as "potentially promising" had the self-explanatory scope of promoting clinical trials and not introducing or even implying a new clinical standard.

Concerning what Caccialanza et al. report to be an inappropriate and premature promotion by the media of the application of fasting in patients with cancer as a medical advance[2], we agree that positive results from large randomized clinical trials should be awaited before these fasting-based interventions can be combined with standard-of-care therapies.

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A.N. and V.D.L. wrote the manuscript. I.C. and S.C. contributed to the discussion of content of the manuscript.

Competing interests
A.N. and I.C. are inventors on three patents of methods for treating cancer by FMDs that have recently been licenced to L-Nutra. V.D.L. is the founder of L-Nutra.