Reply to the letter to the editor 'Can ovarian suppression with gonadotropin releasing hormone analogs (GnRHa) preserve fertility in cancer patients?' by Rodriguez-Wallberg et al.

We thank Rodriguez-Wallberg et al. [1] for their interest in our meta-analysis of randomized studies that assessed the role of gonadotropin-releasing hormone analogs (GnRHa) as a strategy to prevent chemotherapy-induced premature ovarian failure (POF) and preserve fertility of premenopausal women with breast cancer [2].

The authors expressed their concerns on the interpretation of our results due to the lack of information on anticancer treatment administered, the heterogeneity observed among studies, the lack of comparison according to number of patients attempting to become pregnant, and the limited data in terms of disease-free survival (DFS). As we acknowledged, our meta-analysis is not based on individual patient data; hence, it was not possible to investigate the impact of type and dose of chemotherapy administered and use of adjuvant endocrine therapy. Despite the heterogeneity among studies, when restricting the analysis to the trials reporting number of patients with regular menses 1 year after the end of chemotherapy and number of those who achieved pregnancy, the results were statistically significant in favor of the use of GnRHa, with no heterogeneity. As recently reported [3], the most valid denominator for comparing pregnancy outcomes is the entire population as performed in our study, since the number of patients attempting pregnancy might be influenced by the intervention assignment and some pregnancies might occur also in women who did not report an attempt to become pregnant. Despite the limited data on DFS, we did not find any difference between patients undergoing concurrent chemotherapy and GnRHa and those receiving chemotherapy alone. In the POEMS study, a statistically significant improved DFS was observed in patients receiving concurrent GnRHa and chemotherapy [3]. These results are also supported by the excellent survival outcomes of patients enrolled in the TEXT study who received concurrent ovarian suppression and chemotherapy [4].

Rodriguez-Wallberg et al. criticized the exclusion of patients with lymphoma. The reason was that patients with lymphoma are different from those with breast cancer: they are characterized by young age at diagnosis, and some of them are candidates to receive anticancer treatments with low gonadotoxic potential (e.g. ABVD regimen). In this setting, the majority of patients resume ovarian function at the end of chemotherapy irrespective of the use of GnRHa. Long-term follow-up data of the available randomized studies in this setting are warranted to assess the potential role of GnRHa in preserving fertility and delaying age at menopause.

Rodriguez-Wallberg et al. mentioned the meta-analysis by Elgindy et al. showing no significant increase in ovarian function resumption with the use of this strategy. However, these findings should be considered with caution due to several study limitations: the inclusion of patients with different types of cancer, the use of a different definition of POF than those used in each eligible study, the possible biased weighting strategy applied, and mainly the exclusion of some randomized trials [5].

Finally, the authors suggested that GnRHa-induced gonadal suppression has proved ineffective in men. Very limited data exist on the efficacy of this strategy in men, for whom the standard strategy for fertility preservation is semen cryopreservation, a widely available, relatively cheap and not-time consuming procedure. Moreover, spermatogonia are much more sensitive to the cytotoxic effects of chemotherapy when compared with primordial oocytes and spermatogenesis is not a cyclic event, thus making recovery of gonadal function less plausible.

To conclude, a growing amount of data coming from randomized, controlled studies, suggest the efficacy of temporary ovarian suppression with GnRHa during chemotherapy to preserve both ovarian function and fertility. As recently endorsed by the National Comprehensive Cancer Network guidelines (www.nccn.org) and the 2015 St Gallen International Expert Consensus panel [6], this strategy should be offered to young premenopausal breast cancer patients interested in preserving their ovarian function following chemotherapy.

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disclosure

The authors have declared no conflicts of interest.

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Integration between oncology and palliative care: does one size fit all?

For the very first time, the article of Hui et al. sets up indicators of integration of oncology and palliative care programmes: they consider as 'major' indicators of integration the presence of a 'palliative care inpatient consultation team' and a 'palliative care outpatient clinic' [1].

The authors of the article report data from a previous survey showing how in the United States, among centres which are not designated by the National Cancer Institute—and as such, not specifically working in oncology—only 56% have a 'palliative care inpatient consultation' and 22% an 'outpatient clinic' [2].

If this is an image of how things work in a country—the United States—with an advanced health care system, may we be entitled to scale the same criteria to most other countries in the world—even if not having the same logistical standards and favourable economical frame?

The real world is not made of big hospitals, with great resources, in rich countries. On the contrary, most cancer patients are followed in small centres, many of which are located in developing countries.

Among the above-mentioned indicators, we miss the presence of 'community-based palliative care services', which are important, most of all, in small and/or remote communities, yet the authors say that few panellists work within such settings.

This supports our belief, that these indicators are designed for a 'rich' setting, faraway from the real world. Indeed, the same authors state that to meet these integration indicators we need 'proper funding', and we know this is not available in most oncology programmes in the world.

That said, we are fully convinced of the value of Hui et al. work, yet we believe that it can be introduced only in advanced health systems with great economical resources.

Besides, we hope for an expert panel determining 'basic' criteria for integration of oncology and palliative care; criteria that could help developing sustainable integration programmes, taking into account centres with limited resources and foreseeing a key role for 'community-based palliative care services'.

For this, it would be necessary to propose goals (e.g. evaluation and treatment of symptoms, continuity of care, non-abandonment at end-of-life, etc.) rather than pre-set models, so that each single centre is able to develop 'tailored' programmes to their own resources.

According to our experience, it is possible to build custom-tailored programmes for each single economical, cultural, and geographical situation, bearing in mind that, when we talk about health services, 'one size does not fit all' [3, 4].

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Reply to the letter to the editor 'Integration between oncology and palliative care: does one size fit all?' by Verna et al.

We would like to thank Verna et al. [1] for their thoughtful comments regarding our recent *Annals of Oncology* article on the 13 major and 30 minor indictors of integration of oncology and palliative care programs in hospitals with ≥100 beds [2]. They commented on the need to have indicators specific for resource-limited settings, and the importance of community-based palliative care programs.

When we first designed this study, we recognized that indicators are highly specific to the health care setting and local resources. Thus, we explicitly asked our panelists to identify indictors of integration for advanced cancer patients in hospitals with ≥100 beds [2]. Remarkably, a vast majority of the indicators were supported by our international panelists despite their diverse background representing six continents. The major indicators were endorsed by over 90% of panelists, suggesting that there may be some universal themes of integration beyond nationalities, disciplines and cultures.

The *need* for integration is independent of resource availability and further studies are needed to examine indicators of integration specific for low-resource settings. In a recent systematic review, we identified several other aspects of integration [3]. For example, the availability of opioid may be an appropriate indicator in low-resource countries, while a comprehensive home palliative