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Patient benefit rate and guarantee time bias in analysis of outcomes for gynecologic oncology patients receiving targeted treatment after somatic tumor genetic testing

We recently read the article by Somasegar et al. (2021) with great interest. The authors reported 70% of patients with next-generation sequencing (NGS) had actionable mutations and similar survival to those receiving conventional therapy, concluding that most patients with recurrent gynecologic cancer would benefit from NGS testing of their tumor.

The assessment of real-world outcomes including eligibility and benefit from NGS is an important undertaking, as highlighted in the accompanying editorial by Hinchcliff and Westin (2021). Based on the most common molecular alterations in the study and the highest-reported response rates to corresponding targeted therapies, we estimate that only 21% of gynecologic oncology patients are likely to derive benefit from NGS (Table 1). Such methods have been previously validated across all cancer types and broadly estimated at 7% across all cancer types, meaning that only a small minority are expected to benefit from genome-targeted therapy (Marquart et al., 2018; Haslam et al., 2021). If the contributions to patient benefit in recurrent gynecologic cancers are limited to molecular targets uniquely identified by tumor NGS (that is, excluding germline *BRCA* mutations and microsatellite instability which can be ascertained by gene sequencing and immunohistochemistry, respectively), we estimate NGS to confer clinical benefit to an additional 3.9% of patients only (Table 1, excluding *BRCA* mutations and microsatellite instability).

Somsegar et al. do not clarify which patients were considered a match for mTOR inhibitor therapy. While mTOR inhibitors are not currently FDA approved for a gynecologic oncology indication, National Comprehensive Cancer Network guidelines for treatment of uterine cancer do include combination everolimus/letrozole and temsirolimus as treatment options for endometrial cancer without match to a biomarker. For the purposes of calculating benefit from mTOR inhibitors as molecular matched therapy, we refer to a tumor mutational analysis of GOG-248 previously demonstrating that treatment with the mTOR inhibitor temsirolimus is associated with increased PFS (albeit with no increased response rate) in patients with endometrial cancer and *CTNNB1* mutations. Among other potential biomarkers, no association with improved PFS or response rate was observed with *PIK3CA*, *PTEN*, *PIK3R1*, or *KRAS* mutations (Myers et al., 2016). For that reason, we have only included *CTNNB1* in our calculation of benefit from molecular matched mTOR inhibitors.

Importantly, we would describe the observed lack of improvement in overall survival between patients receiving targeted therapies and those receiving chemotherapy as no clinical benefit, rather than no worsening as in the article. The similar survival reported is furthermore confounded by guarantee time bias. Guarantee time bias is introduced in survival analyses when comparison groups are defined by a classifying event—such as initiation of a targeted therapy—that occurs during the follow-up period (Giobbie-Hurder et al., 2013). Patients assigned to group 1 were defined as those who received a targeted therapy, a precondition of which was being well enough to receive a targeted therapy. This was not a condition for patients assigned to group 2, nearly half of whom (n = 20/51, 39%) declined treatment to transition to hospice. As Somasegar et al. calculated overall survival from time of diagnosis, the nonrandom classification of patients into group 1 and group 2 comparatively augments the overall survival estimates for patients in group 1. Patients in group 1 had a significantly longer time between diagnosis and somatic tumor testing than patients in group 2

Table 1

Estimated patient benefit from targeted therapies identified in Somasegar et al. Predicted benefit was calculated from the product of the percentage of patients harboring the indicated alteration and the highest-reported response rate to the matched therapy. Alteration percentages were collected from Somasegar et al. Response rates were collected from the FDA-approved package inserts for patients with the indicated aberration (for PARP inhibitors and checkpoint inhibitors) or, in the case of drugs not approved for a gynecologic oncology indication, from completed clinical trials in recurrent endometrial cancer (for mTOR inhibitors) (Ray-Coquard et al., 2013; Fleming et al., 2014; Slomovitz et al., 2015).

Molecular aberration	Patients harboring alteration, %	Matched therapy class	Highest reported response rate, % (95% CI)	**Patients predicted to benefit, %**	Median duration of response (DOR) or progression-free survival (PFS), months (95% CI)
Ovarian, fallopian tube, and primary peritoneal cancer					
BRCA1 or *BRCA2* mutation	15.6	PARP inhibitor	54 (44, 64)	**8.4**	DOR: 9.2 (6.6, 11.6)
Uterine cancer					
Microsatellite instability	15.2	Checkpoint inhibitor	57.1 (42.2, 71.2)	**8.7**	PFS: 25.7 (2.9 to not reached)
CTNNB1 mutation	12.1	mTOR inhibitor	32 (17, 49)	**3.9**	PFS: 3.0 (1.5 to 15.7)
Summed total	42.9			**21.0**	

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(40 months versus 29 months, $p = 0.024$), illustrating the magnitude of guarantee time introduced for patients classified into group 1. We note that guarantee time bias has been a well-described problem plaguing adjuvant therapy studies in other oncologic subspecialties, and suggest conditional landmark analysis as a particularly useful method to overcome bias in this setting (Newman et al., 2020).

Finally, while the authors report a "favorable toxicity profile" in the targeted therapy group, this conclusion is not clear-cut. Although small sample numbers overall underpowered the study to detect differences in side effects, some reported side effects were more common in the targeted therapy group (9 out of 25 reported effects) and treatment discontinuation due to side effects was similar in both groups (14% with targeted therapy vs. 10% with traditional therapy). This finding suggests targeted agents may have different toxicity profiles from cytotoxic agents, but not necessarily better toxicity profiles.

Overall, we laud the effort to increase available data regarding biomarker-based therapies in gynecologic cancers, but caution the conclusions drawn in regards to survival outcomes and toxicities with targeted therapies. Our calculated predicted patient benefit rate of 19.8% is better than the average expected benefit in other cancer types; however, it falls well below the 70% reported by the authors. For this reason, we should exercise caution when discussing potential clinical benefit to patients with gynecologic cancers when ordering NGS.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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