from work, child care, and transportation could also improve access to clinical trials for lower-income patients. Future research should investigate how to overcome financial barriers to clinical trial participation.

The identification of patient income level as an independent predictor of trial participation is important for multiple reasons. If income is associated with health status, then improving representativeness of lower-income patients in trials would improve the generalizability of study outcomes. Also, greater participation of lower-income patients would allow trials to be conducted more quickly, speeding the development of new treatments. Crucially, since clinical trial treatments represent the newest available treatments, access to this vital resource should be available to individuals of all income levels.

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Critical revision of the manuscript for important intellectual content: Unger, Gralow, Albain, Ramsey, Hershman.

Statistical analysis: Unger.

Obtained funding: Gralow, Ramsey.

Administrative, technical, or material support: Gralow.

Study supervision: Ramsey, Hershman.

Conflict of Interest Disclosures: None reported.

Funding/Sponsor: This work was supported by a Breast Cancer Research Foundation grant and by the National Institutes of Health, National Cancer Institute (NCI) Community Oncology Research Program Research Base grant SUGICA189974-01.

Role of the Funder/Sponsor: The funding organizations had a role in the design and conduct of the study and in the collection and management of the data but had no role in the analysis and interpretation of the data, preparation, review, or approval of the manuscript; or decision to submit for publication.


The Use of Superlatives in Cancer Research

The language used in oncology practice and research may elicit important connotations.1 Whereas most new cancer drugs afford modest benefits,2 approved drugs or those in development may be heralded as “game changers” or “breakthroughs” in the lay press. These news articles may be important sources of information to patients, the public, and investors—with a wider reach than medical journal articles. However, omission of medical context or use of inflated descriptors may lead to misunderstandings among readers.3

We sought to investigate the use of modest and superlative descriptors in contemporary news articles regarding cancer drugs. We sought to determine who uses this inflated language and what classes of drugs were most heralded.

Methods | We searched 10 superlative terms in conjunction with “cancer drug” in Google’s news search (http://news.google.com) between June 21, 2015, and June 25, 2015. Superlative terms included “breakthrough,” “game changer,” “miracle,” “cure,” “home run,” “revolutionary,” “transformative,” “life saver,” “groundbreaking,” and “marvel.” Terms were prespecified and identified through discussion.

All articles resulted were read in full by one reviewer (M.V.A.). The following information was extracted: drug described, mechanism of action, class of medication, whether the agent described had already received US Food and Drug Administration approval, whether the data described concerned human trial results or preclinical (eg, mouse or cell culture) data, and the quoted individual (physician, journalist, industry expert, or patient). An academic hematologist–oncologist (V.P.) researched mechanism of action of all drugs and coded their class as cytotoxic, targeted, immunotherapy—checkpoint inhibitor, immunotherapy—therapeutic vaccine, radiotherapy, gene therapy, or other.

Results | We found 94 news articles from 66 distinct news outlets that made 97 superlative mentions that fit our criteria, referring to 36 specific drugs, with 3 articles not naming the drug. The most common class of drugs referenced was targeted therapy (17 of 36 [47%]). Nine (25%) cytotoxic drugs were discussed, followed by 5 (14%) immunotherapy checkpoint inhibitors, 3 (8%) cancer vaccines, 1 radiotherapy, and 1 gene therapy.

Among 97 superlatives used, 39 (40%) referred to a targeted therapy, 37 (38%) referred to an immunologic checkpoint inhibitor, 10 (10%) referenced a cytotoxic drug, 5 (5%) discussed a therapeutic cancer vaccine, 3 (3%) did not name the drug, 2 (2%) referred to a radiotherapy, and 1 (1%) referred to gene therapy.

Precisely half (18 of 36) of drugs described had not received Food and Drug Administration approval (as of July 15,
Table. Frequency and Characteristics of Cancer Drugs Described With Superlatives

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Superlative Frequency, No. (%) (N = 97)</th>
<th>Superlative(s) Used (Frequency)</th>
<th>Drug Classification</th>
<th>FDA-Approved Drug(s)</th>
<th>Clinical Data?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipiilimumab and nivolumab (Yervoy-Opdivo combination)</td>
<td>20 (21)</td>
<td>Breakthrough (7), miracle (5), game changer (2), revolutionary (2), groundbreaking (1)</td>
<td>Immunotherapy—checkpoint inhibitor</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>12 (12)</td>
<td>Revolutionary (5), game changer (2), groundbreaking (2), cure (2), miracle (1)</td>
<td>Immunotherapy—checkpoint inhibitor</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Palbociclib (Ibrance)</td>
<td>10 (10)</td>
<td>Groundbreaking (6), game changer (2), revolutionary (1), miracle (1)</td>
<td>Targeted therapy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Trastuzumab emtansine (Kadcyla)</td>
<td>7 (7)</td>
<td>Revolutionary (4), miracle (3)</td>
<td>Targeted therapy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dinutuximab (Unituxin)</td>
<td>4 (4)</td>
<td>Game changer (1), groundbreaking (1), breakthrough (1), miracle (1)</td>
<td>Targeted therapy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MPDL3280A</td>
<td>3 (3)</td>
<td>Game changer (2), revolutionary (1)</td>
<td>Immunotherapy—checkpoint inhibitor</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Olaparib (Lynparza)</td>
<td>3 (3)</td>
<td>Revolutionary (2), breakthrough (1)</td>
<td>Targeted therapy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>T-VEC</td>
<td>3 (3)</td>
<td>Breakthrough (3)</td>
<td>Immunotherapy—vaccine</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Pertuzumab (Perjeta)</td>
<td>3 (3)</td>
<td>Groundbreaking (3)</td>
<td>Targeted therapy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Unnamed</td>
<td>3 (3)</td>
<td>Breakthrough (1), miracle (1), game changer (1)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Radium-223 dichloride (Alpharadin or Xofla)</td>
<td>2 (2)</td>
<td>Game changer (2)</td>
<td>Radiotherapeutic drug</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>BPM31510</td>
<td>2 (2)</td>
<td>Revolutionary (2)</td>
<td>Cytotoxic therapy</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviation: FDA, Food and Drug Administration.

* Drugs with 1 (1%) superlative: ABT-199, acelarin, ALM201, bortezomib (Velcade), brentuximab vedotin (Adcetris), Ceravizumab, docetaxel (Taxotere), doxorubicin with vinorelbine, epipodophyllotoxin (Taxol), erlotinib, erlotinib (Tarceva), ibrutinib (Imbruvica), ifosfamide, irinotecan (Camptosar), Keytruda, lenalidomide, letrozole, lenalidomide (Revlimid), nedaplatin, nivolumab (Opdivo), ONT964, PEGADIRUBICIN, protein-bound paclitaxel (Abxirane), rociletinib, TargomiRs, TRXE-O09, vemurafenib (Zelboraf), ZL105.

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Critical revision of the manuscript for important intellectual content: Abola.

Statistical analysis: Abola.

Administrative, technical, or material support: Abola.

Study supervision: Prasad.

Conflict of Interest Disclosures: None reported.


COMMENT & RESPONSE

Neoepitopes and CD3-Positive and CD8-Positive Cells in Polymerase e-Mutated and Microsatellite-Instable Endometrial Cancers

To the Editor We read with interest the Brief Report by Howitt and colleagues. Over the last few years, we have also studied the interesting subgroup of endometrial cancers (ECs) with mutation in the POLE proofreading exonuclease domain, and in particular their association with excellent prognosis, not mentioned by Howitt et al in their report.

In their study, Howitt et al claim that their analysis is the first to demonstrate increased predicted neoepitopes and numbers of CD3-positive and CD8-positive cells in POLE-mutant and microsatellite-unstable (MSI) ECs. However, in a study published earlier this year, we showed that both POLE proofreading-mutant and MSI ECs demonstrate significantly greater CD8-positive cell infiltration and higher numbers of predicted neoantigens than microsatellite-stable ECs. In this analysis, we also demonstrated that POLE-mutant and, to a lesser extent, MSI ECs display increased expression of genes encoding immune checkpoint molecules, including PD-1 and PD-L1. Furthermore, as our study included a substantially greater number of POLE-mutant tumors than that of Howitt et al (47 compared with 3 cases), we were also able to confirm the postulate of Howitt et al that the greater number of neoantigens in POLE-mutant than in MSI ECs is reflected in significantly greater CD8-positive cell infiltration.

Collectively, the small study by Howitt et al, and our earlier, more comprehensive analysis, suggest that both POLE proofreading-mutant and MSI tumors are more immunogenic than other ECs. We therefore agree with Howitt et al that these cancers may be excellent candidates for immune checkpoint inhibitor therapy, as indeed we have previously suggested. We also suggest that the striking immune response observed in POLE-proofreading mutant ECs may contribute to their favorable clinical outcome.

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Conflict of Interest Disclosures: None reported.


In Reply Our study was initially submitted in January 2015 as an abstract for the 2015 American Society of Clinical Oncology Annual Meeting and was accepted in March 2015 as an oral presentation; it was subsequently submitted to JAMA Oncology in April 2015 before the study by van Gool et al appeared online. The goal of our study was to address whether hypermutated (microsatellite-unstable [MSI]/POLE-mutant) endometrial cancers (ECs) were more immunogenic compared with microsatellite-stable (MSS) ECs, and not whether this association may account for the improved survival of POLE-mutated tumors; accordingly, no reference was made to studies reporting an association of POLE-mutated tumors with improved survival.

We would like to highlight 3 important differences between the study by van Gool et al and ours. First, our study also demonstrated that PD-1 expression is significantly increased in tumor-associated lymphocytes of MSI/POLE-mutated ECs. While van Gool et al briefly mentioned the rationale for immunotherapy with PD-1 and PD-L1 inhibitors, they evaluated PD-1 expression by RNaseq on EC samples from the Cancer Genome Atlas data set and inferred it on the basis of CD8A expression. In our study, we directly visualized the increased expression of PD-1 and CD8 by using immunohistochemical analysis on serial sections. Interestingly, van Gool et al did not find a significant difference in PD-1 expression between MSI and MSS tumors, which is in contrast to our findings using immunohistochemical analysis.

Second, we performed immunohistochemical analysis for PD-L1 expression and also described increased PD-L1 expression in intraepithelial immune cells of MSI/POLE-mutated EC compared with MSS EC but did not find significant immunohistochemical expression of PD-L1 in tumor cells (save for 1 POLE-mutated EC with strong diffuse membranous expression). Of note, response to anti–PD-L1 therapy has been shown to correlate with expression of PD-L1 in tumor-infiltrating immune cells but not in tumor cells. We suggest that immuno-