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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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 broader 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,
2015) for at least 1 indication. For 5 of 36 (14%) drugs, superlatives were used in the absence of clinical data (i.e., based solely on mouse, cell culture, and/or preclinical work). The specific drug mentioned, superlative used, and other characteristics are described in the Table.

A variety of speakers were credited with using the superlative (53 journalists [55%], 26 physicians [27%], 9 industry experts [9%], 8 patients [8%], and 1 member of US Congress [1%]). In the majority of cases (55%) the superlative was used by the author of the article without any other attribution.

### Discussion

Our investigation finds that the use of superlatives to describe approved (50%) and nonapproved cancer drugs (50%) is common. Superlatives are used for all types of medications, including those, such as therapeutic cancer vaccines, which historically have low response rates and drugs that have not yet shown overall survival benefits (e.g., palbociclib). Of concern, 14% of drugs were praised without any human data.

Use of superlatives reflects the current “hot fields” of cancer research. Although immunologic checkpoint inhibitors made up only 14% of the unique drugs mentioned, they accounted for 38% of all superlatives. Targeted therapies were the most common drugs mentioned, and they received the most superlatives. One limitation to our work is that it was conducted 3 weeks after the 2015 American Society of Clinical Oncology conference; as such, it may not reflect the use of these terms at other times, as well as in other years.

A range of speakers used superlatives, but the majority were journalists (55%), who may not have the expertise to identify the most promising medical therapies, or what magnitude of benefit warrants a superlative. The use of superlatives is common in cancer research news articles. Some of this use may be questioned.

### Table. Frequency and Characteristics of Cancer Drugs Described With Superlatives

<table>
<thead>
<tr>
<th>Drug</th>
<th>Superlative Frequency, No. (%)</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>Ipilimumab and nivolumab (Yervoy-Opdivo combination)</td>
<td>20 (21)</td>
<td>Breakthrough (7), miracle (5), game changer (5), 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 (%) superlative: ABT-199, acelarim, ALM201, bortezomib (Velcade), brentuximab vedotin (Adcetris), Cimavax, docetaxel (Taxotere), doxorubicin with vinorelbine, epizida (Chidamide), eriburin (Halaven), figitumumab, GI T-28, ibritinib (Imbruvica), ipilimumab, NeuVax, nivolumab (Opdivo), OH4 compound, OTS964, PENAQ, protein-bound paclitaxel (Abraxane), rociletinib, TargomiRs, TRXE-O09, vemurafenib (Zelboraf), ZL105.

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*Author Contributions:* Mr Abola had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Both authors. Acquisition, analysis, or interpretation of data: Both authors. Drafting of the manuscript: Both authors.
COMMENT & RESPONSE

Neoeptopes and CD3-Positive and CD8-Positive Cells in Polymerase ε-Mutated and Microsatellite-Instable Endometrial Cancers

To the Editor We read with interest the Brief Report by Howitt and colleagues.1 Over the last few years, we have also studied the interesting subgroup of endometrial cancers (ECs) with mutation in the POLE proofreading exonuclease domain,2,3 and in particular their association with excellent prognosis,3,4 not mentioned by Howitt et al1 in their report.

In their study, Howitt et al1 claim that their analysis is the first to demonstrate increased predicted neoeptopes 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,2 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 PDCD1 and PD-L1. Furthermore, as our study included a substantially greater number of POLE-mutant tumors than that of Howitt et al1 (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.5

Collectively, the small study by Howitt et al1 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.6 We also suggest that the striking immune response observed in POLE-proofreading mutant ECs may contribute to their favorable clinical outcome.

In Reply Our study1 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 al2 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 al2 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 al2 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 CDA 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 al2 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.3 We suggest that immunom-