blood

To the editor:

Published abstracts at international meetings often over- or underestimate the initial response rate

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Abstracts presented in meetings have a significant effect on decision-making and medical practice. Furthermore, these data may be incorporated in large meta-analyses and systematic reviews and influence therapeutic guidelines.

Considerable pressure is placed on rapid dissemination of response data in clinical trials. Early publication of data is fraught with hazards, as survival outcomes change with time and may not be mature before 3 years.[1] However, initial response rates may be expected to be final at abstract presentation, given the absence of time-dependent variables that can affect the outcome. A comprehensive retrospective analysis was performed to test this hypothesis.

Novel therapeutic agents covering diverse hematological malignancies between 2000 and 2016 were chosen. Then, clinical trials assessing these agents were searched using Medline, PubMed, and Google Scholar databases with the aim of selecting the articles most adjacent to the first clinical report of these drugs. The journals searched, which were determined to be the most likely to report most of the important clinical trials, were limited to the *New England Journal of Medicine*, *Blood*, the *Journal of Clinical Oncology*, *Leukemia*, the *Lancet*, and *Haematologica*. Manuscripts published in these journals were obtained and searched for the most initial abstract presentation at annual meetings of the American Society of Hematology, European Hematology Association, and American Society of Clinical Oncology. Searches were obtained by the website or with help from the journal staff for years before abstracts were digitized. Some articles addressed the specific conference meeting presented in the article, making the search more convenient. Other abstracts were searched in meetings, using the author name or keywords. When an abstract was presented more than once, the earliest described abstract was included in this analysis.

We searched for a discrepancy in response rates of, arbitrarily, at least 10% between abstracts and published manuscripts.

Similarly, we used an 18-month interval between abstract and publication as a cutoff point, on the assumption that a shorter interval would represent the "final" version submitted for publication.

Three thousand papers were reviewed. Of these 3000 articles, review papers, basic science, case reports, and letters were excluded. Three hundred clinical trials were identified and further searched for presentation at 1 of the aforementioned meetings. Ninety-nine studies were identified to have a corresponding abstract (supplemental Table 1, available on the *Blood* Web site). Among the diseases assessed, multiple myeloma comprised 27.3% of trials, followed by non-Hodgkin lymphoma and acute myeloid leukemia in 25.3% and 17.2%, respectively (Table 1).

Eighty-six percent of the abstracts were presented at the American Society of Hematology meetings. Fifty-one abstracts (52%) were eventually published as a full paper in *Blood*, 25% were published in the *Journal of Clinical Oncology*, and 9% were published in the *Lancet* (Table 1).

Fifty-nine studies had discrepant results. Forty-two studies (42.4%) had a discrepancy of 10% or more (Table 2), regardless of the time interval between paper and abstract. Twenty-three (55%) of 42 studies reported an increased response in the publication. Nineteen (45%) of 42 (19.2% of all identified studies) reported a decreased response in the publication. In 30 (71.4%) of 42 cases in which there was a discrepancy of 10% or more, the time interval between abstract and manuscript was 18 months or longer. Discrepancies were less common in phase 3 studies, being mainly demonstrated in phase 1 and 2 studies. In most studies, multiple centers were involved (69%), and among studies with discrepancy, 35 (59%) of 59 were multicenter. Large national and international study groups participated in 11% of all studies and 11.8% of studies with discrepancy. Pharma-sponsored studies were noted in 52% and 44% of all studies and among discrepant studies, respectively.

The most prominent reason for variation in data was additional patients collected by the time the article was published (49.2%).

Presentation of abstracts of clinical trials is crucial for disseminating information and for the planning of subsequent clinical investigations. A common assumption is that initial response data, which are neither time-dependent nor projected, provide reliable information, allowing for the further design of trials. The data provided herein suggest that in more than 40% of cases, a significant discrepancy exists between data reported at initial abstract and subsequent manuscript publication. If one excludes studies from large established trial groups, the discrepancy is still greater (data not shown). Although in some cases this was associated with an increasing patient number as the study progressed, discrepancies also frequently occur when the number of patients is not materially different. This may reflect a somewhat hasty presentation, possibly lacking rigorous review, either local or central. On other occasions, particularly where the initial abstract data were an underestimate, this may be associated with a subtle change in the eligibility criteria to enhance accrual.

Toma et al reviewed abstracts presenting randomized controlled trials of the American College of Cardiology scientific meetings and compared them with full-length publications.[2] Changes in the estimate of primary outcome occurred commonly and were demonstrated in 41% (60/148) of published articles, with a mean change in effect of 0.44 SDs.

Similarly, differences were found in 30 of 51 pairs of abstracts presented in the Interscience Conference on Antimicrobial Agents and Chemotherapy vs the published articles.[3] Indeed, time to publication was mostly associated with this inaccuracy. To the best of our knowledge, this description is in line with previous reports in other medical fields, as described earlier, and has not been looked at in the

Table 1. Basic demographics

		Response			
	Total, n = 99 (%)	Unchanged (n = 40)	Increased (n = 29)	Decrease (n = 30)	Discrepancy, n = 59 (%)
Disease					
AML	17 (17.2)	10	4	3	7 (11.8)
ALL	5 (5)	2	1	2	3 (5.1)
CML	2 (2)	0	2	0	2 (3.4)
CLL	15 (15.2)	6	5	4	9 (15.3)
NHL	25 (25.3)	11	7	7	14 (23.7)
HL	5 (5)	1	2	2	4 (6.8)
MM	27 (27.3)	10	7	10	17 (28.8)
Amyloidosis	1 (1)	0	1	0	1 (1.7)
Myelofibrosis	1 (1)	0	0	1	1 (1.7)
WM	1 (1)	0	0	1	1 (1.7)
Study type					
Phase 1	10 (10)	4	2	4	6 (10.2)
Phase 2	74 (75)	23	27	24	51 (86.4)
Phase 3	15 (15)	13	0	2	2 (3.4)
Centers involved					
Single	31 (31)	7	12	12	24 (41)
Multi	68 (69)	33	17	18	35 (59)
National/international study groups	11 (11)	4	3	4	7 (11.8)
Pharma-sponsored	52 (52)	26	11	15	26 (44)
Meeting					
ASH	85 (86)	34	26	25	51 (86.4)
ASCO	13 (13)	6	3	4	7 (11.9)
EHA	1 (1)	0	0	1	1 (1.7)
Journal					
Blood	51 (52)	20	13	18	31 (52.5)
NEJM	7 (7)	3	1	3	4 (6.8)
Lancet	9 (9)	6	2	1	3 (5.1)
JCO	25 (25)	9	10	6	16 (27.1)
Haematologica	5 (5)	1	2	2	4 (6.8)
Leukemia	2 (2)	1	1	0	1 (1.7)

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; EHA, European Hematology Association; HL, Hodgkin lymphoma; *JCO*, *Journal of Clinical Oncology*; MM, multiple myeloma; *NEJM*, *New England Journal of Medicine*; NHL, non-Hodgkin lymphoma; WM, Waldenstrom macroglobulinemia.

hematology field. Walter et al reviewed characteristics of phase 2 trials in AML.[4] Major problems were identified, with special consideration of absence of control group, patient heterogeneity, and selection bias. This emphasizes the value of a final and complete analysis of data with final recruitment of patients.

There are several limitations to this work. First, several parameters were defined arbitrarily, such as 10% discrepancy and 18-month interval. Obviously, these variables could affect the results of these findings, yet it seems probable that these discrepancies could be significant when decisions regarding proceeding to advanced-phase clinical trials are made. Second, a comprehensive statistical analysis was not provided here, and we recognize the added value of this, as well as sensitivity analysis and a larger study cohort. Third, not all hematology-related journals were included in this analysis, with some highly prestigious and high-impact-factor journals missing. Fourth, older studies (before 2000) were not included because of difficulty in obtaining these abstracts using journal websites.

Table 2. Analysis of trends

		Response		
	Total (n = 99)	Unchanged (n = 40)	Increased (n = 29)	Decrease (n = 30)
Discrepancy of ≥ 10%	42*	NR	23	19
Interval of more than 18 mo	51†	11	17	23
Possible explanation for the change				
Additional patients	29	NR	12	17
Increase in evaluable patients	12	NR	7	5
Unexplained	14	NR	9	5
Other	4	NR	1	3

*Studies with discrepancy irrespective of the time interval.

†Studies with time interval greater than 18 months, irrespective of presence of discrepancy.

NR, not relevant.

There is clearly a need for a broader and more extensive review of data to be followed to determine the approach to presented abstracts in meetings.

These data suggest that initial response data presented in abstracts at international meetings need to be cautiously interpreted, as the outcome may change with time, leading to either an over- or an underestimation of the outcome. Only peer-reviewed publications may be relied on to provide the definitive report of the outcome.

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To the editor:

Brentuximab vedotin in relapsed primary mediastinal large B-cell lymphoma: results from a phase 2 clinical trial

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Primary mediastinal B cell lymphoma (PMBCL) is a rather infrequent aggressive lymphoma, putatively arising from a transformed thymic B cell. It accounts for <5% of all non-Hodgkin lymphomas and typically affects adolescents and young women in their third or fourth decade of life.[1] PMBCL often should be regarded as a hematological emergency and promptly treated: the initial treatment decision is crucial for the management of this disease.

PMBCL has been recognized as a subtype of diffuse large B-cell lymphoma (DLBCL) since 1994, and it has been regarded as a specific clinical and biological entity since 2001 per World Health Organization classification. Apart from its peculiar clinical presentation and pathological features, PMBCL also displays a unique molecular fingerprint, which clearly distinguishes it from the other DLBCLs and partly overlaps with the molecular profile of nodular sclerosis Hodgkin disease (HD, ie at least one-third of its genes, abnormalities on chromosome 9p and, although weaker, the CD30 expression).[2-5]

Relapse tends to occur early during the posttreatment follow-up, mostly within the first 18 months, involving ~15% to 20% of patients (half of the cases are refractory). Disease at relapse generally behaves aggressively: it may remain confined to the mediastinum or spread to subdiaphragmatic organs. Outcomes for patients with relapsed or refractory PMBCL are generally poorer than those observed for a matched population of DLBCL patients. Overall survival (OS) at 2 years after the first relapse is just half of that seen for DLBCL, even when appropriate salvage treatments (eg, platinum-based or other intensive regimens) and autologous stem cell transplantation (ASCT) are timely applied.[6,7] In addition, adding rituximab to first-line treatment improves outcomes.[8,9]

High-dose treatment and ASCT, however, can influence prognosis, mostly in patients who had partial response (PR) before ASCT: a recent retrospective study from Japan documented a significantly higher OS for transplanted versus not-transplanted patients (67% and 31%, respectively),[10] and a chance of cure can be observed in 40% to 80% of patients with disease that favorably responds to salvage treatment, according to different series.[11-14] However, ~15% of patients with refractory disease remain free of progression after ASCT.[6,11]

Brentuximab vedotin (BV) is a potent anti-CD30 antibody drug conjugate that has been approved in relapsed/refractory HD after ASCT and anaplastic large-cell lymphoma (ALCL). Beyond these consolidated indications, BV has been and is being tested in different settings and for different hematologic diseases with promising results. The CD30 antigen is present in the majority of cases of PMBCL (80%), although it is expressed heterogeneously.[1,5] A recently published phase II trial of BV in patients with relapsed/refractory DLBCL also included 6 patients with PMBCL: a 17% overall response rate (ORR) was observed, and half of the patients maintained disease stability. The responses did not correlate with the quantitative CD30 expression on tumor cells.[15]

Based on these premises, a single-arm, open-label, multicenter, phase II clinical trial evaluating the efficacy and safety of BV as a single agent in patients with relapsed/refractory histologically confirmed $CD30^+$ PMLBCL was conceived and conducted by the Italian Lymphoma Foundation. The study was approved by the institutional review board and the ethical committees and has been performed in accordance with the ethical standards as laid out in the Declaration of Helsinki (EudraCT number: 2012-000735-27, NCT02423291). All patients provided written informed consent.

BV was administered at a dose of 1.8 mg per kg as a single IV infusion on day 1 of each 21-day cycle. Patients who achieved stable disease (SD) or better as assessed by the investigator should receive a minimum of 8, but not >16 cycles of study treatment. Measures of anticancer activity were assessed by using the revised response criteria for malignant lymphoma.[16] Dedicated computed tomography scans were scheduled at baseline and at cycles 2, 4, 7, 10, 13, and 16, and positron emission tomography scans were done at baseline and at cycles 4 and 7. The severity of adverse events (AEs) was graded per the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm). The primary endpoint was ORR;