## Title

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Current Perspective

# The iceberg plot, improving the visualisation of therapy response in oncology in the era of sequence-directed therapy

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Graphical representations in oncology;
Statistics in oncology;
Swimmer plot;
Spider plot;
Waterfall plot

**Abstract** Modern clinical cancer research increasingly relies on the visual communication of complex response and treatment sequencing data. Graphical representations used in oncology currently fail to provide adequate information on any prior treatment(s) responses, focussing on current treatment effects in isolation. We have developed a new graphical illustration, the 'iceberg plot,' to allow improved comparison of prior treatment response with current therapy.

To demonstrate the potential clinical utility of this new graphical representation, we have performed an independent reanalysis of a clinical study trialling sequence-directed therapy. In this example, prior therapy responses are contrasted with current treatment response, with further validation using the 'Von Hoff' criteria to assess for exceptional response. This example demonstrates the versatility and clinical utility of the 'iceberg plot,' showing what was previously hidden and provides improved visualisation of prior and current treatment responses together.


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## 1. Introduction

Visualisation of data enables rapid interpretation of complex information and is fundamental to scientific research. In oncology, frequently used graphs include the Kaplan–Meier plot to allow comparison of time to event outcomes between groups, and waterfall, swimmer, and spider plots to display tumour and clinical response changes for individuals receiving therapy [1]. Although these plots provide useful data on current therapy response, they provide limited or no information on responses or stable disease (SD) to prior treatment(s). As the number of anticancer treatments continues to increase, effective sequencing of therapies is becoming more significant across many tumour types [2–4]. Therefore, new graphical representation may help to better appraise prior treatment responses, thus providing context to the potential efficacy of new therapies.

We propose a new graph, coined the 'iceberg plot,' to facilitate easier comparison of prior therapy response with new treatments. To demonstrate the potential utility of this new graphical representation, we have performed a reanalysis of the study by Cobain et al., investigating the clinical benefit of patients with advanced or metastatic solid cancers derived from genomic profiling and sequence-directed therapy (SDT) in comparison to prior therapy response [5].

## 2. Methods

In the study by Cobain et al., among the 1138 included patients, we focused on the 132 (11.6%) patients who received SDT owing to the detection of at least 1 potentially actionable genomic alteration. Using information available within the article (including supplementary material) and, we recapitulated each patient's history by using the unique Mi-Oncseq (Michigan Oncology Sequencing Program) subject identification code [5]. Data were available for 125/132 (94%) patients. Comparative analysis was undertaken to determine the progression-free survival (PFS) of prior therapy lines (if applicable) to the PFS of SDT for each patient. Furthermore, we applied the Von Hoff criterion, which defines molecular profiling or SDT to be of clinical benefit for individual patients if the PFS ratio (PFS on SDT/PFS on prior therapy) is greater than 1.3 to further evaluate therapeutic response and define exceptional responders [6].

[1] See Supplementary Appendix for methodology on construction of iceberg plot.

## 3. Results

We recapitulated the records for 125 (94%) patients receiving SDT in this study and report the first use of the iceberg plot (Fig. 1; Supplementary Appendix [1]). One hundred and two (81.6%) patients had received prior non-SDT therapy before initiating SDT. The median PFS for SDT for treatment-naïve patients was 8.3 months (Interquartile range (IQR): 2.8–8.7) compared with 3.4 months (IQR: 1.4–7.7) for patients who had been receiving prior non-SDT therapy. The authors identified 26 (19.7%) patients as exceptional responders (defined as PFS of >12 months on SDT) including three complete responses (CRs), 14 partial responses (PRs) and nine SDs. Using eligibility for the National Cancer Institute Exceptional Responder Initiative would deem only 17 (13.6%) patients suitable for consideration (includes additional stringent criteria) based on disease response (CR or PR) [7]. The more stringent Von Hoff criterion identifies only 2 (1.5%) patients meeting this criterion for an exceptional response and is shown in Fig. 2.

## 4. Discussion

Understanding response(s) or duration of stable disease to prior therapy is critical to assess the potential benefit of new oncology treatments. Present graphical representations are unsatisfactory. We demonstrate the clinical utility of the iceberg plot (Fig. 1) in this reanalysis of the study by Cobain et al. showing that SDT is underperforming prior response to non-SDT in a significant number of patients. To validate this observation, we have shown that only a low proportion of cases meet the Von Hoff criteria for exceptional response (Fig. 2), demonstrating the usefulness and practicality of the iceberg plot (Fig. 1) as a new data visualisation tool.

This study has limitations which merit consideration. Not having access to full data-limited analysis, only being able to reconstruct 125 patient records. Five Mi-Oncseq codes were repeated, potentially representing patients who went on to successive lines of SDT, however is difficult to fully elucidate and have been included as separate patients. Furthermore, duration on non-SDT was calculated using time between diagnosis and enrolment, this could potentially overestimate this duration, reducing the number of patients meeting the Von Hoff criteria.

Modern clinical cancer research increasingly relies on the visual communication of complex response and treatment sequencing data, including the use of SDT. This requires novel methods of graphical representations to better conceptualise therapy response. The iceberg plot, showing what was previously hidden below the line, provides improved visualisation of prior and current treatment responses. Further validation, such as applying the Von Hoff criteria, will be valuable in

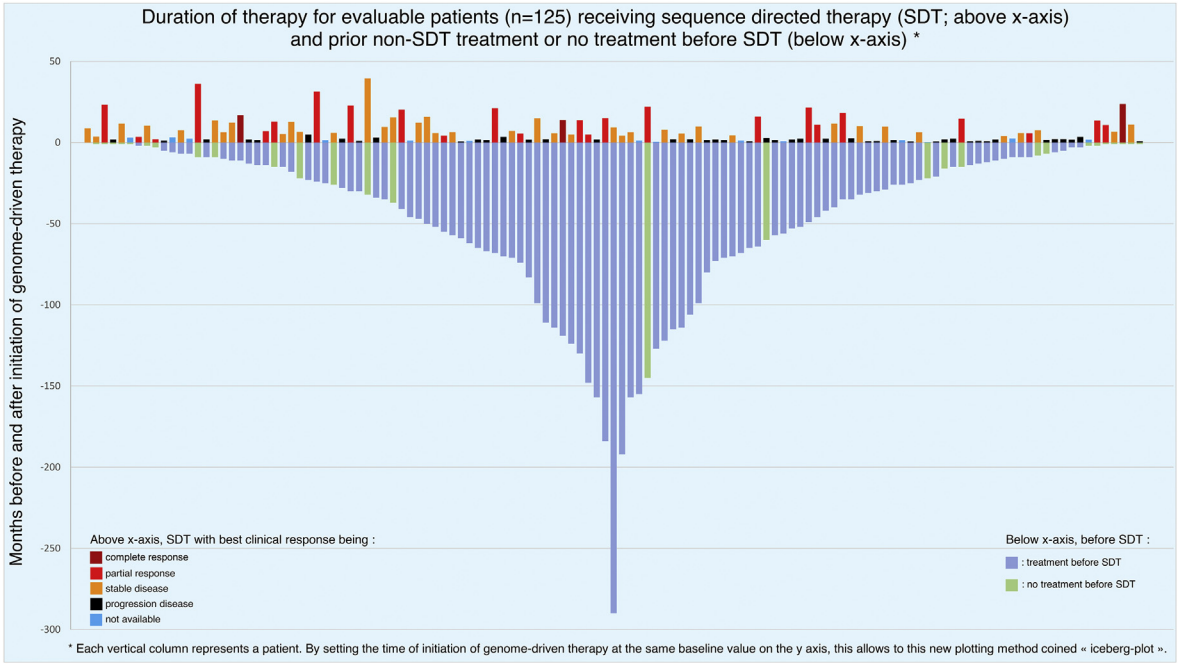


Fig. 1. Duration of therapy for evaluable patients (n = 125) receiving sequence directed therapy (SDT; above x-axis) and prior non-SDT or no treatment before SDT (below x-axis). Each vertical column represents a patient. By setting the time of initiation of sequence directed therapy at the same baseline value on the y axis, this allows a new plotting method, coined the 'iceberg plot'.

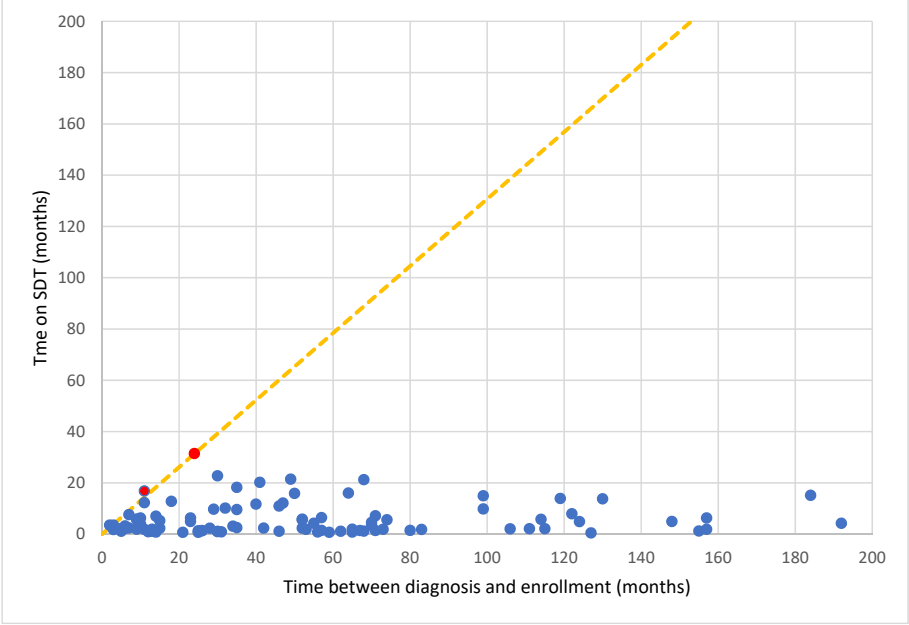


Fig. 2. Comparison of time on SDT and time between diagnosis and enrolment in patients receiving prior systemic anti-cancer therapy prior to SDT. Yellow line represents Von Hoff line (above line meets criteria); Red points (n = 2*) represent individual patients meeting the Von Hoff criteria, and blue points (n = 95*) are those who do not; *This graph does not include patients who did not receive any prior therapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

proving the clinical utility of this new graphical representation.

### Author contributions

Design and conduct of the study: Lythgoe and Prasad.

Original concept, design and terminology for iceberg plot: Olivier.

Collection, management, analysis and interpretation of the data: All authors.

Preparation, review or approval of the article: All authors.

Decision to submit the article for publication: All Authors.

### Access to data and data analysis

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and have included this in the Acknowledgement section of the article.

### Originality of content

The authors verify that all information and materials in the article are original.

### Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Vinay Prasad reports research funding from Arnold Ventures; royalties from Johns Hopkins Press, Medscape and MedPage; consulting fees from UnitedHealthcare; speaking fees from Evicore and New Century Health; and Plenary Session Podcast has Patreon backers. All other authors have no financial nor non-financial conflicts of interest to report.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.09.034.

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