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Original Research

The Fast Real-time Assessment of Combination Therapies in Immuno-ONcology (FRACTION) program: innovative, high-throughput clinical screening of immunotherapies

Katy L. Simonsen [a,*,1], Paula M. Fracasso [b,1], Steven H. Bernstein [c,2], Megan Wind-Rotolo [d], Manish Gupta [e,2], Adriana Comprelli [f], Timothy P. Reilly [b], Jim Cassidy [g,2]

[a] *Global Biometric Sciences – Oncology, Bristol-Myers Squibb, Princeton, NJ, USA*
[b] *Oncology Development, Bristol-Myers Squibb, Princeton, NJ, USA*
[c] *Translational Sciences, Bristol-Myers Squibb, Princeton, NJ, USA*
[d] *Precision Medicine, Bristol-Myers Squibb, Princeton, NJ, USA*
[e] *Clinical Pharmacology and Pharmacometrics – Oncology, Bristol-Myers Squibb, Princeton, NJ, USA*
[f] *Oncology Clinical Operations Strategy, Bristol-Myers Squibb, Princeton, NJ, USA*
[g] *Exploratory Clinical and Translational Research – Early Oncology Development, Bristol-Myers Squibb, Princeton, NJ, USA*

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Abstract ***Background:*** The unprecedented success of immuno-oncology (I-O) agents targeting the cytotoxic T lymphocyte–associated antigen 4 and programmed death-1/programmed death-ligand 1 pathways has stimulated the rapid development of other I-O agents against novel immune targets. Bristol-Myers Squibb has designed a novel phase II platform trial, the Fast Real-time Assessment of Combination Therapies in Immuno-ONcology (FRACTION) Program, to efficiently identify promising combinations for patients with specific malignancies. The concept and study design of the FRACTION Program—currently ongoing in patients with advanced non-small-cell lung cancer (FRACTION-Lung), gastric cancer (FRACTION-Gastric Cancer) and renal cell carcinoma (FRACTION-RCC)—are described.

* *Corresponding author*: Global Biometric Sciences – Oncology, Bristol-Myers Squibb, PO Box 4000, Princeton, NJ, 08543, USA.
E-mail addresses: katy.simonsen@bms.com (K.L. Simonsen), Paula.Fracasso@bms.com (P.M. Fracasso), sbernstein59@gmail.com (S.H. Bernstein), Megan.Windrotolo@bms.com (M. Wind-Rotolo), mangumama@gmail.com (M. Gupta), Adriana.Comprelli@bms.com (A. Comprelli), Timothy.Reilly@bms.com (T.P. Reilly), jcassidy@celgene.com (J. Cassidy).
[1] Co-lead authors. [2] At the time the work was conducted, these authors were employees at Bristol-Myers Squibb.

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Methods: The FRACTION Program comprises open-label, phase II studies that use adaptive randomisation designs with rolling combination regimens. Master Protocols provide the overall study design framework, whereas Sub-Protocols introduced over time provide details on specific I-O combination therapies to which patients may be randomised. In a Master Protocol, patients are enrolled into different Study Tracks based on characteristics such as prior I-O therapy experience. Patients who progress may be rerandomised to other combination regimens from any ongoing Sub-Protocol. Primary objectives are to assess objective response rate, median duration of response and progression-free survival rate at 24 weeks; the secondary objective is to investigate safety and tolerability. Biomarker collection before and on treatment will facilitate identification of patient subsets who benefit most from each therapy.
Conclusions: The FRACTION Program allows for the evaluation of multiple I-O combinations through individual studies for specific tumours using an adaptive trial design and continuous enrolment.

1. Introduction

Immune checkpoints are directly or indirectly dysregulated in tumour microenvironments of many cancers, leading to evasion of antitumour immunity [1,2]. Manipulation of immune checkpoints to reverse suppression of antitumour immune responses has improved survival across a range of different tumour types [3–6]. Nivolumab, a fully human IgG4 monoclonal antibody (mAb), is one such agent that targets the programmed death-1 (PD-1) signalling pathway to inhibit peripheral immune tolerance and to promote or restore antitumour immunity. An overall survival (OS) advantage or clinical benefit has been demonstrated with nivolumab compared with former standard-of-care therapies in melanoma, non-small-cell lung cancer (NSCLC), Hodgkin lymphoma, squamous cell carcinoma of the head and neck, renal cell carcinoma (RCC) and advanced urothelial, gastric, colorectal (microsatellite instability high or mismatch repair deficient) and hepatocellular carcinomas [4,7–12].

Although some patients who are treated with single agent I-O therapy may achieve durable responses that translate into long-term clinical benefit, many will not respond. Combination therapies may improve treatment outcomes relative to monotherapies because of their additive or synergistic effects [13]. In metastatic melanoma, nivolumab is approved in combination with ipilimumab—a fully human IgG1 mAb antagonist of cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) [7]. Nivolumab in combination with ipilimumab provided an objective response rate (ORR) of 58%, whereas respective ORRs of 44% and 19% were observed when these checkpoint inhibitors were used as monotherapies [14]. The success of combination therapy with nivolumab and ipilimumab in melanoma suggests that other combination approaches for modulating immunosuppression may also be applicable to other malignancies (Table 1) [15–17].

1.1. The FRACTION concept

Beyond PD-1 and CTLA-4 blockade therapies, a rapidly growing number of novel I-O agents are in early development, supported by preclinical antitumour activity, including lymphocyte-activated gene 3 (LAG-3), 4-1BB (CD137), killer immunoglobulin-like receptor, OX40 and glucocorticoid-induced tumour necrosis factor receptor [18–21]. The number of new I-O agents in development has increased so rapidly that it is no longer efficient to evaluate all possible combinations in traditional independent phase II studies; therefore, new approaches are needed. Several nontraditional oncology trial designs incorporate a ‘master’ protocol, which refers to a framework in which multiple parallel drug studies occur under an overarching protocol rather than several independent trials in defined cohorts [22,23]. Basket, umbrella and platform trials are examples of

Table 1
Objective responses with nivolumab monotherapy or combination therapy with nivolumab and ipilimumab.

Tumour type	Trial[a]	ORR	
		Nivolumab monotherapy	Nivolumab + ipilimumab
NSCLC	CheckMate 012 [15,37]	23%	47%[b]
Gastric, gastroesophageal junction and oesophageal cancer	CheckMate 032 [16]	12%	24%[c]
Metastatic RCC	CheckMate 025 [17,38]	25%	40%[d]

[a] Given these preliminary results, confirmatory, randomised phase III studies in advanced NSCLC, gastric cancer and RCC are ongoing (CheckMate 227, CheckMate 649 and CheckMate 214, respectively).
[b] Nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 12 weeks.
[c] Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks.
[d] Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks.

trial designs that use master protocols [22–25]. For example, basket trials (eg, NCI-MATCH) [26,27] provide one treatment to patients across many different tumours that have a specific abnormality, whereas umbrella trials (eg, LUNG-MAP) [28] provide several different treatments to patients with a certain tumour type. Platform trials (eg, BATTLE and I-SPY 2) [24,25] provide several different treatments to patients with a certain tumour type, who enter or leave the study on the basis of a decision algorithm.

The Fast Real-time Assessment of Combination Therapies in Immuno-ONcology (FRACTION) Program is a novel phase II platform study, designed to rapidly evaluate new combinations of I-O and targeted therapies. A key feature of the FRACTION Program is that new combination regimens are added to the ongoing study as they become available, whereas ineffective regimens are withdrawn. In addition, patients who do not have a response to an assigned I-O combination regimen will have the option to be re-randomised to new regimens. Continuous enrolment over time will allow early access to investigational therapies for patients who have an urgent need for additional treatment options.

2. The FRACTION design framework

After a typical phase I evaluation has identified a safe dose, establishing distinct, independent phase II trials for every combination therapy is relatively inefficient. Individual phase II studies typically require a 'start-up' time with site visits, contract negotiations and scientific and ethics committee approvals and an 'activation' time as investigators and personnel become familiar with the protocol [23]. Control treatment arms, if used, may also be duplicated across a large number of studies, which is inefficient in terms of patient accrual. Building on other innovative trial designs, the FRACTION Program evaluates combination therapies for cancer in an operationally agile and efficient way within a single trial, allowing evaluation of multiple therapies for patients. In contrast with typical phase II studies focused on the potential benefit of a single new treatment regimen, FRACTION studies are aimed at determining which combinations of therapies are the most promising from among a large number of available therapeutic agents.

The rolling nature of the FRACTION Program design allows new combinations to be added to each study as they become available. The safety, dose, schedule and preliminary antitumour activity of new combinations will be determined separately in prior phase I studies. Combination treatment arms in FRACTION studies that demonstrate futility will be terminated early, whereas those arms that meet early efficacy criteria will enrol additional patients to obtain more precise estimates of treatment effect [29]. Streamlined evaluation of FRACTION regimens will reduce the time and number of patients needed to identify potentially beneficial regimens that merit advancing to phase II/III registrational trials. The Master Protocol for each FRACTION tumour type designates multiple "Study Tracks," thereby allowing patient subgroups within an indication to be randomised and assessed independently (eg, by exposure to prior I-O or other therapies, programmed death-ligand 1 [PD-L1] expression level, histopathology or other biomarker assessments or disease characteristics; Fig. 1). Multiple Sub-Protocols added over time will define different combination therapies to be investigated.

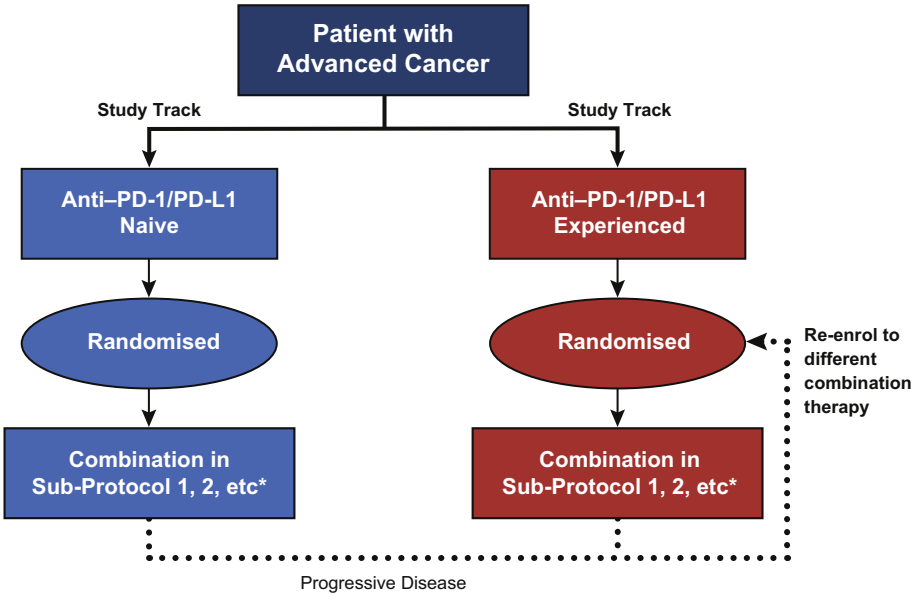

Fig. 1. FRACTION study design. * Patients will be randomised to all possible combinations open at the time of enrolment. Patients will be considered I-O experienced if they previously received ≥4 weeks of anti–PD-1, anti–PD-L1 or anti–CTLA-4 therapy.

2.1. FRACTION Master Protocols and Sub-Protocols

For each of the tumour-specific FRACTION studies, the Master Protocol describes the study objectives, design, duration, inclusion and exclusion criteria, time and event evaluations for screening and follow-up phases, biomarker plan and rationale, statistical considerations and end-points. Patient assignment to Study Tracks based on stratification factors, such as prior exposure to anti–PD-1/PD-L1 therapy or tumour PD-L1 status (if applicable), is also defined. Master Protocol–defined primary end-points for the FRACTION studies are ORR, median duration of response (DOR) and progression-free survival (PFS) rate based on Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 criteria at week 24 of each study regimen. Sample sizes, criteria to discontinue or expand treatment arms and any other aspects common to all treatments are also detailed in the Master Protocol.

The Sub-Protocols provide details on the I-O combination therapies to which patients may be randomised, including background, preclinical and clinical rationale for the combination, preclinical toxicology and clinical safety, drug dose and administration, adverse event (AE) and dosing modifications and time and event evaluations for the treatment phase. When additional combination therapies have sufficient safety data and scientific rationale (from prior phase I trials) to enter FRACTION, they will be introduced via a new Sub-Protocol.

2.2. Biomarkers and other exploratory end-points

Owing to the diverse range of oncogenic drivers and aetiologies within tumour types, patient (sub)populations achieve different responses to therapies; therefore, an exploratory objective of the FRACTION studies is to evaluate biomarkers in tumour tissue and peripheral blood to identify potential predictors of efficacy and/or safety, to investigate mechanisms of resistance and to help inform mechanisms of action for different combination regimens (Fig. 2). Additional exploratory objectives include the assessment of pharmacokinetics, immunogenicity and patient-reported outcomes for disease-related symptom improvement, health status and quality of life.

2.2.1. Identify biomarkers predictive of efficacy and/or safety

A mandatory fresh tumour biopsy will be collected at screening, during treatment and at the end of treatment or progression. Analysis of tumour tissue will include immunohistochemical approaches for the evaluation of infiltrating immune cells as well as determination of the abundance and location of immunoregulatory proteins present on tumour and immune cells. Whole-exome sequencing to quantify tumour mutation burden (including the presence of neo-antigens) and to understand relationships between clinical response and driver mutations or alterations in critical signalling pathways will be performed. RNA sequencing will be completed using tumour tissue, and exploratory analysis to identify gene expression profiles associated with response will be performed. In addition, the interferon gamma gene signature and other gene signatures that may include immunoregulatory genes associated with tumour cells or tumour-infiltrating lymphocytes will be investigated. These analyses may lead to the identification of unique baseline or on treatment expression signatures that could be useful for identifying predictive markers of response. Peripheral blood markers that will be evaluated for their association with response (and potentially safety) include multiparameter flow cytometry evaluated at baseline and during treatment to measure frequency of cell populations and the functional/activation status of immune-effector cells. Cytokines, chemokines and soluble receptors/proteins in serum will also be assessed for their association with response and AEs.

2.2.2. Investigate mechanisms of resistance

Analyses to investigate mechanisms of resistance will focus on evaluation of the tumour from screening and on treatment and, importantly, on changes observed in

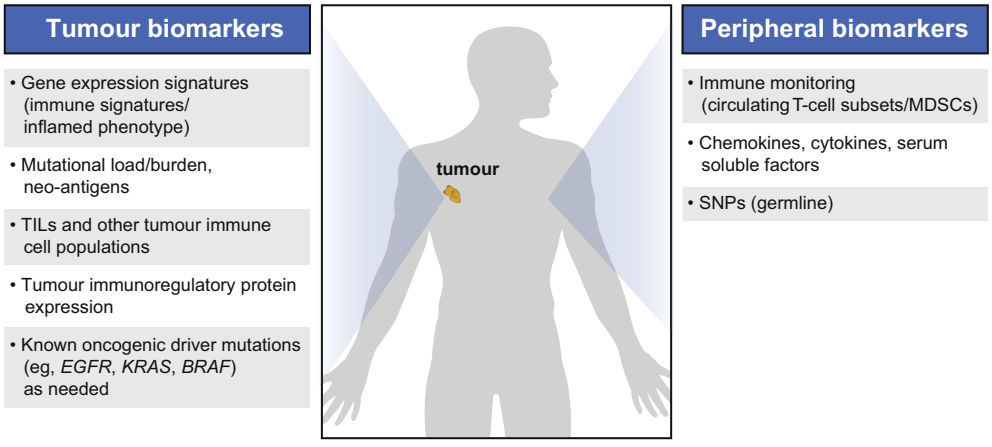

Fig. 2. Tumour and peripheral biomarker plan. MDSC, myeloid-derived suppressor cell; SNP, single nucleotide polymorphism; TIL, tumour-infiltrating lymphocyte.

Table 2
Rules for enrolment continuation and early termination for FRACTION studies.

FRACTION study[a,b]	Track	PD-L1 expression	Historical ORR, %/ target ORR, %	Stage 1 responders/ stage 1 n		Stage 2 responders/ total n (stage 1–2)			Stage 3 responders/ total n (stage 1–3)		Stage 4 responders/ total n (stage 1–4)		Expected n with historical ORR/expected n with target ORR
				Consider futility	Go to stage 2	Consider futility	Go to stage 3	Consider efficacy	Consider futility	Go to stage 4	Consider futility	Consider efficacy	
Non-small-cell lung cancer	1.b	–	–	≤3/20	≥4/20	≤6/35	≥7/35	≥11/35	≤11/50	≥12/50	≤13/70	≥14/70	–
	2	–	–	≤2/20	≥3/20	≤4/35	≥5/35	≥9/35	≤8/50	≥9/50	≤9/70	≥10/70	–
	3	–	–	≤1/12	≥2/12	≤5/35	–	≥6/35	–		–		–
	4	<1%	–	≤3/19	≥4/19	≤10/36	–	≥11/36	–		–		–
	4	≥1% & <50%	–	≤11/28	≥12/28	≤20/41	–	≥21/41	–		–		–
	4	≥50%	–	≤11/16	≥12/16	≤20/25	–	≥21/25	–		–		–
	5[c]	–	–	–	–	–	–	–	–		–		–
Gastric cancer	1	Positive	30/50	≤8/24	≥9/24	≤24/63	–	≥25/63	–		–		34.5/60.0
	1	Negative	15/35	≤3/19	≥4/19	≤10/44	–	≥11/44	–		–		16.8/42.5
	2	–	5/20	≤1/21	≥2/21	≤4/41	–	≥5/41	–		–		26.6/39.8
Renal cell carcinoma	1	–	30/50	≤8/24	≥9/24	≤24/63	–	≥25/63	–		–		34.5/60.0
	2	–	5/20	≤1/21	≥2/21	≤4/41	–	≥5/41	–		–		26.6/39.8

[a] Nested Simon-Fleming 4-stage, Simon 2-stage and single-stage designs were used for the non-small-cell lung cancer study; Simon 2-stage (optimal) designs were used for the gastric cancer and renal cell carcinoma studies [30–35].
[b] Numbers of responses serve as a guideline; however, the totality of efficacy data will be considered when making decisions to terminate or continue an arm; n values presented in this table are per treatment arm.
[c] Stage 1 (n = 35).

tumour tissue at the end of treatment or progression. The focus of these analyses will be characterisation of the tumour microenvironment, including genomic profiling and the presence of immune cell infiltrates and immunoregulatory proteins expressed on tumour and immune cells. In particular, the ability to make an immunologically 'cold' tumour into a more immunogenic tumour is a focus of the correlative projects within FRACTION.

2.3. Statistical considerations

Traditional phase II studies usually have either a single experimental treatment arm (non-comparative) or a randomised experimental treatment arm compared with a control arm. Different experimental treatments are evaluated in different studies. A major advantage of the FRACTION approach is that randomisation to multiple treatment arms as well as a potential control allows direct comparisons to be made among treatments, with a gain in efficiency through a common control arm.

The number of patients randomised to each treatment (ie, arm) in a given Study Track is guided by statistical requirements for establishing a favourable efficacy profile in that population (see the Methods in the Supplementary Material for details specific to the FRACTION trials). The adaptive design specifies that treatments that do not achieve promising activity may be discontinued early from a particular Study Track with no further randomisation of patients. A treatment arm may be discontinued in one Study Track while continued in another. The goal is to minimise the number of patients assigned to ineffective treatments, while randomising new patients to therapies that demonstrate preliminary evidence of sufficient efficacy or to new treatments added through new Sub-Protocols. Since efficacy expectations and historical performance of the standard of care for each indication are different for different Study Track populations, the maximum sample size and minimum efficacy criteria may also vary by Study Track. Multistage designs, such as Simon or Fleming 2-stage designs, provide a reasonable approach for each Study Track [30,31]; however, single-stage designs or Bayesian continuous monitoring could also be used [32]. For simplicity, decision criteria for stopping or continuing a treatment arm are typically based on the number of objective responses observed. However, other aspects of clinical benefit that may better predict OS benefit, such as DOR and PFS, and safety and pharmacodynamic changes in markers that may be associated with immune response should also be reviewed before making a determination to terminate or continue a treatment. The rules for enrolment continuation and early termination for each of the FRACTION studies are presented in Table 2, with further details provided in the Supplementary Material.

3. Ongoing FRACTION studies

The ongoing FRACTION studies are continually enrolling patients with advanced NSCLC [33], gastric cancer (or gastroesophageal junction cancer) [34] or RCC [35], allowing them an opportunity to access multiple new combinations of I-O therapies, including the combination of nivolumab with investigational I-O or targeted agents (Fig. 1). As many as 8 to 10 combinations of early-stage therapeutic combinations are planned for the FRACTION studies.

Initially, all study regimens will include nivolumab with or without I-O or targeted agents (eg, anti–LAG-3, ipilimumab and other pipeline agents). Efficacy assessments occur approximately every 8 weeks. If a patient is responding or has stable disease, the patient continues with treatment until a maximum of 6 cycles is reached (24 weeks); however, if treatment with a combination regimen ends with stable disease, patients may continue treatment for an additional 6 cycles at the investigator's discretion. All patients who experience progressive disease on treatment and maintain eligibility will have the option to continue in the study by receiving another randomised therapy (a subsequent randomised therapy cannot repeat a previously assigned therapy) or enter the follow-up period (Fig. 1). Patients who achieve a complete response will have the option to discontinue treatment before completing therapy. At the end of treatment, all patients will enter the follow-up phase and will be monitored for safety events, ongoing response to therapy (if applicable) and survival. Retreatment with a randomised regimen will be possible for patients who end treatment (for reasons other than toxicity) with disease control and who subsequently experience disease progression within 12 months of ending therapy.

4. Summary

Current strategies for improving the clinical benefit of I-O therapies increasingly rely on a combination of I-O agents. The FRACTION Program is a new, efficient approach for rapid assessment of I-O therapies that have high potential for clinical success. FRACTION studies combine key design features of platform oncology trials [22,23], including the ability to phase in new combination I-O therapies as they emerge as candidates from phase I studies. Adaptive randomisation in FRACTION studies based on pretreatment biomarker status, similar to the BATTLE and I-SPY 2 trials [24,25,36], is envisioned in the future as these data elucidate the biology behind effective combinations. Concurrent signal-finding evaluation of many I-O combinations will initially involve small numbers of patients; therefore, the FRACTION design will avoid unnecessary treatment of patients with I-O combinations with little or no chance of demonstrating a significant change in survival.

The FRACTION design has certain limitations. The design is primarily focused on signal finding for multiple I-O combinations rather than prospective confirmation for a single combination. Early decisions regarding efficacy will be based on surrogate measures of survival such as best overall response and PFS, with a relatively small number of participants. Thus, successful combination regimens will likely require subsequent traditional phase II/III studies to confirm the signal and obtain registrational approval, although data obtained in FRACTION would be supportive. In addition, as currently implemented, the FRACTION studies rely on prospective assignment and equal randomisation to all available treatments, with biomarker subgroups potentially identified after the fact; an adaptive randomisation approach would potentially allow biomarkers for individual treatments to be identified more efficiently in the future.

In the FRACTION Program, multiple I-O treatment combinations will be evaluated in various tumours using a Master Protocol with a continuous-throughput, adaptive trial design. Patients with advanced cancers will have an opportunity to receive subsequent combination regimens if they do not achieve a response with their initial regimen. The rapid evaluation of several I-O combination regimens simultaneously will help accelerate availability of those that are efficacious, providing additional treatment options to patients with a high unmet need.

Authors' contributions

KL Simonsen, PM Fracasso, SH Bernstein, M Wind-Rotolo, M Gupta, A Comprelli, TP Reilly and J Cassidy contributed to concept and design. KL Simonsen, PM Fracasso, SH Bernstein, M Wind-Rotolo, TP Reilly and J Cassidy contributed to development of methodology. KL Simonsen and M Gupta contributed to analysis and interpretation of data (eg, statistical analysis, biostatistics, computational analysis). KL Simonsen, PM Fracasso, SH Bernstein, M Wind-Rotolo, M Gupta, A Comprelli, TP Reilly and J Cassidy contributed to writing, review and/or revision of the manuscript. PM Fracasso and A Comprelli contributed to administrative, technical or material support (ie, reporting or organising data, constructing databases). PM Fracasso and A Comprelli contributed to study supervision.

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Conflict of interest statement

KL Simonsen, PM Fracasso, M Wind-Rotolo, A Comprelli and TP Reilly are employees of Bristol-Myers Squibb. SH Bernstein, M Gupta and J Cassidy were employees of Bristol-Myers Squibb at the time the work was conducted.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2018.07.127.

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