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Exaggeration of PFS by blinded, independent, central review (BICR)

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Abstract

Background: Recent published studies have shown meaningful discrepancies between local investigator and blinded, independent, central review (BICR) assessed median progression-free survival (PFS). When the local review but not BICR shows progression, generally, no further assessments are performed and patients are censored in the BICR analysis, leading to violation of the statistical assumptions of independence between censoring and outcome used in survival analysis methods.

Methods: We performed a simulation study to assess methodological reasons behind these discrepancies and corroborated our findings in a case study of three *BRCA*-mutated ovarian cancer trials. We briefly outline possible methodological solutions that may lead to improved estimation of the BICR medians.

Results: The Kaplan-Meier curve for the BICR PFS can often be exaggerated. The degree of bias is largest when there is reasonably strong correlation between BICR and local PFS, especially when PFS is long compared to assessment frequency. This can result in an exaggeration of the medians and their difference; however, the hazard ratio (HR) is much less susceptible to bias. Our simulation shows that when the true BICR median PFS was 19 months, and patients assessed every 12 weeks, the estimated Kaplan-Meier curves were materially biased whenever the correlation between BICR and local PFS was 0.4 or greater. This was corroborated by case studies where, in the active arm, the BICR median PFS was between 6 and 11 months greater than the local median PFS. Further research is required to find improved methods for estimating BICR survival curves.

Conclusions: In general, when there is a difference between local and BICR medians, the true BICR Kaplan-Meier curve is likely to be exaggerated and its true median will probably lie somewhere between the observed local and BICR medians. Presentation of data should always include both BICR and local results whenever a BICR is performed.

Word count: 299 (300 words or fewer)

Introduction

Progression-free survival (PFS) is an accepted measure of clinical activity and an effect on PFS may also be regarded as a clinical benefit if the magnitude of effect is sufficiently large. Increasingly, it is used as a registration endpoint, especially when post-progression survival is long or confounded by post-progression treatment. Therefore, it is imperative that the size of any benefit is accurately represented.

Unlike overall survival, the date of progression is not known exactly, only that it occurs within an interval between two successive scans. As a result, there are a number of additional methodological considerations when analysing PFS. These include the need for identical timing of scans between arms, pre-defined censoring rules for the handling of patients who take other anti-cancer therapy prior to progression or PFS events that occur after a number of missed assessments. These issues have been described by a number of authors [1–3].

While objective criteria, such as response evaluation criteria in solid tumours (RECIST) [4], are routinely used to decide when a patient has progressed radiologically, there can be high levels of disagreement between readers, which has the potential to cause bias in the estimated treatment effect. This is often called ascertainment bias and has driven the requirement to have scans read by a central group of radiologists who are blinded to treatment arm, the local investigator assessment of progression and other clinical outcomes. This is commonly referred to as a blinded, independent, central review (BICR).

It would be natural to expect that the treatment effects estimated using the BICR-derived PFS would result in an unbiased estimate of outcome in each arm. This may

largely be the case when assessing response rate; however, for PFS there are special issues related to censoring [5]. When the treating physician (local assessment) determines that the patient has progressed, sometimes on the basis of clinical events not visible to the BICR readers, no further scans are normally performed. In the analysis of BICR progression, if the central reviewer does not believe the patient has progressed, they are censored at the time of the local progression. This applies regardless of whether the data are analysed using the log-rank test or Cox model or presented using a Kaplan-Meier (KM) curve. With the advent of immunotherapy protocols increasingly requesting a confirmatory scan of progression [6], this design feature only partially offsets the issues described here.

A positive correlation between the true local and BICR PFS times leads to a level of agreement between local and BICR reviewers that is usually higher than would be expected due to chance. This violates the statistical assumptions of independence between censoring and outcome used in survival analysis methods. This type of censoring is often termed informative [5].

A number of authors have assessed whether the presence of informative censoring biases the hazard ratio (HR), the primary measure of treatment effect. Separate meta-analyses of double-blind and open-label studies have shown that in general local and BICR PFS HRs are highly consistent [7,8]. Therefore, in the case of the estimation of the HR, non-differential informative censoring may not necessarily result in material bias even when discordance rates are as high as 50% [9]. However, simulation studies have identified that, for individual studies, if there is a between-arm difference in the proportion of local PFS times earlier than BICR, there is likely to be bias in the estimate of the HR [10–12].

HRs are not the only measures used to describe and gauge the extent of clinical benefit; KM estimates of medians are also routinely presented. There are many issues with the use of a median to describe an average outcome of a treatment arm: it can understate benefit if the treatment effect is delayed or overstate benefit when the treatment effect wanes with longer follow-up. For PFS, the median has additional problems due to the stepped nature of the KM curves. These steps may randomly just fall short, or just pass the 50th percentile and consequently, the medians may substantially either over- or underestimate the true value, especially if the numbers at risk are relatively small. Despite these problems, and in the absence of a universally accepted alternative, medians are still routinely used in labelling and their difference used as an important measure of clinical benefit. Therefore, the impact of informative censoring on the KM curve of PFS needs to be clearly understood. The same considerations also apply to other measures taken from the KM curves, such as mean survival or landmark times, for example, the proportion of patients progression-free at 1 year.

Here, we present a simulation study and a case study in ovarian cancer from a series of related trials. We also briefly introduce possible alternatives to analysis, but these require further in-depth assessment and we hope this paper stimulates further research.

Simulation

We performed a simulation study in which each patient was assumed to have exponentially distributed progression times for the BICR and local review, which were aligned to assessments every 12 weeks and with varying levels of correlation. Full details of the methodology are provided in the supplementary appendix and expanded upon below Table 2.

When there was truly no difference in the true local and BICR PFS medians, the observed BICR survival curve and consequently median can be exaggerated. The presence and extent of bias depended on the correlation between local and BICR PFS times and how frequently patients were assessed prior to progression (Table 1). When the true BICR median PFS was 19 months, and with patients assessed every 12 weeks, the Kaplan-Meier curves were materially biased whenever the correlation between BICR and local PFS times was 0.4 or greater. The median was exaggerated on average by 5.8 months when the correlation was 0.9, with the bias applying to the entire KM curve (Figure 1). In contrast, when the true BICR median was 6 months, and with an assessment frequency of 12 weeks, the extent of bias was much lower and unlikely to be apparent. Our simulations also confirm previous findings that the HR is much less susceptible to bias.

Further simulation results are provided in the supplementary appendix, which describe the extent of bias with the same assessment frequency but with medians of 9, 12 and 14 months and situations where the true local and BICR PFS medians differed.

Case study in *BRCA*-mutated ovarian cancer

We examined three closely related maintenance trials of poly-ADP ribose polymerase inhibitors (PARPis) olaparib, niraparib and rucaparib in platinum-sensitive ovarian cancer [13–15]. The patient populations, endpoint definitions and assessment frequencies were highly consistent between trials (supplementary appendix). For the niraparib and rucaparib trials we present data from only the *BRCA*-mutated subgroups; however, the pattern of findings in the non-*BRCA* subgroups is consistent with the *BRCA*-mutated groups. The olaparib trial only recruited *BRCA*-mutated patients.

While the treatment effect, as measured by the HR, is similar regardless of whether the scans were reviewed locally or by BICR, the KM estimates of the PARPi arm median vary greatly (Table 2, Figure 2). In these trials the BICR median is between 6 and 11 months longer than the local median in the treatment arm. In the placebo arm, where fewer assessments were performed prior to progression, there is no such difference in the medians. Furthermore, the difference in medians between-arm is also much greater, 67%–91%, on the BICR review compared to the local review.

These findings are consistent with the simulation study. Therefore, given that the HRs are broadly similar between the local and BICR assessment, this suggests that the true increase in PFS, as measured by BICR, probably lies somewhere between that observed and that measured by the local review.

Alternative methods

If current approaches to the estimation of survival curves for BICR data are inadequate, what alternatives exist? There has been little attention paid to this topic in the statistical literature but some possible solutions exist that were designed for related situations. The performance of these methods will however require further scrutiny before any preferred approach can be chosen. We summarise the options here.

One approach is to impute a BICR event at the next scheduled visit every time a progression is called only by the investigator. Indeed, this approach was applied by the US Food and Drug Administration (FDA) as a sensitivity in the review of niraparib and olaparib [16, 17]. When applied to the SOLO2 and NOVA trials, the estimated BICR medians were 19.6 m and 5.5 m for the olaparib and placebo arms respectively [17], and 13.6 m vs 5.4 m [16] for the niraparib and placebo arms respectively. However, while such a sensitivity analysis is helpful to assess for possible bias with the HR, our simulations show that they can greatly underestimate the true BICR median (supplementary appendix), especially when patients are assessed multiple times prior to progression. Therefore, a more sophisticated approach is probably needed to get closer to the true median value.

Of the published methods, one possible alternative approach is to apply the inverse probability of censoring weights (IPCW) method [18]. This is often used to estimate overall survival in trials where patients in the control arm switch to experimental therapy. A related, multiple imputation method [19], could also be applied in this situation. In this approach, patients with local-only progression are matched with other patients who most resemble them and their outcomes are randomly imputed.

Discussion

We have shown that KM estimates of the BICR PFS survival curve can be exaggerated even when the local and true BICR curves are identical – methodological bias. The exaggeration is most evident when the median PFS is a large multiple of the assessment frequency and there is a reasonable correlation between the local and BICR PFS times. In the SOLO2 trial, we estimated this correlation to be in excess of 0.9, using a joint-modelling approach. In the simulations, when median PFS was more than five times the assessment frequency, the median was falsely extended by at least 2 months, as long as the correlation was larger than 0.6. In some scenarios, it was shown that median BICR PFS might be exaggerated by as much as 6 months solely due to methodological bias. In contrast, when the median was twice the assessment frequency or less, the extent of bias was negligible. Perhaps surprisingly, scanning patients more frequently does little to improve power [2], so these findings provide another reason to apply the same scanning frequency in trials as used in clinical practice. The source of the bias in the BICR median is the handling of patients with local-only progression in standard analyses. This explains why bias is greatest when patients are assessed more often relative to their rate of progression as there is a higher chance of a disagreement in progression status between visits.

A case study of maintenance trials in *BRCA*-mutated platinum-sensitive ovarian cancer corroborated the findings of the simulation study. This general pattern also seems to be replicated in other situations where other highly active therapies have been studied, such as CDK4/6 inhibitors in advanced breast cancer; the median BICR vs local PFS was 22.4 vs 16.4 and 30.5 vs 24.8 for the active arms of trials of abemociclib [20], palbociclib [21], respectively.

Having identified the circumstances where there is the greatest potential for bias, how would we know whether this applies to a particular trial? Our research suggests there is no universal threshold of a single observable metric of discordance rates between the local and BICR assessments that would identify whether or not methodological bias was present. However, given that relatively, the HR is not susceptible to methodological bias, it could be used to gauge the extent to which an extended BICR median is real. For example, if the HRs are reasonably consistent, as they were in the case studies, if the BICR PFS is longer than the local PFS only in the arm with longest PFS, it would suggest the BICR Kaplan-Meier curves and hence median is biased and its true value lies somewhere between the two.

We have focused on quantifying the bias in the estimation of the median because it is routinely presented. As a measure of average benefit, it has many problems, one of which was highlighted in the case study. When applied to PFS, in a well conducted trial, using standard analysis approaches, the KM curve will have clearly defined steps, the location of which can have a large bearing on the estimated median. For both olaparib and niraparib the KM curve just failed to reach the 50th percentile at least 5 months before reaching the median. This further increases the bias described in this paper, especially when absolute benefit is quantified by a difference in medians from a BICR analysis and the experimental therapy is highly effective. A related issue can occur in advanced cancer studies, when a high proportion of patients, sometimes >50%, progress prior to the first scan. In this situation, while the BICR analysis may not be biased, the reported medians for both the local and BICR review can be highly dependent on the chosen assessment frequency.

If there are problems with the median, it would be tempting to turn to alternative measures of average outcome, and in turn average benefit, such as landmark times, for example 1- or 2-year PFS or restricted mean survival [22]. However, as shown in Figure 1, the entire BICR survival curve can be exaggerated artificially increasing these other measures too.

In theory, the bias associated with informative censoring could be removed by requiring investigators to continue to scan patients until they have progressed according to the BICR, which would entail a real-time BICR review. This approach has proven successful in studies where patients can switch from control to the experimental arm [23], but only after central confirmation of progression. There are a number of practical and clinical issues that we believe are a major barrier to its routine use in a more general setting – it removes the responsibility for the care of patients by the treating physician and it should be considered whether the BICR assessment can be returned to the investigator sufficiently quickly. However, the development of immunotherapies and the possibility of pseudo progression has led to the idea of requiring a second scan to confirm progression [6]. If these confirmatory scans were consistently performed in both treatment arms, while not completely removing the bias caused by informative censoring, they would probably help to reduce its effect.

There are also broader implications for the findings presented in the paper. The median BICR PFS can cause confusion when presented alongside other endpoints. For SOLO2 [13], the BICR median in the olaparib arm, 30.2 months, is longer than the median time to first subsequent therapy or death, 27.9 months, falsely implying that investigators added subsequent therapy prior to progression. Likewise, for NOVA [14] the median PFS2 (the time to second progression according to local review), 25.8 m

in the niraparib arm, was only 4.8 m longer than the BICR median for PFS raising concerns that resistance to subsequent therapy had developed.

Finally, given the data presented in this paper, BICR PFS data should not be presented in isolation, either in publications or prescribing information even if it is designated as the primary endpoint; currently, this is not always the case. The olaparib prescribing information only contains the results of the local review for PFS, whereas for niraparib it only contains only the BICR review in platinum-sensitive ovarian cancer, rendering any between-study comparison unreliable.

Key messages

- BICR may exaggerate PFS data including the median
- The HR remains the most reliable measure to describe the benefit of a BICR PFS analysis
- Further research is required to find better alternatives to more accurately estimate the survival curve for BICR PFS
- Presentation of data should routinely present the results of both the local and BICR evaluations

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Disclosure

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Table 1. Simulated median local and BICR PFS according to correlation

a) No underlying bias: Median of 19 m with 12-week assessment frequency

Correlation	True local median	Observed local median (5th, 95th percentile)	True BICR median	Observed BICR median (5th, 95th percentile)	Local HR*	BICR HR*
0.9	19.0	19.1 (16.3, 21.8)	19.0	24.8 (20.1, 30.1)	0.29	0.28
0.8	19.0	19.0 (16.3, 21.9)	19.1	24.5 (19.6, 30.0)	0.29	0.28
0.6	19.1	19.1 (16.3, 21.9)	19.1	22.3 (18.7, 27.5)	0.29	0.28
0.4	19.0	19.1 (16.3, 22.0)	19.1	20.9 (16.8, 25.1)	0.29	0.27
0.2	19.1	19.1 (16.2, 22.0)	19.0	19.3 (16.2, 22.7)	0.29	0.27
0	19.0	19.1 (16.3, 21.8)	19.1	17.5 (16.3, 21.8)	0.29	0.26

b) No underlying bias: Median of 6 m with 12-week assessment frequency

Correlation	True local median	Observed local median (5th, 95th percentile)	True BICR median	Observed BICR median (5th, 95th percentile)
0.9	6.0	6.0 (5.6, 7.8)	6.0	6.2 (5.6, 8.1)
0.8	6.0	6.0 (5.6, 7.8)	6.0	6.1 (5.6, 8.1)
0.6	6.0	6.0 (5.6, 7.7)	6.0	6.0 (5.5, 7.9)
0.4	6.0	6.0 (5.6, 7.8)	6.0	5.8 (5.4, 7.7)
0.2	6.0	6.0 (5.6, 7.8)	6.0	5.7 (5.3, 6.6)
0	6.0	6.0 (5.6, 7.8)	6.0	5.6 (5.2, 6.0)

1000 simulations of 200 patients per arm have been simulated. Data were simulated from bivariate normal distributions with the specified correlation coefficients and back transformed to create correlated exponential distributions with medians of 17.35 months panel a) and 5 months panel b). Patients were assessed every 12 weeks and normally distributed variability was imposed around the intended timing with a standard deviation of

0.5 months. The observed local PFS time was set at the time of the first visit occurring after the underlying local PFS time. The same approach was used to create observed BICR times, except that if the underlying BICR PFS time occurred later than the visit at which the local progression was detected, the BICR PFS time was censored at the time of local progression. This resulted in true medians of 19 and 6 months having aligned to visits. Finally, patients were assumed to enter the trial randomly over 15 months and a fixed minimum follow-up of 24 months was introduced, where patients who had not had an event by the end of the follow-up period were censored at their latest visit. This resulted in 70% and 98% maturity (events/patients) for local PFS with 19 and 6 months respectively.

*The HR compared PFS between panel a) and b) for the local and BICR data separately with the same correlation, where the true HR was 0.29. Further details are provided in the supplementary appendix.

Table 2. Hazard ratio and median PFS in maintenance trials of PARPi in platinum-sensitive *BRCA*-mutated ovarian cancer

	Local		BICR	
	Median	**HR (95% CI)**	**Median**	**HR (95% CI)**
SOLO2 (n=295)	19.1 v 5.5	0.30 (0.22–0.41)	30.2 vs 5.5	0.25 (0.18–0.35)
NOVA (n=203)	14.8 v 5.5[a]	0.27 (0.18–0.40)[a]	21.0 vs 5.5	0.27 (0.17–0.41)
ARIEL3 (n=196)	16.6 v 5.4	0.23 (0.16–0.34)	26.8 vs 5.4	0.20 (0.13–0.32)

[a]Data published in the FDA review [16]

Figure legends

Figure 1. Estimated and true KM BICR curves

Curves displayed are for a correlation of 0.9 between BICR and local PFS times and a 12-week assessment frequency. True 6 m and True 19 m represent the KM curves for the true BICR PFS times having been aligned to visit with a 6 and 19 m median, respectively. Est 6 m and Est 19 m represent the corresponding BICR KM curves estimated in the presence of censoring

Figure 2. Kaplan-Meier curves for (a) olaparib, (b) niraparib and (c) rucaparib

(a) Reproduced with permission from Pujade-Lauraine et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18(9):1274–1285 © 2017 Elsevier Ltd. (b) Reproduced with permission from Mirza MR et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 2016;375(22):2154–2164 © 2016 Massachusetts Medical Society and Niraparib GBA review. Available at: https://www.g-ba.de/downloads/92-975-2225/2017-12-14_Modul4A_Niraparib.pdf [24]. (c) Reproduced with permission from Coleman RL et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;390(10106):1949–1961 © 2017 Elsevier Ltd

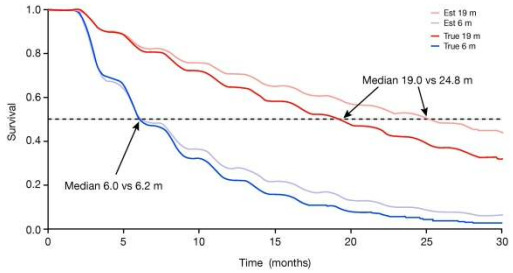

Figure 1

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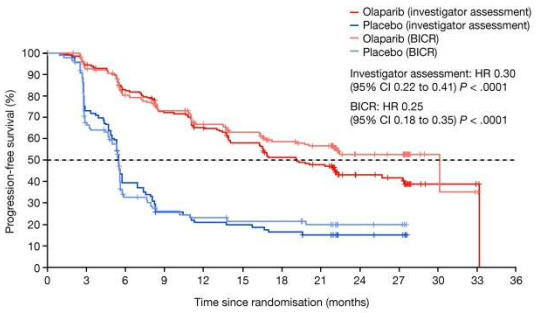

Figure 2a

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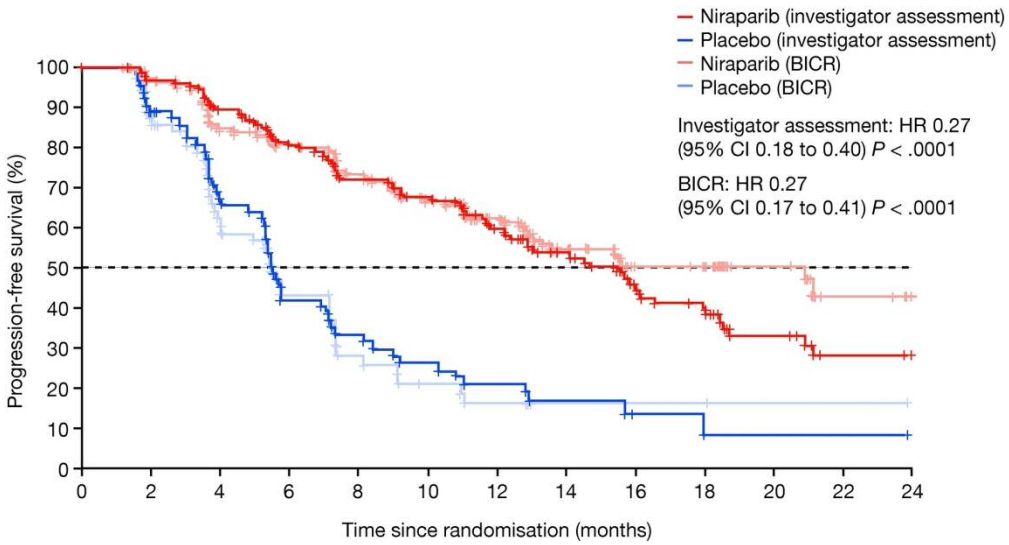

Figure 2b

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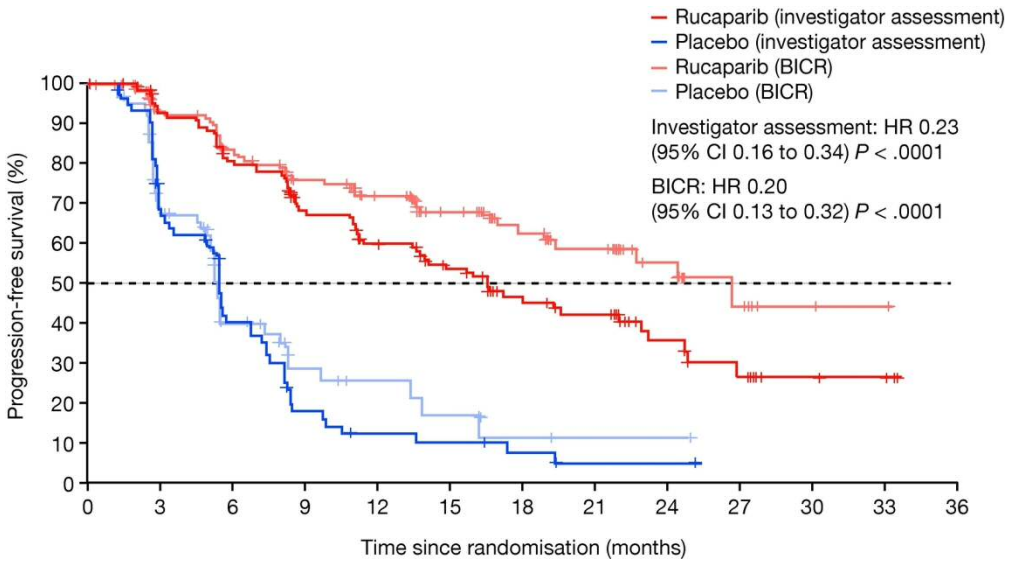

Figure 2c

152x84mm (300 x 300 DPI)