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Original Research

Development and validation of a prognostic nomogram for overall survival in patients with platinum-resistant ovarian cancer treated with chemotherapy

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Abstract ***Background:*** Platinum-resistant ovarian cancer (PROC) is associated with a variable prognosis and unpredictable survival times. We have developed and validated a prognostic nomogram with the objective of improving the prediction of overall survival (OS) in patients treated with chemotherapy.

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Prognostic nomogram

Methods: The nomogram was developed using data from a training cohort of patients from two trials, including the chemotherapy-only arm in AURELIA and all randomised patients in CARTAXHY. Multivariable proportional hazards models were generated based on pretreatment characteristics to develop a nomogram that classifies patients based on OS. We subsequently assessed the performance of the nomogram in terms of discrimination and calibration in independent validation patient cohorts: PENELOPE and the bevacizumab-chemotherapy arm of AURELIA.

Results: The nomogram included six significant OS predictors, in order of importance: performance status, ascites, size of the largest tumour, CA-125, platinum-free interval and primary platinum resistance (C-statistic 0.69). In the training cohort, the median OS in the good, intermediate and poor prognosis groups was 25.3, 15.2 and 7.4 months, respectively. In the PENELOPE validation cohort (C-statistic 0.59), the median OS in the good, intermediate and poor prognosis groups was 18.5, 10.3 and 5.8 months, respectively. In the AURELIA bevacizumab-chemotherapy validation cohort (C-statistic 0.67), the median OS in good, intermediate and poor prognosis groups was 26.7, 13.8 and 10.0 months, respectively.

Conclusions: This nomogram with six pretreatment characteristics allows prediction of OS in PROC and could be used for stratification of patients in clinical trials as well as for counselling patients about prognosis.

1. Introduction

Patients with platinum-resistant ovarian cancer (PROC) are a very heterogeneous group with a variable prognosis and unpredictable survival times. The median overall survival (OS) of patients with PROC ranges from 9 to 17 months in clinical trials [1,2]. Traditionally, the term 'platinum-resistant' is applied to patients who experience recurrence or progression within 6 months of completing prior platinum-based chemotherapy. The original definition of platinum resistance was based predominantly on clinical or radiological evidence of recurrence after first-line platinum-based chemotherapy. However, platinum resistance is used far more loosely today to include asymptomatic patients with a rising CA125 or those with small volume disease on computed tomography or positron emission tomography–computed tomography. As CA125 rise and radiologic findings commonly precede clinical or symptomatic recurrence by several months [3], many patients now classified as platinum-resistant would have previously been considered to be platinum-sensitive. Furthermore, this term has also been extended to those who receive multiple lines of chemotherapy. These patients, classified differently as being platinum-resistant, are typically all grouped together as a single entity in clinical trials. These differences in patient classification contribute to the heterogeneity in OS outcomes.

There is currently a limited understanding of the prognostic factors in patients with PROC. With the exception of performance status, there has not been any uniform approach in accounting for baseline prognostic factors in PROC clinical trials. Prior work on the CALYPSO trial [4,5] identified prognostic factors in patients with platinum-sensitive recurrent ovarian cancer. Prognostic indices have also been developed for recurrent disease but have included both platinum-sensitive and platinum-resistant populations [6–9]. To the best of our knowledge, no studies have comprehensively investigated clinical, radiologic and laboratory-based pretreatment factors to help predict OS in PROC patients receiving chemotherapy.

Accurate and reliable information on OS is essential to support communication between oncologists and patients about prognosis and making decisions regarding chemotherapy, particularly in the subset who may only have months to live. This information is also vital for the design and analysis of future PROC trials. We address these needs by developing and validating a prognostic nomogram for OS in PROC. Our objective was to develop a tool that would be accurate and simple to use and allow for the stratification of PROC patients before chemotherapy based on their predicted survival times using routinely available pretreatment clinical information.

2. Methods

2.1. Training cohort

We used data from the control chemotherapy-only arm in AURELIA trial [2] and all randomised patients in the CARTAXHY trial [10] to develop the nomogram. AURELIA was an open-label randomised phase III trial comparing the addition of bevacizumab to chemotherapy versus chemotherapy alone in patients with

PROC. CARTAXHY was an open-label randomised phase II trial comparing weekly paclitaxel, weekly paclitaxel plus carboplatin and weekly paclitaxel plus weekly topotecan. In both studies, eligible patients must have progressive disease during or have evidence of relapse within 6 months of completing platinum-containing therapy. Patients must have received at least one prior regimen of platinum-based chemotherapy. None of the study mandated methods are for detection of disease progression. Both of these trials mandated randomised treatment to continue until disease progression or unacceptable toxicity. The primary end-point was progression-free survival, with OS as a main secondary end-point.

2.2. Validation cohorts

We validated the performance of our nomogram on all patients enrolled in the PENELOPE trial [11]. PENELOPE was a randomised phase III trial evaluating the addition of pertuzumab to investigator's choice of chemotherapy (topotecan, weekly paclitaxel or gemcitabine) versus chemotherapy alone in patients with PROC. Treatment was continued until disease progression or unacceptable toxicity. The primary end-point was progression-free survival, with OS as a main secondary end-point.

A second validation was also performed by applying the nomogram on patients randomised to the bevacizumab plus chemotherapy arm of AURELIA.

2.3. Statistical analysis

OS was defined as the time from randomisation to the date of death or last follow-up. The univariate relationship between each baseline clinical, radiologic and laboratory pretreatment variable and OS was analysed using a Cox proportional hazards models. These candidate variables were considered based on their prognostic values in advanced ovarian cancer reported previously [12–14]. The data for these variables must also be available from all three trials used for training and validation. Those with $P < .10$ in univariable analyses were included as candidate variables for Cox multivariable modelling, and a stepwise selection procedure was implemented. To construct the nomogram, only significant variables ($P < .05$) retained in the final multivariable Cox model were used. Nomogram points were assigned based on the weights for the relative importance of each variable in the final model. The total score (scaled to range from 0 to 100) for each patient was calculated as a weighted sum based on the contribution from the individual risk factors.

We arbitrarily categorised patients into three groups based on the quartiles of the OS predicted probabilities. For simplicity, the first quartile formed the 'good prognosis' group, the middle two were combined to form the 'intermediate prognosis' group and the final quartile formed the 'poor prognosis' group.

We validated the nomogram using two procedures. First, the model discrimination was assessed using Harrell's discrimination concordance index statistic (which is the equivalent of an area under the receiver-operating characteristics curve for survival data) as well as Kaplan–Meier curves and log-rank tests to illustrate the discriminatory ability of the nomogram-derived categorisation of patients. Second, calibration was assessed by comparing the nomogram-predicted probabilities for OS at 1 year with the corresponding observed OS probability. Plots that resemble a 45-degree line indicate that the nomogram predictions are well calibrated.

3. Results

The training cohort consisted of 331 patients, had a median follow-up of 30 months (range, 0.6–54 months) and a total of 249 (75%) deaths. The PENELOPE cohort had a median follow-up of 26.6 months (range, 0.5–29 months) and a total of 130 (83%) deaths, and the AURELIA bevacizumab had a median follow-up of 27.2 months (range, 1.4–37.0 months) with 119 (72%) deaths. The training cohort had a significantly longer OS than the PENELOPE cohort (median OS 15.7 versus 9.6 months, $P < .001$), but there was no difference with the AURELIA bevacizumab arm (median OS 15.7 versus 16.3 months, $P = 0.77$; Supplementary Fig. 1). The baseline characteristics of patients are summarised in Table 1.

3.1. Nomogram for overall survival

Fig. 1 shows the nomogram to predict the probability of 1-year OS and median survival. A web-based version of this nomogram is available (http://proconline.ctc.usyd.edu.au) to provide individualised estimates of 1 year and median OS. Performance status had the greatest prognostic significance, contributing a maximum of 38 points out of 100. Ascites (19 points), size of largest tumour documented on imaging (14 points maximum), CA-125 $\geq$ 100 (13 points), platinum-free interval $<$ 3 months (PFI) (9 points) and primary platinum resistance (7 points) were also individually important predictors of OS. All variables were statistically significant predictors in univariable and multivariable analyses (Supplementary Table 1).

Fig. 2A illustrates the discriminatory value of the nomogram when the patients were stratified into good (nomogram score less than 24, $N = 93$, median OS 25.3 months), intermediate (nomogram score 24–47, $N = 151$, median OS 15.2 months) and poor risk (nomogram score greater than 47, $N = 87$, median OS 7.4 months) prognostic groups (log-rank $P < .001$). When compared with the good-risk group, the poor-risk and the intermediate-risk groups were associated with a

Table 1
Baseline demographics.

Baseline characteristics		AURELIA and CARTAXHY (N = 331)	PENELOPE (N = 155)	AURELIA (Bev arm) (N = 166)
Age at baseline (range)		60.5 (25–84)	61.5 (26–80)	59.8 (25–80)
Performance status	0	162 (49%)	83 (54%)	100 (60%)
	1	146 (44%)	59 (38%)	55 (33%)
	2	23 (7%)	13 (8%)	11 (7%)
Serous histology	No	89 (27%)	35 (23%)	38 (23%)
	Yes	242 (73%)	120 (77%)	128 (77%)
CA125	<100 IU/ml	68 (21%)	36 (23%)	33 (20%)
	≥100 IU/ml	263 (79%)	119 (77%)	133 (80%)
Ascites	No	212 (64%)	112 (72%)	112 (67%)
	Yes	119 (36%)	43 (28%)	54 (33%)
Measureable disease	Non-measurable	86 (26%)	26 (17%)	34 (20%)
	Largest lesion measured < 5 cm	141 (43%)	51 (33%)	58 (35%)
	Largest lesion measured ≥ 5 cm	104 (31%)	78 (50%)	74 (45%)
Primary platinum resistance	Yes	236 (71%)	90 (58%)	126 (76%)
	No	95 (29%)	65 (42%)	40 (24%)
Progression-free interval	<3 months	211 (64%)	47 (30%)	118 (71%)
	3–6 months	120 (36%)	108 (70%)	48 (29%)
Lines of therapy	1	211 (64%)	64 (42%)	102 (61%)
	2	116 (35%)	86 (57%)	64 (39%)
	3	2 (<1%)	1 (<1%)	
	4			
	5+	2 (<1%)	1 (<1%)	

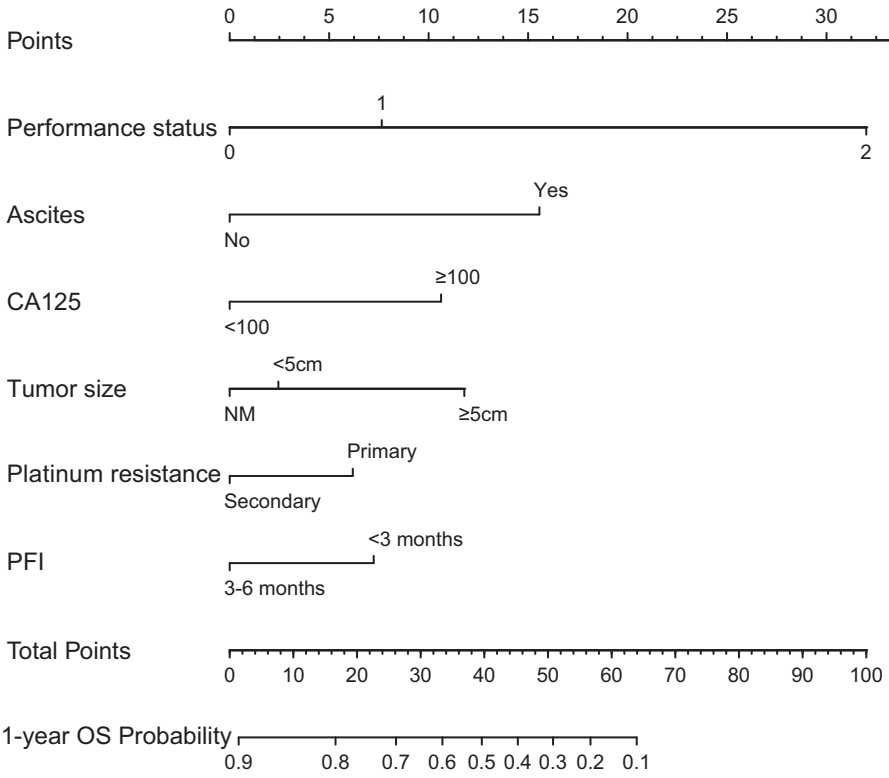

Fig. 1. Nomograms to predict the probability of 1-year OS. Points were assigned for performance status, ascites, size of largest tumour detected on imaging, CA-125, PFI and platinum resistance, by drawing a line upward from the corresponding values to the 'Points' line. The sum of these six points, plotted on the 'Total Points' line, corresponds to the prediction of probability of 1-year OS and median OS. PFI, platinum-free interval; NM, non-measurable; OS, overall survival.

4.60-fold increase (hazard ratio [HR] 4.60, 95% confidence interval [CI] 3.20–6.63) and 2.08-fold increase (HR 2.08, 95% CI 1.50–2.88) in the risk of death, respectively. The *C*-statistic was 0.66. Therefore, 66% of the time the nomogram correctly predicted the ordering of the OS outcome of two randomly selected patients.

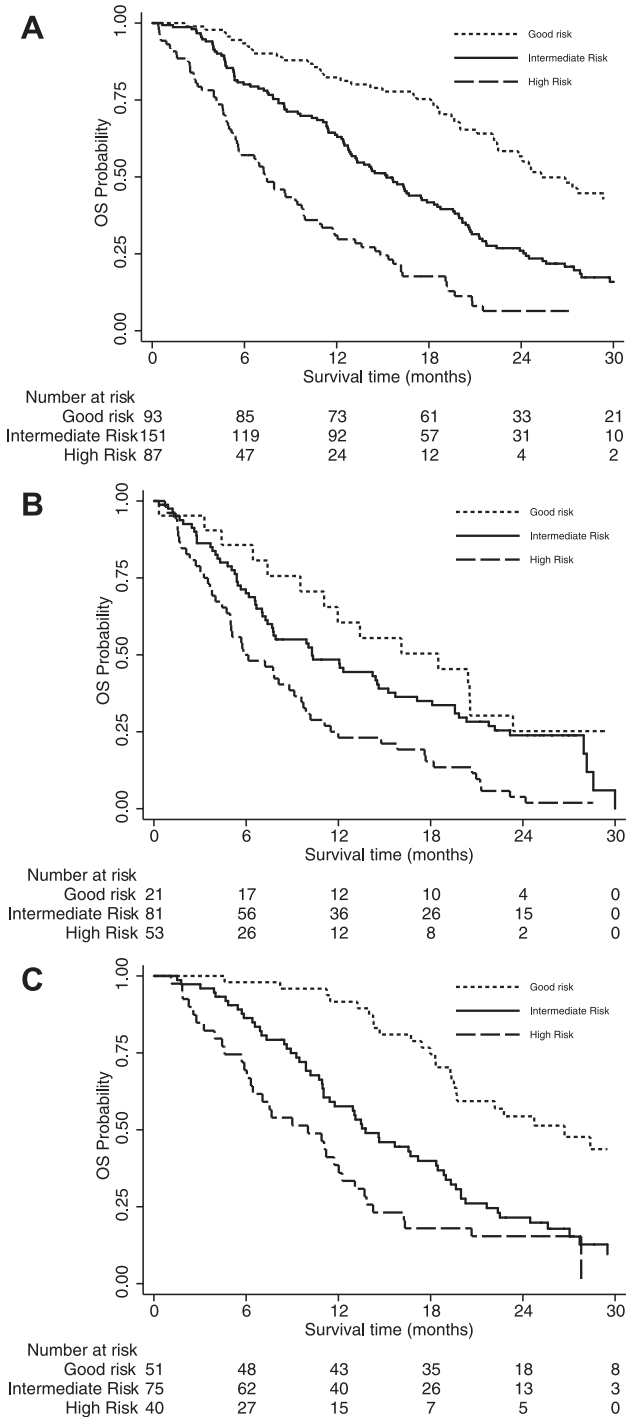

Fig. 2. OS of the training and validation cohorts according to risk groups. Kaplan-Meier estimates according to good, intermediate and poor risk groups of PROC patients treated with chemotherapy, based on a subset of patients enrolled in the (A) training cohort and (B) validation cohort (PENELOPE) and (C) another validation cohort (AURELIA bevacizumab arm). OS, overall survival; PROC, platinum-resistant ovarian cancer.

3.2. Validation

When the nomogram was applied to the PENELOPE validation cohort, the *C*-statistic was 0.59. Fig. 2B illustrates the good discriminatory value of the nomogram when applied to the PENELOPE cohort. There were significant differences in OS between good ($N = 21$, median OS 18.5 months), intermediate ($N = 81$, median OS 10.3 months) and poor risk ($N = 53$, median OS 5.8 months) prognostic groups (log-rank $P < .001$). When compared with the good-risk group, the poor-risk and the intermediate-risk groups were associated with a 2.54-fold increase (HR 2.54, 95% CI 1.42–4.54) and 1.34-fold increase (HR 1.34, 95% CI 0.76–2.36) in the risk of death, respectively.

When the nomogram was applied to the AURELIA bevacizumab cohort, the *C*-statistic was 0.67. Fig. 2C illustrates the good discriminatory value of the nomogram when applied to the AURELIA bevacizumab cohort. There were significant differences in OS between good ($N = 51$, median OS 26.7 months), intermediate ($N = 75$, median OS 13.8 months) and poor risk ($N = 40$, median OS 10.0 months) prognostic groups (log-rank $P < .001$). When compared with the good-risk group, the poor-risk and the intermediate-risk groups were associated with a 4.38-fold increase (HR 4.38, 95% CI 2.58–7.43) and 2.72-fold increase (HR 2.72, 95% CI 1.70–4.36) in the risk of death, respectively.

3.3. Calibration

Fig. 3 (A, PENELOPE; B, AURELIA bevacizumab cohort) demonstrates agreement between the predicted versus observed 1-year OS for the good, intermediate and poor risk groups.

4. Discussion

We have developed and validated a nomogram to help categorise patients with PROC being considered for palliative chemotherapy with respect to OS using information readily available in the clinic. This simple tool, available as both a web-based and a paper version, overcomes the complexity of assessing the effects of multiple prognostic factors simultaneously. It can help inform and support clinical decision-making as well as communication with patients and their families. To our knowledge, this is the first prognostic classifier specifically developed for patients with PROC being treated with chemotherapy.

Traditionally, the definition of platinum-resistant disease has been based on a PFI of 6 months or less, but there is an increasing recognition and acceptance that PFI alone is inadequate to estimate the survival times of PROC patients, who in reality comprise a very heterogeneous group with respect to prognosis [1]. We have shown that incorporating other prognostic factors, including patient factors (performance status), tumour volume (ascites, CA125 and size of largest tumour) and tumour biology (primary versus secondary platinum

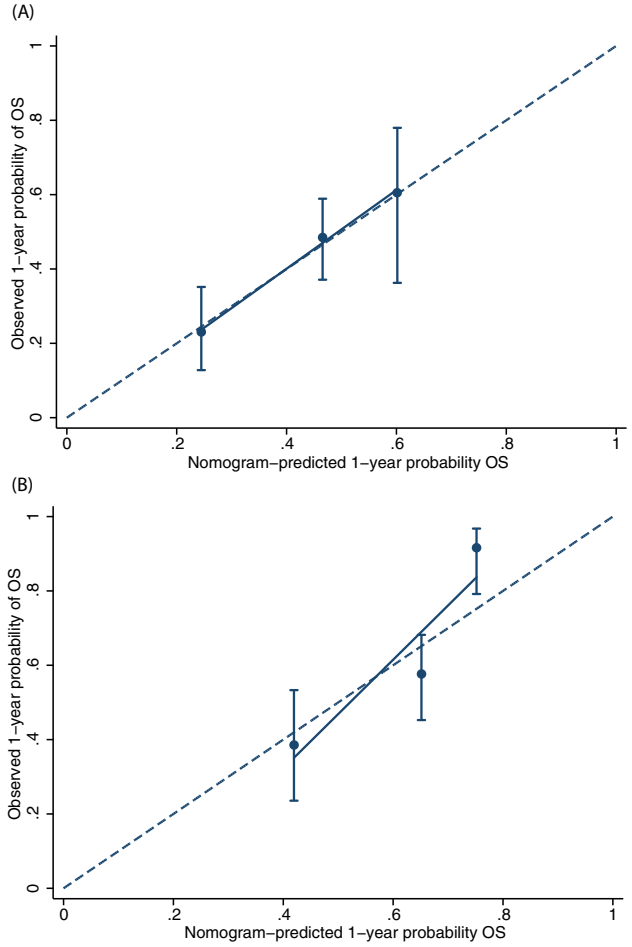

Fig. 3. Observed compared with nomogram-predicted 1-year OS rate for the good, intermediate and poor risk groups in (A) the PENELOPE validation cohort and (B) the AURELIA bevacizumab cohort. OS, overall survival.

resistance), provides significant prognostic information beyond PFI.

Although the prognostic factors identified in our study are of recognised significance in PROC, and in contrast to other methods of prognostic assessment, our nomogram is novel as it ranks and assigns weights according to importance of the variables relative to each other. A popular approach used to estimate prognosis of patients is to simply sum the presence or absence of prognostic factors, with more adverse factors equating to poorer outcomes. However, such an approach is too simplistic and does not account for the interaction of these prognostic factors with each other, which will lead to potentially underestimating the survival outcomes of these patients [15]. Providing accurate prognostic information is important in this vulnerable patient population [16], particularly when counselling these women about the role of palliative chemotherapy. There is evidence that many patients want to be informed of their likely prognosis. This information empowers patients to make informed decisions and to receive treatment that will align with their own goals and preferences [17]. Our online nomogram will facilitate further doctor-patient communication, where we provide the level of uncertainty surrounding individual estimates of survival outcomes for the typical (half to double the median survival), best-case (triple the median) and worst-case (one quarter of the median) scenarios using the approach developed for use in advanced breast cancer [18]. Physicians generally overestimate prognosis [19], and having a reliable and simple tool to counsel patients will be of benefit in women with PROC.

This study has a number of strengths. This nomogram has good practical applicability because the variables utilised are routinely collected and available pretreatment. It has been developed and validated based on the clinically important end-point of OS using high quality data from three contemporary PROC clinical trials. Although developed in patients treated with chemotherapy, this nomogram has performed well even in patients treated with chemotherapy and bevacizumab, which is the current standard of care for PROC. However, this study also has some limitations. Since the nomogram was developed and validated using data from the highly selected patients enrolled in clinical trials, its applicability to routine care non-trial patients, such as those with a performance status of 2, requires further research. The online version of this nomogram provides predicted OS estimates and the associated range of uncertainties. Providing prediction intervals is a compromise between providing patients with more objective information and avoiding the perception associated with the precise single OS time [20]. We also accept that the performance of our nomogram remains relatively modest (C-statistic = 0.65), and we have not included any genomic factors [21] that might also be associated with prognosis. Nevertheless, the nomogram is superior to simply counselling patients based on clinical impression or median OS, as reported in PROC clinical trials. The nomogram could act as a platform to incorporate new prognostic factors, including genomic prognostic biomarkers, as our understanding of the biology of PROC improves over time. Furthermore, the discriminatory value of any new prognostic factor identified in future research could be benchmarked against those we have identified in this study.

In conclusion, we have developed and validated a prognostic nomogram to help better predict OS in patients with PROC planning to commence palliative chemotherapy. This is readily available for use to counsel patients with PROC being considered for chemotherapy. This tool could also be used to stratify patients with PROC in clinical trials and facilitate the design and interpretation of future PROC trials.

Conflict of interest statement

C.K.L. received research grant paid to his institution from AstraZeneca, Roche and advisory board fees and lecture fees from AstraZeneca, Roche, Novartis and Takeda and reimbursement of travel/accommodations expenses from AstraZeneca. M.F. received grant support, advisory board fees and lecture fees from AstraZeneca and advisory board fees from MSD. A.G-M. received advisory board fees, lecture fees and travel support from Roche, Tesaro and AstraZeneca and advisory board fees from Clovis. C.K. received honoraria from Roche and AstraZeneca, advisory role for Roche, AstraZeneca and Pfizer and reimbursement of travel/accommodations expenses from Roche, Tesaro and AstraZeneca. F.H. received honoraria from Roche, PharmaMar, AstraZeneca, Clovis and Tesaro, advisory role for Roche, PharmaMar, AstraZeneca, MSD and Tesaro and reimbursement of travel/accommodations expenses from Roche, Tesaro, PharmaMar and AstraZeneca. A-C. H–B. received honoraria from Roche, Norvatis, AstraZeneca, Tesaro, Pfizer and Ipsen and advisory role for Roche, Norvatis, AstraZeneca, Tesaro, Pfizer and Ipsen. A.P. had advisory role for Roche, PharmaMar, AstraZeneca, Clovis and Tesaro andreimbursement of travel/accommodations expenses from AstraZeneca and Tesaro. E.P-L. received research grant paid to his institution from Roche, Pfizer, AstraZeneca, Clovis, Tesaro and Merck and received honoraria from Roche, Pfizer, AstraZeneca, Clovis, Tesaro and Incyte and advisory role for Roche, Pfizer, AstraZeneca, Clovis, Tesaro and Incyte and reimbursement of travel/accommodations expenses from Roche, Tesaro and AstraZeneca. All other authors declare no conflict of interest.

Role of study sponsor

This research received funding from F. Hoffmann-La Roche. Any views, opinions, findings, conclusions or recommendations expressed in this material are those solely of the authors. F. Hoffmann-La Roche did not play any role in study design; collection, analysis and interpretation of data; in the writing of the report and in the decision to submit the article for publication.

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Appendix A. Supplementary data

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