Hyperprogression under Immune Checkpoint Inhibitor: a potential role for germinal immunogenetics

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Hyperprogressive disease (HPD), an unexpected acceleration of tumor growth kinetics, is described in cancer patients treated with anti-PD-1/anti-PD-L1 agents. Here, our aim was to take into consideration the host and explore whether single nucleotide polymorphisms (SNPs) in key genes involved in immune response might predispose to HPD. DNA was extracted from blood-samples from 98 patients treated under CPI monotherapy. Four candidate genes (PD-1, PD-L1, IDO1 and VEGFR2) and 15 potential SNPs were selected. The TGKₑ (ratio of the slope of tumor growth before treatment and the slope of tumor growth on treatment) was calculated. Hyperprogression was defined as a TGKₑ ≥ 2. TGKₑ calculation was feasible for 80 patients (82%). HPD was observed for 11 patients (14%) and was associated with shorter overall survival (P = 0.003). In univariate analysis, HPD was significantly associated with age ≥ 70 y (P = 0.025), immune-related toxicity (P = 0.016), VEGFR2 rs1870377 A/T or A/A (P = 0.005), PD-L1 rs2282055 G/T or G/G (P = 0.024) and PD-L1 rs2227981 G/A or A/A (P = 0.024). Multivariate analysis confirmed the correlation between HPD and age ≥ 70 y (P = 0.006), VEGFR2 rs1870377 A/T or A/A (P = 0.007) and PD-L1 rs2282055 G/T or G/G (P = 0.018). Immunogenetics could become integral predictive factors for CPI-based immunotherapy.
Results

Patient characteristics and outcome. Patient baseline characteristics are given in Table 1. All patients were treated for an advanced malignancy. Non-small cell lung cancer (NSCLC) (n = 48) was the largest subgroup followed mainly by head and neck squamous cell carcinoma (HNSCC) (n = 16), renal cell carcinoma (RCC) (n = 14) and melanoma (n = 13). Importantly, all patients were treated by CPI monotherapy alone (anti-PD-1 or anti-PD-L1), with a majority of anti-PD1 (87%). Median age was 68 (range: 32–85), 65 were males (66%) and 70 were smokers (83%). Sixty-six patients had received previous irradiation (69%). The SNP genotype, gene information and genotype frequency are shown in Table 2.

Median follow-up was 13.3 months (95% confidence interval [CI]; 10.6 months to 15.4 months). Median irPFS was 16.8 months (95% confidence interval [CI]; 10.2 months to NA) and median OS was not reached. Twelve-month OS and 12-month PFS were 80% (95% confidence interval [CI], 72% to 90%) and 47% (95% confidence interval [CI]; 5% to 60%), respectively.

Fifteen patients experienced grade 3–4 IrAEs (15.5%), 67 grade 1–2 IrAEs (68.2%) and 16 patients had no IrAE (16.25%). Overall response was complete for 8 patients (8%), partial for 43 patients (44%), stable disease for 28 patients (28.5%) and progressive disease for 19 patients (19.5%). TGK could be calculated for 80 patients (15 patients had CPI as first line for advanced disease; pre-baseline scanner was not available for 3 patients). HPD was observed in 11 patients (14%). HPD was correlated with shorter OS (Fig. 1) compared with non-HPD patients (P = 0.003).

HPD predictive factors. In univariate analysis (Table 3), HPD was significantly associated with age ≥70 years (25% versus 6%; P = 0.025), immune-related toxicity grade ≥3 (38.5% versus 9.5%; P = 0.016); VEGFR2 rs1870377 A/T or A/A (26% versus 4%; P = 0.005), PD-L1 rs2282055 G/T or G/G (23% versus 2.5%; P = 0.024) and PD-L1 rs2227981 G/G (4.5% versus 23.5%; P = 0.024). HPD was not significantly correlated with lactate dehydrogenase (LDH) blood levels at baseline (p = 0.055). Similarly, the neutrophil-to-lymphocyte ratio (NLR) was not linked to HPD (p = 0.936). Also, tumor burden was not associated with HPD (p = 0.732). Multivariate analysis revealed an independent association between HPD and age ≥70 years (OR = 14.42; 95% confidence interval [CI]; 2 to 100; P = 0.006), rs1870377 T/A or A/A, and VEGFR2 (OR = 15.36; 95% confidence interval [CI]; 1.92 to 119; P = 0.007) and rs2282055 T/G or G/G, PD-L1 (OR = 17.73; 95% confidence interval [CI]; 11.55 to 227; P = 0.01).

A risk score was calculated by logistic regression and integrated the 3 independent variables (age, rs2282055, rs1870377) for predicting HPD. The risk for HPD was optimally estimated (OR = 18.34; 95% confidence interval [CI]; 3.38 to 99.58; P < 0.001) (Table 4).

Discussion

We observed HPD in 14% of treated patients by CPI, a figure in the range of figures reported in independent series. We identified older age as a predictive variable for HPD in accord with previously reported series. However, this point is controversial and observations have been reported in recent studies by Kim et al. and Ferrara et al. showing no association between HPD and age. These discrepancies may be due to the different evaluation methods used to evaluate HPD as well as to the retrospective nature of these studies. In agreement with others, we noted that patients with HPD had higher baseline LDH levels but which did not reach statistical significance in our hands. Our negative finding contrasts with that of Kim and coworkers reporting that patients with HPD had baseline NLR values higher than those of patients without HPD. This discrepancy can be explained by the retrospective nature of both studies and also by the relatively small number of patients. Clearly, prospective studies based on a larger set of patients would be more likely to provide firmer conclusions regard of this possible association between baseline NLR and the risk to developing HPD under CPI. To the best of our knowledge, the present study is the first cohort that explores the link between host gene polymorphisms and HPD under CPI. Our data highlight two germinal variations with rs2282055 (PD-L1) and rs1870377 (VEGFR2) having a significant and independent influence on the occurrence of HPD.

The group of patients with rs2282055 (PD-L1) G allele, either homozygous or heterozygous, was found to be significantly associated with a higher risk of developing HPD in comparison with T/T genotype, the locus being located on chromosome 9p24.1. When expressed on tumor cells, this gene down-regulates the activation of T effector cells through a key mechanism responsible for immune response evasion. However, the real impact of tumor PD-L1 expression on treatment outcome under CPI remains controversial. The regulation of tumoral and non-tumoral PD-L1 expression is a complex phenomenon and is influenced by multiple molecular pathways. rs2282055 (PD-L1) is associated with 10 other SNP all inserted in different introns of the PD-L1 gene. It has been shown that introns may have a direct or indirect influence on mRNA expression: GTEX portal (https://gtex-portal.org/home) indicates that rs2282055 is associated with down-regulated expression of PD-L1 (CD274 gene) in brain tissue while it is overexpressed in the pancreas, suggesting that rs2282055 may impact PD-L1 expression differently in different tissues. rs2282055 (PD-L1) was recently evaluated for its association with survival of patients not treated by CPI. In this latter study, the impact of rs2282055 (PD-L1) polymorphism on survival was found to be non-significant, thus suggesting a non-prognostic role of this polymorphism. Since PD-L1 expression was not available in our cohort, we could not examine potential links between this rs and the level of expression of PD-L1 protein. In conclusion, it can be suggested that rs2282055 (PD-L1) may interfere with CPI-HPD development, while the underlying mechanism remains to be elucidated.

VEGFR2 is a gene encoding for vascular endothelial growth factor receptor 2 expressed on both endothelial cells and various immune cells. VEGFR2 is a key regulator of tumor angiogenesis and tumor microenvironment by mainly promoting a high level of Tregs and by reducing the ability of T effector cells to penetrate the tumor cell bed. Of note, rs1870377 (KDR, VEGFR2, NM_002253.3:c.1416A>T) induces a missense substitution Q472H in the fifth (out of seven) extracellular Ig-like motifs that has been shown to increase VEGF-A binding.
| Variable                        | No of patients | %   |
|--------------------------------|----------------|-----|
| **Median Age (min-max)**       | 60, 83         |     |
| **Gender**                     |                |     |
| Female                         | 33             | 34  |
| Male                           | 65             | 66  |
| **Histology**                  |                |     |
| Non-small cell lung cancer     | 48             | 49  |
| Head and neck squamous cell    | 16             | 16  |
| Carcinoma Melanoma             | 13             | 13.5|
| Renal cell carcinoma           | 14             | 14.5|
| Others (2 bladder, 2 ovarian, 2 hematological, 1 gastrointestinal) | 7   | 7   |
| **Smoker**                     |                |     |
| No                             | 14             | 17  |
| Yes                            | 70             | 83  |
| **Previous irradiation**       |                |     |
| No                             | 30             | 32  |
| Yes                            | 66             | 68  |
| N/A                            | 2              |     |
| **Number of lines before recurrence** |          |     |
| 0                              | 15             | 15.5|
| 1                              | 53             | 54  |
| 2                              | 20             | 20.5|
| 3                              | 6              | 6   |
| ≥4                            | 4              | 4   |
| **Anti-PD-1/PD-L1**            |                |     |
| Anti-PD-1                      | 85             | 84  |
| Anti-PD-L1                     | 13             | 14  |
| **Reason for stopping treatment** |            |     |
| Progression                    | 33             | 75  |
| Toxicity                       | 6              | 14  |
| Prolonged response             | 4              | 9   |
| Patient                        | 1              | 2   |
| N/A                            | 54             |     |
| **Response**                   |                |     |
| Complete response              | 8              | 8   |
| Partial response               | 43             | 44  |
| Stable disease                 | 28             | 28.5|
| Progressive disease            | 19             | 19.5|
| **irAE**                       |                |     |
| 0                              | 16             | 16.25|
| 1–2                            | 67             | 68.25|
| 3–4                            | 15             | 15.5|
| **Type IrAE**                  |                |     |
| Hematologic                    | 18             | 20  |
| Dermatologic                   | 18             | 20  |
| Thyroid                        | 13             | 14.5|
| Digestive                      | 7              | 7.5 |
| Metabolic                      | 5              | 5.5 |
| Articular                      | 12             | 13.5|
| Rhinitis                       | 5              | 5.5 |
| Others                         | 12             | 13.5|
| **TGKR**                       |                |     |
| <2                             | 69             | 86  |
| ≥2                             | 11             | 14  |
| N/A                            | 18             |     |

Table 1. Patient characteristics. Abbreviations: N/A = Not Available; Anti PD-L1 = Anti-programmed cell death ligand1; Anti PD-1 = Anti-programmed cell death; TGKR= Tumor growth kinetic rate.
and activity inducing increased microvessel density in tumor tissue of patients with non-small cell lung cancer. In our series, carriers of rs1870377 (VEGFR2) with any A genotype were more prone to develop HPD. Thus, VEGFR2 substitution Q472H may play a potential role in increased tumor size due to increased angiogenesis and microvessel development in these patients. It is thus conceivable that the impact of VEGFR2 on tumor and its microenvironment may differ according to the allelic inheritance of the host with an influence on HPD development under CPI.

Collectively, one can formulate a working hypothesis with HPD occurring in a subset of patients harboring unfavorable alleles which modulate the expression of different genes inducing tumor progression under CPI.

It was interesting to identify key immunology-linked genes like PD-L1 and VEGFR2 gene variants using this approach. The present reported results remain challenging in clinical practice with particular attention given to the fact that most allelic variations are present at relatively low frequencies. However, this study contains a number of limitations which do not allow drawing definitive conclusion: the sample size is relatively small (11 HPD cases) and patients received two different classes of PD-1 and PD-L1 CPI. TGKR was not assessable for first-line treated patients. The study covered different histological types and some patients had been more or less heavily pretreated. According to the meta-analysis by Kim and coworkers, the histological type of the tumor is not predictive value for the occurrence of HPD. However, it has been reported that renal cell carcinoma (RCC) patients may be at a lesser risk of HPD. Of note, our cohort was also enriched with long-responding patients as all patients alive and treated with CPI in the department were asked their consent to dedicated blood sampling for the study. This explains the high response rate reported in our series (52%). Above all, the study remains original leading to identification of potential host-linked biomarkers for HPD prediction. Interestingly, it was possible to establish a powerful (OR = 18.34; 95% confidence interval [CI]; 3.38 to 99.58; P < 0.001) predictive score combining host characteristics such as age and germinal gene polymorphisms. Evaluating the risk of HPD by testing host immunogenetics must remain probabilistic in nature and may differ according to ethnic population, thus limiting extrapolation of the present study outside the Caucasian population. Efforts to expand other candidate

Table 2. Summary of genotyping results by MassARRAY (AGENA) of 98 patients.

| Gene SNPs | PD-1 | PD-L1 | VEGFR2 | IDO1 |
|-----------|------|-------|--------|------|
| rs10204525 | C/C (81) | C/C (74) | A/A (12) | T/T (49) |
| rs11568821 | G/G (52) | G/G (16) | G/G (12) | G/G (68) |
| rs2227981 | C/C (13) | C/C (11) | A/A (4) | A/A (28) |
| rs2228355 | T/T (63) | T/T (64) | C/C (14) | C/C (14) |
| rs2297136 | A/A (3) | A/A (25) | G/G (23) | G/G (23) |
| rs2297137 | A/G (23) | A/A (25) | G/G (57) | C/C (65) |
| rs3443815 | A/G (23) | A/G (23) | G/G (57) | C/C (53) |
| rs10815225 | T/T (52) | T/T (52) | A/A (28) | A/A (28) |
| rs3205948 | A/A (12) | A/A (12) | T/T (3) | T/T (3) |
| rs1870377 | G/G (42) | G/G (42) | C/C (11) | C/C (11) |
| rs1798777 | G/G (50) | G/G (50) | A/G (50) | A/G (50) |
| rs2305948 | G/G (68) | G/G (68) | G/G (68) | G/G (68) |
| rs1870377 | T/T (52) | T/T (52) | A/A (28) | A/A (28) |
| rs2071559 | A/A (28) | A/A (28) | T/T (4) | T/T (4) |
| rs7393319 | G/G (23) | G/G (23) | A/A (23) | A/A (23) |
| rs3080606 | A/G (23) | A/G (23) | G/G (23) | G/G (23) |
| rs739331 | C/C (11) | C/C (11) | G/G (23) | G/G (23) |
| rs9657182 | T/T (2) | T/T (2) | A/A (23) | A/A (23) |

Figure 1. Association between HPD and OS: Kaplan Meier estimates of OS of patients treated with anti PD1/anti PDL1 according to ir-RECIST criteria: clinical benefit (complete response, partial response, stable disease), PD non HPD (progressive disease) and HPD.
| Parameters                              | Univariate Analysis | Multivariate Analysis |
|----------------------------------------|---------------------|----------------------|
|                                        | TGKR<2 (N = 69)     | TGKR<2 (N = 11)      | OR 95% CI  | P value | Estimate | SE  | P value | Estimate | SE  | OR [95% CI] | P value |
|                                        |                     |                     | P value  |         |          |     |         |          |     |             |         |
| Age (year old)                         |                     |                     |          |         |          |     |         |          |     |             |         |
| <70                                    | 45 (94)             | 3 (6)               | 1        | reference |         |     |         |          |     | Reference   | 1       |
| ≥70                                    | 24 (75)             | 8 (25)              | 5        | [1.21–20.61] | 0.025 | 2.17 | 1.28   | 0.009    | 2.66 | 0.97        | 14.42   | 0.006 |
| Gender                                 |                     |                     |          |         |          |     |         |          |     |             |         |
| Male                                   | 19 (76)             | 6 (24)              | 1        | reference |         |     |         |          |     |             |         |
| Female                                 | 50 (91)             | 5 (9)               | 0.31     | [0.08–1.16] | 0.089 | 0.078 | 0.078  | 0.078    |      |             |         |
| Histology                              |                     |                     |          |         |          |     |         |          |     |             |         |
| Non-small cell lung cancer             | 14 (93.5)           | 1 (6.5)             | —        | —       |         |     |         |          |     |             |         |
| Head and neck squamous cell            | 38 (86.5)           | 6 (13.5)            | —        | —       |         |     |         |          |     |             |         |
| Carcinoma Melanoma                     | 4 (100)             | 0 (0)               | —        | —       |         |     |         |          |     |             |         |
| Renal cell carcinoma                   | 11 (91.5)           | 1 (8.5)             | —        | —       |         |     |         |          |     |             |         |
| Others f                               | 2 (40)              | 3 (60)              | —        | —       | 0.078   | 0.078 | 0.078  | 0.078    |      |             |         |
| Smoker                                 |                     |                     |          |         |          |     |         |          |     |             |         |
| No                                     | 9 (100)             | 0 (0)               | 1        | reference |         |     |         |          |     |             |         |
| Yes                                    | 51 (85)             | 9 (15)              | 1.17     | [1.05–30] | 0.594 | 1.17  | 1.05   | 0.025    | 2.17 | 1.28        | 0.009   | 14.42  | 0.006 |
| Previous irradiation i                 |                     |                     |          |         |          |     |         |          |     |             |         |
| No                                     | 17 (85)             | 3 (15)              | 1        | reference |         |     |         |          |     |             |         |
| Yes                                    | 51 (86.5)           | 8 (13.5)            | 0.88     | [0.21–3.73] | 1   | 0.88  | 0.21   | 0.016    | 1.71 | 1.14        | 0.13    | 17.73  | 0.018 |
| Number of lines before recurrence      |                     |                     |          |         |          |     |         |          |     |             |         |
| 0                                      | 5 (100)             | 0 (0)               | —        | —       |         |     |         |          |     |             |         |
| 1–4                                    | 64 (85)             | 11 (15)             | 1        | reference |         |     |         |          |     | Reference   | 1       |
| Anti-PD-1/PD-L1                        |                     |                     |          |         |          |     |         |          |     |             |         |
| Anti-PD-1                              | 59 (87)             | 9 (13)              | 1        | reference |         |     |         |          |     |             |         |
| Anti-PD-L1                             | 10 (83)             | 2 (17)              | 1.3      | [0.24–6.9] | 0.667 | 1.3   | 0.24   | 0.025    | 1.71 | 1.14        | 0.13    | 17.73  | 0.018 |
| Immune related Adverse Event d         |                     |                     |          |         |          |     |         |          |     |             |         |
| <3                                     | 47 (90.5)           | 5 (9.5)             | 1        | reference |         |     |         |          |     | Reference   | 1       |
| ≥3                                     | 8 (61.5)            | 5 (38.5)            | 5.87     | [1.38–25.01] | 0.016 | 1.71  | 1.38   | 0.016    | 1.71 | 1.14        | 0.13    | 17.73  | 0.018 |
| Lactate dehydrogenase (LDH, UI/L) j    |                     |                     |          |         |          |     |         |          |     |             |         |
|                                        | 338.5 (109–1269)    | 414 (252–770)       | 0.055    |          |         |     |         |          |     |             |         |
| NLR k                                  | 3.6 (0.72–63.52)    | 2.6 (2.64–37)       | 0.936    |          |         |     |         |          |     |             |         |
| Tumor burden i                         | 57 (12–189)         | 59 (10–143)         | 0.732    |          |         |     |         |          |     |             |         |
| VEGFR2 rs1870377                        |                     |                     |          |         |          |     |         |          |     |             |         |
| T/T                                    | 46 (96)             | 2 (4)               | 1        | reference |         |     |         |          |     | Reference   | 1       |
| A/T or A/A                             | 23 (74)             | 8 (26)              | 9        | [1.79–45.1] | 0.005 | 3.98  | 1.69   | 0.018    | 2.73 | 1.02        | 15.36   | 0.007 |
| G/T or G/G                             | 33 (77)             | 10 (23)             | 10.90    | [1.32–89.90] | 0.024 | 2.93  | 1.59   | 0.06     | 2.93 | 1.24        | 17.73   | 0.018 |
| PD-L1 rs2282055                        |                     |                     |          |         |          |     |         |          |     |             |         |
| T/T                                    | 36 (97.5)           | 1 (2.5)             | 1        | reference |         |     |         |          |     | Reference   | 1       |
| G/T or G/G                             | 33 (77)             | 10 (23)             | 10.90    | [1.32–89.90] | 0.024 | 2.93  | 1.59   | 0.06     | 2.93 | 1.24        | 17.73   | 0.018 |
| PD-L1 rs2227984 i                       |                     |                     |          |         |          |     |         |          |     |             |         |
| G/A or A/A                             | 26 (76.5)           | 8 (23.5)            | 1        | reference |         |     |         |          |     |             |         |
| G/G                                    | 41 (95.5)           | 2 (4.5)             | 6.30     | [1.24–32.05] | 0.024 | 1.83  | 1.30   | 0.15     |      |             |         |

Table 3. Univariate and multivariate analyses for hyperprogressive disease. Significant p values are bolded; aInitial model: including all variables with P < 0.05 in univariate analysis; bFinal model: same model after backward stepwise algorithm; cNS = not significant after stepwise algorithm; dData available for 65 patients; eData available for 77 patients; f2 bladder, 2 ovarian, 1 gastrointestinal; gRelative Risk [95% CI]; hFisher's exact or Wilcoxon’s test; iData available for 79 patients; jmedian (min-max), Baseline data available for 55 patients: N = 48 for TGKR<2 and N = 7 for TGKR≥2; kNeutrophil-to Lymphocyte Ratio; median (min-max); lSum of the largest diameter of target lesions at baseline, median (min-max).
genes and their polymorphisms are currently ongoing in larger prospective cohorts. Particular attention should be paid to allelic variations of HLA class I genes.

Finally, our results support the notion of a genetic susceptibility potentially impacting the development of HPD in a Caucasian population. In a broader perspective, it is hoped that the present data can stimulate further studies integrating both somatic and germinal variability aimed at satisfying the still unmet need for faithful predictive biomarkers to ensure enhanced management of cancer therapy by CPI.

Patients and Methods

Study design and patients. This is a retrospective study covering the period April to August 2018. All data were retrieved from the clinical database of the Centre Antoine Lacassagne (Nice, France). Tumor responses were evaluated after monotherapy according to RECIST 1.1 criteria (complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD)). Objective response was evaluated as previously published. Immune-related adverse events (irAEs) were evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE V5). Pre-baseline, baseline, and initial imaging results were recorded and were used to calculate the TGKR (ratio of the slope of tumor growth before treatment and the slope of tumor growth during treatment), as previously reported. The sum of the largest diameter of target lesions at baseline indicated the tumor burden at baseline. HPD was defined as a TGKR ≥ 2. Written informed consent was systemically obtained before collecting a study-dedicated blood sample. Patient characteristics, at baseline, also included age, gender, histology, smoker status, lactate dehydrogenase (LDH), neutrophil-to-lymphocyte (NLR) and tumor burden.

SNP selection and genotyping. Seventeen SNPs of PD-1 (rs10204525; rs11568821; rs22727981), PD-L1 (rs2282055; rs2297136; rs2297137; rs4143815; rs10815225; rs822339), IDO1 (rs3739319; rs3808606; rs373931; rs9657182; rs34820341) and VEGFR2 (rs2305948; rs1870377; rs2071559) were selected according to their functional and/or clinical relevance. Genomic DNA was extracted from a blood sample using the commercially-available Maxwell® 16 LEV Blood DNA Kit (#AS1290, Promega). The assay to screen the 17 SNPs was created by using Assay Design Suite v2.0 (AGENA Bioscience online software) with the “Genotyping Design” option. We had created the assay to screen the 17 SNPs. Data were verified and compatible with DNA controls polymorphism for 15 SNPs; the remaining 2 SNPs had been eliminated. The optimal number of risk groups for predictive models was obtained using the Y ounden method. Statistical considerations. The link between the 15 SNPs and clinico-radiological parameters and CPI response according to ir-RECIST criteria and irAEs was examined. Statistical comparisons were performed using χ² test or Fisher’s exact test for categorical data and Student’s test or Wilcoxon’s test for continuous variables. Immune-related progression-free survival (irPFS) and Overall Survival (OS) were respectively calculated from the baseline CT scan to progression (according to ir-RECIST criteria) or death and presented graphically using the Kaplan-Meier method. All variables significant at the 5% level in both univariate and multivariate logistic regression models were included. Co-linearity between all variables of the initial multivariate model was evaluated. The choice of the final model was made by performing a backward stepwise selection model. A fitted score for each participant by logistic regression was used to define two risk groups of patients (low or high risk of HPD). The optimal number of risk groups for predictive models was obtained using the Youden method. Statistical analyses were performed using R version 3.5.0 on Windows.

Ethical approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (French National Committee for Informatics and Liberties N°17010).

Informed consent. All patients provided written informed consent before enrollment.

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Competing interests
Gérard Milano is a member of an advisory board at B.M.S., M.S.D. and Merck. Frédéric Peyrade is a member of an advisory board at M.S.D. and Merck. Delphine Borchiellini is a member of an advisory board at M.S.D., Pfizer, Astra-Zeneca, Roche, B.M.S. Joel Guigay is a member of an advisory board at Merck. The remaining authors declare no competing interests.

Additional information
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