Preliminary Communication

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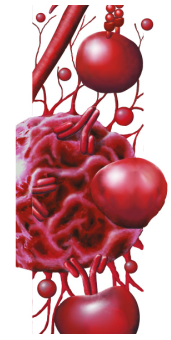
Immunotherapy



Family history of cancer as surrogate predictor for immunotherapy with anti-PD1/PD-L1 agents: preliminary report of the *FAMI-L1* study

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Aim: Tumors related to hereditary susceptibility seem to have an immunosensitive phenotype. **Materials & methods:** We conducted a multicenter retrospective study, to investigate if family history of cancer, multiple neoplasms and early onset of cancer could be related to clinical outcomes of anti-PD-1/PD-L1 therapy. Activity and efficacy data of 211 advanced cancer patients (kidney, non-small-cell lung cancer, melanoma, urothelium, colorectal and HeN), treated at seven Italian centers with anti-PD-1/PD-L1 agents, were analyzed. **Results:** In this preliminary report at multivariate analyses, positive family history of cancer showed a statistically significant relationship with a better objective response rate (p = 0.0024), disease control rate (p = 0.0161), median time to treatment failure (p = 0.0203) and median overall survival (p = 0.0221). Diagnosis of multiple neoplasms significantly correlates only to a better disease control rate, while interestingly non-early onset of cancer and sex (in favor of female patients) showed significant correlation with a better median overall survival (p = 0.0268 and p = 0.0272, respectively). **Conclusion:** This pilot study seems to individuate easily available patient's features as possible predictive surrogates of clinical benefit for anti-PD-1/PD-L1 treatments. These preliminary results need to be confirmed with a greater sample size, in prospective trials with immunotherapy.

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Keywords: family history of cancer • immunotherapy • multiple neoplasms

The advent of immune checkpoint inhibitors (ICIs) has led to a revolution in the classical paradigm of cancer care. In some cases, responses are durable with extended median progression-free survival and median overall survival (OS) beyond previous standard of care therapies. Although it was initially hoped that ICIs could be '*The Remedy*' for many types of cancers, limitations of clinical efficacy of this class of drugs are now emerging, and it is now clear that a large part of patients does not benefit from ICIs treatment. Currently in use checkpoint

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inhibitors, all of which are monoclonal antibodies, fall into three main classes: anti-CTLA4, which target CTLA4 (such as ipilimumab), anti-PD-1, which target PD-1 (such as nivolumab and pembrolizumab) and anti-PD-L1, which target PD-L1 (such as atezolizumab, durvalumab and avelumab). Common clinical practice and health economics still suffer a lack of validated predictive biomarkers to select patients who would benefit from ICIs. PD-L1 protein expression, evaluated by immunohistochemistry staining, both in tumor and immune cells, has been investigated as a potential predictive biomarker [1], even in prospective trials [2], but its correlation with ICIs efficacy is still debated [3–5]. Different companion diagnostics, with different immunohistochemistry techniques and platforms were used in clinical trials, creating difficulties in routine use in clinical practice, despite the efforts of many 'harmonization' studies [6–9]. PD-L1 expression is probably a dynamic process influenced by many events, such as previous and/or concomitant treatments, and has a wide intra-/inter-patient variability [10–12]. The only exception that has led to reliable and routine use of the test came from positive experience of the Keynote-024 Trial, which established PD-L1 tumor expression >50% as predictive factor of benefit from pembrolizumab in first-line metastatic non-small-cell lung cancer (NSCLC) setting [13]. A different possible approach to predict immunotherapy efficacy is to analyze the somatic mutational landscape of the tumor, since a high mutational tumor burden has been shown to correlate with benefit from immunotherapy [14–16]. Microsatellite instability (MSI), a condition of genetic hypermutability that results from mismatch repair deficiency, correlates with the number of somatic mutations (especially in MSI-high cases), and many studies confirmed its positive correlation with ICIs treatment, particularly with anti-PD-1 antibodies [17,18]. MSI is known to be the hallmark of Lynch syndrome (LS), a familial clustering of colorectal and endometrial cancers. LS is caused by several germline mutations, which result in a defective mismatch repair and is inherited as dominant autosomal character. Similarly, *BRCA 1* and *2* mutations, which have been associated with hereditary breast–ovarian cancer syndrome, may correlate with tumor mutational burden, because of the homologous recombination repair deficiency. 'BRCA-like' phenotype may be more sensitive to anti-PD-1/PD-L1 [19], thus prospective clinical trials with anti-PD1 for patients with germline *BRCA 1/2* mutations are currently ongoing [20]. LS and breast–ovarian cancer syndrome are just two forms of inherited cancer susceptibility; even if notoriously only about 5–10% of all cancers result directly from germline mutations, we can hypothesize that much about family cancer syndromes and cancer predisposition is still unknown. Starting from this hypothesis and from the suggestion that tumors related to syndromes with inherited susceptibility to cancer seem to have an 'immune-sensitive phenotype', we investigated if positive family history of cancer (FHC) and diagnosis of metachronous and/or synchronous multiple neoplasms (MN), could be used as possible surrogate predictors of clinical benefit for anti-PD-1/PD-L1 treatments. Furthermore, among families with syndromes of inherited susceptibility to cancer, patients' age at cancer diagnosis is typically lower when compared with those of non-hereditary cancer cases [21–23]. Thus, we hypothesized that there could also be a relationship between clinical outcomes with immunotherapy and early onset (EO) of cancer.

Materials & methods

Patient eligibility

This study evaluated advanced cancer patients who underwent treatment with anti-PD-1/PD-L1, regardless of the treatment line, at Medical Oncology Units of seven Italian centers. The patients were eligible if they had histologically confirmed diagnosis of measurable stage IV cancer, with filled records about FHC (positive or negative), and eventual history of metachronous or synchronous MN. All patients provided written, informed consent to the treatment with immunotherapy. The procedures followed were in accordance with the ethical standards of local responsible committees on human experimentation and precepts of Good Clinical Practice.

Study design

A multicenter, retrospective, observational analysis of advanced cancer patients, treated with anti-PD-1 or anti-PD-L1 monotherapy, as any treatment line, was performed. The aim of this study was to evaluate the correlations between FHC, MN, EO of cancer and clinical outcomes mostly used in clinical practice: objective response rate (ORR), disease control rate (DCR), median time to treatment failure (TTF) and median OS. ORR was defined as the portion of patients experiencing an objective response (complete response or partial response) as best response to immunotherapy; DCR was defined as the portion of patients which experienced an objective response or demonstrated stable disease as best response to treatment. TTF was defined as the time from treatment's start to discontinuation for any reason, including disease progression, treatment toxicity, patient preference or death; OS as the length of time between the beginning of treatment and death or to last contact. The correlations tests

were performed between clinical outcomes and the following patients' features: FHC status (positive vs negative), diagnosis of MN (yes vs no), age at diagnosis (EO vs non-EO), sex (male vs female), Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (0–1 vs ≥2), number of metastatic sites (including nonregional lymph nodes metastases) (≤2 vs >2) and treatment line (first vs nonfirst). Responses were evaluated with immune-related RECIST criteria [24]. $\chi 2$ and Fisher's exact test were used to correlate ORR and DCR with patient's characteristics [25,26], using the appropriate test according to the sample size in contingency tables for each comparison. Odds ratio with 95% CI was used to estimate the association between ORR, DCR and predictor variables [27]. In the multivariate analysis, logistic regression was used to evaluate the role of parameters which resulted to be significant at the univariate analysis (including FHC and MN status) of ORR and DCR [28]. Median TTF and median OS were evaluated using the Kaplan–Meier method [29]. Median period of follow-up was calculated according to the reverse Kaplan–Meier method [30]. Cox proportional hazards model [31] was used to evaluate predictor variables in univariate and multivariate analysis for median TTF and median OS. Data cut-off period was November 2017. All statistical analyses were performed using MedCalc Statistical Software version 17.9.7 (MedCalc Software bvba, Ostend, Belgium; www.medcalc.org; 2017).

Definition of family history of cancer, multiple neoplasms & early onset

Family history was collected in straight and collateral lines, till the fourth degree of relatedness (cousins, children of parents' siblings); positive FHC was defined, with at least one diagnosis of cancer found among the relatives. Diagnosis of metachronous and/or synchronous MN was defined according to the international association of cancer registry rules [32]. EO of cancer was defined for each primary tumor as follows: for NSCLC ≤60 years [33], for kidney cancer ≤46 years [34], for urothelial cancer ≤40 years [35–37], for melanoma ≤39 years [38,39], for colorectal cancer <50 years [40] and <45 years for head and neck carcinomas [41].

Results

Patients' features

From April 2015 to October 2017, 211 stage IV cancer patients underwent a treatment with anti-PD-1/PD-L1 at 7 Italian centers (Medical Oncology units of: University Hospital of L'Aquila, University Hospital of Chieti, University Hospital of Parma, University Hospital of Cagliari, Hospital of Frosinone, Pulmonary Oncology Unit of St. Camillo-Forlanini Hospital of Rome and outpatient cancer care center of Aprilia). Median age was 68 years (range: 32–85), ECOG-PS 0–1, 179 patients (84.8%), ECOG-PS ≥2, 32 patients (15.2%). Primary tumors were: renal cell carcinoma 41 patients (19.4%), melanoma 51 patients (24.2%), NSCLC 104 patients (49.3%), urothelial cancer 10 patients (4.7%), colorectal cancer three patients (1.4%) and head and neck carcinomas two patients (1%). Administered immunotherapies were: anti-PD-1 in 199 patients (94.3%) (pembrolizumab and nivolumab), anti-PD-L1 in 12 patients (5.7%) (atezolizumab and avelumab). Anti-PD-1/PD-L1 were administered as first-line treatment in 36 patients (17.1%), second-line in 103 patients (48.8%), third-line in 45 patients (21.3%), fourth-line in 19 patients (9.0%) and fifth-line in 8 patients (3.8%). Thirty-two patients (15.2%) had diagnosis of metachronous MN (no synchronous malignances were reported), 107 patients (50.7%) had positive FHC. The patients with EO of cancer were 21 (9.9%). All patients' features, distinct by subgroup, are listed in Table 1.

Activity & efficacy

All activity data are summarized in Table 2. Among 211 patients, 190 (90.1%) were evaluable for activity; the other 21 patients (9.9%) had not yet evaluated the disease at the time of the data cut-off analysis. ORR and DCR in overall population were 37.4 and 60.5%, respectively. ORR and DCR among patients with positive FHC were 45.2 and 68.8%, while in patients with negative FHC were 24.7 and 52.6%. ORR and DCR among patients with diagnosis of MN were 53.8 and 84.6%, while in patients without diagnosis of MN were 31.7 and 56.7%. ORR and DCR among patients with EO of cancer were 25 and 55%, while in patients with non-EO of cancer were 35.9 and 61.2%. As the forest plot for univariate analysis shows (Figure 1), the variables which were significantly related to ORR are FHC ($p = 0.0032$), diagnosis of MN ($p = 0.0280$) and ECOG-PS ($p = 0.0273$). At multivariate analysis, FHC and ECOG-PS were confirmed as independent predictors for ORR ($p = 0.0024$ and $p = 0.0295$, respectively) while not diagnosis of MN ($p = 0.0546$) (Figure 2). Also regarding DCR, FHC ($p = 0.0024$), diagnosis of MN ($p = 0.0085$) and ECOG-PS ($p = 0.0019$) were significantly related at univariate analysis (Figure 3), and they all were confirmed as independent predictors at multivariate analysis ($p = 0.0161$, $p = 0.0217$ and $p = 0051$, respectively) (Figure 4).

Table 1. Patients' features.

	Number (%)	Positive FHC	Negative FHC	Positive MN	Negative MN	EO	Non-EO	Female	Male
Patients (n)	**211**	**107 (50.7)**	**104 (49.3)**	**32 (15.2)**	**179 (84.8)**	**21 (9.9)**	**190 (90.1)**	**69 (32.7)**	**142 (67.3)**
Age, years									
Range	32–85	36–85	32–85	45–85	32–85	32–60	43–85	36–85	32–85
Median	68	67	68	74	67	53	68	66	68
ECOG-PS									
0–1	179 (84.8)	90 (84.1)	89 (85.6)	31 (96.9)	148 (82.7)	15 (71.4)	164 (86.3)	61 (88.4)	118 (83.1)
≥2	32 (15.2)	17 (15.9)	15 (14.4)	1 (3.1)	31 (17.3)	6 (28.6)	26 (13.7)	8 (11.6)	24 (16.9)
Primary tumor									
NSCLC	104 (49.3)	56 (52.3)	48 (46.2)	16 (50.0)	88 (49.1)	18 (85.7)	86 (45.3)	27 (39.1)	77 (54.2)
Melanoma	51 (24.2)	22 (20.6)	29 (27.9)	7 (21.9)	44 (24.6)	2 (9.5)	49 (25.8)	23 (33.3)	28 (19.7)
Renal cell carcinoma	41 (19.4)	21 (19.6)	20 (19.2)	6 (18.7)	35 (19.6)	1 (4.8)	40 (21.0)	15 (21.7)	26 (18.3)
Urothelial cancer	10 (4.7)	6 (5.6)	4 (3.8)	3 (9.4)	7 (3.9)	-	10 (5.3)	2 (2.9)	8 (5.7)
Colorectal	3 (1.4)	2 (1.9)	1 (1.0)	-	3 (1.7)	-	3 (1.6)	1 (1.5)	2 (1.4)
HeN	2 (1.0)	-	2 (1.9)	-	2 (1.1)	-	2 (1.0)	1 (1.5)	1 (0.7)
Number of metastases									
≤2	112 (53.1)	55 (51.4)	57 (54.8)	20 (62.5)	92 (51.4)	11 (52.4)	101 (53.2)	41 (59.4)	71 (50)
>2	99 (46.9)	52 (48.6)	47 (45.2)	12 (37.5)	87 (48.6)	10 (47.6)	89 (46.8)	28 (40.6)	71 (50)
Type of immunotherapy									
Anti-PD1	199 (94.3)	100 (93.5)	99 (95.2)	30 (93.7)	169 (94.4)	20 (95.2)	179 (94.2)	66 (95.7)	133 (93.7)
Anti-PDL1	12 (5.7)	7 (6.5)	5 (4.8)	2 (6.3)	10 (5.6)	1 (4.8)	11 (5.8)	3 (4.3)	9 (6.3)
Line of immunotherapy									
First	36 (17.1)	17 (15.9)	19 (18.3)	4 (12.5)	32 (17.9)	2 (9.5)	34 (17.9)	16 (23.2)	20 (14.1)
Second	103 (48.8)	50 (46.7)	53 (51.0)	15 (46.9)	88 (49.1)	12 (57.1)	91 (47.9)	34 (49.3)	69 (48.6)
Third	45 (21.3)	25 (23.4)	20 (19.2)	8 (25.0)	37 (20.7)	5 (23.8)	40 (21.0)	13 (18.8)	32 (22.5)
Fourth	19 (9.0)	11 (10.3)	8 (7.7)	4 (12.5)	15 (8.4)	1 (4.8)	18 (9.5)	5 (7.2)	14 (9.9)
Fifth	8 (3.8)	4 (3.7)	4 (3.8)	1 (3.1)	7 (3.9)	1 (4.8)	7 (3.7)	1 (1.5)	7 (4.9)

EO: Early onset; FHC: Family history of cancer; MN: Multiple neoplasm; NSCLC: Non-small-cell lung cancer.

Table 2. Activity data for overall population, and subgroups: positive family history of cancer, negative family history of cancer, diagnosis of multiple neoplasms, absence of multiple neoplasms, early onset of cancer and non-early onset of cancer.

	Overall	FHC	Non-FHC	MN	Non-MN	EO	Non-EO
Number of evaluable patients	190	93	97	26	164	20	170
Objective response rate	37.4 (95% CI: 26.8–44.1)	45.2 (95% CI: 32.5–61.0)	24.7 (95% CI: 15.8–36.8)	53.8 (95% CI: 29.4–90.3)	31.7 (95% CI: 23.6–41.5)	25.0 (95% CI: 8.1–58.3)	35.9 (95% CI: 27.4–46.1)
Partial/complete response	66	42	24	14	52	5	61
Disease control rate	60.5 (95% CI: 49.9–72.6)	68.8 (95% CI: 53.0–87.8)	52.6 (95% CI: 39.1–69.1)	84.6 (95% CI: 65.1–95.6)*	56.7 (95% CI: 45.7–69.4)	55.0 (95% CI: 27.4–98.4)	61.2 (95% CI: 49.9–74.1)
Stable disease	49	22	28	8	41	6	43

EO: Early onset; FHC: Family history of cancer; MN: Multiple neoplasm.
*Used binomial confidence interval, beacuse of the small sample size of the subgroup.

All the patients were evaluable for efficacy analysis; after a median follow-up of 12.6 months median TTF in overall population was 7.3 months (95% CI: 5.9–13.1) and median OS was 14.8 months (95% CI: 12.1–21.8) (Figure 5). At univariate analysis FHC ($p = 0.0108$), number of metastatic sites ($p = 0.0370$), ECOG-PS ($p < 0.0001$) and sex ($p = 0.0301$) were significantly related to median TTF, while only FHC ($p = 0.0203$) (Figure 6) and ECOG-PS ($p < 0.0001$) were confirmed as independent predictors at multivariate analysis (Table 3). At univariate analysis FHC ($p = 0.0192$), EO of cancer ($p = 0.0293$), number of metastatic sites ($p = 0.0127$), ECOG-PS ($p < 0.0001$) and sex ($p = 0.0051$) were significantly related to median OS. FHC ($p = 0.0221$), ECOG-PS ($p < 0.0001$), sex

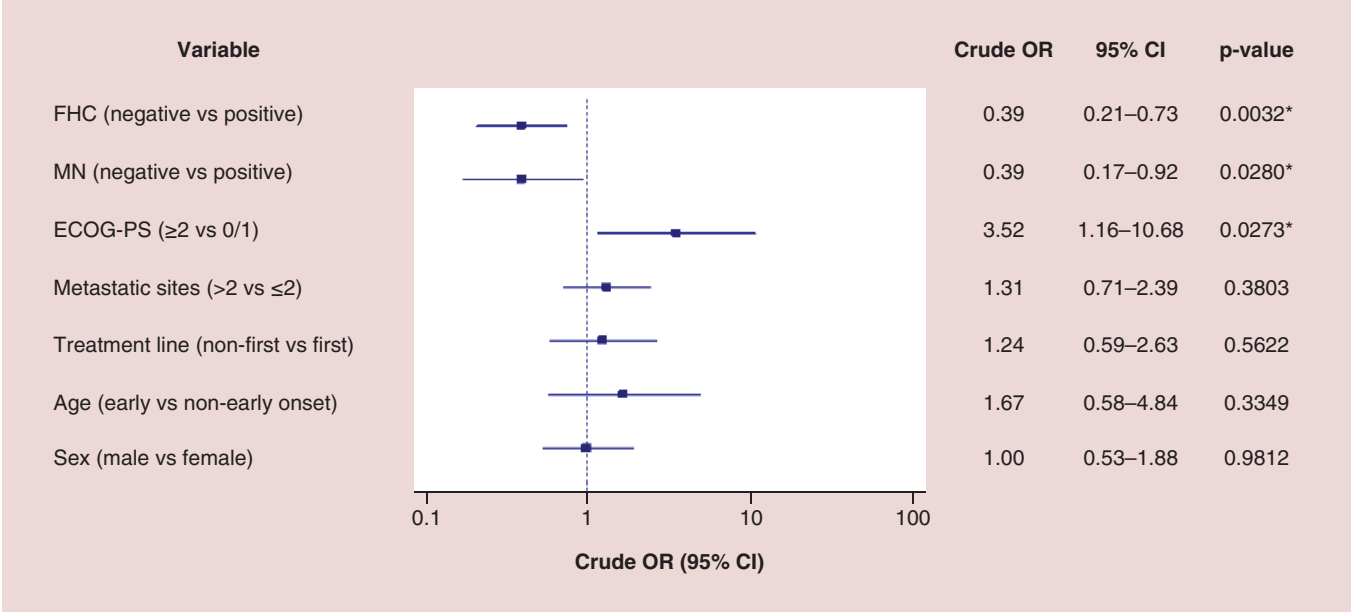

Figure 1. Forest plot graph of univariate analysis of objective response rate.
*Statistically significant.

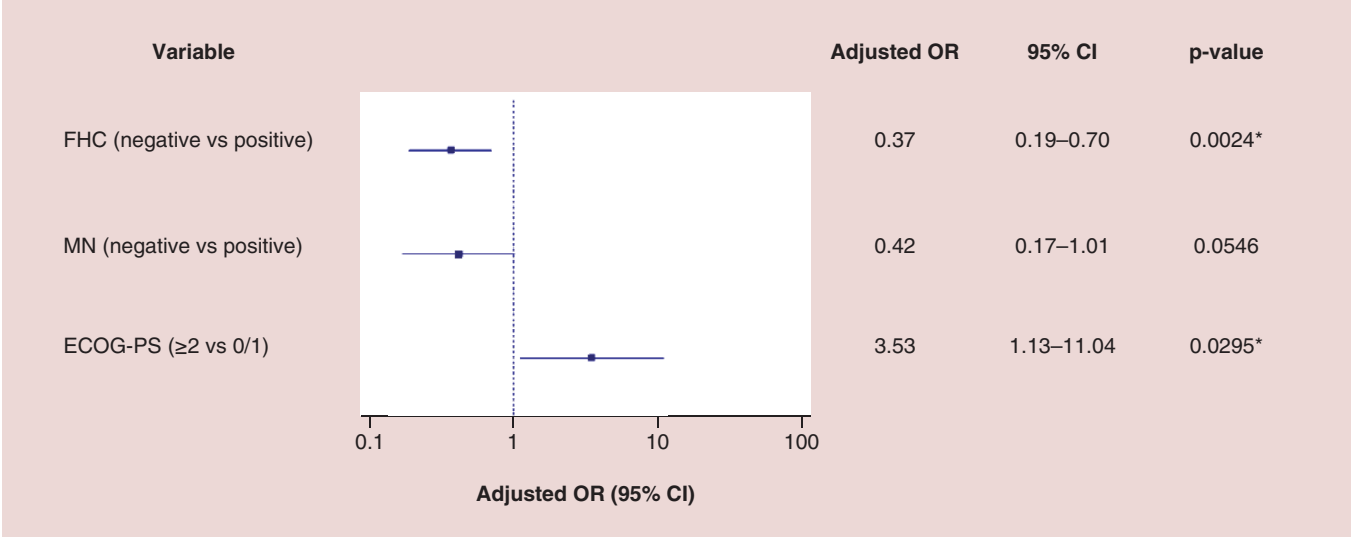

Figure 2. Forest plot graph of multivariate analysis of objective response rate.
*Statistically significant.

(p = 0.0272) and EO of cancer (p = 0.0268) were confirmed as independent predictors at multivariate analysis (Figure 7 & Table 3).

Discussion

The statistically significant correlations, at multivariate analyses, with a benefit in ORR, DCR, median TTF e (time to treatment failure calculated with kaplan-meier as a survival interval) median OS in favor of positive FHC, allow us to say that our preliminary results appear to confirm the hypothesis that FHC could be used as predictive surrogates of clinical benefit to anti-PD-1/PD-L1 therapy. Diagnosis of MN seems to have a less defined role, being significant related only to DCR. The lack of clinical decisional parameters for immunotherapy choice in advanced cancer patients makes it challenging to select the best treatment option, especially when not supported by the

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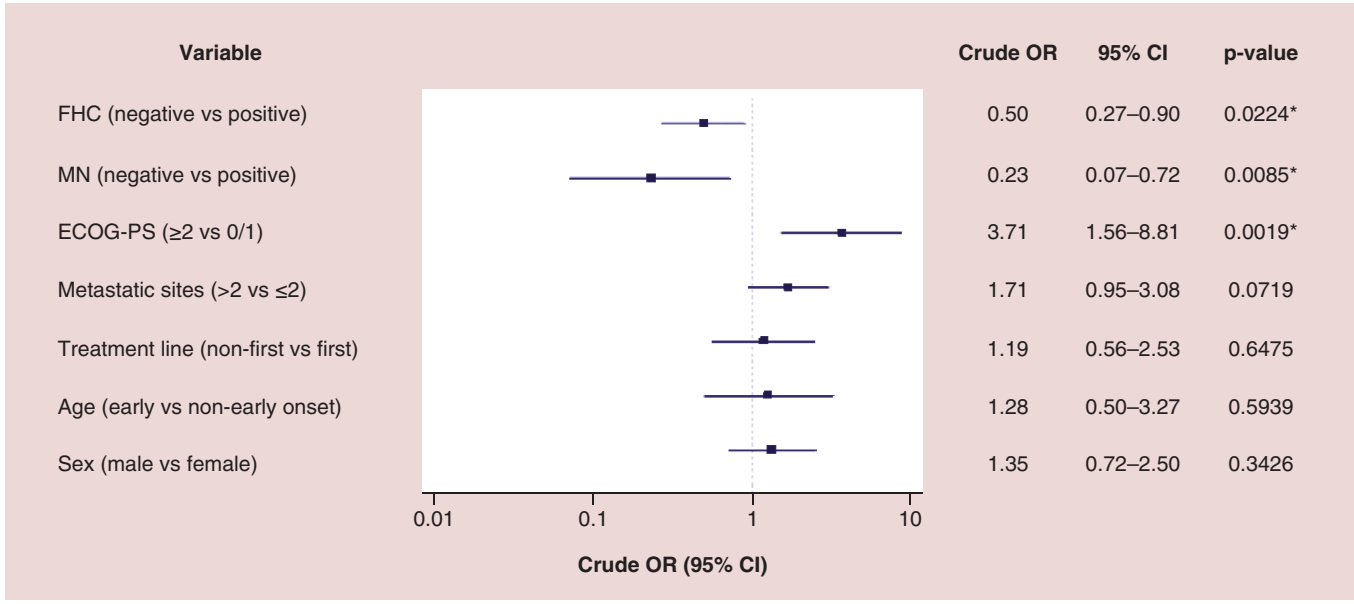


Figure 3. Forest plot graph of univariate analysis of disease control rate.
*Statistically significant.

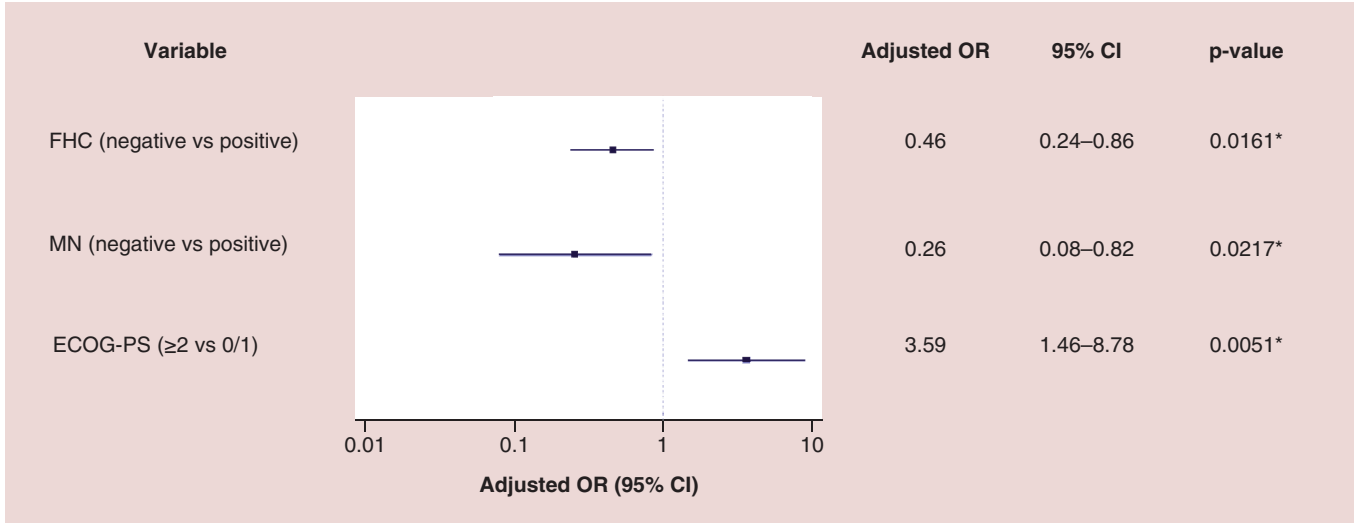
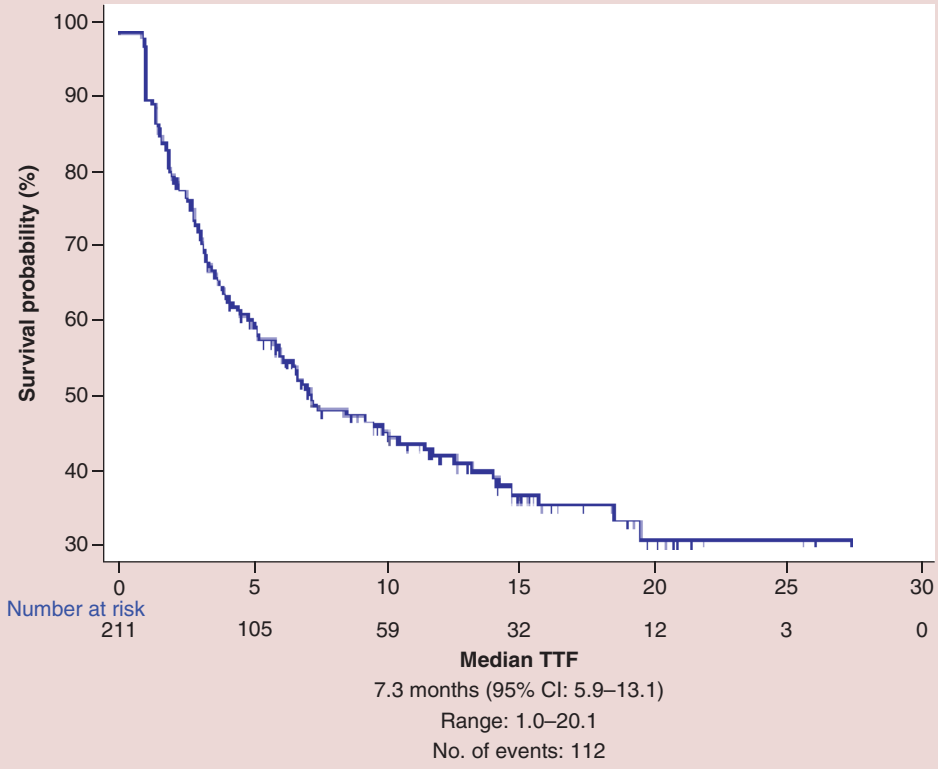


Figure 4. Forest plot graph of multivariate analysis of disease control rate.
*Statistically significant.

presence of an indisputable biomarker. Sometimes, despite offering immune-checkpoint blockade as the probably best treatment chance for patients, we would like to improve our counseling to inform patients about their chance of benefit from this therapy. A simple anamnestic parameter, such as FHC, could be easily used, rather than as a method of selection, to provide a more tailored prediction of treatment outcomes. The hypothesis that there could be a relationship between clinical benefit with anti-PD-1/PD-L1 therapy and EO of cancer, was unexpectedly denied by our preliminary data, showing an opposite trend in favor of non-EO of cancer. A possible explanation could be represented by the higher incidence, among young patients, of very aggressive forms of cancers (such as renal carcinoma with Xp11.2 translocation). Our result of a statistically significant benefit in OS for patients with non-EO of cancer compared with whom with EO of cancer meets halfway the opposite evidences of immunosenescence and residual immunocompetence in elderly patients [42,43]. The statistically significant correlation between sex and median OS at multivariate analysis, in favor of female patients, remains partly unexplained, and needs further



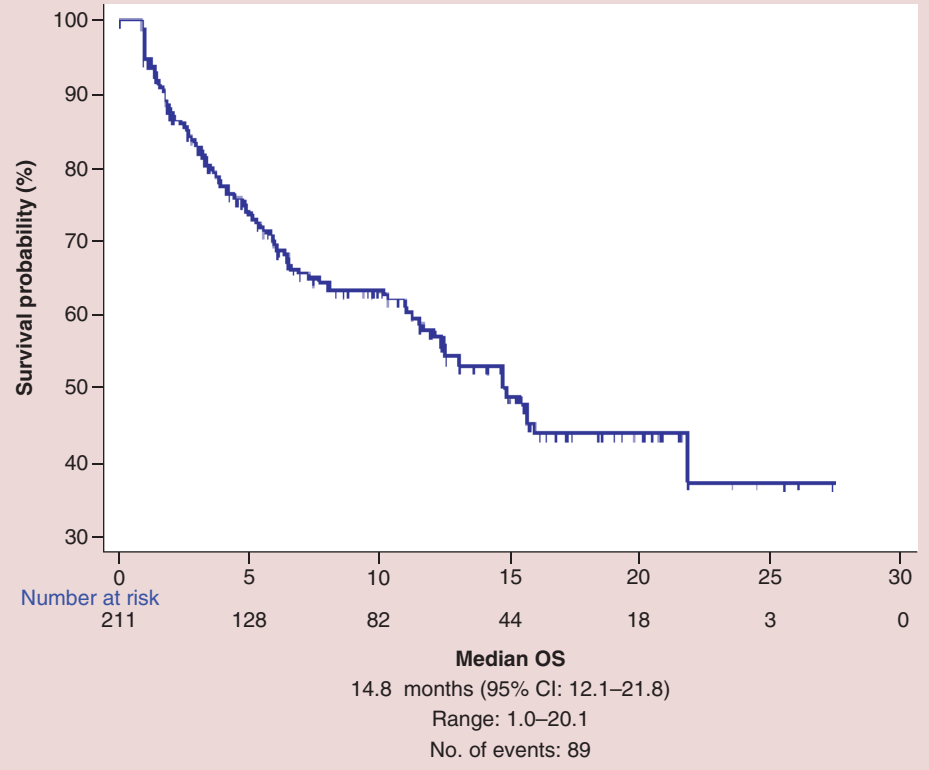


Figure 5. Kaplan–Meier survival estimate for median time to treatment failure and median overall survival in overall population.

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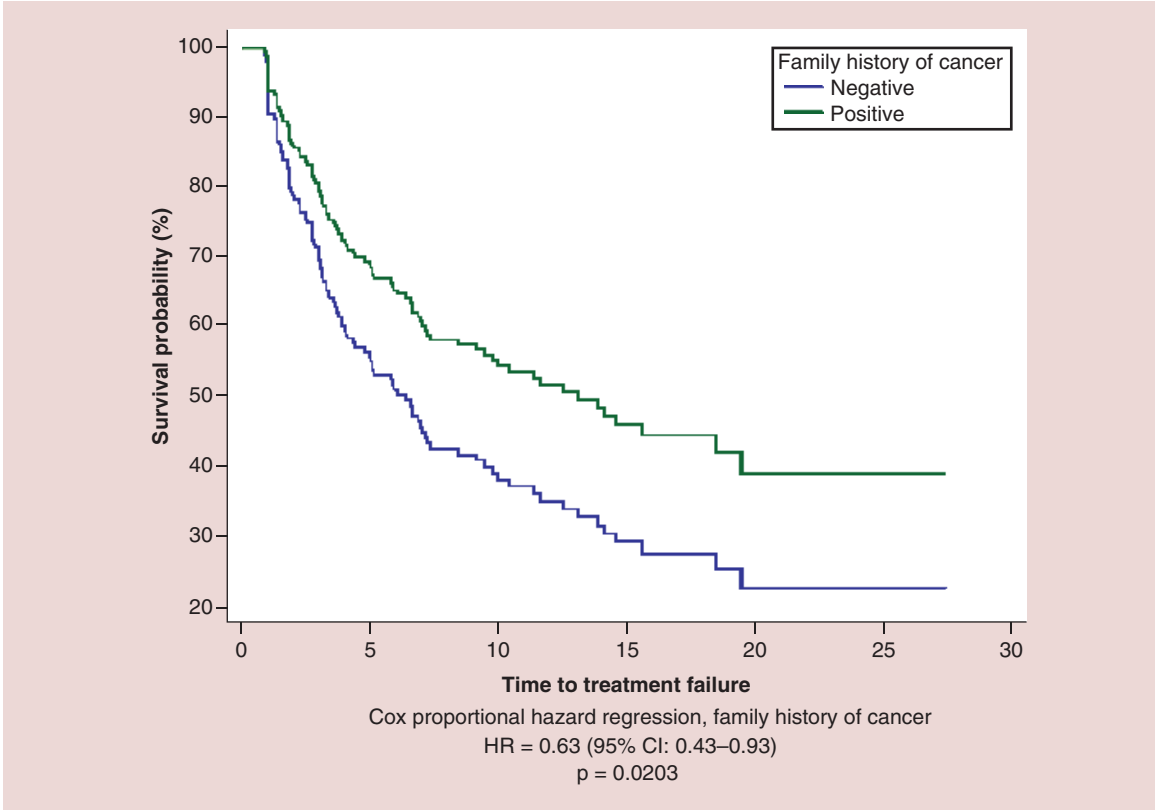

Figure 6. Cox proportional hazard regression survival estimate for positive versus negative family history of cancer in multivariate analysis.

confirmations. Even if it starts to be known that there are sex-driven differences in immunological responses, which could bring to different patterns of response to immunotherapy for male and female patients [44], as Table 1 shows, male and female populations were unbalanced in two important categories: primary tumors (e.g., more NSCLC among male patients and more melanoma among female patients) and number of metastatic sites.

Among limits of the present study, the retrospective design with its selection biases, could partly explain that clinical outcomes in overall population are higher than what is generally reported with anti-PD-1/PD-L1 agents. We must also discuss about the heterogeneity of our population: analyzing in the same time different type of cancer and different treatment lines could bring us to misestimate results. In contrast of that, Table 1 shows that patients' features among patients with positive and negative FHC (ECOG-PS, age, primary tumor, number of metastases and line of immunotherapy) are well balanced in two subgroups. Even if TTF is a composite end point, influenced by factors unrelated to efficacy, in our opinion it better fits to our population, which came from clinical practice and had a spurious nature. We must further cite the lack of centralized imaging revision, and of a discussion about possible implications of previous/subsequent systemic treatments, which will be better analyzed in the future development of the study. As we said in the introduction, probably most of the genetic and molecular mechanisms that underlie inherited susceptibility to cancer are still unknown; in a similar way we still have not understand the mechanisms that allow some patients to benefit from immunotherapies more than others. For these reasons, the aim of this preliminary analysis is just to validate the hypothesis, deliberately without biomarkers assessment; our intention was to find a correlation between FHC and anti-PD1/PD-L1 therapy, *"explaining from afar a phenomenology that we are still not able to describe closely"*.

We have already planned to extend the study to other centers: with a bigger sample size and a longer follow-up, we could investigate the role of FHC, diagnosis of MN and EO of cancer in each type of primary tumor and in patients with homogeneous characteristics (e.g., second-line setting in NSCLC patients), planning a stratification for 'burden' of positive FHC. A tissue bank for biomarkers assessment will be included in the next phase of the

Table 3. Univariate and multivariate analysis data for time to treatment failure.

Univariate analysis – TTF		
Variable (n)	**HR (95% CI)**	**p-value**
FHC – Positive (107) Negative (104)	0.61 (0.41–0.89)	0.0108*
MN – Yes (32) – No (179)	0.86 (0.49–1.48)	0.5889
Onset – Early (21) – Non-early (190)	0.68 (0.38–1.19)	0.1798
Number of metastases – ≤2 (112) – >2 (99)	1.48 (1.02–2.15)	0.0370*
ECOG-PS – 0–1 (179) – ≥2 (32)	3.23 (2.08–5.01)	<0.0001*
Sex – Male (142) – Female (69)	1.58 (1.04–2.39)	0.0301*
Treatment line – First (36) – Nonfirst (175)	1.04 (0.63–1.70)	0.8682
Multivariate analysis		
FHC	0.63 (0.43–0.93)	0.0203*
ECOG-PS	3.16 (1.99–5.01)	<0.0001*
Number of metastases	1.17 (0.79–1.73)	0.4127
Sex	1.48 (0.97–2.25)	0.0680

ECOG-PS: Eastern Cooperative Oncology Group Performance Status; FHC: Family history of cancer; MN: Multiple neoplasm; TTF: Time to treatment failure.
*Statistically significant.

study. In case of confirmation of such interesting results, these evidences will deserve to be confirmed also in prospective trials.

Conclusion

In a scenario with lack of useful factors to make a proper selection among patients to treat or not with anti-PD-1/PD-L1 therapy, this pilot study seems to individuate easily available patient's features as possible predictive surrogates of clinical benefit. These preliminary results need to be confirmed with a greater sample size, in order to extend the follow-up in each type of primary tumor. Assessment of FHC and MN should be preplanned in prospective trials with immunotherapy, to provide an external validation of their predictive role (Table 4).

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A Cortellini received honoraria as speaker at a scientific event from Boehringer Ingelheim. C Ficorella received honoraria for advisory role and as a speaker at scientific events from Sanofi and Pfizer. M Bersanelli received honoraria for advisory role and as speakers form Bristol-Myers Squibb, Pfizer and Novartis. S Buti received honoraria for advisory role and as a speaker from Bristol-Myers Squibb, Pfizer, Novartis and AstraZeneca, Roche and Merck, Sharp & Dohme. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

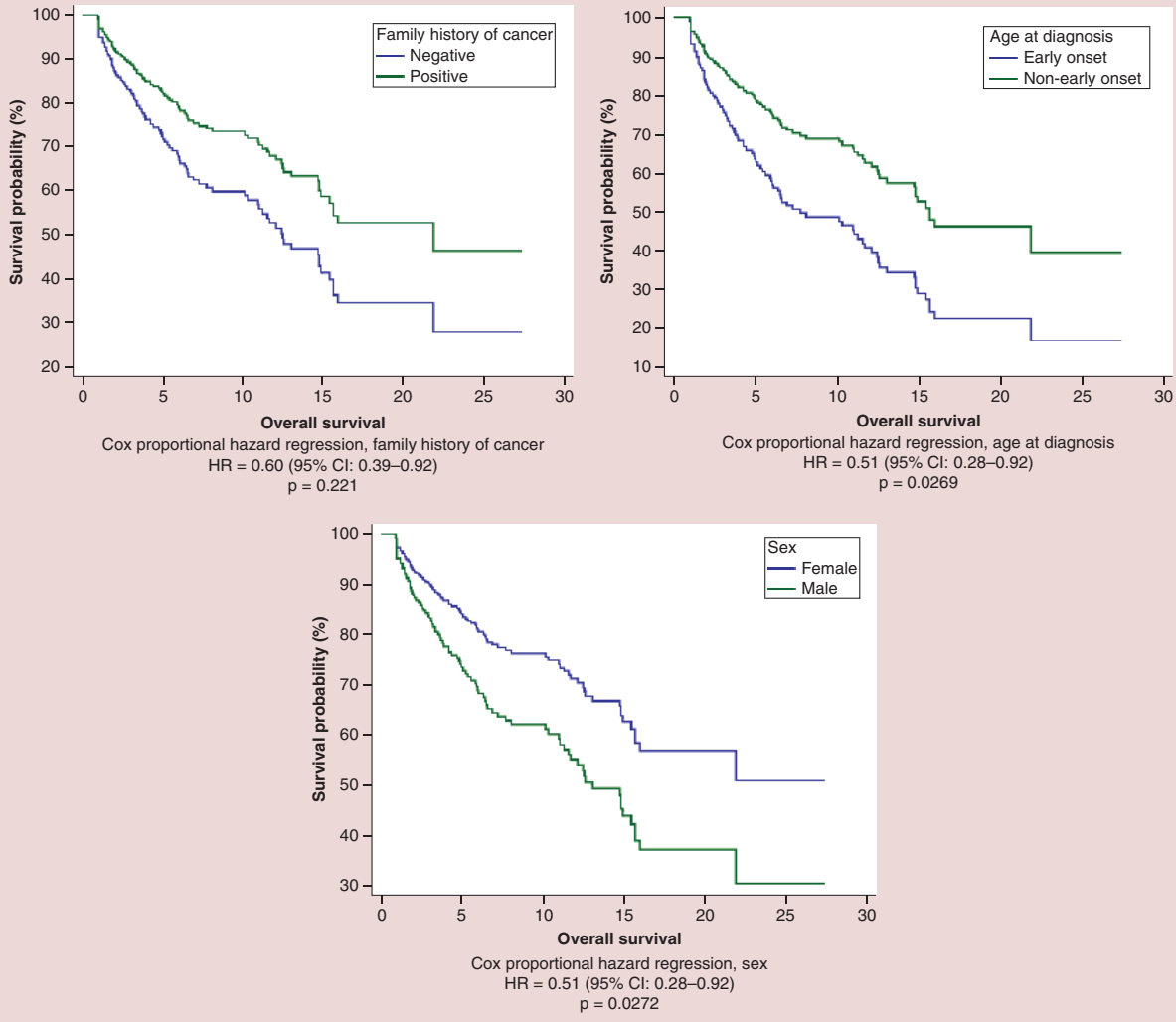

Figure 7. Cox proportional hazard regression survival estimate for positive versus negative family history of cancer, early onset versus non-early onset of cancer and male versus female in multivariate analysis.

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Table 4. Univariate and multivariate analysis data for overall survival.

Univariate analysis – OS		
Variable (n)	**HR (95% CI)**	**p-value**
FHC Positive (107) Negative (104)	0.60 (0.39–0.92)	0.0192*
MN Yes (32) No (179)	0.89 (0.48–1.63)	0.7090
Onset Early (21) Non-early (190)	0.52 (0.29–0.93)	0.0293*
Number of metastases ≤2 (112) >2 (99)	1.70 (1.12–2.59)	0.0127*
ECOG-PS 0-1 (179) ≥ 2 (32)	4.18 (2.62–6.66)	<0.0001*
Sex Male (142) Female (69)	2.01 (1.23–3.29)	0.0051*
Treatment Line First (36) Non-first (175)	1.14 (0.64–2.02)	0.6498
Multivariate analysis		
FHC	0.60 (0.39–0.92)	0.0221*
ECOG-PS	3.74 (2.26–6.20)	<0.0001*
Number of metastases	1.24 (0.79–1.96)	0.3392
Sex	1.75 (1.06–2.88)	0.0272*
Onset	0.51 (0.28–0.92)	0.0268*

ECOG-PS: Eastern Cooperative Oncology Group Performance Status; FHC: Family history of cancer; MN: Multiple neoplasm; OS: Overall surival.
*Statistically significant.

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