

Molecular profiling and access to treatment for rare cancers in Europe

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Arcagen is a clinical study proposing a comprehensive analysis of molecular and clinical characteristics of rare adult solid cancers (11 domains: sarcomas, gynecology, uro-genital, GI, NET, head and neck, thoracic, skin and eyes, CNS and CUP) across Europe, utilizing the EORTC-SPECTA platform with the EURACAN ERN. This study enrolled 1235 advanced stage patients. 893 were evaluable for molecular profiling toward a potential access to personalized therapy. In the 11 different domains, 69.4% (620/893) of patients had actionable mutations, among whom 93 (15% of 620 patients with currently actionable alterations) received targeted- or immune (IO)-therapies. The median overall survival of the patient population without treatment adaptation, with switch to targeted therapy, or immunotherapy was 1.1, 3.3 years, and not reached, respectively. Across Europe, high prevalence and diversity of molecular alterations for rare solid tumors were observed as well as significant disparities regarding access to personalized medicine approaches.

Rare cancers are defined by an annual incidence <6 per 100,000 people¹. While individual rare cancer are low incidence, when combined, they correspond to 22% (~650,000 new diagnoses annually) of overall cancer incidence and cause over 30% of cancer mortality in the EU¹. It is estimated that 5.1 million people live with a rare cancer in

Europe. In 2017, 4 European reference networks (ERN) were launched to address the challenges of rare cancer (including hereditary syndromes) management with the aim to improve patient pathways, diagnosis, care, and dedicated research². EURACAN is the ERN dedicated to rare adult solid cancers.

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The optimal management of rare cancers is hindered by difficulties in accessing timely and expert diagnosis with molecular biology support, lack of access to expert cancer care centers, limited clinical research involvement, more restricted access to new therapies, and the generation of isolation and financial burden due to living with a rare cancer condition³. Clinical studies are complicated to conduct, not prioritized, with methodological challenges given the low numbers of patients and the diversity of tumor subtypes^{4–7}. While management of rare cancer in reference centers has been shown to improve the quality of diagnosis of cancer and survival¹, access to expert diagnosis and molecular biology remains often a challenge for many EU regions and countries, despite some clinical trials such as DART⁸.

Within EURACAN, in partnership with the EORTC, the Arcagen study (NCT02834884) was initiated to address the question of access to molecular profiling to guide treatment strategies and better classify rare cancers.

This study aimed to assess the feasibility and impact of using tissue and liquid comprehensive genomic profiling in a real-world setting to facilitate personalized treatment approaches across multiple rare cancer domains. Here, we seek to describe the spectrum of molecular alterations in rare cancers across Europe and assess the clinical outcomes of patients receiving treatments based on their molecular profile.

Results

Study cohort

Between July 2020 and January 2023, Arcagen registered 1235 patients with advanced rare cancers across 13 countries in Europe (Fig. 1a, b), within the EORTC-SPECTA platform (NCT02834884). Overall, 893 (72.3%) were ultimately evaluable for this study, with 165 (13.4%) patients failing to meet the clinical eligibility criteria (cancer not considered as rare (57/34.5%), not advanced (44/26.7%), missing samples or clinical information (64, 38.8%) and 75 (6%) patients from all domains with unsuccessful molecular profiling (from FFPE and/or ctDNA, Fig. 1a), and considered as screening failure.

CUP was added as a cohort in this study as a rare form of cancer, though not included so far in the EURACAN list of diseases.

As main eligibility criteria, we requested that all patients were reviewed by a EURACAN center or an expert center on the given rare cancer, according to ESMO/EURACAN recommendations⁹.

Most molecular profiling was performed on tumor tissue (FFPE, $n = 657$, 73.6%). In case of unsuccessful sequencing or inadequate FFPE material, analysis on ctDNA was performed for 236 (26.4%) patients, using the tests from Foundation Medicine. FFPE adequacy was the most common reason for using ctDNA (block older than 2 years ($n = 51$, 21.6%), insufficient quantity of FFPE material ($n = 60$, 25.4%) or central FFPE QC failure ($n = 49$, 20.8%). A rescue was possible using ctDNA ($n = 76$, 32.2%). Median turn-around time was similar for both analysis (14.0 vs 12.5 days) from sample reception to molecular report (Fig. 1a). In addition, TAT from patient registration in Arcagen (signature of consent) to eligibility confirmation is 27 days for FFPE and 44 days for blood. Accrual was made mostly in 3 countries, France ($n = 392$, 43.9%), Portugal ($n = 226$, 25.3%) and Belgium ($n = 121$, 13.5%) (Fig. 1b). The highest and fastest recruitment was seen for rare gastro-intestinal (GI, domain 5, $n = 119$, 13%, in particular for cholangiocarcinomas ($n = 72$)), whereas for rare genito-urinary (GU, domain 3, $n = 23$, 3%) and domain 9 enrolling rare skin cancer and uveal melanoma ($n = 49$, 5%) recruitment was slow (Fig. 1c).

Clinical characteristics of the patient population

Patient clinical characteristics per domain are displayed in Table 1, and clinical characteristics for domain 1–10 and CUP separately are provided in Supplementary Fig. 3c, d. The sex ratio was 0.98 (441 males and 452 females). The median age at diagnosis was 56 (range 6–90) and 60 at registration (range 12–91). Most patients had received chemotherapy in first-line metastatic settings (1L, $n = 543$, 60.8%). As expected, strong disparities in the treatment landscape between domains were observed, with CNS malignancies (domain 10) being the outlier (only 11.5% of patients receiving chemotherapy vs 57.4% of patients receiving RT in 1L). Specifically for CUP, we assessed the risk

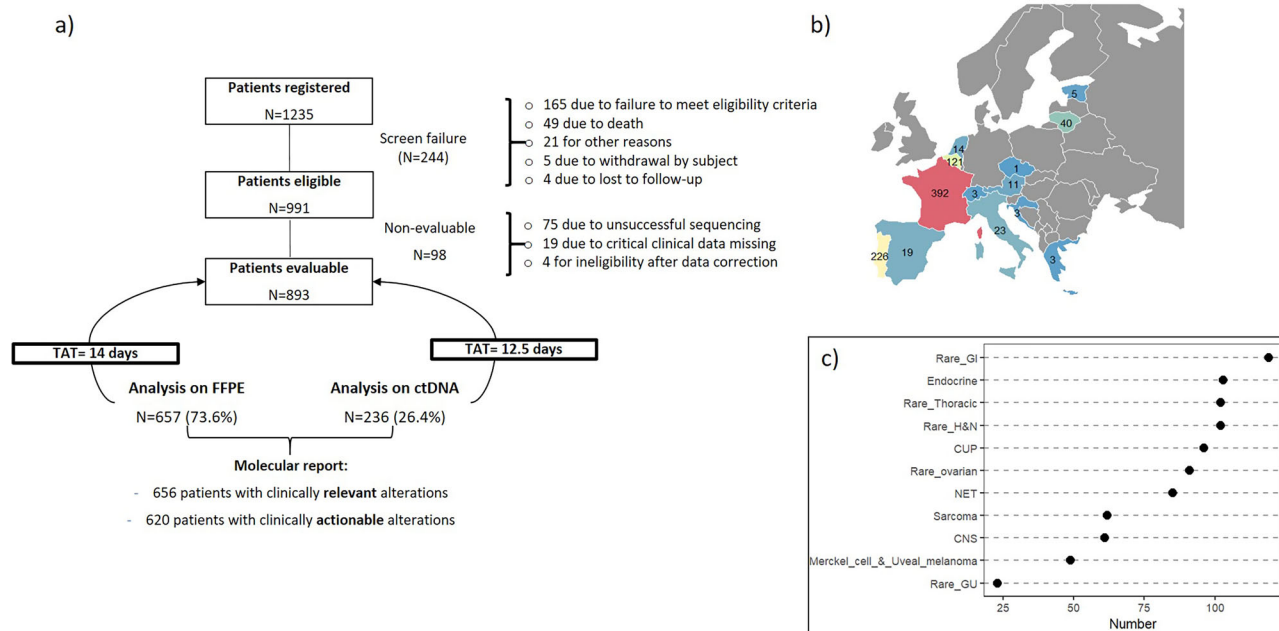


Fig. 1 | Description of patient accrual. a Flowchart of the Arcagen study. Clinically relevant alterations are defined as alterations relevant for diagnosis, staging and treatment. Clinically actionable alterations are defined as alterations linked to a treatment option, incl. clinical trial (as per FMI reporting in the test report). The TAT is calculated from sample collection to the reception of the molecular report.

In addition, TAT from patient registration in Arcagen (signature of consent) to eligibility confirmation is 27 days for FFPE and 44 days for blood. **b** Map of Europe highlighting the recruitment. **c** Recruitment (evaluable patients) per EURACAN domain. TAT: Turn-Around Time; ctDNA: circulating tumor DNA; FFPE: Formalin-Fixed Paraffin-Embedded.

Table 1 | Clinical characteristics of Arcagen patients per domain and global population

	Domain										Total (N = 893)	
	Domain 1 (N = 62) N (%)	Domain 2 (N = 90) N (%)	Domain 3 (N = 24) N (%)	Domain 4 (N = 85) N (%)	Domain 5 (N = 119) N (%)	Domain 6 (N = 103) N (%)	Domain 7 (N = 102) N (%)	Domain 8 (N = 102) N (%)	Domain 9 (N = 49) N (%)	Domain 10 (N = 61) N (%)	CUP (N = 96) N (%)	N (%)
Sex												
Female	25 (40.3)	90 (98.9)	0 (0.0)	38 (44.7)	56 (47.1)	67 (65.0)	44 (43.1)	37 (36.3)	25 (51.0)	25 (41.0)	45 (46.9)	452 (50.6)
Male	37 (59.7)	0 (0.0)	24 (100.0)	47 (55.3)	63 (52.9)	36 (35.0)	58 (56.9)	65 (63.7)	24 (49.0)	36 (59.0)	51 (53.1)	441 (49.4)
Age at registration												
<60	48 (77.4)	63 (70.0)	21 (87.5)	37 (43.5)	58 (48.7)	36 (35.0)	51 (50.0)	26 (25.5)	10 (20.4)	44 (72.1)	41 (42.7)	435 (48.7)
≥60	14 (22.6)	27 (30.0)	3 (12.5)	48 (56.5)	61 (51.3)	67 (65.0)	51 (50.0)	76 (74.5)	39 (79.6)	17 (27.9)	55 (57.3)	458 (51.3)
Median	48.0	52.5	37.0	61.0	60.0	64.0	59.5	69.5	67.0	48.0	61.5	60.0
Range	12.0–78.0	12.0–87.0	20.0–71.0	29.0–85.0	14.0–88.0	22.0–89.0	22.0–86.0	16.0–91.0	38.0–86.0	13.0–72.0	23.0–90.0	12.0–91.0
Mean	47.0	51.8	39.6	60.3	58.9	63.0	58.5	65.5	67.3	47.5	60.8	58.0
Std Dev	17.0	16.0	13.6	12.6	13.4	14.2	15.1	12.9	9.9	14.0	12.6	15.4
Age at diagnosis												
<60	50 (80.6)	69 (76.7)	22 (91.7)	43 (50.6)	64 (53.8)	53 (51.5)	65 (63.7)	30 (29.4)	21 (42.9)	50 (82.0)	41 (42.7)	508 (56.9)
≥60	12 (19.4)	21 (23.3)	2 (8.3)	42 (49.4)	55 (46.2)	50 (48.5)	37 (36.3)	72 (70.6)	28 (57.1)	11 (18.0)	55 (57.3)	385 (43.1)
Median	43.0	47.5	35.0	59.0	58.0	58.0	55.0	69.0	61.0	47.0	61.5	56.0
Range	9.0–77.0	12.0–86.0	20.0–69.0	23.0–85.0	12.0–88.0	18.0–89.0	15.0–86.0	15.0–87.0	33.0–86.0	6.0–72.0	23.0–90.0	6.0–90.0
Mean	43.0	47.2	36.7	58.7	57.5	57.8	53.5	63.5	63.7	44.1	60.4	55.0
Std Dev	17.5	16.2	13.9	13.0	13.6	15.2	16.0	14.6	11.3	16.4	12.8	16.3
PS												
0	20 (32.3)	33 (36.7)	12 (50.0)	23 (27.1)	23 (19.3)	39 (37.9)	45 (44.1)	31 (30.4)	20 (40.8)	16 (26.2)	34 (35.4)	296 (33.1)
1	18 (29.0)	47 (52.2)	7 (29.2)	48 (56.5)	66 (55.5)	43 (41.7)	40 (39.2)	46 (45.1)	19 (38.8)	23 (37.7)	48 (50.0)	405 (45.4)
2	4 (6.5)	4 (4.4)	1 (4.2)	7 (8.2)	6 (5.0)	13 (12.6)	5 (4.9)	7 (6.9)	1 (2.0)	6 (9.8)	8 (8.3)	62 (6.9)
3	3 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)	1 (1.0)	8 (0.9)
Unknown/Missing	17 (27.4)	6 (6.7)	4 (16.7)	7 (8.2)	22 (18.5)	8 (7.8)	12 (11.8)	18 (17.6)	9 (18.4)	14 (23.0)	5 (5.2)	122 (13.7)
Any family history of cancer												
No	34 (54.8)	40 (44.4)	12 (50.0)	48 (56.5)	67 (56.3)	51 (49.5)	71 (69.6)	65 (63.7)	27 (55.1)	42 (68.9)	41 (42.7)	498 (55.8)
Yes	28 (45.2)	49 (54.4)	12 (50.0)	36 (42.4)	52 (43.7)	52 (50.5)	30 (29.4)	37 (36.3)	21 (42.9)	19 (31.1)	55 (57.3)	391 (43.8)
Missing	0 (0.0)	1 (1.1)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	4 (0.4)
Metastatic disease at registration												
Yes	62 (100.0)	89 (98.9)	24 (100.0)	84 (98.8)	119 (100.0)	102 (99.0)	102 (100.0)	101 (99.0)	49 (100.0)	60 (98.4)	96 (100.0)	888 (99.4)
No or unknown	0 (0.0)	1 (1.1)	0 (0.0)	1 (1.2)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.6)	0 (0.0)	5 (0.6)
First treatment received												
Chemotherapy	27 (43.5)	39 (43.3)	7 (29.2)	59 (69.4)	87 (73.1)	36 (35.0)	19 (18.6)	74 (72.5)	10 (20.4)	7 (11.5)	76 (79.2)	441 (49.4)
RO surgery	25 (40.3)	50 (55.6)	17 (70.8)	20 (23.5)	30 (25.2)	62 (60.2)	45 (44.1)	12 (11.8)	22 (44.9)	19 (31.1)	13 (13.5)	315 (35.3)
RT	10 (16.1)	1 (1.1)	0 (0.0)	6 (7.1)	2 (1.7)	5 (4.9)	38 (37.3)	16 (15.7)	17 (34.7)	35 (57.4)	7 (7.3)	137 (15.3)
Status												
Alive/Lost to FU	29 (46.8)	36 (40.0)	13 (54.2)	30 (35.3)	46 (38.7)	55 (53.4)	46 (45.1)	46 (45.1)	12 (24.5)	32 (52.5)	34 (35.4)	379 (42.4)
Dead	33 (53.2)	54 (60.0)	11 (45.8)	55 (64.7)	73 (61.3)	48 (46.6)	56 (54.9)	56 (54.9)	37 (75.5)	29 (47.5)	62 (64.6)	514 (57.6)

Domain 1: sarcoma, Domain 2: rare ovarian cancer, Domain 3: rare GU malignancies, Domain 4: neuro-endocrine tumors, Domain 5: rare GI malignancies, Domain 6: thyroid and adrenal gland cancers, Domain 7: rare thoracic malignancies, Domain 8: rare Head and Neck cancers, Domain 9: Merkel-cell carcinoma and uveal melanoma, Domain 10: CNS tumors, CUP: Cancer of Unknown Primary.

status based on ECOG PS and LDH at registration⁹. Most patients ($n = 46$, 48%) had an unfavorable status, 38 (39.5%) had a favorable status, and we could not calculate it based on the available data for 12 patients (12.5%) (Supplementary Fig. 3d).

At inclusion in Arcagen, patients had received, on average, 2 lines of treatment in the metastatic setting (range 1 to 11). Patient had a good average Performance Status (PS) score, with 296 (33.1%) patients with a PS of 0 and 405 (45.4%) patients with a PS of 1. A family history of cancer was observed in 391 patients (43.4%). Suspected germline mutations were identified in 9 patients: 2 in mismatched repair genes (*MLH1* and *MSH2*), associated with an MSI-high status, 3 in HRD genes (1 in *PALB2* and 2 in *BRCA1*, associated with an HRD+ status for the *BRCA1* mutations), 1 in *APC*, and 3 in *TP53* (Supplementary Fig. 1a).

At the time of database lock, 514 (57.6%) patients were dead, with a median follow-up of 2.3 years [IQR = 1.5–3.1]. The median Overall Survival from registration in Arcagen (OSreg) for the global Arcagen population was 1.6 [1.5–2] years.

Molecular alterations in the different domains

Clinically relevant alterations (i.e. alterations relevant for diagnosis, staging and treatment) were identified in 656 out of 893 (73.5%) patients (Fig. 2a). The average number of clinically relevant alterations per sample was 3.6 (range [0:77], Table 2). Across cohorts, the CNS cohort had the lowest number of alterations (2 per sample on average, range [0:11]) and the CUP had the highest number (5.1 on average, range [0:17]) (Table 2).

Clinically actionable alterations were identified in 620 out of 893 evaluable patients (69.4%)^{10–13}. The average number of clinically actionable alterations per sample in the whole study was 1.45 (range [0:25]), with CUP being the highest with 2 (range [0:8]) actionable alterations per sample on average and sarcoma the lowest with only 1 (range [0:5]) (Table 2). As expected, the diagnostic impact of the molecular analysis was limited in this population of rare cancer patients (no diagnosis adaptation, nor restaging occurred), with a diagnosis review in reference centers.

In the evaluable population ($n = 893$), the most altered gene was *TP53* ($n = 358$, e.g. identified in 40% of evaluable patients, Fig. 2a), followed by *CDKN2A/B* ($n = 161$, 18%, Fig. 2a and Table 2). We observed a high variability of prevalence of *TP53* mutation between cohorts, with only 4.2 % of samples with a *TP53* mutation in refractory testicular germ cell tumors (domain 3) vs 67.1% of neuroendocrine tumor

samples (NET, domain 4). *CDKN2A/B* loss also varied considerably, with 41.2% of samples with this alteration in rare thoracic malignancies (domain 8) versus only 6.1% for rare skin cancers and uveal melanomas (domain 9) (Table 2). *KRAS* mutations were found in 89 patients (10%, Fig. 2a), mostly SNVs (70, 7.8%, Table 2), the majority being in the G12 position. *RAS* amplifications were observed in 10 patients, 8 in testicular germ cell tumors. Up to 20% of NET had a *KRAS* mutation. On the other hand, no mutation in *KRAS* was detected for sarcoma, rare skin cancer or uveal melanoma (Table 2).

PIK3CA mutations were identified in all domains in 75 patients (8.4%). *BRAF* mutations were observed in 35 patients (3.9%, 19 with a V600 mutation and 16 with a different mutation), including 15/35 (42.9%) in patients with thyroid cancer. Losses in *PTEN* and *MTAP* were highly prevalent ($n = 64$, 7.2% and $n = 76$, 8.5% of patients, respectively) (Fig. 2a). *MTAP* deletions were identified in all domains, with the highest prevalence in CNS malignancies (23%) and pleural mesothelioma (22.5%) (Table 2). Loss of *PTEN* was found in all but domain 3 (rare GU malignancies), with a higher prevalence in CNS tumors (11, 2%) (Table 2).

To note, testicular germ cell tumors are known to have a distinct mutational profile with a low rate of somatic point mutations and more frequent gains and losses¹⁴. In our cohort, indeed, 76.2% of the alterations were gene losses and amplifications, and 23.8% were SNVs¹⁵. Interestingly, we had 3 patients with ovarian germ cell tumors (2 teratomas and 1 germ cell). In this population, only 24.4% of the alterations are linked to CNVs, the majority of alterations being SNVs (70.7%), in accordance with other published reports¹⁶.

On FFPE material, actionable alterations (according to FMI reports) were detected in 75.5% of patients ($n = 496$), but only in 52.5% of patients ($n = 236$) when the analysis was performed on ctDNA, with a similar proportion of Variant of Unknown Significance (VUS) in both cases (28.5% vs 27.5%, respectively) (Supplementary Fig. 2a, blue bars for VUS, yellow bar for actionable alterations. Detection of losses and deletions, as well as amplifications, was hindered in ctDNA analysis (Supplementary Fig. 2b), mainly due to samples with undetected tumor fraction (Supplementary Fig. 2c, green bar).

Rearrangements (including inversions and fusions) were identified in 166 patients (18.6% of evaluable patients), and clinically relevant ones (actionable and relevant for diagnosis) in 102 (11.4%) patients, mainly observed in patients with rare sarcoma (10 out of 66, 15%, mainly diagnostic fusions), CNS (8 out of 63, 12.7%, including 4 GBM)

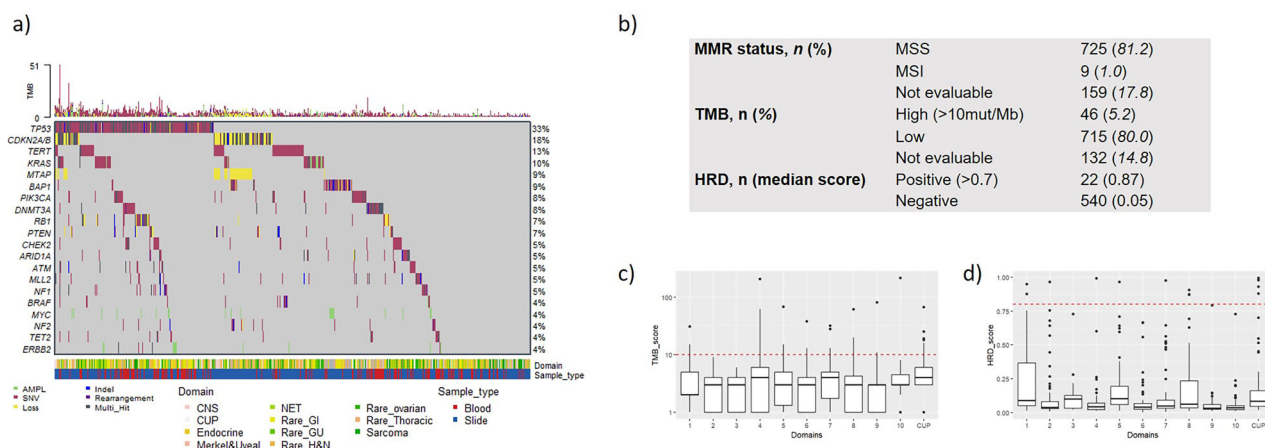


Fig. 2 | Molecular alterations in the different domains. a Oncoplot of the clinically relevant alterations identified in the evaluable patients (656 out of 893), EURACAN domains and type of samples are highlighted at the bottom. **b** MMR, TMB status and HRD status in the global population **(c)** TMB score in each EURACAN domain (NA for 132 samples). **d** Prevalence of HRD per EURACAN domain (for patients with analysis on FFPE, $n = 562$, NA for 95 samples). Box plots show the

median (black center line), interquartile range (box bounds), and whiskers extending to 1.5× the interquartile range. Points beyond the whiskers represent outliers. Red dashed lines indicate the threshold. MMR: mismatch repair; MSS: microsatellite stable; MSI: microsatellite instability; TMB: tumor mutational burden; HRD: Homologous recombination deficiency.

Table 2 | Total number of clinically relevant and actionable alterations per domain and (average per sample)

	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Domain 7	Domain 8	Domain 9	Domain 10	CUP	p value (Chi2)
Clinically relevant alterations (n = 3251, average per sample = 3.6)	183 (2.9)	264 (2.9)	80 (3.3)	397 (4.7)	375 (3.1)	315 (3)	387 (3.8)	358 (3.5)	149 (3)	125 (2)	480 (5.1)	1.09 × 10 ⁻²⁸
Actionable alterations (n = 1301, average per sample = 1.4)	62 (1)	117 (1.3)	36 (1.5)	152 (1.8)	161 (1.3)	121 (1.2)	144 (1.4)	134 (1.3)	68 (1.4)	114 (1.9)	192 (2)	1.10 × 10 ⁻⁷
TP53 (n = 358)	22 (35.5%)	28 (31.1%)	1 (4.2%)	57 (67.1%)	51 (42.8%)	44 (42.7%)	39 (38.2%)	36 (35.3%)	2 (4.1%)	26 (42.6%)	52 (54.2%)	1.02 × 10 ⁻⁶
CDKN2A/B loss (n = 161)	10 (16.1%)	14 (15.5%)	4 (16.7%)	12 (14.1%)	14 (11.8%)	11 (10.7%)	16 (15.7%)	42 (41.2%)	3 (6.1%)	19 (31.1%)	16 (16.7%)	8.41 × 10 ⁻⁷
KRAS SNV (n = 70)	0 (0%)	13 (14.4%)	1 (4.2%)	17 (20%)	18 (15.1%)	5 (4.9%)	3 (2.9%)	2 (2%)	0 (0%)	1 (1.6%)	10 (10.4%)	2.09 × 10 ⁻⁷
PIK3CA (n = 75)	3 (4.8%)	8 (8.9%)	2 (8.3%)	9 (10.6%)	10 (8.4%)	1 (1%)	17 (16.7%)	2 (2%)	5 (10.2%)	5 (8.2%)	13 (13.5%)	5.82 × 10 ⁻³
BRAF (n = 35)	0 (0%)	1 (1.1%)	0 (0%)	5 (5.9%)	2 (1.7%)	15 (14.6%)	4 (3.9%)	1 (6%)	2 (1%)	0 (0%)	6 (6.2%)	7.35 × 10 ⁻⁶
MTAP loss (n = 76)	1 (1.6%)	6 (6.7%)	3 (12.5%)	5 (5.9%)	5 (4.2%)	2 (1.9%)	7 (6.9%)	23 (22.5%)	3 (6.1%)	14 (23%)	7 (7.3%)	1.00 × 10 ⁻⁷
PTEN loss (n = 64)	4 (6.4%)	3 (3.3%)	0 (0%)	11 (12.9%)	2 (1.7%)	9 (8.7%)	9 (8.8%)	6 (5.9%)	1 (2%)	11 (18%)	8 (8.3%)	4.39 × 10 ⁻³

Clinically relevant alterations are defined as having an impact on diagnosis, staging and treatment, whereas actionable alterations are specific alterations linked to a treatment, independently of clinical scores such as ESCAT. Statistical significance was assessed using a two-sided chi-square test. No adjustment for multiple comparisons was performed. The lowest and/or highest prevalence are highlighted in bold.

and GI malignancies (11 cholangiocarcinoma and 1 peritoneal mesothelioma, e.g. 12 out of 119, 10%). Clinically actionable rearrangements were observed in 55 (6.1%) of evaluable patients, most commonly on *FGFR2* (n = 17), *EGFR* (n = 6), *ALK* (n = 4) and *NTRK* (n = 2).

MSI and TMB status were evaluable in most of the population (82.2% and 85.2%, respectively, Fig. 2b, c). No difference was observed in TMB evaluation between ctDNA and FFPE analysis (Supplementary Fig. 2d). No major differences were observed between the different domains for TMB (Fig. 2c). Most of the patients were MSS (n = 725, 81.2%) and most had a TMB < 10 (n = 715, 80%) (Fig. 2b). All patients with MSI status with a calculated TMB showed a TMB > 10 (2 NA, 65[11–216], Supplementary Fig. 1b). As previously discussed, 2 MSI-high patients had suspected germline mutations in *MLH1* and *MSH2* (Supplementary Fig. 1a).

HRD evaluation with HRD signature was also possible on FFPE material (n = 562). Using the FMI-selected cut-off of 0.7^{17,18}, 22 patients (3.9%) were classified as HRD-signature positive (Fig. 2b, d). Within those patients, 3 had an alteration in *BRCA1*, and 5 in *BRCA2* (Supplementary Fig. 1c), including 2 suspected germline *BRCA1* mutations (Supplementary Fig. 1a). However, in the global cohort, we identified 30 patients with *BRCA* alterations (including 4 with TMB-high, excluded from the analysis) and 3 with a *PALB2*, suggesting a poor correlation between *BRCA/PALB2* alterations and HRD-signature positive score (8 out of 29, 27.6%) in this cohort, in accordance to previous reports¹⁹ (REF). Positivity for HRD-signature was identified in 6 (6.2%) patients with CUP, 4 (6.4%) sarcoma (3 undifferentiated pleomorphic sarcoma and 1 with osteosarcoma), 2 (2.7%) biliary tract cancers, 3 (5.4%) pleural mesothelioma, and 7 with other rare cancers (Supplementary Fig. 1c).

No pathologist review of the alteration for diagnosis review was systematically performed. Therefore, no impact on diagnosis was shown by this study.

Treatment adaptation based on molecular profiling

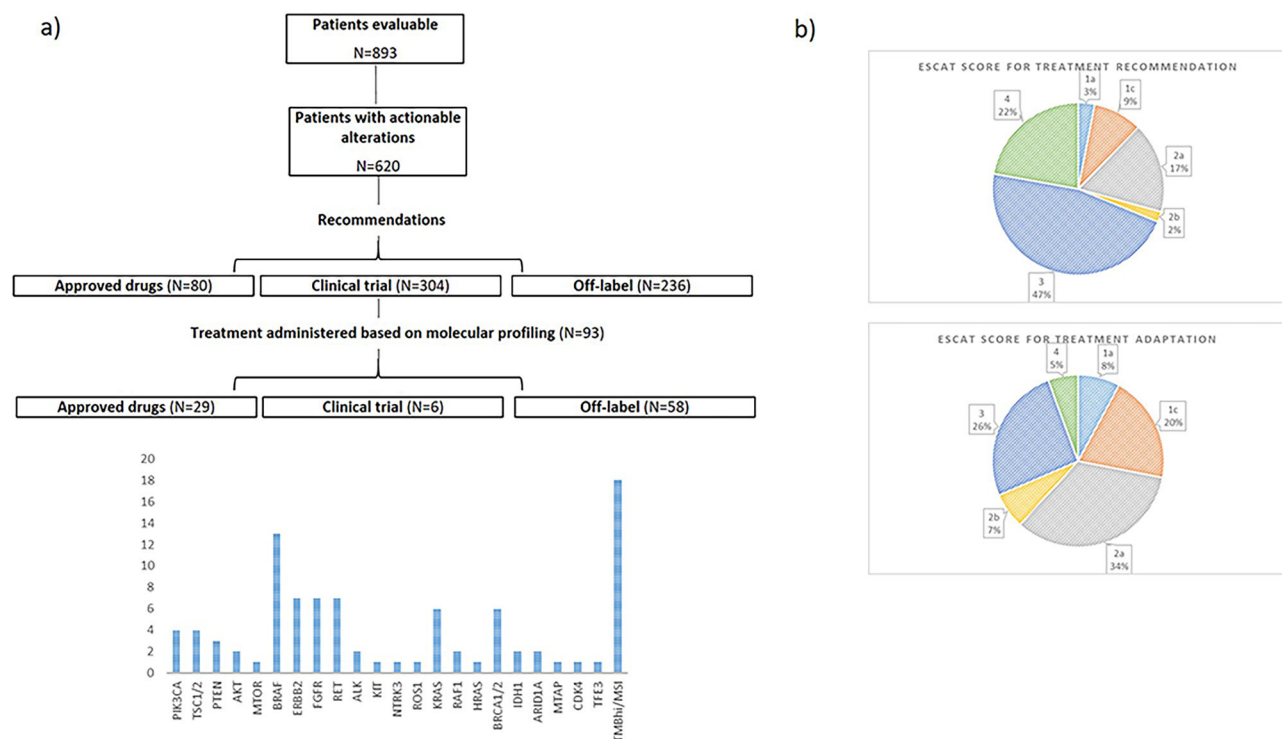
Based on the FMI clinical report and ESCAT/ESMO PMWG recommendations^{10–13}, treatment recommendations were proposed for 620 (69.4%) patients, mainly clinical trials (n = 304, 49%) or off-label use of marketed drugs (n = 236, 28%) (Fig. 3a). However, despite good PS status in the population (Table 1, PS status 0/1 for 701 (78.5%)), recommended treatment was given only to 93 of these 620 (15%) patients (Fig. 3a). Of note, for 19 patients (20.4%), the actionable alterations had previously been identified at the local site and treatment was given prior to enrollment in Arcagen. Most patients (n = 58, 62.4%) received a targeted treatment based on an off-label use of the drug, whereas very few (n = 6, 6.4%) were included in clinical trials despite 304 recommendations for clinical trial inclusion proposed on the FMI clinical report, highlighting the difficulty in enrolling patients with rare cancers into clinical trials^{20,21}. No routine molecular tumor boards were set up for this study, which might have improved the inclusion in clinical trials, especially by broadening the knowledge of trial availability in neighboring hospitals.

Importantly, 29 (31.2%) patients ended up receiving a therapy approved for their cancer, including 8 with the alterations identified at the site, highlighting the importance of frontline molecular screening of rare cancer in routine care.

Immunotherapy in high TMB or MSI high was the most common reason for treatment adaptation (n = 18 out of 93, 19.4%), followed by kinase inhibitors for alterations in *BRAF* (n = 13, 14%), *ERBB2*, *FGFR*, *RET*, *KRAS* (n = 7, 7.5%, each) and PARP inhibitors for *BRCA1/2* (n = 7, 7.5%).

For the switch to immunotherapy, 5 (29.4%) analysis were performed on ctDNA and 13 (70.6%) on FFPE blocks. For targeted therapy, 11 (15.1%) treatment adaptations were done based on ctDNA analysis and 62 (84.9%) on FFPE.

Start of a new line of targeted therapy, based on the results of the molecular profiling, was the most common (n = 75 out of 93 treatment



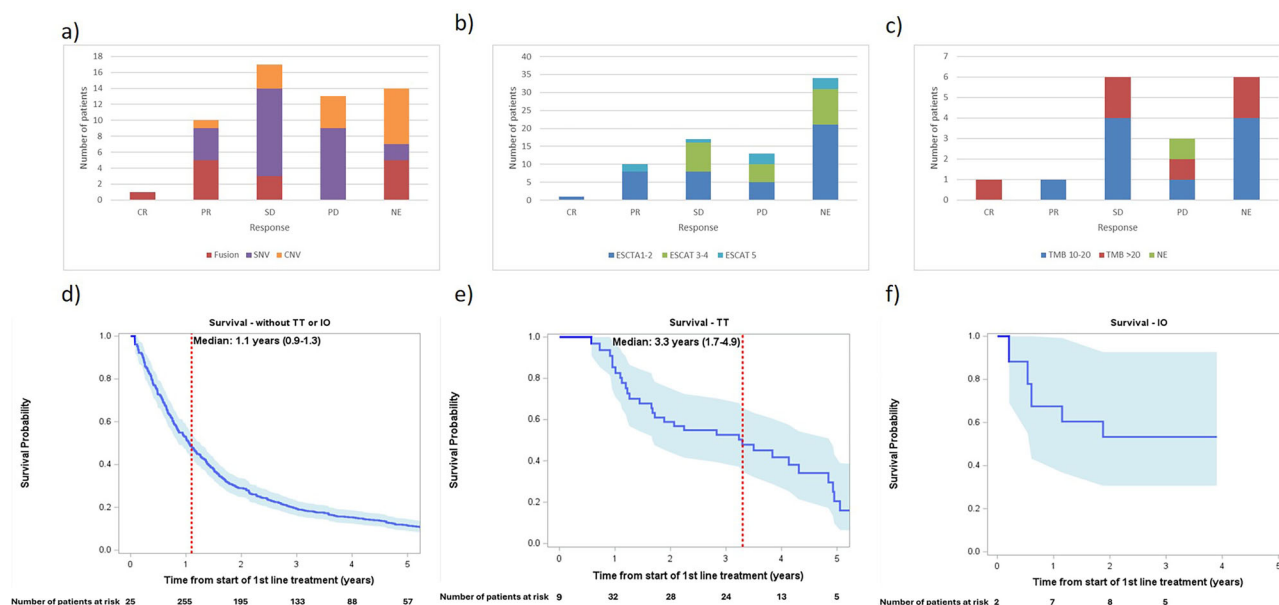


Fig. 4 | Access to personalized treatment and response. **a** Best response for the 60 patients with targeted treatment depending on the type of molecular alteration (red for fusion, blue for SNV and orange for CNV) and **(b)** depending on the clinical status of the alteration (dark blue for ESCAT 1–2, green for ESCAT 3–4, and light blue for ESCAT 5). **c** Best response for the 14 patients with ICI (blue for TMB10–20, red for TMB > 20 and green for Non-evaluable patients) **(d)** Kaplan-Meier Curve estimate of Overall survival (OSf) in the total population without targeted

treatment or ICI ($n = 744$) **(e)** Kaplan-Meier Curve estimate of Overall survival (OSf) in the population with targeted therapy ($n = 75$) **(f)** Kaplan-Meier Curve estimate of Overall survival (OSf) in the population with immunotherapy ($n = 17$). Numbers at risk are shown after delayed entry at the time of sample availability; therefore, the number of patients at risk is low at early time points despite overall survival being measured from first-line initiation. Shaded bands represent 95% confidence intervals estimated using Greenwood's formula. ICI: Immune Checkpoint Inhibitor.

right graph), we noticed that the majority of adaptations were done for ESCAT scores of 1 (25 patients, 28%) or 2 (36 patients, 41%).

Access to personalized treatment and outcomes

Based on the Arcagen molecular profiling, 60 out of 75 patients were treated with molecular-profile matching targeted therapy and 14 out of 17 with immunotherapy, based on their high TMB or MSI status (see above and Supplementary Table 2). A specific analysis for patients in domain 1–10 (exclusion of CUP) and CUP only is displayed in Supplementary Fig. 3.

Among the 60 patients who received targeted therapy at any line following treatment adaptation and inclusion in Arcagen, 1 (1.7%) had a complete response (CR), 5 (8.3%) had a partial response (PR), 15 (25.0%) had stable disease (SD) as best response, 9 (15.0%) showed progressive disease (PD), and 30 (50.0%) were non-evaluable (NE) (incl. 2 early deaths) or missing. Treatment adaptation by type of molecular alteration is displayed in Fig. 4a and by ESCAT tier in Fig. 4b. A swimmer plot for the 12 patients with treatment adaptation based on fusion (out of 31 with an actionable fusion) is displayed in Supplementary Fig. 4. The median time to next treatment or death for targeted therapy was 617 days for the patient in CR, 310 days for the patients in PR, and 267 days for SD (Supplementary Table 2).

Of note, among the 15 patients who received targeted therapy based on the molecular profiling performed at site, 6 (40.0%) had a PR (1 Fusion/4 SNV/1 CNV, and 3 ESCAT 1–2/1 ESCAT 3–4/2 ESCAT 5), 1 (6.7%) had stable disease (CNV and ESCAT 1–2), 4 (26.7%) showed PD (4 SNV, and 2 ESCAT 1–2/1 ESCAT 3–4/1 ESCAT 5), and 4 (26.7%) were NE or missing (4 SNV and 2 ESCAT 1–2/1 ESCAT 3–4/1 missing). As the molecular profiling performed in Arcagen was done after targeted therapy, we investigated the resistance mechanism to targeted treatment in the Arcagen molecular data. The Arcagen analysis was performed on post-targeted treatment samples for 10/19 (52.6%) patients (8 FFPE and 2 blood samples). Analysis of 2 new FFPE materials identified additional actionable alterations for the patients (*IDH1* R132C for

one patient and *EGFR* Q787R for the other), and for 1 additional patient, the new FFPE sample showed an additional *BRCA2* deletion, in addition to the original *BRCA2* mutation, which is consistent with reversion, especially as the patient received olaparib between the 2 samples. Finally, for 1 patient with analysis in Arcagen performed in the same FFPE material as the site, we identified an additional actionable alteration (a *MET* amplification), not identified by the original analysis on site. However, no treatment adaptation was given to those patients based on their new molecular profile.

Among the 14 patients who received immunotherapy at any line following treatment adaptation, after registration, 1 patient (7.1%) had a CR, 0 patient (0.0%) had a PR, 5 patients (35.7%) had SD, 2 patients (14.3%) showed PD, and 6 (42.9%) were NE (incl. 2 early deaths) or missing (Fig. 4c). The median time to next treatment or death for patients treated with immunotherapy was 1311 days for the patient in CR, and 529 days for SD (Supplementary Table 2).

Altogether, the majority of identified alterations were ESCAT 3 (47%) or 4 (22%). There were only 93 of the 620 (15%) alterations that led to actual clinical treatment, among which 27 of the 93 (29%) had either a PR, CR or SD following treatment installation.

For the global population (all metastatic patients receiving at least 1 prior line of treatment, $n = 744$), excluding patients having received matched therapy, 446 deaths were observed. Median OS (from start of 1L treatment to death or last follow-up, OSf) was 1.1 years (95% CI = 0.9–1.3) (Fig. 4d). For all patients who received targeted therapy following a treatment adaptation ($n = 75$), 36 events were observed, and median OSf was 3.3 years (95% CI = 1.7–4.9) (Fig. 4e). For all patients who received immunotherapy following a treatment adaptation ($n = 17$), 6 events were observed and the median OSf was not reached (Fig. 4f).

Because patients had to survive long enough to undergo molecular profiling, be evaluable, and potentially receive a treatment adaptation, we performed a sensitivity analysis restricted to those who actually began the adapted treatment after registration. In this cohort,

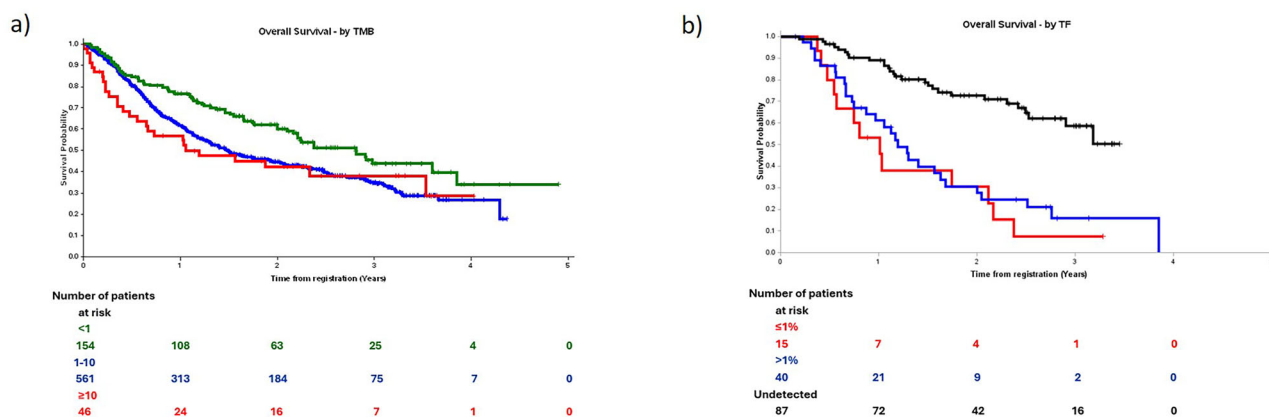


Fig. 5 | TMB and tumor fraction as potential prognostic biomarkers, HRD as predictive BM. a Kaplan-Meier Curve estimate of Overall survival (OSreg) for high (≥ 10 , red line), medium ($1 < \text{TMB} \leq 10$, blue line) or low (< 10 Mb/Kb, green line) TMB (**b**) Kaplan-Meier Curve estimate of Overall survival (OSreg) in the population

median OS measured from the start of the adapted treatment was 1.9 years with TT, was not reached with IO, and was 1.3 years in patients without treatment adaptation.

TMB and tumor fraction as exploratory prognostic biomarkers
TMB and tumor fraction (TF) scores were evaluated for descriptive and exploratory purposes in the ARCAGEN cohort, given its biological and histological heterogeneity. Among patients with a TMB value ($N = 761$), 46 patients (6.0%) exhibited high TMB (≥ 10 mut/mg), 561 patients (73.7%) had TMB levels between 1 and 10, and 154 patients (20.2%) had TMB levels below 1. Regardless of treatment, the median overall survival from 1L therapy was 1.1 [0.6–3.5] years for patients with high TMB, 1.5 [1.3–1.9] years for those with TMB between 1 and 10, and 2.8 [2.2–3.9] years for patients with TMB lower than 1 (Fig. 5a). Similar descriptive trends were observed when analyses were restricted to samples analyzed from ctDNA or FFPE tissue (Supplementary fig 5, red curves for blood, blue curves for FFPE), with a median OS of 0.9 years vs 2.5 years for low TMB.

TF was assessable in only 142 patients (21.6%) with ctDNA analysis. Among these 142 patients, TF was undetectable (below the limit of detection) in 87 patients (61.3%). Of the 55 patients (38.7%) with detectable TF, 15 (27.3%) had levels below 1%, while 40 (72.7%) had levels above 1%. Overall survival from 1L therapy was comparable for patients with detectable TF, regardless of the tumor fraction detected, with a median survival of 1.0 years (95% CI: 0.5–2.1) for those with TF below 1% and 1.2 years (95% CI: 0.7–1.6) for those with TF above 1%. In contrast, the median survival for patients with undetected TF was not reached.

Long-term benefit of personalized treatment

We identified 10 patients treated based on Arcagen molecular profiling results alive and progression free at 500 days. 2 patients have thyroid cancer (with high-TMB, treated with immunotherapy), 4 CUP (1 with *ALK* fusion treated with TKI, 1 with *BRCA1* deletion treated with PARP inhibitor, and 2 with high-TMB treated with immunotherapy), 1 ovarian cancer (with *BRAF* mutation treated with TKI), 1 parotid gland tumor (with *NTRK* fusion, treated with TKI), 1 Merkel-cell carcinoma (with high-TMB treated with immunotherapy), 1 astrocytoma (with *IDH1* mutation treated with TKI). 4 were male and 6 female, the median age at registration was 65.9 [43:77] and 5 patients received treatment in 1st (median PFS: 908.8 days), 2nd (median pfs: 712 days), or 3rd line (median PFS: 588 days), highlighting the need for an early molecular profile for rare cancers, for personalized therapy.

analyzed with ctDNA with high ($> 1\%$, red line), low ($\leq 1\%$, blue line) or undetected TF (black line). TMB: tumor mutational burden, TF: Tumor Fraction HRD: Homologous recombination deficiency.

Discussion

To our knowledge, this is the largest series exploring somatic molecular alterations in rare cancers in a multinational format in Europe. This is also the first study of this nature proposed by an ERN. Plugged to the preexisting SPECTA study (NCT02834884) of the EORTC, the accrual was steady despite the COVID period and proved the concept that such a study was feasible to enable the access of rare cancers to the tools applied more commonly in frequent cancers. When tissue was not available, the analysis of ctDNA enabled the detection of actionable alterations in additional patients not able to be analyzed with tissue CGP due to a lack of adequate tissue. The use of liquid biopsy allowed the “rescue” of analysis for 25% of patients; however, a decrease in detection of fusions and CNVs when using the molecular profiling on plasma was noticed²². Accrual was possible in all countries for all domains (Fig. 1b), showing the feasibility of this multinational diagnosis strategy in rare cancers, which was one of the objectives of the ARCAGEN study.

A second important finding was that the proportion of patients with actionable molecular alterations, or in whom these served to classify or prognosticate the patients, was similar to that of common cancers^{23,24}. A large proportion of patients were proposed for a specific treatment, mostly in the context of a clinical trial or off label. However, only 15% of the patients with targetable alterations could get access to a targeted treatment. The proportion was even smaller for IO treatment. For those patients who could get access to a treatment guided by molecular characterization (TT or IO), OSfl was found superior to that of other patients (median OSfl of 3.3 years for TT, not reached for IO vs 1.1 years for standard of care). However, whether treatment (TT or IO) guided by molecular characterization improves patient outcome over the standard of care should be confirmed in properly designed randomized studies.

The Arcagen study highlighted several critical insights

The molecular diversity of such a group of rare cancers was as high as expected: A high frequency of actionable molecular alterations was identified across the rare cancer spectrum, without significant differences observed between FFPE and plasma samples, but for CNVs. The most prevalent alterations were in *KRAS*, *PIK3CA*, *PTEN*, and *MTAP*, aligning with known oncogenic drivers in other more common cancer types. As expected, we identified important differences across domains in terms of molecular profile (Fig. 2e), even in *TP53* SNVs, with alterations found in less than 5% of rare GU tumors (germ cells and teratoma) but in more than 60% of NET, often associated with *PTEN* and *RBI* loss. Sarcoma had a lower number of clinically relevant

alterations (average of 2.9 per sample) and actionable alterations (average of 1 per sample), despite the use of a specific panel (F1Heme) for these patients, with a focus on fusions. To note, some diagnostic fusions were identified in this cohort, such as EWSR1-ERG/WT1/CREBL3 in 4 patients or TFE3-ASPSCR1 in 3 patients²¹. These data support the development of histology-agnostic approaches for these rare alterations, which may be common if assessed across rare and common tumor types²⁵.

Treatment adaptation was possible for a small fraction of patients: While molecular profiling facilitated personalized treatment recommendations for a substantial proportion of patients, actual adaptation of treatment based on these recommendations was limited. Altogether, we identified 1301 alterations (out of 3251, 40%) in 620 patients affecting the treatment propositions, including 93 (7%) which led to actual therapy change. The global median TAT was 41 days for analysis on FFPE and 56.5 days on plasma, which can hinder the treatment adaptation for patients²⁶. This underscores the challenges in translating molecular insights into clinical practice, particularly in the context of rare cancers where evidence-based guidelines are less robust and access to treatment is challenging. This proportion of patients treated per molecular analysis is, however, not very different from that observed in common cancers^{27,28}.

Access to trials is exceptionally low: Strikingly, access to clinical trials was extremely low, with only 6 patients enrolling, out of 304 (1.2%) with recommendation for clinical trial inclusion. Similar results were demonstrated for CNS tumors in a prior extensive analysis²⁹. This illustrates the difficulty of making clinical trials accessible to a population with rare cancers, dispersed across the EU. Tumor heterogeneity, heterogeneity of actionable targets, heterogeneity of possible treatments, and regulatory differences specific to each country all hinder the accessibility of clinical trials in this context. Pragmatic, platform-based trials at the European level should be considered.

The clinical outcome observed in this series provides guidance for future research. Evidence of the activity of the treatment prescribed was observed in some patients of this series. The OS of the population treated is also encouraging. A larger series is now needed to explore the impact of this treatment approach in larger subgroups of patients, with more homogenous histotypes and/or organs of origin, and the value of agnostic treatments. A follow-up study of the EORTC is intending to generate such a large cohort.

The study enabled the exploration of specific prognostic biomarkers: The study also enabled the exploratory assessment of selected molecular features, including tumor mutational burden (TMB), tumor fraction (TF), and HRD, in a large and heterogeneous cohort of rare cancers. Exploratory analyses of TMB and TF suggested differences in overall survival across predefined categories; however, these findings should be interpreted with caution. The cohort included multiple unrelated tumor entities; TMB and TF were not available for all patients, and analyses were not powered for entity-specific evaluation. Similarly, we assessed the role of HRD as a predictive biomarker for progression-free survival in patients who received first-line treatment with platinum-based chemotherapy (FFPE only, $N = 191$). The number of HRD-positive patients treated with first-line platinum-based chemotherapy was limited, with only 5 patients (2.6%) identified. Other patients were HRD negative ($N = 167$, 87.4%) or HRD unknown ($N = 19$, 9.9%). Based on this very small population, we were unable to detect any correlation between HRD-positivity and response to platinum-based chemotherapy (Supplementary Fig 5). TMB, TF, and HRD are context-dependent biomarkers: their use for rare cancers in general cannot be assessed for the present study, and their analysis should be interpreted as exploratory and hypothesis generating, not as definitive evidence.

This study has several limitations. Despite a large overall sample size, the heterogeneity and specificities of each rare cancer domain complicated the analysis and interpretation of data to measure the

utility of molecular characterization. No systematic review of the molecular profile by a pathologist was performed in Arcagen, thus, we can not conclude on the diagnostic utility of molecular profiling for this patient population. The median follow-up of the series remains limited, precluding an analysis of the long-term impact of the diagnostic strategy. Furthermore, interpretation and comparability of observed survival times were limited by potential selection and immortal time biases. Indeed, only patients with a valid molecular sample were included in the study, and patients had to survive long enough to undergo molecular profiling and potentially receive a treatment adaptation.

As already reported, the gap between molecular profiling and the practical application of personalized medicine was evident, with numerous barriers, including regulatory, financial, and logistical challenges commonly seen in rare cancers. A limitation of this study is that there was no centralized MTB to discuss options (only domain 8, thoracic). The trial options were solely reviewed by the treating physician on the basis of 1) the presence of a molecular alteration, 2) the availability of a clinical trial for this alteration in the center, in the country or with cross-border healthcare, 3) the availability of the drug in a compassionate or off-label basis. Because of the heterogeneity of the centers, countries, and access to trials and off-label drugs, it is not feasible to assess the proportion of patients in whom each option was discussed in a consolidated manner.

However, this study remains a significant step for a better application of the methods of precision medicine in the underserved population of rare cancers, which represents about a million new patients per year in the EU. The observed favorable survival outcomes call for continued research into more effective treatment options and combinations, potentially incorporating emerging therapies and novel clinical trial designs.

Future research should focus on enhancing the integration of molecular profiling into routine clinical practice for rare cancers, as for common cancers, as recommended by Mission Cancer and the Beating Cancer Plan, with inclusion of already existing tools, such as ETAC-SII¹¹. Not enough trials were accessible to these patients: the generation of basket trials^{30–32} and their dissemination within the EU, funded projects such as PRIME-ROSE (PRIME-ROSE: Advancing Precision Cancer Medicine in Europe) project should facilitate; novel methodologies for clinical trials must be used for rare cancers, potentially using adaptive designs that allow for the exploration of multiple therapies⁸. Trials within cohorts could be solutions to the rarity of a very large (and growing number) of entities when agnostic therapies are not applicable. These could also serve the identification of novel biomarkers and technologies in predicting treatment response and outcomes in rare cancer patients.

The Arcagen study provides valuable insights into the molecular landscape of rare cancers and demonstrates the potential benefits and current limitations of personalized medicine in this challenging field. Ongoing efforts to refine molecular diagnostics, coupled with advances in therapeutic options, are essential to improve the prognosis and quality of life for patients with rare cancers. Furthermore, early genomic testing in patients with better performance status may add to the chance of translation of molecular findings into a molecular-based treatment.

Methods

Study design and participants

Patients older than 12 with a diagnosis of metastatic or advanced rare cancer (according to the EURACAN guidelines³³), regardless of the number of treatment lines received, were recruited. A recent tumor specimen was requested for analysis (sampling within 2 years of registration). If unavailable or failed quality control at the central biobank, a blood draw was performed. Clinical-pathological data were collected according to the EORTC-SPECTA protocol (NCT02834884).

All patients provided written informed consent for sample collection and genomic analysis. The SPECTA Arcagen study was approved by ethical committees—Commissie voor Medische Ethiek ZNA (Belgium), reference 4881, date 10/03/2021—Comissao de Etica para a Saude de CHLO (Portugal), reference 2150, date 28/06/2021—Eticka komise pro Multicentricka Klinicka Hodnoceni, Fakultini Nemocnice v Motole (Check Republic), reference 017/08, date 01/12/2021. This study has been conducted in accordance with international standards of ethical principles for medical research (Declaration of Helsinki, Good Clinical Practice guidelines). This study was conducted in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonization and the Declaration of Helsinki, as well as relevant French and European laws and directives.

Comprehensive genomic profiling

Analysis was performed on tumor formalin-fixed paraffin-embedded (FFPE) tissue samples (when available and obtained within 2 years) or blood samples, using the Foundation Medicine platform (F1CDx or F1LCDx). FFPE material was obtained either a primary or recurrent tumor. A hematoxylin and eosin (H&E) stained section was prepared for each FFPE block and reviewed by an expert pathologist to assess tissue quality and tumor content. Based on the pathologist review, high quality samples, with a minimum surface area of 25 mm² and containing at least 20% of viable cells were selected for molecular analysis. (17). If the block was older than 2 years or of poor quality, a blood sample was taken for genomic analysis.

Comprehensive genomic profiling was performed with a targeted hybrid capture next-generation sequencing (NGS) test (FoundationOne®CDx) with >300 genes, including MSI, TMB, and HRDsig, using DNA isolated from FFPE tumor tissue specimens; or by FoundationOne®Liquid CDx, on ctDNA isolated from plasma with >300 genes, including ctDNA tumor fraction (TF).

MTB and patient follow-up

For the thoracic cohort, the genomic report was reviewed and discussed by the EORTC-SPECTA multidisciplinary MTB, which met monthly and was composed of experienced oncologists and biologists. The MTB evaluated the pathogenicity and the targetability of individual molecular alterations according to the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Only pathogenic or likely pathogenic variants were considered. Matched therapies and targeted agents were recommended where possible based on existing pre-clinical and clinical data, available within clinical trials not restricted to EORTC trials, or outside a trial.

All patients were followed up every 3 to 6 months, according to the SPECTA protocol.

Statistics

Categorical clinical variables were summarized using frequencies and percentages. Continuous variables were expressed using the median and range. The median follow-up time from the date of registration was estimated among patients still alive at the time of database lock. Overall survival (OS) was analyzed from two reference points: the date of registration (OSreg) and the start of first-line treatment (OSfl). OSreg and OSfl were defined as the time from the date of registration and the time from the start of first-line treatment to the date of death from any cause, respectively. Both were censored at the last date the patient was known to be alive.

For OSreg, survival distributions were estimated using the Kaplan–Meier method. The results were presented as the number of events, median survival time (95% CI), and survival rates at 3 years. For OSfl, survival analyses were performed using the Kaplan–Meier method with left truncation. Left truncation was necessary because patients became at risk only after the start of the study; some

patients had sample collection, an eligibility requirement after registration or treatment initiation. By modeling delayed entry, we ensured that patients contributed to the risk set only after their entry time^{34,35}. This entry time was defined as the interval between the start of first-line treatment and the later of the sample collection date or eligibility date.

Confidence intervals for survival estimates were calculated using Greenwood's formula, and the median survival time was defined as the earliest time at which the survival probability fell below 50%. Kaplan–Meier curves were presented with shaded 95% confidence intervals, and median survival times were indicated for reference.

The OSfl analyses were performed in all study patients (main analysis) and in patients who initiated first-line treatment after registration (sensitivity analysis). The comparison of the estimates helped to assess whether the timing of treatment start significantly impacts survival outcomes. If the estimates differ substantially, it may indicate that the timing of treatment plays a role in patient prognosis.

All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The sequencing data generated in this study have been deposited in the European Genome-phenome Archive (EGA), dataset reference numbers EGAD50000000902 (domain 1) [<https://ega-archive.org/studies/EGAS50000000639>], EGAD50000001315 (domain 2) [<https://ega-archive.org/studies/EGAS50000000900>], EGAD50000000914 (domain 3) [<https://ega-archive.org/studies/EGAS50000000645>], EGAD50000000913 (domain 4) [<https://ega-archive.org/studies/EGAS50000000644>], EGAD00001008826 and EGAD00001008968 (domain 5) [<https://ega-archive.org/studies/EGAS00001006299>], EGAD50000000886 (domain 6) [<https://ega-archive.org/studies/EGAS50000000626>], EGAD50000000885 (domain 7) [<https://ega-archive.org/studies/EGAS50000000625>], EGAD50000000168 (domain 8) [<https://ega-archive.org/studies/EGAS50000000123>], EGAD50000000705 (domain 9) [<https://ega-archive.org/studies/EGAS50000000491>], EGAD50000001468 (domain 10) [<https://ega-archive.org/datasets/EGAD50000001468>], EGAD50000000256 (CUP) [<https://ega-archive.org/studies/EGAS50000000177>]. The clinical data and molecular are available under restricted access due to data privacy laws and GDPR, in line with EORTC data sharing policy (<https://www.eortc.org/app/uploads/2023/06/L-01-POL-01.pdf>). Access can be obtained by submitting a request to the EORTC: <https://www.eortc.be/services/forms/erp/request.aspxQueries> will be answered within 2 weeks of request by the EORTC. No restrictions on how long data will be made available for have been foreseen. Source data are provided as source data file for the relevant figures. Source data are provided with this paper.

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Author contributions

M.M. and J.Y.B. designed the study. M.M., F.H., T.G., and J.Y.B. analyzed the data with input from all authors. M.M., F.H., and J.Y.B. wrote the manuscript with input from all authors. M.M. and J.Y.B. got the funding.

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Competing interests

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