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### Authors

Ambrosini, Margherita

Del Re, Marzia

Manca, Paolo

et al.

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# ALK Inhibitors in Patients With ALK Fusion–Positive GI Cancers: An International Data Set and a Molecular Case Series

Margherita Ambrosini, MD<sup>1</sup>; Marzia Del Re, MSc<sup>2</sup>; Paolo Manca, MD<sup>1</sup>; Andrew Hendifar, MD<sup>3</sup>; Alexander Drilon, MD<sup>4</sup>; Guilherme Harada, MD<sup>4</sup>; Anne Hansen Ree, MD<sup>5,6</sup>; Samuel Klempner, MD<sup>7</sup>; Gunhild Mari Mælandsmo, MD<sup>8</sup>; Kjersti Flatmark, MD<sup>9</sup>; Hege G. Russnes, MD<sup>10,11</sup>; James M. Cleary, MD<sup>12</sup>; Harshabad Singh, MD<sup>12</sup>; Elisa Sottotetti, MSc<sup>1</sup>; Antonia Martinetti, MSc<sup>1</sup>; Giovanni Randon, MD<sup>1</sup>; Andrea Sartore-Bianchi, MD<sup>13</sup>; Iolanda Capone, MSc<sup>14</sup>; Massimo Milione, MD<sup>14</sup>; Maria Di Bartolomeo, MD<sup>1</sup>; and Filippo Pietrantonio, MD<sup>1</sup>

**PURPOSE** In GI cancers, anaplastic lymphoma kinase (*ALK*) rearrangements are extremely less frequent than in non–small-cell lung cancer but may be important to offer personalized strategies of treatment in selected patients. Data about the activity and efficacy of ALK inhibitors (ALKi) in GI cancers are scarce.

**MATERIALS AND METHODS** We assembled a clinical and molecular international data set of pretreated patients with metastatic or nonresectable cancers of GI primary tumor origin with documented *ALK* rearrangement treated with at least one line of ALKi. Measurable disease as per RECIST 1.1 was required for response analysis.

**RESULTS** Primary tumor sites were distributed as follows: 5 (38%) pancreas, 3 (23%) right colon, and 1 (8%) for each one of gastric, duodenal, rectal, left colon, and biliary tract sites. Seven patients (54%) were treated with alectinib, 5 (38%) with crizotinib, and 1 (8%) with entrectinib. After disease progression, five patients (38%) received a subsequent ALKi treatment line, and at the time of data cutoff date, treatment was still ongoing in two patients. Five of 12 evaluable patients (41%) achieved a partial response to first-line ALKi, five patients (41%) had stable disease, and 2 (17%) had progressive disease. No complete responses were registered. At a median follow-up of 39.6 months (interquartile range: 19.8–59.5), the median progression-free survival was 5.0 months (95% CI, 3.68 to no response) and the median overall survival was 9.3 months (95% CI, 5.46 to no response).

**CONCLUSION** Treatment with ALKi provides remarkable responses and clinical benefit in pretreated patients with ALK fusion–positive GI malignancies. Despite the rarity, *ALK* rearrangements represent an important therapeutic target in individual pretreated patients with GI solid tumors. Further work providing prospective clinical validation of this target is needed.

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## INTRODUCTION

Anaplastic lymphoma kinase (*ALK*) gene encodes for a classical transmembrane tyrosine kinase receptor that belongs to the superfamily of insulin receptors and was first discovered in hematologic malignancies. It is involved in cancer promotion and growth mainly by translocation with a partner gene, creating a fusion protein with self-sufficient kinase activity, that triggers various downstream pathways such as phosphatidylinositol 3–kinase-protein kinase B–mammalian target of rapamycin (PI3K-AKT-mTOR), phospholipase C, Janus kinase–signal transducers and activators of transcription (JAK-STAT), and mitogen-activated protein kinase (MAPK) signaling.<sup>1,2</sup> Regarding solid tumors, the dual ALK/mesenchymal-epithelial transition factor (MET) inhibitor crizotinib and the selective tyrosine kinase inhibitors alectinib, ceritinib, brigatinib, and lorlatinib are approved for treatment of patients with *ALK* fusion–positive advanced non–small-cell lung cancer (NSCLC), given the superior outcomes achieved

by these agents when compared with standard chemotherapy.<sup>3,4</sup>

In gastrointestinal cancers, the frequency of *ALK* rearrangements is much lower than NSCLC (< 1% of colorectal and 0.2% of pancreatic and different frequencies for gastric according to reports and methods of detection).<sup>5–8</sup> However, despite the variability in different reports, *ALK* fusions have been documented among colorectal, gastric, biliary, and pancreatic tumors, often displaying peculiar features.<sup>5–11</sup> *ALK* fusion–positive metastatic colorectal cancers (mCRCs) define a distinct rare subtype together with *ROS1* and *NTRK* rearranged mCRC, characterized by older age at diagnosis, right-sided primary tumor location, *RAS* and *BRAF* wild-type status, microsatellite instability high, lymph node spreading, and evidence of significantly worse survival.<sup>11,12</sup> In a series of patients with resected gastric cancer, *ALK* overexpression (by immunohistochemistry [IHC] with cytoplasmic staining positivity set at ≥ 10% tumor cells) was found in 8.4% of samples

Author affiliations and support information (if applicable) appear at the end of this article.

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## CONTEXT

### Key Objective

Anaplastic lymphoma kinase (ALK) rearrangements are emerging in clinical practice as a rare oncogenic driver of therapeutic potential in GI tumors. Because of the rarity, data about the activity of ALK inhibitors (ALKi) in GI cancers are scarce. We describe clinical and molecular characteristics and response to ALKi of an international series of patients with ALK rearranged GI cancers, with the aim to provide useful data for oncologists to sustain the use of ALKi in this setting and to stimulate further research.

### Knowledge Generated

We demonstrate remarkable activity of ALKi in pretreated patients with ALK rearranged GI cancers (overall response rate 41%, disease control rate 82%). Some patients (38%) were able to receive a second line of ALKi after disease progression, with further clinical benefit and ongoing responses at the time of data cutoff date.

### Relevance

The use of ALKi in selected pretreated patients with GI malignancies could provide significant clinical benefit when no other standard-of-care treatment is available.

and was associated with signet ring cell component and young age, as well as worse disease-free survival and overall survival (OS).<sup>6</sup> Pancreatic cancers with *ALK* fusions, most frequently with *EML4* as the partner gene, may be associated with young onset (< 50 years), male sex, and *KRAS* wild-type status.<sup>5</sup>

Data about the activity and efficacy of ALK inhibitors (ALKi) in *ALK* fusion–positive GI cancers are scarce, and those available mainly derive from case reports, thus representing an important unmet need in the era of expansion of personalized strategies in several tumor types including GI cancers. Drawing from this background, we conducted an international effort to collect clinical and molecular data of patients with *ALK* rearranged GI cancers treated with ALKi with the aim of analyzing patients' characteristics and outcomes and providing useful data for GI oncologists.

## MATERIALS AND METHODS

### Patient Population

We assembled an international data set of 13 published<sup>5,12-15</sup> (n = 6) and nonpublished (n = 7) cases of *ALK* fusion–positive GI cancer patients treated with ALKi. We collected information about social and demographic characteristics of patients, primary tumor site and histology, *ALK* fusion partner or site of breakpoint, microsatellite status, or other baseline next-generation sequencing (NGS)/mutational data. Other data were about clinical history, including time and type of prior local treatments (surgery/others), metastatic disease diagnosis, and systemic treatments.

The method and site of detection of ALK rearrangement were not known for five patients. For the others, *ALK* rearrangement was determined by using NGS (n = 6), NGS and IHC (n = 1), IHC, and fluorescent in situ hybridization (FISH; n = 1); the analysis was conducted on primary tumor tissue (n = 3) on metastases (n = 2) or both (n = 3). Metastatic or unresectable GI cancers from any site of

origin in the GI tract and of any histology were included in the data set and in the final analysis. Patients with a documented *ALK* rearrangement had to have undergone at least one systemic treatment with ALKi to be included, regardless of the number of prior lines of systemic treatment and type of ALKi agent. Information about second or further lines of ALKi treatment was collected, when available. Measurable disease as per RECIST 1.1 was required for response analysis, and percentual RECIST response at each scan was collected, when available.

All the patients provided written informed consent in sharing and using nonidentifiable personal data, each one according to own institutional policy and ethics committee.

### Statistical Analyses

Progression-free survival (PFS) was defined as the time from the start of the ALKi agent to disease progression (PD) or death, whichever occurred first. OS was calculated from the start date of the ALKi agent to death from any cause. The cutoff date was set as June 30, 2021. Response of disease was assessed according to the RECIST 1.1 criteria. Overall response rate (ORR) was calculated as the sum of complete responses (CR) plus partial responses (PR) divided by the number of total evaluable patients. Disease control rate (DCR) was calculated as the sum of ORR plus the ratio between the number of disease stabilizations (SDs) and totality of evaluable patients. Data were imported and handled in R v 4.1. Kaplan-Meier curves were used to represent right-censored variables (PFS and OS).

## RESULTS

### Patient Characteristics

Thirteen patients with *ALK* rearranged GI cancers were selected and included in the final population. Detailed clinical and molecular patients' characteristics are provided individually in [Table 1](#). Cumulative frequency of each characteristic is described in [Table 2](#). The median age was

**TABLE 1.** Patients' Clinical and Molecular Characteristics

No.	Age	Sex	Ethnicity	Primary Tumor Site	Histology	Stage at Diagnosis	Surgery/Locoregional Treatment	Lines of Systemic Treatment Before ALKi	ALK Fusion Partner/Breakpoint	MSI/ MSS Status	Other NGS Data	First-Line ALKi Agent	Best Tumor Response	First-Line ALKi PFS (months)	Further ALKi Agent
1	50	F	White	Gastric	Adenocarcinoma	III	Surgery	3	HMBOX1 <sup>a</sup>	MSS	<i>See molecular case report</i>	Alectinib	PR	6.0	Lorlatinib
2	58	F	NA	Biliary tract	Cholangiocarcinoma	IV	None	1	Unknown <sup>b</sup>	MSS	PIK3CA, BAP1, PTCH1, TP53, RB1	Crizotinib	SD	3.9	No
3	46	M	NA	Rectum	Adenocarcinoma	IV	None	2	EML4 <sup>b</sup>	MSS	KDR, SMAD4, APC, TP53	Crizotinib	PD	2.3	No
4	75	M	White	Pancreas	Adenocarcinoma	IV	None	1	Intron 19 rearrangement <sup>c</sup>	MSS		Alectinib	PD	0.9	No
5	34	M	White	Pancreas	Adenocarcinoma	III	Surgery	1	STRN <sup>c</sup>	MSS		Crizotinib	PR	28.4	Alectinib
6	41	F	White	Pancreas	Adenocarcinoma	IV	Surgery	1	PPFIBP1 <sup>d</sup>	MSS	CDKN2A loss, CDKN2B loss, MTAP loss, P53, NF-1	Alectinib	PR	5.0	Lorlatinib
7	45	M	White	Right colon	Adenocarcinoma	IV	None	2	EML4	MSS	TP53 splice site, APC truncating mutation	Crizotinib	PR	9.1	No
8	70	M	Asian	Duodenum	Adenocarcinoma	IV	None	2	KIF5B	MSS	TP53, SMAD4	Alectinib	SD	7.8	No
9	51	F	White	Right colon	Adenocarcinoma	IV	None	2	CAD <sup>e</sup>	MSS	TP53	Crizotinib	SD	3.7	Alectinib <sup>12</sup>
10	50	F	White	Right colon	Adenocarcinoma	IV	Surgery	2	CAD <sup>e</sup>	NA		Entrectinib	PR	4.6	No
11	63	M	White	Pancreas	Adenocarcinoma	IV	None	1	EML4	MSS	TP53, CDKN2A, VTCN1, FAM46C, GLI1, CDK4, PRDM1, SESN1, NTRK3, KMT2D, RHOA, FANCA, DNMT3A, CREBBP	Alectinib	SD	5.4	No
12	67	M	White	Left colon	Adenocarcinoma	IV	Surgery	1	STRN	MSS	TP53, PIK3CG, PTPRS, PTPRT, MYC	Alectinib	SD	13.6	Ceritinib
13	72	M	White	Pancreas	Adenocarcinoma	III	Surgery	2	EML4	MSS	TP53, SMAD4, CDKN2B, CDKN2Ap14ARF, FBXW7, CDKN2Ap16INK4A, ASXL1, CDKN2Ap16INK4A, INHBA, NTRK3, PRKD1, ZFH3, TEX14	Alectinib	NA	1.6	No

Abbreviations: ALKi, anaplastic lymphoma kinase inhibitors; IHC, immunohistochemistry; MSI, microsatellite instability high; MSS, microsatellite stable; NA, not applicable; NGS, next-generation sequencing; PD, disease progression; PFS, progression-free survival; PR, partial response; SD, disease stabilization.

<sup>a</sup>Detected by NGS on primary tumor sample before systemic treatments for metastatic disease and on metastases before ALKi treatment.

<sup>b</sup>Detected by NGS on metastases before ALKi treatment.

<sup>c</sup>Detected by NGS on diagnostic primary tumor sample.

<sup>d</sup>Detected by NGS and IHC on primary tumor sample and metastases before systemic treatments.

<sup>e</sup>Detected by IHC and fluorescent in situ hybridization on primary tumor sample and metastases before ALKi treatment.

**TABLE 2.** Cumulative Frequencies of Patients' Characteristics

Characteristic	Patients, No. (%)
Age, years	
Median (range)	51 (34-75)
Sex	
Male	8 (62)
Female	5 (38)
Ethnicity	
White	10 (77)
Asian	1 (8)
Unknown	2 (15)
Primary tumor site	
Gastric	1 (8)
Duodenum	1 (8)
Right colon	3 (23)
Left colon	1 (8)
Rectum	1 (8)
Biliary tract	1 (8)
Pancreas	5 (38)
Stage at diagnosis	
I-II	0
III	3 (23)
IV	10 (77)
Metastasis presentation	
Synchronous	3 (23)
Metachronous	10 (77)
No. of metastatic sites	
1	4 (31)
≥ 2	9 (69)
Liver metastases	
Yes	9 (69)
No	4 (31)
Nodal metastases	
Yes	8 (62)
No	5 (38)
Lung metastases	
Yes	3 (23)
No	10 (77)
Peritoneal metastases	
Yes	2 (15)
No	11 (85)
Brain metastases	
Yes	2 (15)
No	11 (85)
No. of prior lines of systemic treatment	
1	6 (46)

(Continued in next column)

**TABLE 2.** Cumulative Frequencies of Patients' Characteristics

(Continued)

Characteristic	Patients, No. (%)
≥ 2	7 (54)
MSI/MSS status	
MSI-H	0
MSI-L/MSS	12 (92)
NA	1 (8)
First line ALKi (agent)	
Alectinib	7 (54)
Crizotinib	5 (38)
Entrectinib	1 (8)
Further lines of ALKi	
Yes	5 (38)
No	8 (62)
Further lines of ALKi (agent)	
Alectinib	2 (40)
Lorlatinib	2 (40)
Ceritinib	1 (20)

Abbreviations: ALKi, anaplastic lymphoma kinase inhibitors; MSI-H, microsatellite instability high; MSI-L, microsatellite instability low; MSS, microsatellite stable; NA, not applicable.

51 years (range 34-75 years). Most of patients were male ( $n = 8$ , 62%), 10 were White ethnicity (77%), one was Asian (8%), and two patients' ethnicity was not known. Five patients (38%) had pancreatic adenocarcinoma as the primary site, 3 (23%) had right colon cancer; gastric, duodenal, left colon, rectal, and biliary tract cancers presented the same frequency in our data set ( $n = 1$ , 8% for each one). From a molecular point of view, *ALK* rearranged colorectal and pancreatic adenocarcinoma of our data set did not harbor any mutation in the most common driver genes such as *RAS* and *BRAF*. All the patients had received at least one prior line of standard systemic treatment for metastatic disease. At the time of start of ALKi, brain metastases were present in two patients (15%), liver metastasis in nine patients (69%), and peritoneal metastasis in two patients (15%). Regarding the specific ALKi used, seven patients (54%) were treated with alectinib, 5 (38%) with crizotinib, and 1 (8%) with entrectinib. After PD on ALKi first-line treatment, five patients (38%) received a subsequent ALKi treatment line: Alectinib was given after crizotinib in two patients, whereas lorlatinib and ceritinib were used after failure of prior alectinib in two and one patients, respectively. At the time of data cutoff date, two patients were still receiving second-line treatment.

#### Activity of ALK Inhibitors

One patient was not evaluable for disease response because of the occurrence of a stroke, not drug-related but

leading to treatment permanent discontinuation and early death; therefore, the patient was included only in survival analysis. Figure 1 represents the spider plot of the response dynamics and the waterfall plot of individual best responses for the 12 evaluable patients according to the primary site of origin (Figs 1A and 1B) and the type of ALKi received (Figs 1C and 1D). Five patients (41%) achieved a PR to first-line ALKi treatment, whereas no CRs were registered. The ORR was 41%. SD was achieved by five patients (41%), with a DCR of 82%. The remaining two patients (15%) had PD at the first evaluation.

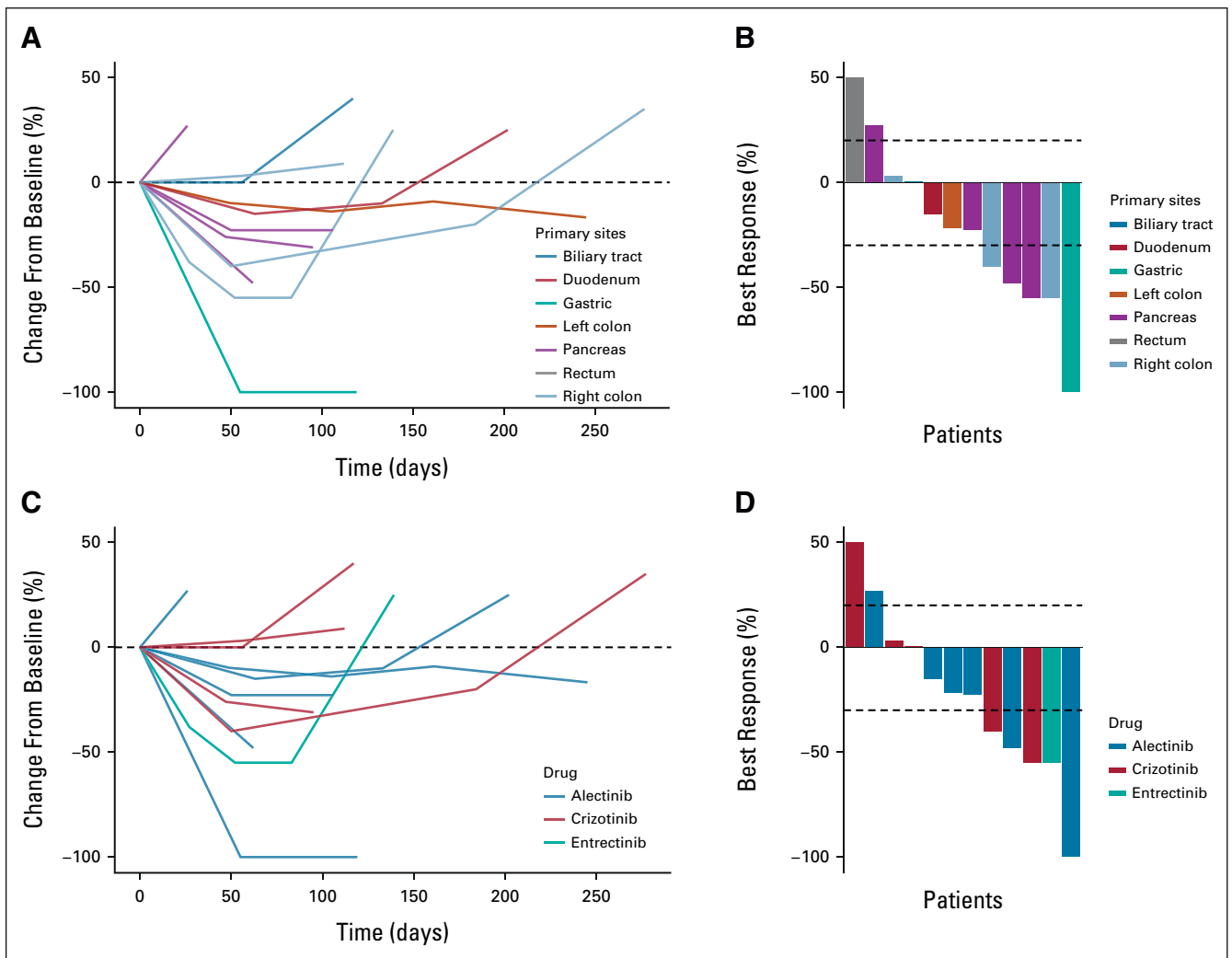
Among the five patients who were able to receive second-line ALKi treatment, two patients (40%) achieved PR as best response while three (60%) achieved SD, with one patient per group continuing treatment at the time of data cutoff date.

**Efficacy of ALK Inhibitors**

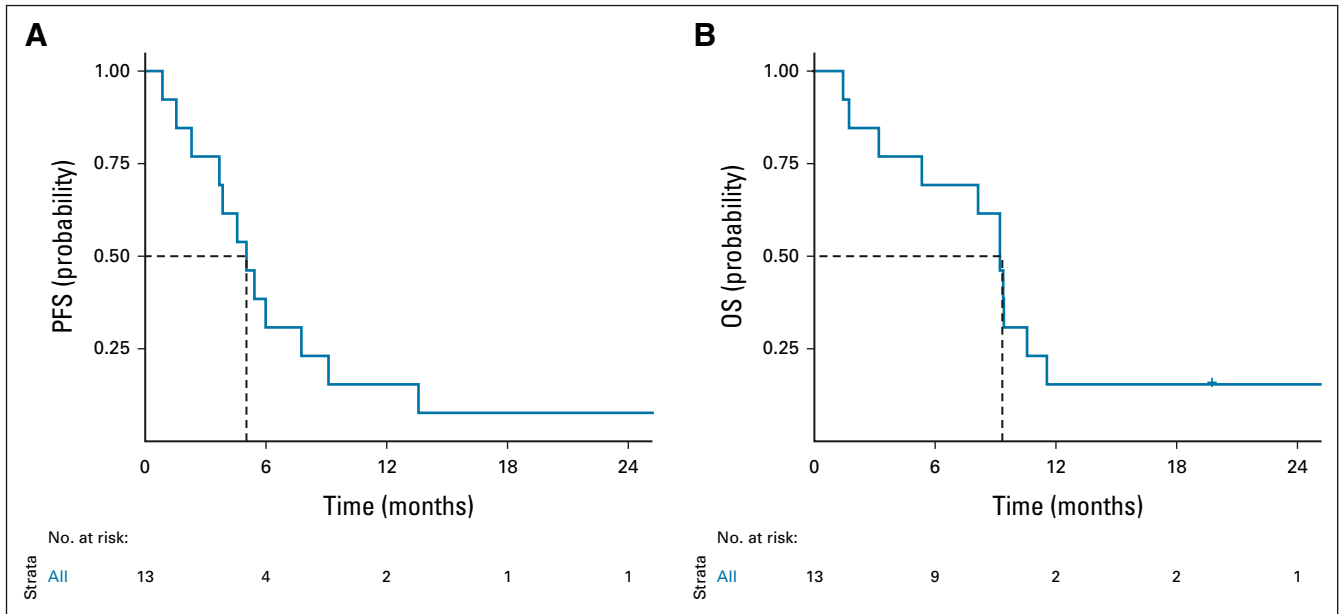
The median follow-up time was 39.6 months (interquartile range: 19.8-59.5 months). At the time of data cutoff date, all patients experienced PD to first-line ALKi or death, whereas 11 (85%) died. The median PFS was 5.0 months (95% CI, 3.68 to no response), and the median OS was 9.3 months (95% CI, 5.46 to no response; Fig 2). Figure 3 represents the time on treatment with ALKi for each patient.

**Molecular Case Report of ALK Rearranged Gastric Cancer on Alectinib-Lorlatinib Sequential Strategy**

We report the longitudinal molecular profiling of a patient with ALK fusion-positive advanced gastric cancer treated with alectinib followed by lorlatinib. Figure 4 depicts the timeline of the patient’s clinical history and details on molecular analyses. Briefly, a 51-year-old woman with locally advanced gastric adenocarcinoma received perioperative FLOT regimen. Histologic examination of total gastrectomy described poorly



**FIG 1.** Spider plot of response dynamics according to (A) the primary site of origin and (C) the type of ALKi received and waterfall plot of individual best responses according to (B) the primary site of origin and (D) the type of ALKi received for the 12 evaluable patients. ALKi, anaplastic lymphoma kinase inhibitors.

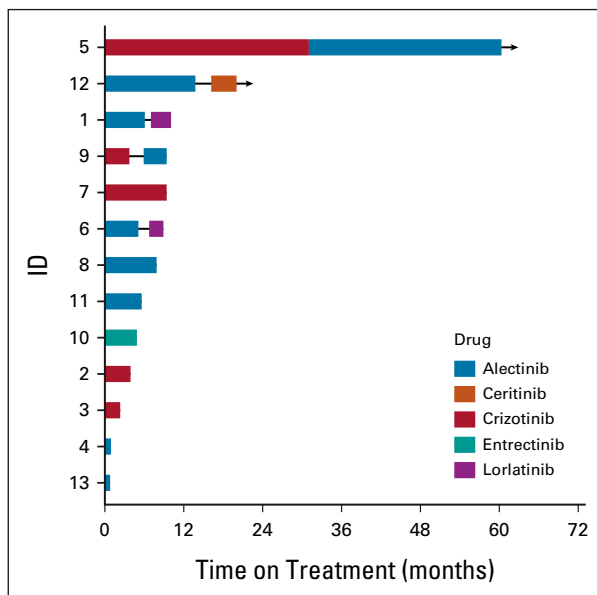


**FIG 2.** PFS and OS of the 13 patients. OS, overall survival; PFS, progression-free survival.

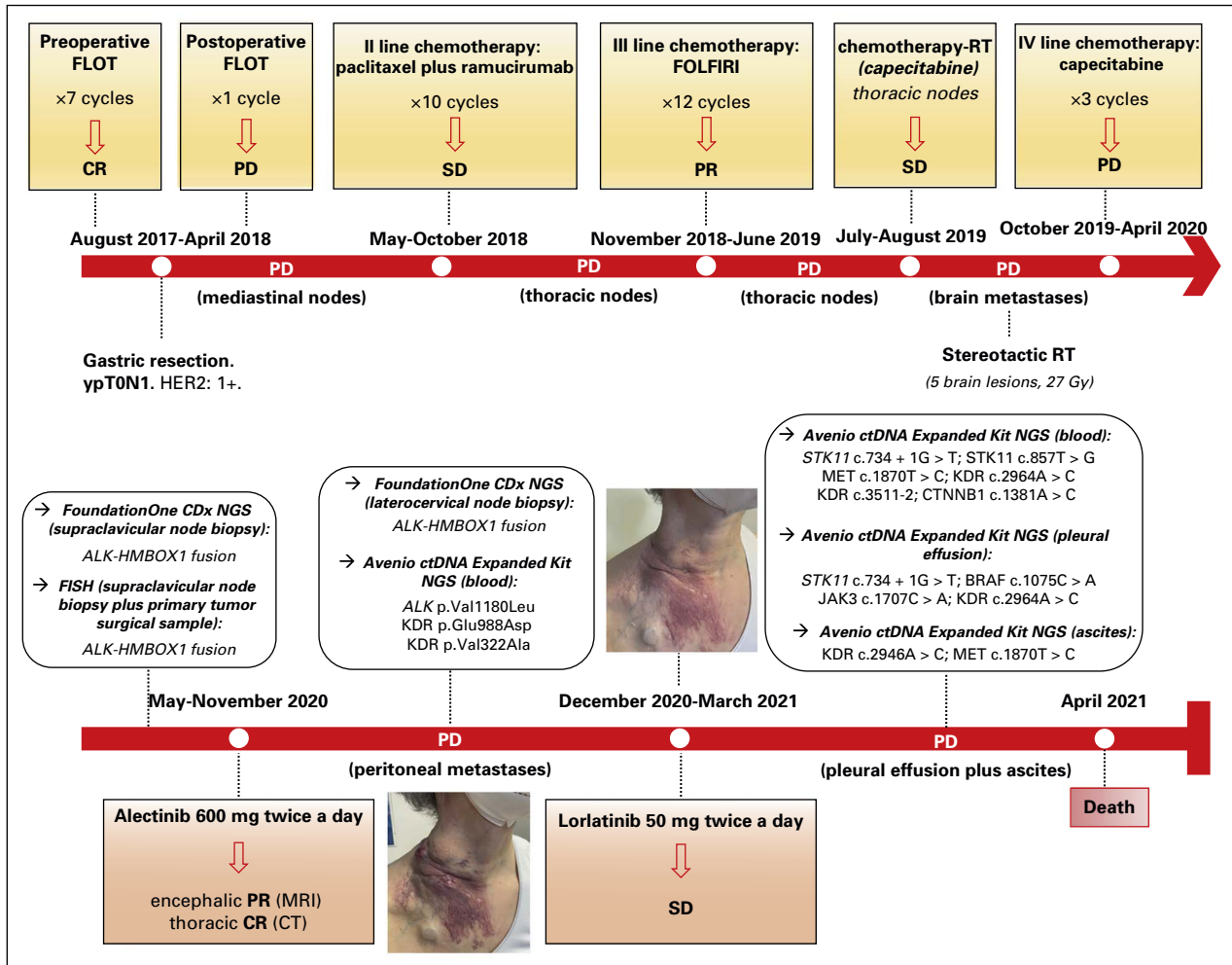
differentiated gastric adenocarcinoma with a nearly CR (stage ypT0N1). Immunohistochemical analysis showed focal positive staining for Caudal Type Homeobox 2 (CDX2), negative staining for paired box gene 8 (PAX8), thyroid transcription factor 1 (TTF1), and human epidermal growth factor receptor 2 (HER2) (1+), as well as intact expression of mismatch repair proteins. Unfortunately, early recurrence at the mediastinal lymph nodes was observed.

The patient received subsequent treatments with paclitaxel/ramucirumab and fluorouracil, leucovorin, and irinotecan,

followed by capecitabine-based chemoradiation to the mediastinal lymph nodes as a site of isolated PD and stereotactic radiotherapy to symptomatic brain metastases. A new molecular profiling with FoundationOne CDx (F1CDx) was performed after a new biopsy on laterocervical lymph nodes, site of PD, revealing the presence of the *ALK-HMBOX* fusion protein. This finding was confirmed by FISH on the same specimen and in the primary tumor surgical sample (ALK Break Apart FISH Probe Kit, CE-IVD-FDA, Abbott, Vysis, IL), with *ALK* rearrangement in 100% of analyzed cancer cells. On the basis of these molecular findings, the patient started alectinib 600 mg twice a day in May 2020, with an Eastern Cooperative Oncology Group performance status of 3 mainly because of symptomatic brain metastases. The treatment yielded a rapid and significant symptomatic improvement consistent with Lazarus response: After few weeks, the neurologic symptoms had almost completely disappeared and the Eastern Cooperative Oncology Group performance status was 1. Radiologic re-evaluation in July 2020 showed CR on thoracic and cervical localizations and PR on brain. Alectinib was interrupted in October 2020 because of abdominal PD. Repeated profiling with a second FoundationOne CDx test was performed on a new tissue specimen from a cervical lymph node, site of PD, with the evidence of retained *ALK-HMBOX* fusion, but no acquired resistance mechanisms to alectinib. A liquid biopsy was performed and analyzed with the Avenio ctDNA Expanded Kit (Roche Sequencing, Pleasanton, CA) on a 550 Next Generation Sequencing instrument (Illumina, San Diego, CA). The analysis showed the presence of one *ALKi* resistance mutations: the p.Val1180Leu (allele frequency 0.19%). The patient started on second-line lorlatinib 50 mg twice a day in December 2020, with further clinical benefit and radiologic SD until March 2021. Then, PD



**FIG 3.** Swimmer plot representing time on treatment with anaplastic lymphoma kinase inhibitors for each patient.



**FIG 4.** Timeline of the patient's clinical history and sequential tumoral molecular profiling. CR, complete response; CT, computed tomography; ctDNA, circulating tumor DNA; FISH, fluorescent in situ hybridization; FLOT, fluorouracil, leucovorin, oxaliplatin, docetaxel; FOLFIRI, fluorouracil, leucovorin, and irinotecan; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; NGS, next-generation sequencing; PD, disease progression; PR, partial response; RT, radiotherapy; SD, disease stabilization.

occurred with the worsening of peritoneal disease, ascites and pleural effusion, with drainage and collection of both fluids and plasma, that were analyzed again with the Avenio ctDNA Expanded Kit, Roche. As a result, cell clones carrying the *ALK* point mutation previously detected were depleted by lorlatinib treatment, which is reported to be active against the p.Val1180Leu. However, a *STK11* intronic loss-of-function mutation (c.734+1G>T) emerged as a mechanism of resistance at an allele frequency of 5.95% and 0.72% in the pleural effusion and in plasma, respectively.

The patient died in April 2021 because of PD.

**DISCUSSION**

In this study, we demonstrated the activity of ALKi in pretreated patients with *ALK* fusion-positive advanced GI cancers, with the evidence of tumor responses both as a single line of therapy and as sequences of different agents, switched after PD.

Cancer genome sequencing assays are not recommended by guidelines in several cancer types, including GI tumors, since their clinical usefulness for the clinical practice has not been definitively established yet.<sup>16</sup> However, increased utilization of NGS and comprehensive genomic profiling may allow us to obtain useful information on tumor targets with potential relevance for patients' treatment. As a matter of fact, genomic profiling can be useful in individual patients to detect rare but potentially actionable gene alterations, thus allowing to offer a therapeutic chance when no further evidence-based options are available for the single patient.

In this scenario, *ALK* rearrangements are extremely rare in GI cancers, but similar to other gene fusions may be regarded as oncogenic drivers. In colorectal cancer, *ALK* fusions are invariably associated with *RAS* and *BRAF* V600E wild-type status, and thus, they are mutually exclusive with the commonest driver mutations in *RAS* or *BRAF*.<sup>11</sup> In addition, *ALK/ROS1/NTRK1-3* and *RET*



rearrangements were selected to build our PRESSING panel that includes uncommon alterations associated with primary resistance, lack of clinical benefit, and unfavorable outcomes to anti-epidermal growth factor receptor (anti-EGFR) agents in patients with *RAS/BRAF* wild-type mCRC.<sup>17,18</sup> Regarding pancreatic cancer, available data show that potentially actionable alterations, such as *BRAF* mutations and *FGFR2-3*, *NTRK*, *RET*, *MET* and *ALK* fusions, are restricted to *KRAS* wild-type tumors, suggesting their role as cancer drivers.<sup>19,20</sup>

Recently, various studies have evaluated the activity of new selective inhibitors of fusion proteins across different cancer types. The *NTRK* inhibitors entrectinib and larotrectinib were evaluated in *NTRK1-3* fusion–positive solid tumors of any site origin, including GI tract, showing tumor-site independent dramatic responses, thus leading to US Food and Drug Administration and European Medicines Agency agnostic approval of both drugs.<sup>21,22</sup> Activity data of these agents have been reported specifically for GI cancer patients. A cohort of eight patients with GI cancer enrolled in three global trials involving *NTRK1-3* fusion–positive tumors showed clinically meaningful and durable responses to entrectinib, with four PR (1 colorectal cancer, 2 pancreatic cancers, and 1 cholangiocarcinoma).<sup>23</sup> Larotrectinib demonstrated rapid responses and high survival rates in 14 patients with *NTRK* fusion–positive GI cancers enrolled in the phase II NAVIGATE clinical trial.<sup>24,25</sup>

Similarly, the new selective *RET* inhibitors selpercatinib and pralsetinib have shown promising antitumor activity in small cohorts of *RET* fusion–positive solid tumors other than NSCLC and thyroid cancer (in which the two drugs are already approved), including treatment refractory GI malignancies.<sup>26,27</sup>

All these studies are industry-sponsored and have developed these drugs with a potentially agnostic indication since the initial phases of the drugs development. This was clearly necessary for entrectinib and larotrectinib because of the extremely low frequency of *NTRK* fusions across almost all cancer types, with a large-scale screening being the only chance to reach the evidence of tissue-independent activity and clinical approval. For selpercatinib and pralsetinib, despite the enrichment of *RET* alterations in NSCLC and thyroid cancers, agnostic clinical development was pursued in parallel because of the possibility to detect *RET* fusions virtually in all cancer types, even if with low prevalence.

A similar concept may be valid for *ALK* fusions in solid tumors, found in approximately 4% of NSCLC and with significantly lower frequencies in GI cancers, as previously described.

However, when the clinical development of selective ALKi was started, the use of master protocols and the design of basket trials were relatively uncommon. As a matter of fact, several randomized controlled trials have focused on *ALK* fusion–positive NSCLC with the aim of

testing the efficacy of ALKi as compared with standard chemotherapy. These efforts have led to a practice changing of the frontline strategy from chemotherapy to targeted treatment and later to the approval of sequential strategies of treatment with the next generations of ALKi.<sup>3,4</sup> Similar data are not available, to date, for solid tumors other than NSCLC. In GI cancers, the only data supporting therapeutic ALK targeting derived from case reports, that, although being proof-of-concept, remain anecdotal and are not sufficient to support off-label ALKi use in many countries.

With all this background in mind, waiting for stronger prospective evidence from ongoing basket trials (ClinicalTrials.gov identifier: [NCT04644315](#), [NCT03868423](#), [NCT01284192](#), [NCT04439266](#)), we assembled an international cohort of 13 patients with *ALK* fusion–positive GI cancer and demonstrated remarkable activity of different ALKi in heavily pretreated patients (ORR 41%, DCR 82%). Notably, five patients (38%) were able to receive a second line of ALKi after PD, with two patients still receiving second-line treatment at the time of data cutoff date.

Our molecular case report in a patient with *ALK* fusion–positive gastric cancer showed that lorlatinib may suppress tumor clones with mutations of secondary resistance to alectinib. The emergence of *STK11* mutations at resistance to lorlatinib warrants further investigation on the mTOR pathway as a crucial resistance pathway that may be targeted; however, nongenomic mechanisms of resistance should be investigated in this setting. Indeed, the emergence of p.L1196Q gatekeeper mutation in *ALK* kinase domain was found in a PDX model obtained at PD to the second line of ALKi in patient 9 of our series, as previously described by Singh et al.<sup>12</sup> This finding may explain the modest benefit with first-generation and second-generation ALKi since *ALK* p.L1196Q may drive cross-resistance to both crizotinib and alectinib.

Our study has clearly some limitations, mainly related to the small sample of patients treated, the retrospective nature of the analysis, and the heterogeneity of ALKi drugs used. These limitations did not let us to explore possible differences in responses according to patients' clinical and molecular characteristics, such as specific gene fusion partners, or different ALK targeted agents. Notably, some patients were treated with the first-generation ALKi crizotinib that may be less efficacious compared with new generation drugs.

Despite being rare, *ALK* translocations represent an important therapeutic target in GI and other nonlung solid tumors. Patients with GI malignancies harboring *ALK* translocations are at risk of being neglected and excluded from a personalized treatment that could have significant impact on their cancer. Efforts in prospective validation of *ALK* rearrangement as a clinically useful therapeutic target and in the characterization of determinants of tumor response are greatly needed.

**AFFILIATIONS**

<sup>1</sup>Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

<sup>2</sup>Clinical Pharmacology and Pharmacogenetics Unit, Department of Clinical and Experimental Medicine, University Hospital of Pisa, Pisa, Italy

<sup>3</sup>Division of Hematology and Oncology, Cedars-Sinai Medical Center, Los Angeles, CA

<sup>4</sup>Memorial Sloan Kettering Cancer Center, New York, NY

<sup>5</sup>Department of Oncology, Akershus University Hospital, Lorenskog, Norway

<sup>6</sup>Institute of Clinical Medicine, University of Oslo, Oslo, Norway

<sup>7</sup>Massachusetts General Hospital Cancer Center, Boston, MA

<sup>8</sup>Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway

<sup>9</sup>Department of Gastroenterological Surgery, Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway

<sup>10</sup>Division of Laboratory Medicine, Department of Pathology, Oslo University Hospital, Norway

<sup>11</sup>Division of Cancer Medicine, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway

<sup>12</sup>Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

<sup>13</sup>Department of Oncology and Hemato–Oncology, University of Milano (La Statale), Milan, Italy

<sup>14</sup>Pathology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

**CORRESPONDING AUTHOR**

Filippo Pietrantonio, MD, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milan, Italy; Twitter: @FilippoPietran4; e-mail: filippo.pietrantonio@istitutotumori.mi.it.

**AUTHOR CONTRIBUTIONS**

**Conception and design:** Margherita Ambrosini, Marzia Del Re, Andrew Hendifar, Massimo Milione, Maria Di Bartolomeo, Filippo Pietrantonio

**Financial support:** Marzia Del Re

**Provision of study materials or patients:** Marzia Del Re, Andrew Hendifar, Alexander Drilon, Guilherme Harada, Anne Hansen Ree, Samuel Klempner, Gunhild Mari Mælandsmo, Kjersti Flatmark, Hege G. Russnes, James M. Cleary, Harshabad Singh, Elisa Sottotetti, Andrea Sartore-Bianchi, Maria Di Bartolomeo, Filippo Pietrantonio

**Collection and assembly of data:** Margherita Ambrosini, Andrew Hendifar, Alexander Drilon, Guilherme Harada, Anne Hansen Ree, Gunhild Mari Mælandsmo, Kjersti Flatmark, Hege G. Russnes, James M. Cleary, Harshabad Singh, Elisa Sottotetti, Antonia Martinetti, Giovanni Randon, Andrea Sartore-Bianchi, Iolanda Capone, Maria Di Bartolomeo, Filippo Pietrantonio

**Data analysis and interpretation:** Margherita Ambrosini, Marzia Del Re, Paolo Manca, Andrew Hendifar, Guilherme Harada, Anne Hansen Ree, Samuel Klempner, Harshabad Singh, Maria Di Bartolomeo, Filippo Pietrantonio

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

**Accountable for all aspects of the work:** All authors

**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](http://www.openpayments.org)).

**Marzia Del Re**

**Consulting or Advisory Role:** Sanofi, Celgene, Janssen-Cilag, Ipsen, Roche Molecular Diagnostics

**Speakers' Bureau:** Sanofi, Pfizer, Novartis, Janssen-Cilag, Ipsen, AstraZeneca, Astellas Pharma, Roche, MSD Oncology

**Paolo Manca**

**Patents, Royalties, Other Intellectual Property:** I have a patent for a method for the identification of gene panels optimal for TMB estimation (Inst)

**Andrew Hendifar**

**Consulting or Advisory Role:** Novartis, Ipsen, Perthera, Celgene, AbbVie, Eisai

**Research Funding:** Ipsen, NGM Biopharmaceuticals (Inst)

**Travel, Accommodations, Expenses:** Halozyme

**Other Relationship:** FibroGen

**Alexander Drilon**

**Honoraria:** Pfizer, Loxo/Bayer/Lilly, IASLC

**Consulting or Advisory Role:** Ignyta, Loxo, AstraZeneca, Pfizer, Blueprint Medicines, Genentech/Roche, BeiGene, Hengrui Therapeutics, Exelixis, Bayer, Tyra Biosciences, Takeda/Millennium, BerGenBio, MORE Health, Lilly, AbbVie, 14ner Oncology/Elevation Oncology, Monopteros Therapeutics, Novartis, EMD Serono/Merck, Repare Therapeutics, Melendi, Archer, Nuvalent Inc, Janssen, Amgen, Merus, Axis Pharma, Medscape, Liberum, Med Learning, PeerView, EPG Health, JNCCN/Harboardside, Ology, Clinical Care Options, touchIME, Entos, Treeline, Prelude Therapeutics, Applied Pharmaceutical Science Inc

**Speakers' Bureau:** Helsinn Therapeutics, Beigene, Remedica Ltd, TP Therapeutics, Verastem, Ignyta/Genentech/Roche, AstraZeneca, Liberum, Loxo/Bayer/Lilly, Lungevity, NIH, PER, OncLive/MJH Life Sciences, Clinical Care Options/NCCN, Lung Cancer Canada, AIOT, Chugai Pharma, Chugai Pharma, Sirio Libanes Hospital, Answers in CME, Faculty RTP, RV More

**Research Funding:** Foundation Medicine

**Patents, Royalties, Other Intellectual Property:** Wolters Kluwer (Royalties for Pocket Oncology)

**Other Relationship:** Merck, GlaxoSmithKline, Teva, Taiho Pharmaceutical, Pfizer, PharmaMar, Puma Biotechnology, Merus, Boehringer Ingelheim

**Guilherme Harada**

**Speakers' Bureau:** MSD, AstraZeneca, Pfizer

**Anne Hansen Ree**

**Honoraria:** MSD Oncology, BMSi

**Research Funding:** BMSi (Inst)

**Samuel Klempner**

**Stock and Other Ownership Interests:** TP Therapeutics, Nuvalent Inc

**Honoraria:** Natera

**Consulting or Advisory Role:** Lilly, Astellas Pharma, Bristol Myers Squibb, Pieris Pharmaceuticals, Merck, Daiichi Sankyo/UCB Japan, Sanofi/Aventis, Mersana

**Research Funding:** Leap Therapeutics (Inst), BeiGene (Inst), Silverback Therapeutics (Inst)

**Other Relationship:** NCCN

**Gunhild Mari Mælandsmo**

**Patents, Royalties, Other Intellectual Property:** Patent application submitted for a nine-protein/gene panel predicting response to anti VEGF therapies in combination with chemotherapy (Inst)

**Hege G. Russnes**

**Honoraria:** AstraZeneca (Inst), Pfizer (Inst), InCyte (Inst), Merck (Inst), Roche (Inst)

**Research Funding:** Foundation Medicine (Inst)

**James M. Cleary****Honoraria:** Blueprint Medicines, Syros Pharmaceuticals**Consulting or Advisory Role:** Bristol Myers Squibb**Research Funding:** Merck, Tesaro, AstraZeneca, Esperas Pharma, AbbVie (Inst), Merus (Inst), Roche/Genentech (Inst), BMS (Inst)**Travel, Accommodations, Expenses:** Roche, Agios, Bristol Myers Squibb**Andrea Sartore-Bianchi****Consulting or Advisory Role:** Amgen, Bayer, Sanofi, Servier, Novartis**Maria Di Bartolomeo****Honoraria:** Lilly, MSD Oncology, Servier, BMSi**Consulting or Advisory Role:** Lilly, MSD Oncology**Research Funding:** Lilly**Travel, Accommodations, Expenses:** Roche, Sanofi**Filippo Pietrantonio****Honoraria:** Servier, Bayer, AstraZeneca/MedImmune, Lilly, Sanofi, MSD Oncology, Amgen**Consulting or Advisory Role:** Amgen, Servier, MSD Oncology, Merck**Research Funding:** Bristol Myers Squibb (Inst), AstraZeneca (Inst)

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