Evolving Landscape of Molecular Prescreening Strategies for Oncology Early Clinical Trials

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abstract

Most academic precision oncology programs have been designed to facilitate enrollment of patients in early clinical trials with matched targeted agents. Over the last decade, major changes were seen both in the targetable molecular alteration landscape and in drug development trends. In this article, we describe how the Vall d'Hebron Institute of Oncology molecular prescreening program adapted to a dynamic model of biomarker-drug codevelopment. We started with a tumor-agnostic hotspot mutation panel plus in situ hybridization and immunohistochemistry of selected markers and subsequently transitioned to tumor-specific amplicon-based next-generation sequencing (NGS) tests together with custom copy number, fusion, and outlier gene expression panels. All assays are optimized for archived formalin-fixed paraffin-embedded tumor tissues without matched germline sequencing. In parallel, biomarker-matched trials evolved from a scenario of few targets and large populations (such as PI3K inhibitors in *PIK3CA* mutants) to a complex situation with many targets and small populations (such as multiple targetable fusion events). Recruitment rates in clinical trials with mandatory biomarkers decreased over the last 3 years. Molecular tumor board meetings proved critical to guide oncologists on emerging biomarkers for clinical testing and interpretation of NGS results. The substantial increase of immunotherapy trials had a major impact in target prioritization and guided clinical implementation of new markers, such as tumor mutational burden, with larger exon-based NGS assays and gene expression signatures to capture microenvironment infiltration patterns. This new multiomics era of precision oncology is expected to increase the opportunities for early clinical trial matching.

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INTRODUCTION

During the last decade, when targeted agents entered the phase I clinical trial arena and next-generation sequencing (NGS) became a standard molecular prescreening test to identify actionable alterations, oncologists experienced a major shift toward biomarker-driven drug development.[1] There was a lot of enthusiasm with this approach, which culminated with the approval of many targeted drugs in molecularly selected patients on the basis of nonrandomized data. More recently, another important milestone was reached with the approval of tissue-agnostic therapies in biomarker-selected population, first the immune checkpoint inhibitor pembrolizumab in microsatellite instable (MSI) tumors and then TRK inhibitors larotrectinib and entrectinib in cancers harboring *NTRK* fusions. Given these exciting advances, many reference institutions initiated precision oncology programs with longitudinal patient cohorts undergoing tumor molecular profiling nested to early clinical trials with matched targeted agents.[2]

In parallel, as advances in immuno-oncology are changing the standard of care of many cancer types, the phase I oncology community experienced another paradigm shift in drug development, with an unprecedented number of new investigational agents entering clinical testing.[3] Not only different anti–PD-1/L1 inhibitors but also multiple combination regimens are being investigated in early clinical trials. Initially, a tumor type fishing approach was used to select patients for immuno-oncology investigational drugs. More recently, genomic biomarkers are inclusion criteria to select patients for immune checkpoint inhibitor therapy, such as tumor mutation burden (TMB) and mutations in DNA damage repair (DDR) pathway genes.

In this evolving scenario, early clinical trial units had to constantly adapt to new biomarker-drug codevelopment trends. Because the molecular prescreening program was established at our institution, we customized the techniques and procedures to accurately identify molecular alterations in tumors from patients eligible for early clinical trials. In this article, we describe the expanding landscape of phase I clinical

CONTEXT

Key Objective

Our objective was to describe how an academic molecular prescreening program adapts to a dynamic landscape of early clinical trials.

Knowledge Generated

Genomically matched trials evolved from a scenario of few targets and large populations to one of many targets and small populations with complex multimodality biomarkers for immuno-oncology drugs.

Relevance

Multiplicity of trials for emerging targets and academic-industry partnership for biomarker-drug codevelopment are needed to retain the clinical use of molecular prescreening programs.

trials in a reference institution and how molecular testing is being modified to facilitate precision oncology and immunotherapy drug development.

VALL D'HEBRON INSTITUTE OF ONCOLOGY MOLECULAR PRESCREENING PROGRAM

The Vall d'Hebron Institute of Oncology (VHIO) molecular prescreening program consists of a multidisciplinary team with experts in cancer biology and genomics, bioinformatics, molecular pathology, genetic counseling, and medical oncology. The program initiated in 2010 with the main objective of using emerging cancer biomarkers to optimize the selection of therapies for patients being considered for phase I clinical trials. The team meets periodically to discuss existing molecular tests and new biomarkers of interest to be added to our prescreening program. Cancer biologists and genomicists participate in weekly molecular tumor board meetings with medical oncologists to provide guidance on the interpretation of NGS results and discuss new markers for clinical testing in patients eligible for early clinical trials.

As detailed in Figure 1A, we started with a targeted single base extension mutation assay covering hotspot events in 20 oncogenes and tumor suppressor genes (Sequenom) plus fluorescent in situ hybridization (FISH) or immunohistochemistry (IHC) analysis of selected genes and proteins. In 2013 we implemented an nCounter RNA platform (NanoString) fusions and gene expression (GEX) analysis of 26 genes—Fusion and GEX nCounter. In 2014 we substituted the hotspot mutation panel with a custom amplicon-based NGS assay covering 59 genes (MiSeq), and 1 year later we replaced the FISH analysis with a targeted copy number nCounter DNA panel of 44 genes—CNA nCounter. During 2015 we also added *BRCA1/BRCA2* genes to the NGS panel, introduced PDL1 IHC and MSI testing by IHC (with polymerase chain reaction–based test in equivocal cases). In 2018 we developed an exon-based NGS assay (HiSeq) with 420 genes, encompassing DDR plus epigenetic pathway genes and fine-tuned for TMB quantification and other genomic signatures, such as MSI. So far, this assay is limited to selected cases of

particular interest, as per discussions in weekly molecular tumor boards, but will eventually replace the amplicon NGS and NanoCopy DNA panels in the coming year. To identify patients eligible for antibody-drug conjugates, different IHC assays were developed in collaboration with pharmaceutical companies, which allowed local testing instead of sample shipment for central profiling. Most pharmaceutical companies also accept our in-house–developed genomic testing as screening for biomarker-guided trials, but we noticed that a growing number of early clinical trials mandate central NGS companion diagnostic tests, specifically in lung, bladder, and biliary tract cancers.

All assays were optimized for archived formalin-fixed paraffin-embedded tumor tissues. We prioritized analysis of metastatic samples if available, but de novo biopsies were not mandatory. Importantly, NGS assays had frequent modifications in gene coverage to capture emerging biomarkers being investigated in clinical trials at our institution, such as the recent additions of *NOTCH* family genes to the mutation panel, *NTRK* breakpoints to the fusion assay, and *CD274* (PD-L1) to the CNA nCounter test. Until 2017, all tests were tumor-type universal. In 2018, the amplicon-based NGS panel was tailored as multiple tumor-type–specific panels, with coverage limited to genes that have been previously found to be mutated in each malignancy. This modification allowed partial coverage of genes with emerging actionability in specific tumor types, such as *BRCA1* and *BRCA2*. Finally, circulating tumor DNA (ctDNA) mutation detection panels are under development but still limited to patient cohorts with predefined tumor types participating in validation studies.

Each oncologist has the responsibility to define a patient's eligibility for molecular prescreening on the basis of clinical features, tumor type, and disease setting. The medical team also defines which test is indicated for each patient, given the targets of interest in different tumor types. Clinicians follow previously outlined flow charts for NGS testing, which are not rigid or formal in any sense. As a general rule, a test request is indicated in a particular tumor type at a specific time point when its actionability
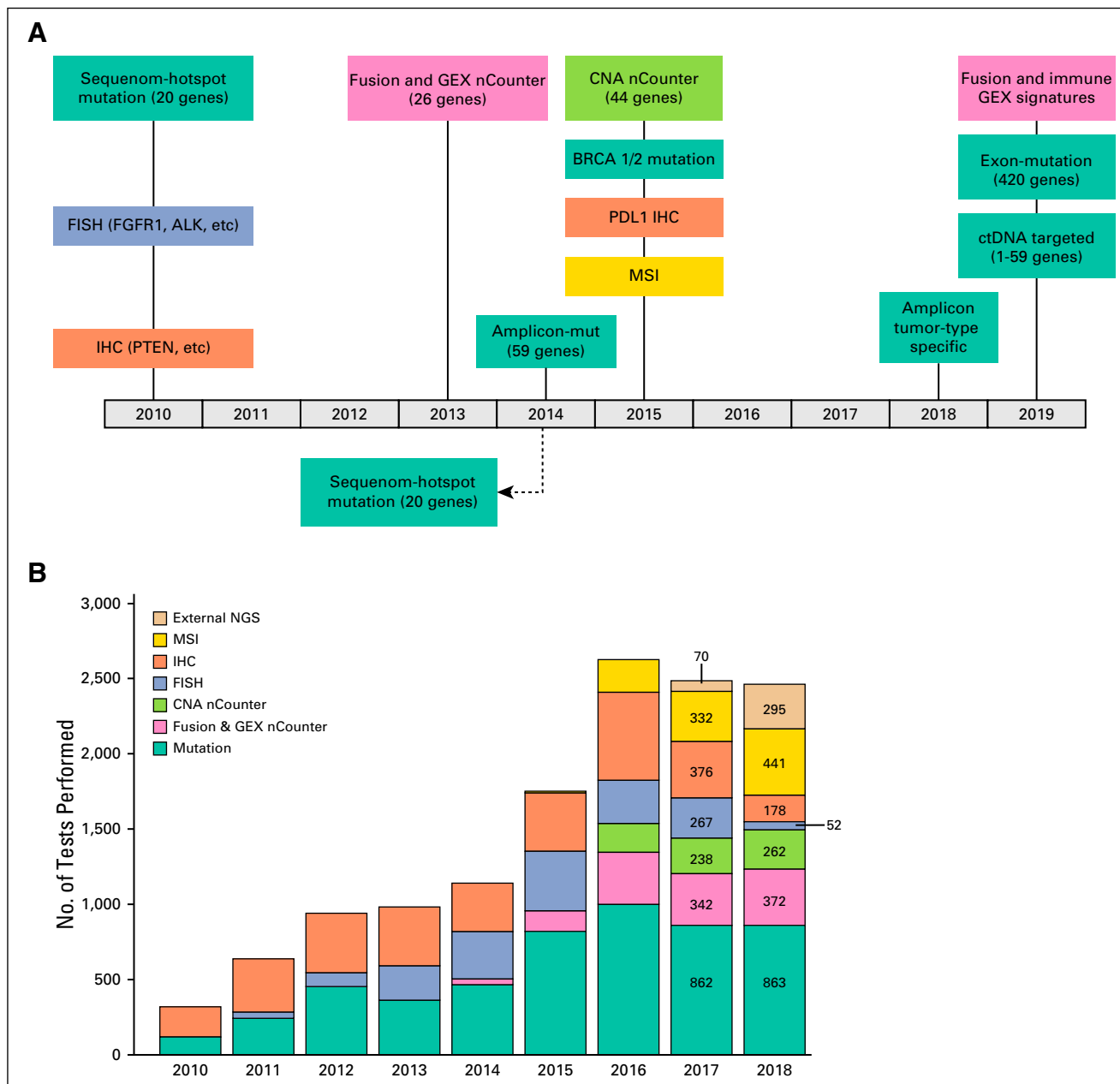
FIG 1. Vall d'Hebron Institute of Oncology molecular prescreening program. (A) Timeline detailing most important changes in prescreening tests in the last years. (B) Number of tests performed each year by category. CNA nCounter, Copy Number Alteration NanoString Panel; FISH, fluorescent in situ hybridization; Fusion and GEX nCounter, Fusion and gene expression NanoString Panel; IHC, immunohistochemistry; MSI, microsatellite instability; NGS, next-generation sequencing.

yield (combined prevalence of targetable molecular alterations) exceeds 3%. Depending on the tumor type, molecular tests are performed up front (such as in lung cancer when sufficient tissue is available for NGS), while patients receive standard-of-care chemotherapies (such as biliary tract cancer and hormone receptor–positive breast cancer), or after progression to approved regimens (such as cervical cancer). We educate clinicians not to indicate NGS as a rescue diagnostic test to identify targets for experimental therapies when patients have fast clinical deterioration, but also to avoid the "all-comers up-front" strategy, given the potential reduced cost effectiveness of this approach for all advanced tumor types. Approximately 50% of the population with metastatic cancer treated at the institution every year participates in the molecular prescreening program. Even though it was originally developed as a research platform, with advances in precision oncology over the last years we noticed that the program is also serving our standard diagnostics needs.

After the patient signs informed consent for broad tumor molecular profiling, requests are submitted to the Molecular Oncology Unit for sample retrieval, qualification, and preparation, and to perform IHC/FISH tests. Minimal tumor purity for mutation and fusion–GEX nCounter testing is 20%, whereas CNA nCounter and exon-based NGS tests require at least 50% of tumor cells. Subsequently, samples are sent to the Cancer Genomics laboratory for DNA and RNA assays. Both laboratories follow ISO15189 standards. Overall, 90% of the patients who participated in the program had at least one test result available for treatment decision. Turnaround time is < 1 week for IHC or FISH tests and approximately 2 weeks for the amplicon-based NGS panel; nCounter results are reported within 2-3 weeks and exon-based NGS panel in 3-4 weeks. As previously mentioned, patients may have their tumor tested in external diagnostics laboratories according to specific clinical trial eligibility criteria. Depending on the assay's coverage, it serves as a substitute for the internal program.

Our molecular prescreening program is free of charge to patients and financed with both internal resources acquired through competitive grants or donations (institutional patronage) and external funds from agreements with pharmaceutical companies running early clinical trials with mandatory biomarker matches. In the latter case, which represents 15% of total budget, the cofinancing models can be a molecular prescreening fee for each patient recruited in the trial or a pay-per-test fee while the trial is recruiting patients (with monthly reports detailing number of tests performed and positive results).

As shown in Figure 1B, close to 2,500 molecular tests were performed in 2018, a 10-fold increase as compared with 2010. Major increments were noticed in 2015-2016, after the introduction of amplicon-based NGS mutation panel and the nCounter platform for RNA and DNA profiling. This went along with a stepwise increase in the number of cases profiled in-house, from 207 patients in 2010 to 1,121 in 2018, representing a 5-fold increase.

VHIO PHASE I CLINICAL TRIAL UNIT

In the last 9 years, the number of phase I clinical trials at our institution increased from 13 in 2010 to 161 in 2018, as illustrated in Figures 2A and 2B. In 2010, most early therapeutic trials tested PI3K pathway inhibitors (n = 11), whereas in 2018, immunotherapy trials represented the great majority (n = 75), followed by antibody-drug conjugates (n = 9), epigenetics (n = 9), FGFR inhibitors (n = 9), PI3K pathway inhibitors (n = 8), MEK/ERK inhibitors (n = 8), and EGFR/ERBB2 inhibitors (n = 7). Regarding phase I trials with targeted drugs (Fig 2A), we observed a gradual increase in the number of targets of interest for clinical development from 2010 to 2016, including *ALK/ROS1*, *FGFR1-3*, *BRAF*, *MET*, *NOTCH1-2*, DDR pathways alterations, and others (*HDM2*, *KIT*, *PDGFR*, *IDH1-2*, *RET*, *NTRK1-3*, cyclin, and Wnt pathways). A substantial

increase in the number of drugs matched to the same targets was noted in 2016. Interestingly, between 2017 and 2018 we had a consistent decrease in the number of clinical trials with targeted agents (Fig 2A). This was accompanied by a major increase in the number of immuno-oncology trials, which escalated since 2015 (Fig 2B).

The criteria for patient enrollment in a given trial go beyond genomic markers. However, as a general rule, when an oncogene alteration is found, clinical trials with targeted agents are prioritized. In cases of borderline evidence of clinical actionability of molecular targets (enrichment criteria) or no oncogene alteration, alternative therapies are considered, taking into consideration tumor type and availability of slots in trials with immunotherapies and other drugs. More recently, immune-related markers are used as positive selection criteria for clinical trials with novel immune-oncology drugs and combinations.

Out of 161 early clinical trials actively recruiting patients in 2018, 57 investigated targeted agents (Fig 2A), 24 of them (42%) were combination regimens, and 48 (84%) had mandatory or enrichment molecular inclusion criteria, the most common being FGFR, MAPK, PI3K, EGFR/ERBB2, and DDR pathway alterations. This high rate of genomics-guided recruitment in early clinical trials with targeted agents remained stable since 2010. Regarding immunotherapy trials, 57 out of 75 (76%) were combination regimens and 32 (43%) had mandatory or enrichment molecular criteria for recruitment, with PD-L1 expression and MSI status being the most common biomarkers (Figs 2B and 2D). In 2017, only 8 out of 56 immunotherapy trials (14%) used biomarkers to select patients. We also gradually increased the number of clinical trials testing antibody-drug conjugates, most of them with mandatory IHC analysis for patient selection, and epigenetic targets, rarely recruiting patients on the basis of genomic profiling (as *BRD4-NUT* fusions for BET inhibitors).

Inclusions in clinical trials with targeted agents fluctuated from 2010 to 2018 (Fig 2C). In 2018, 142 patients were recruited in molecularly guided targeted phase I trials. The multiplicity of drug targets under investigation coupled with a growing number of molecular tests being performed during this period allowed recruitment of more patients in phase I trials assessing novel biomarkers, including *FGFR1-3*, *NOTCH1-2* alterations, and *BRCA1-2* mutations, among others. Interestingly, agents targeting MAPK pathway and HER2 alterations had increased interest in 2018 as compared with 2017. We observed a major decrease in recruitment rates in phase I trials with targeted agents in 2017, in part related to lower interest in some targets, such as PI3K pathway inhibitors, but also a 3-fold increase in the number of patients referred to phase II or III trials with molecular matches, from 84 in 2016 to 224 in 2018. In parallel, we noticed a substantial increase of enrollment in immuno-oncology phase I clinical trials with biomarker inclusion criteria, illustrated in Figure 2D. Indeed, out of
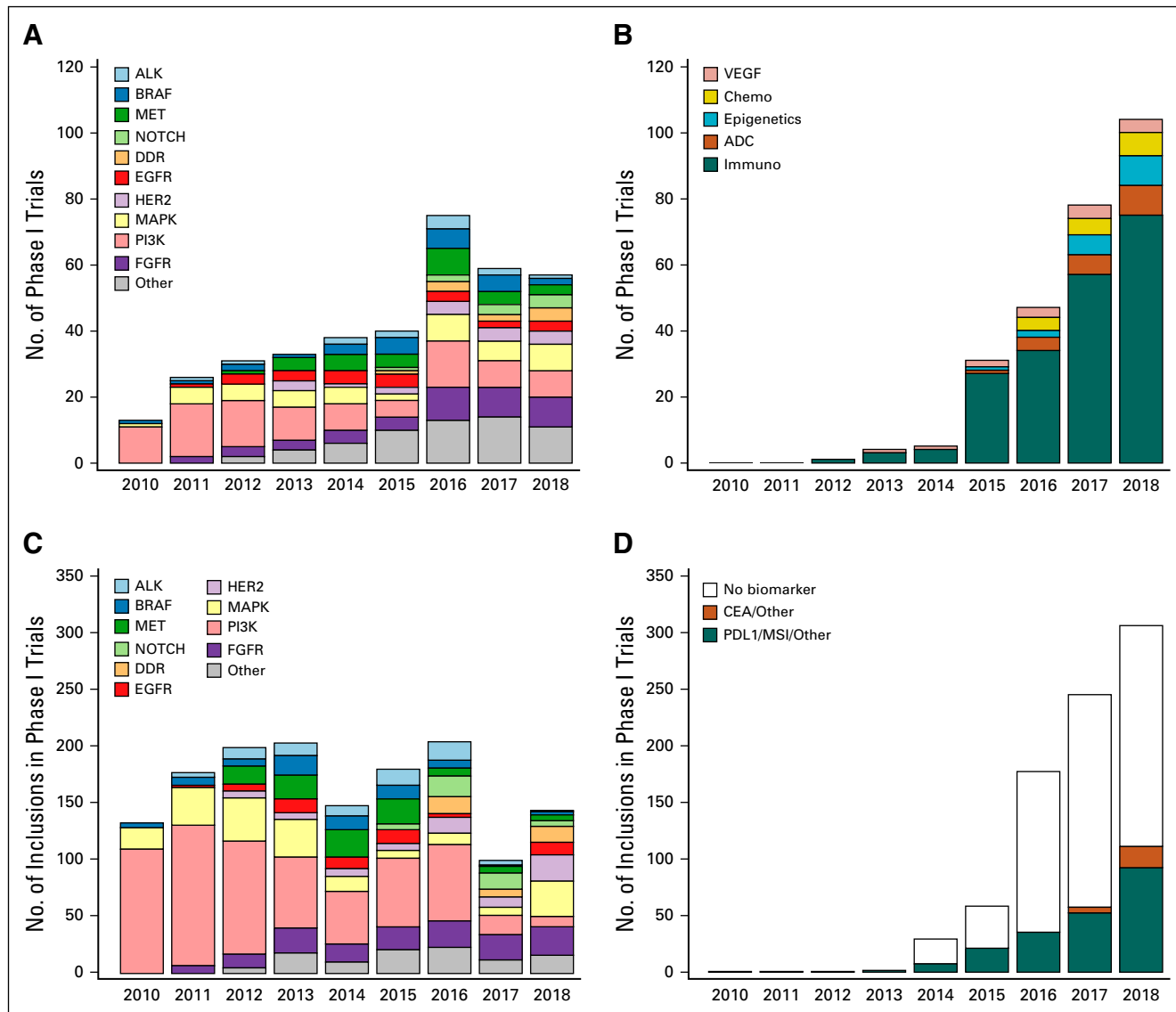
FIG 2. Vall d'Hebron Institute of Oncology phase I clinical trial unit. (A) Evolution of phase I clinical trials with targeted agents over time. (B) Phase I clinical trials investigating drugs with other mechanisms of action. (C) Inclusions in biomarker-based phase I trials of targeted agents. (D) Inclusions in biomarker-based phase I trials investigating drugs with other mechanisms of action. Other biomarkers: *HDM2, KIT, PDGFR, IDH1-2, RET, NTRK1-3*, CDK, and Wnt pathway alterations. Chemo, chemotherapy; Immuno, immunotherapy; MSI, microsatellite instability.

306 patients recruited in immunotherapy trials during 2018, 92 (30%) were based on biomarkers.

To investigate the clinical utility of our program, we assessed how the results of profiling (both in-house and external) affected the immediate treatment decision of each patient. The most common tumor types undergoing molecular profiling in the last 3 years are shown in Figure 3A. In 2018, we noticed an increase in lung, breast, and pancreatobiliary cancers being tested in line with major advances in precision cancer therapy across these tumor types. It is important to emphasize that these represent patients not eligible for standard-of-care genomically guided therapy, such as BRAF inhibitors in *BRAF*^V600E^-mutated melanomas, or HER2-targeted therapy in *ERBB2*-

amplified breast cancer. Recruitment rates in molecularly matched trials reduced in the last years, from 15% in 2016 to 11% in 2017 and 2018 (Fig 3B). Matched trial inclusions in 2016 were largely explained by PI3K pathway inhibitors, which reduced significantly since 2017 (Fig 2C). Recruitment rates in alternative unmatched trials also gradually reduced in the same period, from 21% in 2016 to 12% in 2018 (Fig 3B). Nontargeted unmatched trials are mostly immuno-oncology drugs, with patient enrollment on the basis of lack of a promising molecular match or patient and physician preference. Still, in 2018, close to 80% of the patients participating in our molecular prescreening program were not enrolled in clinical trials immediately after tumor profiling, despite the multiplicity of molecularly
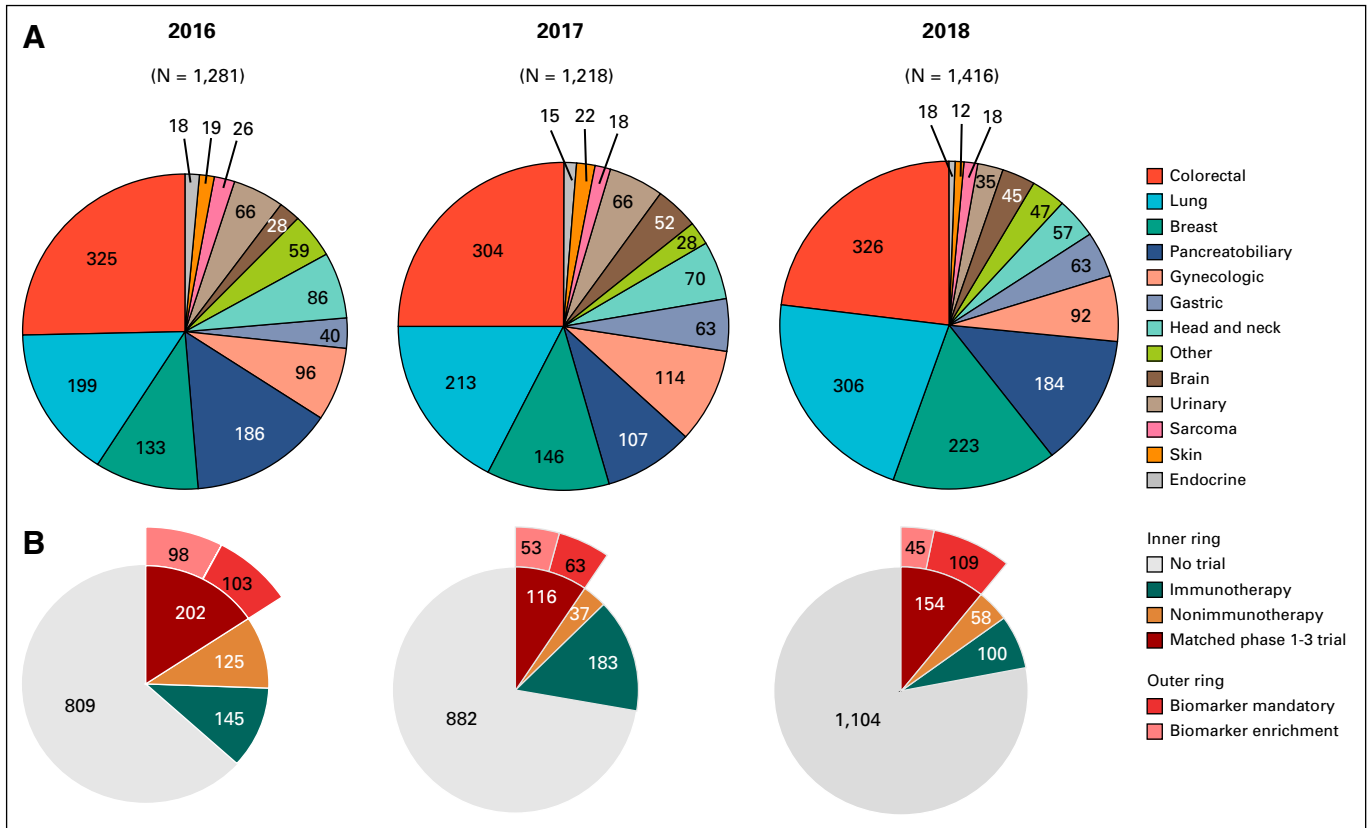
FIG 3. Vall d'Hebron Institute of Oncology molecular prescreening impact on clinical trial recruitment during the last 3 years. (A) Distribution of tumor types over the years. (B) Recruitment in biomarker-guided (mandatory or enrichment) and other alternative trials (immunotherapy or nonimmunotherapy).

guided targeted agents, antibody-drug conjugates, and immunotherapies.

DISCUSSION

The Vall d'Hebron Institute of Oncology (VHIO) molecular prescreening program is constantly adapting to the needs of our early clinical trial portfolio. We observed a dramatic change in the landscape of phase I clinical trials, now focused on targeted agents for rare molecular alterations, immunotherapy combinations, antibody-drug conjugates, and epigenetic agents. In parallel, different NGS assays were developed for accurate detection of rare actionable mutations, copy number alterations, fusion events, and novel IHC tests were introduced.

From the beginning, we followed a personalized pre-screening approach, whereby oncologists are empowered to decide which patients are eligible for testing based on clinicopathological features and which molecular tests are indicated in each disease setting. By avoiding the one-test-for-all strategy, we were able to optimize the use of our prescreening program and educate the clinicians on molecular epidemiology of each tumor type as well as emerging diagnostic tests. The decision to transition from smaller tumor-specific panels to a larger exon-based NGS that covers both mutation and copy number tests is related to the need to accommodate emerging biomarkers in the

DDR and epigenetic pathways as well as TMB quantification. But we still maintain the Fusion and GEX nCounter assays as separate tests, indicated in specific clinical settings. Overall, 1 out of 10 patients profiled are ultimately enrolled in matched targeted trials, which is in line with other academic molecular prescreening programs with nested clinical studies.[4] Regarding germline sequencing, we follow guideline-directed testing and have regular meetings with genetic counselors to discuss secondary incidental findings in tumor sequencing.[5]

In the last decade, biomarker-matched trials evolved from a scenario of few targets and large populations to a complex situation with many targets and small populations. Even with a growing number of targets being investigated in phase I trials, and the multiplicity of trials per target, we observed a relative reduction in the number of patients enrolled in molecularly guided trials in the last years. This is the result of shifting interests in drug development and a clear focus on a limited number of promising biomarkers, such as rare fusion events in *FGFR1-3*, *RET*, and *NTRK1-3* genes. On top of the expected individual patient benefit with therapies targeting these alterations, to retain the clinical utility of our program and build long-term relationships with pharmaceutical companies, our approach is to keep low-accruing trials

open, despite associated impact on personnel, infrastructure, and resource use. More often, molecularly guided trials are recruiting patients with acquired resistance to targeted agents. In this scenario, liquid biopsies for target identification are becoming quite useful, which has guiding our current development of a ctDNA amplicon-based NGS test and prompted collaborations with commercial partners for molecular prescreening.

The substantial increase in immunotherapy trials had a major impact on trial prioritization. Inclusion criteria of immuno-oncology phase I trials are frequently limited to tumor type and treatment line, with few trials having a mandatory molecular match, which facilitates patient recruitment. We noticed an increase in biomarker-guided immunotherapy trial recruitment in 2018, which is guiding implementation of a multimodality biomarker strategy that moves beyond TMB quantification, such as immune cytotoxic/suppressive microenvironment signatures measured through the GEX nCounter panel,[6] as well as multiplex IHC panels.[7]

To conclude, we believe that to accelerate progress in precision oncology, clinical trials with adaptive designs to enroll patients on the basis of multiomics enrichment criteria are needed. The previous era of molecularly guided targeted agents is restrictive, and larger portfolios of drugs that include immunotherapeutic and antibody-drug conjugates with recruitment guided by molecular tests must be pursued. In our view, the future of cancer drug development will encompass sequential genomic profiling to guide matched targeted therapies, complex multimodality biomarkers for immune-oncology agents, individualized immunotherapeutics, novel combination regimens with epigenetic drugs, and antibody-drug conjugates. As precision oncology becomes a more paved road, clinicians in the community oncology setting must be cognizant of its full potential and reference institutions must establish patient referral networks to increase the access to innovative experimental therapies. To improve clinical decision making, particularly in rare cancers and rare genomic variants, international collaboration among leading cancer research centers is needed. VHIO is an active member of international data-sharing projects, including Cancer Core Europe[8] and the American Association for Cancer Research Genomics, Evidence, Neoplasia, Information, Exchange (GENIE),[9] with a strong belief that sharing cancer genomic data and linked clinical annotation has the potential to expand real-world evidence on biomarker-drug matches.

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Consulting or Advisory Role: Bayer, Boehringer Ingelheim, Eli Lilly, MSD, Merck Serono, Novartis, Sanofi, Taiho Pharmaceutical, Merrimack, Peptomyc, Rafael Pharmaceuticals, Symphogen, Chugai Pharma, Ipsen, Merus, Pfizer, Seattle Genetics, Array BioPharma, AstraZeneca, BeiGene, Genentech, Genmab, Halozyme, Imugene Limited, Inflection Biosciences Limited, Kura, Menarini, Molecular Partners, Pharmacyclics, ProteoDesign, Roche, Seattle Genetics, Servier, VCN Biosciences, Biocartis, Foundation Medicine, HalioDX, Roche Diagnostics

Jordi Rodon
Consulting or Advisory Role: Peptomyc, Kelun Pharmaceuticals, Merck Sharp & Dohme, Spectrum Pharmaceuticals, Pfizer, Roche/Genentech, Ellipses Pharma, Certera, Bayer, Ionctura
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Honoraria: Bayer, Novartis, MSD Oncology, MSD Oncology
Consulting or Advisory Role: Bayer, MSD Oncology
Travel, Accommodations, Expenses: Novartis

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Consulting or Advisory Role: Guardant Health, Novartis, Bayer Health

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