

Methodology of clinical trials in lung cancer

Jessica Menis¹, Benjamin Besse², Denis Lacombe¹

¹EORTC Headquarters, Brussels, Belgium; ²Gustave Roussy Cancer Campus Grand Paris, Villejuif, France

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Correspondence to: Benjamin Besse. Gustave Roussy Cancer Campus Grand Paris, Villejuif, France. Email: benjamin.besse@gustaveroussy.fr.

Author's introduction: Jessica Menis is a medical oncologist currently working as clinical research physician of the EORTC Lung Cancer Group and Head and Neck Group at the EORTC Headquarters. She gained her medical oncology degree in 2012 at the University of Udine (Italy) where she was involved in the in-patient and out-patient unit and regularly attended the Multidisciplinary Meetings of Thoracic Malignancies. In 2010 she attended the Flims workshop where she developed a protocol in small cell lung cancer. Her main research interests are application of molecular abnormalities to personalize treatment, phase I/II/III trials in thoracic tumors. She has been sub-investigator of more than ten phase II and III trials in the past 10 years.

Benjamin Besse is a full time cancer specialist at Gustave Roussy. He gained his medical oncology degree in 2005 from Paris University and holds a doctoral degree in translational research. Currently, Dr. Besse is Head of the Thoracic Oncology Unit at Gustave Roussy. His main research interests are application of molecular abnormalities to personalize treatment, phase I trials in thoracic tumors and thymic malignancies. Dr. Besse has been the principal investigator of more than 30 phase I and phase II trials in the past 5 years. In 2014, he has been elected Chair of the EORTC Lung Group. He coordinates the French network for thymic malignancies (www.ryhtmic.org). He is associate editor of *European Respiratory Journal*. He was Chair of the systemic treatment part of the ESMO Consensus Conference on Lung Cancer published in *Annals of Oncology* last year.

Denis Lacombe graduated with his MD from the University of Marseilles (France) in 1988 and obtained a Master Post Doctoral Fellowship at The Roswell Park Cancer Institute (Buffalo, NY, USA) for research in pharmacology and pharmacokinetics from 1989 to 1991. From 1991 to 1993, he worked as a clinical research advisor in charge of the development of a new drug in oncology in the pharmaceutical industry. Dr. Lacombe joined the EORTC in 1993 as a research fellow and quickly became a very active and productive clinical research physician involved in the conduct of clinical research from protocol development through publication for a number of oncology indications from phase I to phase III. Dr. Lacombe contributed to the strategic evolution of the EORTC pan-European clinical and translational research infrastructure by setting up various supportive assets such as regulatory and pharmacovigilance expertise as well as partnership models with the pharmaceutical industry. Dr. Lacombe rose to the position of Director EORTC Headquarters in 2010, and in April 2015 was appointed EORTC Director General. In his current position, Denis Lacombe is now involved in the coordination and administration of all EORTC activities in order to promote the EORTC as a major European organization in cancer clinical and translational research and is responsible for the organization of scientific activities, public relations and medium term strategies as defined by the EORTC Board as well as for internal and external communications. Dr. Lacombe is the author of well over 100 peer reviewed publications and communications that have had a positive impact on the future of cancer therapy.



Jessica Menis



Benjamin Besse



Denis Lacombe

Abstract: The identification of new targets in cancer biology has changed the traditional approach to cancer diagnosis and treatment and therefore also to drug development. The classical ‘one size fits all’ approach needed to be modified into a tailored approach that took into account the patient-to-patient variation. Innovative trials are warranted, based on the integration of new types of design and integrating the knowledge coming from new disciplines like bioinformatics, biostatistics, epidemiology and health economics. Several initiatives have started at national levels but also in large pan-European academic organizations [like the European Organization for Research and Treatment of Cancer (EORTC)] in the scope of generating a harmonized healthcare landscape across Europe.

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The rapid advances in the knowledge of cancer molecular biology together with technological progresses in new targets identification have challenged the traditional drug development.

Although the classical ‘one size fits all’ approach has revolutionized medical practice, it does not take into account the patient-to-patient variation in the molecular drivers of both cancer and drug sensitivity.

As a consequence of this rapidly evolving landscape, an urgent need has been felt to reshape the clinical trials design.

Large randomized multi-centre studies that aim to definitively prove the superior efficacy of new therapies compared with the gold standard, generally without molecular stratification of patients and resulting in small efficacy improvements of limited clinical significance are not affordable anymore both for stakeholders in an era of economical restrictions. This model can still be valid

for very selected agents, those that show early and strong efficacy signal, such as PD-1/PD-L1 inhibitors.

Therefore, a new strategy has emerged that involves the use of customized, adaptive, hypothesis-testing early trial designs incorporating analytically validated and clinically qualified biomarkers from the earliest possible stage.

Although traditional drug development has involved “trials designed to learn”, there is increasing evidence that this should now change to “trials designed to conclude” (1,2).

Optimizing drug development

In the past years, several drug candidates went into clinical trial without appropriate understanding and documentation of the biology. Due to a ‘kill early’ philosophy and the lack of biological understanding, too many promising drugs were abandoned. Another contributing factor to such failure

might be the lack of appropriate risk-assessments to identify the variables that could affect the end points of the study.

On an average, only 5% of the compounds in development reach the clinical phase although, but reaching the clinical phase is no guarantee of success. More than 51% of new drugs fail in clinical phase II trials due to a lack of efficacy, and even more, 66%, fail in phase III. Roughly 5,000-10,000 compounds need to be developed and screened to realize a single approved drug (3).

Decreasing the number of not optimal-designed clinical trials by a stronger collaboration between industry and academia where both partners can contribute their expertise will lead to a win-win situation for industry and academia, reduce the current high attrition rate and minimize futile exposure of patients to ineffective investigational therapies (4).

Industry has recently started establishing broader cooperation around specific research areas with the aim of reducing costs and attrition rates (5).

The entire drug development cycle, from discovery to final approval, takes about 10-15 years on average, and the average cost to develop and market a new drug, including the cost for failures, has increased by more than 60% from 2000 to 2005 (6).

Indeed, while the understanding of molecular biology evolves, it has become increasingly critical to model clinical research methodology and drug development approaches.

This can be achieved through the incorporation of translational medicine in the design of clinical trials with the ultimate goal to treat the right patient, the right tumor, at the right time with the right agent. Biomarkers might play another important role in the future as testing before treating can save money by avoiding unnecessary treatments and may predict adverse drug reactions (7) but therefore intensive research about the different disease mechanism is inevitable. At the moment, approximately 10% of all United States Food and Drug Administration (FDA)-approved drugs have some evidence of a genomic-based response to treatment but only for very few drugs there is enough evidence to use these tests for treatment decisions (8). Moreover, many drugs fail at a late stage of the development process and the number of drugs approved by the FDA and the European Medicines Agency (EMA) remains in the range of 20-25 per year (9).

In a sustainable partnership with cross-functional synergies everybody can benefit from the expertise of each other while avoiding duplications and minimizing the impact of individual conflicts of interest by the working

principles mentioned above (10).

Nevertheless possible obstacles like the challenge of data-sharing, intellectual property and marketing for a strategy of combining different drugs of several companies within one trial should not be underestimated.

Moreover, integration among all stakeholders including regulators might not be sufficient, as regulatory approval does not imply that payers will reimburse the drug. Therefore, creating meaningful data for reimbursement i.e., active and affordable drug is of key relevance (2).

Thus, new cost-sharing models and solutions are needed to ensure a broad access to high-quality community samples, to secure regulatory and ethical approvals, reimbursement, and promote harmonization and standardization. The previous business model of development needs to be modified, as the society needs new strategies for health care and sustainable costs.

The last 5-year developments in NSCLC treatment strategy

Lung Cancer, among all thoracic malignancies, has become the prototype for genetically tailored targeted therapy.

Non-small cell lung cancer (NSCLC) diagnosis and treatment have been consistently revolutionized in the last years thus leading to improvements in patients' prognosis.

As a matter of fact, the identification of new molecular alterations and the development of specific targeted agents have completely changed the diagnostic and therapeutic approach to these patients, switching from a one size fits all approach to tailored treatment strategies and providing remarkable efficacy results.

Among these molecular alterations, the EML4-ALK fusion oncogene, first described in 2007, present in 1.5% to 6.7% of unselected NSCLC patients results from a small inversion within chromosome 2p which leads to the formation of a fusion gene that contains the exons 1-13 of the echinoderm microtubule-associated protein-like 4 (*EML4*) gene and exons 20-29 of the anaplastic lymphoma kinase (*ALK*) gene (11-15). Tumors that harbor the EML4-ALK fusion gene have a dramatic clinical response to ALK-directed therapy. Crizotinib, an orally bioavailable inhibitor of ALK-tyrosine kinase firstly developed as a MET inhibitor, demonstrated its antitumor efficacy in phase I, II studies, achieving 55% ORR (16,17).

Two phase III trials assessed the efficacy of crizotinib versus chemotherapy in ALK rearranged NSCLC patients with advanced disease: PROFILE 1014, where crizotinib

was compared to pemetrexed plus a platinum compound in previously untreated patients (18); PROFILE 1007, where crizotinib was compared to single-agent docetaxel or pemetrexed in previously treated patients (19). Both trials demonstrated a significantly longer median progression free survival (PFS) [10.9 *vs.* 7.0 months, hazard ratio (HR), 0.45; 7.7 versus 3.0 months, HR, 0.49, respectively] and higher objective response rates (ORR) (74% versus 45% and 65% versus 20%, respectively). Crizotinib was approved by FDA and EMA in 2011 (20), 4 years after the first data on published on the EML4-ALK fusion.

Several other EML4-ALK inhibitors are under development. Among them, ceritinib was also recently approved based on phase I data (21) where it demonstrated high activity (58% ORR) (22).

New clinical trials

The crizotinib example is one more confirmation that the distinction between a phase II trial aiming at identifying potentially effective drugs and a phase III trial designed to determine efficacy or clinical (relevant) benefit and licensing should no longer be justified. Cleverly designed phase II trials (or expansion cohort of phase I trial) with reasonable endpoints based on a strong biological rationale and good outcome can lead to drug approval so that phase III trials are not an essential requirement for approval (23).

Moreover, pragmatic trials or prospective large community based multicenter observational cohort studies are the best to investigate real life situations and to provide information concerning resource utilization, practicability in real life and outcome measures such as overall survival (OS) (2,24).

Clinical trials designed to enrich for a target population by a predictive biomarker or statistically powered to prospectively evaluate a biomarker, as co-primary or secondary endpoint, will most likely demonstrate the benefitting patient subgroups (25,26). The main requirements are an adequate amount of tissue for molecular profiling, early co-development of biomarker and targeted agent and recognition of intratumor heterogeneity.

The study can be classified in: unselected or all-comers design, when the compound is tested in the overall population first and then in the marker-defined subpopulation or vice versa; targeted or enrichment design, when all patients are screened for molecular alteration but only the subpopulation who either express or not a specific molecular alteration is enrolled in the clinical trial; and

hybrid design (27).

Two main enrichment strategies have been used:

- Basket trials, they allows patients with one or multiple diseases and one or more targets to be enrolled in cohorts or groups in one trial (the basket) so that researchers will separately analyze the responses of patients with each cohort of cancer as well as to assess the impact of the drug on all of the patients as a group (28). There are three main categories: one drug for several tumor types, one drug for one molecular alteration in several tumor types and one drug for several molecular alterations in several tumor types (29). Basket trials usually belong to the 'trial to learn' category;
- Umbrella trials are designed to test, on the basis of a centralized molecular portrait performed after the informed consent, the impact of different drugs on different mutations in a single type of cancer: one disease, several molecular subtypes, several therapies embrace both a centrally performed molecular portrait and molecularly selected cohorts with matched drug (30); they fall in the 'trial to conclude' category.

Both types of studies have the potential to accelerate the drug development process so that the right therapies can be quickly delivered to the right patients.

Finally, in situations when the biological characteristics of the target are uncertain or in absence of a clearly understood mechanism of action of the compound, adaptive designs may provide a more distinct advantage.

Adaptive designs foresee modifications on some aspects of the trial can be prospectively planned so that changes ("adaptations") may take place while the study is ongoing: a treatment arm or a subgroup of patients could be dropped, dose levels could be altered, the trial size could be increased, if the tested compound proved to be less effective than expected at the interim analyses. Adaptive designs are increasingly used as there is a growing acceptance and a general encouragement from regulators (FDA guidance) (29) that have approved some compounds on the basis of phase I and II studies adopting enrichment strategies or expansion cohorts strategies as a consequence of the recruitment difficulties in rare tumor types (31). These trials can also lead to validate a strategy. The SAFIRO2 trial (32) aims to evaluate whether treatment with targeted agents guided by high throughput molecular analyses (CGH array, NGS) improves PFS as compared to standard maintenance therapy in patients with metastatic NSCLC. This program is sponsored by the cooperative group UNICANCER. In

this study, a biopsy is being performed in a metastatic site for each patient after signature of an informed consent. This is an open-label multicentric phase II randomized trial, using high throughput genome analysis as a therapeutic decision tool, comparing a medical treatment administered according to the identified molecular anomaly of the tumour with a medical treatment administered without considering the tumour genome analysis (pemetrexed in non-squamous patients and erlotinib in squamous cells).

European Organization for Research and Treatment of Cancer (EORTC)

The identification of multiple targeted pathways and of gene alterations has determined the reclassification of each tumor type in small subsets. These small subsets have the same incidence of rare tumors so that feasibility of clinical trials in such small populations has dramatically fallen both in terms of costs and timelines.

Fragmentation of diseases based on molecular sub-entities requires international cooperation: large numbers of patients must be screened in order to accrue meaningful sized patient populations bearing the alterations of interest.

In Europe, currently, no systematic and efficient scheme exists that enables sharing efforts of molecular characterization of the tumors among all stakeholders, and could guarantee structured access for patients to multiple clinical trials. Several countries have already developed their own strategies for the process for deciding reimbursement. However, since different countries have different guidelines for what is reimbursable, this could lead to a diverse healthcare landscape across Europe.

A possible solution might then come from tight networks across each continent in order to build large transversal screening platforms to efficaciously detect these subpopulations and to offer them the possibility to participate to specific clinical trials.

The main aim would be to offer to largest number of patients both the possibility to get their tumor being screened for each known alteration and to participate to clinical trials testing drugs that target those alterations. Such opportunity has not been feasible so far for each patient in each institution across Europe and across the world.

A pan-European approach to develop a comprehensive research program might reduce costs and bias compared to national studies by reducing efforts and delays thus leading to a harmonized healthcare landscape across Europe (2,33).

In this scenario the EORTC might be the perfect

institution leading and running these revolutionary trials.

The EORTC is an academic, no-profit organization that aims to explore novel models of clinical cancer research and development, to consider new opportunities for partnerships between industry, academia, regulatory agencies and other major cancer organizations, and, most importantly, to describe a new form of clinical trial access currently emerging in Europe.

The EORTC has connected leading clinical centers across Europe to set-up the SPECTA program.

By screening patients for biomarkers relevant to targeted clinical trials, the SPECTA program aims to increase the opportunities for patients to access clinical trials with new molecularly defined approaches and simultaneously decreases the cost and logistical pressure of setting up new translational research-based clinical trials. This new strategy can be and also will be applied to colorectal tumors (SPECTAcolor), lung cancer, mesothelioma and thymic malignancies (SPECTAlung), melanoma (SPECTAmel) and brain tumors (SPECTAbrain).

SPECTAlung is a screening program of the EORTC in collaboration with the European Thoracic Oncology Platform (ETOP) for efficient clinical trial access for patients with thoracic tumors. It is the first European standardized, quality-assured molecular testing platform for thoracic tumor characterization with the overall goal of offering patients specifically targeted downstream clinical trials.

After signature of the informed consent, existing tumor tissue will be collected, centralized and processed according to defined international quality control standards at Gustave Roussy Biobank (Villejuif, France). Next generation sequencing (NGS) will be performed at 14 MG (Cambridge, UK) where a panel of about 360 genes will be analyzed for somatic mutations, rearrangements and gene copy number.

Eligible patients will be those having a pathological diagnosis of any thoracic tumor (lung cancer, malignant pleural mesothelioma and thymic malignancies) at any stage of disease evolution, the availability of tumor tissue, age >18 years, PS 0-2, life expectancy >3 months, no active malignancy in the 5 years before study entry and absence of any exclusion criteria that may prevent inclusion into clinical trials. NGS results will be sent to EORTC, a molecular report will be then released to the investigator highlighting the trials in which the patients might be eligible.

The study will be active and recruiting in 2015, as soon as approved by ethic committees, in 15 selected highly

specialized and qualified thoracic centres in 12 countries in Europe.

SPECTALung is an open screening program expected to test 500 to 1,000 patients each year, EORTC and ETOP will promote the implementation of clinical trials in molecularly selected groups of patients at the SPECTALung centers. It offers innovative and attractive models of collaboration with commercial and research organizations and therefore is positioned as a unique platform for supporting the development of personalized medicine and a first in class partnership model (33-35).

Others consortiums

NSCLC has become a very complex disease so that investigators of different institutions have felt the need to merge their efforts in order to better study and treat this disease.

In the US the Lung cancer Mutation Consortium (LCMC) represents the largest academic-initiated national initiative to prospectively examine NSCLC tumors, and match patients to the best possible therapies. The LCMC is coordinated by a cross-institutional group of researchers and the National Lung Cancer Partnership. Currently, the LCMC includes 16 leading cancer centers across the country and centralizes molecular analysis in few core centers. The LCMC primary goal is to provide the most up-to-date care for lung cancer patients, while collecting valuable information about the frequency and characteristics of molecular aberrations found in lung tumors to further improve patient care.

The LCMC has created a unique national data set that tested for the national investigators the frequency of certain mutations and also assured large enrollment in clinical trials (36).

In Europe, the landscape is fragmented into national initiatives being France and United Kingdom the two most advanced examples.

In France, since 2009, the French National Cancer Institute (INCa) and French Ministry of Health have set up and funded a national network of 28 regional molecular genetics centres. The centres, located throughout the country, were selected through competitive calls managed by INCa in 2006 and 2007 and they quickly become operational, as selection was based on pre-existing, although scattered, expertise. Each molecular genetics centre is a partnership between several university hospital and cancer centre laboratories with complementary expertise.

The goal was to ensure uniform nationwide test provision and fast implementation of molecular tests for new tumour biomarkers as cancer was identified as a national cause. Cancer Plans were sequentially launched by the government to coordinate and fund research projects, implement actions in public health and quality of care and provide information about cancers to all health-care practitioners, patients and the public.

INCa is responsible for coordinating the 28 regional molecular genetics centres at the national level. This project involves monitoring national activities, making recommendations for the implementation of new molecular tests, managing funding allocation, drafting quality assurance and organization guidelines, and setting up external quality evaluation programmes. INCa also promotes the development of a collaborative network between centres to share expertise and facilitate troubleshooting. Thus, all the professionals involved in molecular testing are part of a multi-level national network that optimizes organization, fosters standardization and ensures top-quality molecular testing.

Each molecular genetics centre performs innovative molecular tests for all patients in its region, regardless of the institution where they are treated (university hospitals, cancer centres, public local hospitals or private institutions). The activities of the 28 centres are not limited to assessment of predictive markers, they also perform diagnostic tests, prognostic tests and tests for monitoring of minimal residual disease. Molecular tests are free of charge for patients or health institutions and the centres compensate local pathologists for tumour block shipment, a logistical burden with the increasing number of samples to be tested.

The centres coordinate their activities at the regional level and are responsible for optimizing logistics for the circulation of prescriptions, tumour samples and molecular reports in order to minimize test result delivery times.

Beyond offering widespread access and nationwide coverage, achieving and maintaining quality is crucial. A regulatory evolution makes it mandatory for all medical laboratories to obtain an accreditation to ISO 15189 standard before 2016 in order to be able to continue their clinical activity.

The French screening and targeted cancer treatment initiative is unique. It offers equal access to molecular testing for all patients in France and represents a real benefit in terms of public health. It illustrates that molecular stratification can be successfully integrated into the health-care system and, as an additional benefit, is a cost-effective

strategy (37).

A similar initiative, sponsored by Cancer Research UK (CRUK), is currently ongoing in the UK and could be expanded to other European countries or Canada, who have a similar provincial organization. The Stratified Medicine Programme is a multi-site model that aims to demonstrate how large scale testing could be achieved within the National Health System (NHS), while driving forward research into targeted therapies by creating a centralised data repository of molecular and associated clinical data. Based at eight CRUK Experimental Cancer Medicine Centres (ECMCs) and incorporating 26 referring hospitals, the clinical hubs gain consent from patients diagnosed with the most common tumour types (breast, lung, prostate, ovarian, colorectal cancer and advanced malignant melanoma) for the use of their samples and data in research. In total, ten genes were selected for NGS analysis and arranged into panels of 4 or 5 for each tumour type. The molecular results were returned to the referring clinical hub electronically through a secure online server to be combined with patient clinical data (diagnostic, treatment and outcomes) (38).

Also single institutions have to face such challenges and a successful example in Europe is the Gustave Roussy Cancer Campus Grand Paris (Villejuif, France) that has set up a large panel of ongoing and future prospective trials with the aim of implementing high throughput technologies and develop software for target identification in order to identify potential therapeutic targets for cancer patients. This program foresees also the integration of immunotherapy and treatment toxicities to develop predictive biomarkers on host response to conventional or new agents. Among those, one example is MOSCATO (Molecular Screening Approach for Treatment Optimization), that will reach a total of 900 patients in 2015, that will benefit from molecular profiling including array CGH and a panel of hot spots mutations in 96 amplicons from a biopsy performed in the metastatic site. Patients will be driven into specific phase I trials according to the presence of a molecular alteration. The primary endpoint is the efficacy of such approach measured as improvement in PFS with the use of high throughput technologies is improved.

Open issues/grey areas/feasibility

By selecting rare subsets, not only we have fewer patients but also we really miss clear information on the specific and appropriate standard of care. However, the laws of

probability on which our statistical tools are built do not change because of the scarcity of the sample and also assumptions need to be correct and valid for the statistical plan.

A second challenge is the methodology as the biomarkers validation is currently affected by severe challenges such as the multitude of the assessment methods (i.e., immunohistochemistry, FISH, NGS, etc.), the reliability in terms of sensitivity and specificity, the reproducibility of the test, the feasibility of obtaining an adequate and representative tumor sample, and finally the overall costs related.

Another common confounder is to consider the disease as unicum. An advanced knowledge has been reached in the NSCLC characterization not only by determining the primary genetic alterations but also for describing intra-tumor heterogeneity both in the primary tumor and within different metastatic sites. The identification of the presence of a dominant clonal and/or of subclones, both if untreated and under drug pressure, might be warranted to decide the treatment strategy for these patients. However, at the same time, it is important to analyze multiple samples to get a comprehensive picture of a patient's entire tumor. Fine needle aspirates and core needle aspirates may under or over represent high-grade areas in the tumor. Analysis of portions of tumors by biochemical or molecular biology assays may provide quantitative data about a tumor sample that is an average or aggregate value, but the contribution of a minor fraction of high-grade cells may be hidden by a large fraction of low-grade cells (39,40). TRACERx [TRACKing NSCLC evolution through therapy (Rx)], a prospective study of patients with primary NSCLC, aims to define the evolutionary trajectories of lung cancer in both space and time through multi-region and longitudinal tumour sampling and genetic analysis. TRACERx mainly aims to identify novel therapeutic targets for NSCLC and may also serve as a model applicable to other cancer types (41).

Another crucial aspect in clinical trial methodology is the definition of the endpoint, as it is the way we measure the treatment benefit.

Until the present moment, identifying an endpoint that truly represents an indication of compound effectiveness is still subject of argument in randomized clinical trials.

Powering a trial to show an OS benefit can be challenging, as it requires a large number of patients consequently slowing drug development, increasing the cost of medical care, and using patient resources. However at the same time, it is the only solid defined endpoint. PFS has been

increasingly used as surrogate endpoint, particularly in trials on targeted agents (42). However, with some of the new immune compounds the definition of progression has been challenged.

Among the most difficult tumor response pattern to face for a clinician there is the “tumor flare”: it has been described as an initial increase in the tumor burden that is afterwards followed by tumor shrinkage. Recognizing tumor flare and differentiating it from true treatment failure (PD) is key for clinicians and require both a training and the development of new tools merged with the clinical insight brought by the patients (modification of performance status and/or symptoms).

Immune-related response criteria (Ir-criteria) have been proposed by a collaborative group of approximately 200 oncologists, immunotherapists, and regulatory experts on the basis of clinical observations. For the Ir-criteria only index and measurable new lesions are taken into account and antitumor response is based on the total measurable tumor burden (43). However these criteria are time consuming (bi-dimensional measurement) and still need to be validated and should be further investigated.

Moreover, once tumor progression is defined, there are a variety of choices for the patient and the physician: continue the same regimen, cross-over to the other arm, switch to another treatment (for example next generation inhibitors) or no treatment at all and commonly this choice is not randomized and therefore not comparable between the arms. An example of successful treatment beyond progression is the one of ALK positive NSCLC patients that continued crizotinib beyond PD according to RECIST 1.1 resulting in a significant prolongation of the SPP and consequently of OS (44).

Last but not least, ensuring equal access to personalized cancer treatment is a public health requirement. Several challenges must be overcome: nationwide applicability of molecular tests into clinical practice, the timeliness of test results must be compatible with normal patient care, and the quality of tests must be guaranteed to avoid uninformative, false-positive or false-negative results and mis-interpretations that could adversely affect patient prognosis or expose them to unnecessary adverse effects.

As a matter of fact, in US there is an easy access to comprehensive genomic profiling via commercial laboratories with all related debates on appropriateness and adequacy: a reported example is the publication of Schwaederle *et al.* with the analysis being performed by Foundation Medicine Inc. (45).

Conclusions

Advances in the molecular profiling of tumour tissues have opened up an era of personalized, or biologically adapted, cancer treatment where therapies are matched to the molecular profile of the individual tumor. The challenge is to give the right drug to the right patient by selecting the right molecular alteration.

As there are lots of new cancer therapies in development, there is a huge need for designing and implementing innovative trials, warranting the integration of all involved disciplines including bioinformatics, biostatisticians, epidemiologist and health economist.

The ultimate goal is to identify the most effective therapy and avoid ineffective, toxic and expensive treatments.

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Footnote

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