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# The dream and reality of histology agnostic cancer clinical trials

*Denis Lacombe*[a,*], *Susen Burock*[a], *Jan Bogaerts*[a], *Patrick Schoeffski*[b], *Vassilis Golfinopoulos*[a], *Roger Stupp*[a,c]

[a]*EORTC Headquarters, Brussels, Belgium*
[b]*U.Z. Leuven Gasthuisberg, Leuven, Belgium*
[c]*UniversitaetsSpital and University of Zurich – Department of Oncology and Cancer Center, Zurich, Switzerland*

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ABSTRACT

Emerging technologies and progress in data processing allowed for new insights on gene expression, genomics and epigenomics, and mechanisms of cancer genesis and progression. The development of new therapeutic strategies should therefore be triggered by the understanding of the underlying biology through sophisticated clinical trials. Therefore, the methodology and the design of cancer clinical trials as well as the methods of their implementation are under profound changes. Targeting specific pathways has open the hope of a more focused and personalized medicine which has the potential to bring more efficient and tailored treatments to patients. It has been questioned therefore whether clinical trials traditionally designed for specific tumor types could not re-visited towards trials gathering patients based on molecular features rather than pure pathology criteria. The complexity of the cancer biology being the result of so many different interactive mechanisms whether driving or not the process of cancer cells is an additional level of complexity to approach more inclusive clinical trial access. Nevertheless, a number of innovative solutions to address biological challenges across histologies have been initiated and the question of whether histology agnostic trials could be conceived is a logical next question. This paper questions the advantages and the limits of clinical trials performed across tumor types bearing similar selected molecular features and looks further into the feasibility of such histology agnostic trials.

## 1. Background

Recent discoveries in molecular medicine combined with technological progress, such as genome sequencing have led to the development of a number of innovative drugs over the past few years. The United States Food and Drug Administration (FDA) approved an average of 25–30 first-in-class agents per year from 2004 through 2012 (U.S.Food and Drug Administration Center for Drug and Research, 2014). In 2013 the FDA's Center for Drug Evaluation approved 27 "new molecular entities" (NMEs), and nine of these were for treating cancer. In Europe, cancer remains a significant burden with an estimated 3.45

* *Corresponding author.*
E-mail address: denis.lacombe@eortc.be (D. Lacombe).
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million new cancer patients and 1.75 million cancer-related deaths in 2012 (Ferlay et al., 2013) and is projected to further increase. Mortality has been steadily decreasing, most notably for hematological malignancies, while many epithelial and most mesenchymal cancers remain largely incurable despite the use of rationally engineered targeted drugs (Watson, 2013).

Emerging technologies and progress in data processing allowed for new insights on gene expression, genomics and epigenomics, and mechanisms of cancer genesis and progression. New molecular entities tailored according to the molecular profile of the patient and their cancer interfere with cell signaling pathways that are, for example, responsible for proliferation or apoptosis. This should make modern treatments not only more effective, but also associated with less toxicity and tailoring treatment to the tumor and patient will expose fewer patients to ineffective therapy.

Targeted therapies have met some success, e.g. the development of B-RAF inhibitors for treating melanoma or ALK inhibitors for a subtype of non-small cell lung cancer. The active incorporation of biological insights into drug development and the subsequent design of the clinical trials were a prerequisite. Can we extrapolate the results obtained with targeted therapies in certain tumor types and histologies to tumors of different origin provided they share some of the molecular aberrations? Some targeted therapeutics may be active only in the context of a specific histology and tumor type. Other pathways may carry a driving role in multiple tumor types and, consequently, justify a pan-cancer approach (Weinstein et al., 2013).

Although different histological tumor types exhibit different frequencies of certain genomic alterations, they possess some similarities. A clinical example of a pathway and agent explored in various tumor types is the amplification of human epidermal growth factor receptor 2 (HER2). This critical oncogene for proliferation and survival of tumors is frequently expressed in breast but also in gastric cancers. Trastuzumab (Herceptin®, Roche, Basel, Switzerland), a monoclonal antibody that irreversibly binds to the extracellular domain of the HER2/neu receptor, was initially specifically developed for the treatment of HER2 overexpressing breast cancer and approved in this indication in the year 2000. Only years later it was found to be a relevant drug for treating Her2-overexpressing metastatic gastric cancers, and extension of the indication was granted in 2010. Response in histological tumor types that occasionally overexpress HER2, for example cholangiocarcinoma, gallbladder cancer, and salivary gland malignancies have been described in several case reports for these various histological cancer types (Kadowaki et al., 2013; Cappuzzo et al., 2006; Sorscher, 2013; Bronchud et al., 2012; Law, 2012).

A comprehensive view of the mutational landscape, and therefore of potential therapeutic targets across the different histological tumor types, is nowadays available. The challenge for research is to discern whether similar aberrations in different histologies (cross-cancer similarity) have a comparable biological significance and can be successfully targeted with the same agents. The histological context may be of importance, and intratumoral heterogeneity (Ciriello et al., 2013) adds to the complexity in evaluating the value of novel targeted treatments.

### 1.1. *Terminology*

The term "histology agnostic trials" has been proposed when referring to trials aiming at including various tumor types with only the molecular aberration or target as common denominator. The word "agnostic" stems from the ancient Greek and literally means "without" (a) "knowledge" (gnōsis). Strictly speaking, histology agnostic trials would imply that nothing is known about the histology of the tumor in such trials, but in practice the term refers to studies where patients harboring identical or related molecular profiles are treated with a specific targeting drug for this molecular profile regardless of the pre-specified histological tumor type or anatomical site of origin. This kind of trial can provide insights into the functionality of the respective genomic alteration across various histological tumor types and can also provide a better understanding of the clinical importance of histological and anatomical factors of a given malignancy. It may also provide insight into the importance of a particular biological context that might modify the importance of the drug target. Currently, pure histology agnostic trials do not exist, although there are clinical trials that have been opened across tumor types, and these could pave the way towards innovative clinical trial approaches.

## 2. From whence we came

Traditional clinical drug development usually starts with small phase I trials to define dose and toxicity usually across tumor types and histologies. Once the maximally tolerated dose and a dosing regimen have been established, phase II trials within one histology will provide some initial indication on efficacy before the true value of a new therapeutic strategy is established in typically comparative definitive large phase III trials aimed at regulatory approval. Cancer drugs are conventionally tested, approved, and prescribed for a specific tumor type based on the tissue of origin of the cancer and the histomorphology of the tumor cells.

Although some NMEs have been approved for several tumor types, the approval is commonly based on the results of separate organ- and histology-specific phase III trials. Sunitinib (Sutent®, Pfizer, New York, NY), an oral multi-targeted receptor tyrosine kinase inhibitor, was simultaneously approved for gastrointestinal stromal tumors (GIST) and renal -cell carcinoma in 2006 and subsequently for pancreatic neuroendocrine tumors in 2010. However, these approvals were based on three independent, histology- and organ-specific trials, and Sunitinib is currently being evaluated in a broad range of other solid tumors in additional clinical trials, despite the fact that the relevant biological target is not identified (Dror et al., 2009; Santini et al., 2013; Grivas et al., 2013; Curigliano et al., 2013; Crown et al., 2013; Kreisl et al., 2013; Carr et al., 2010; Yi et al., 2012).

A logical question, therefore, is whether a modified approach for drug development could be established that allows enhancing our knowledge more efficiently while bringing new treatments rapidly to patients. The *in silo* drug development with separate, independent and often only partially rational clinical trials aiming at repeated single drug approval

needs to be revisited. This can be considered as inefficient, time-consuming and expensive.

In the era of targeted cancer therapy, the clinical research landscape is slowly changing. Recently, it was proposed that a new vision for drug development should be embraced, and we should consider generating different types of continued data sets from early clinical trials with a strong translational research component that lead to biologically solid pivotal studies followed by long term outcome research and health technology assessments (Burock et al., 2013a,b).

## 3. Where are we going to?

We propose to expand early clinical trials and to incorporate a strong translational component, exploit window of opportunity studies for patients subsequently undergoing tumor resection or biopsy, evaluate relevant pathways across numerous tumor types, and ideally identify potential predictive biomarkers. Only after obtaining such knowledge should we embark on large pivotal phase III studies, and within these it should be possible to include several tumor types for which the pathway under investigation is considered relevant. Already at this juncture, we should consider incorporating real world data (e.g. expanded access program for patients that do not formally meet the restrictive eligibility criteria of the pivotal protocol), patient-centered outcome data before and after evaluation of the primary end-point of the trials as well as health economics (e.g. resource utilization).

Some examples of clinical trials that, even though cannot be considered completely histology agnostic, do already provide insights into the risks and benefits of opening trial access beyond a single histology are shown in Table 1. The principle of grouping patients with a range of histologies under the same treatment protocol, is referred to as a basket trial. It includes parallel cohorts with a separate statistical design for each cohort. Addressing specific clinical situations such as brain metastases, regardless of the origin of the primary cancer, or grouped entities that are driven by the same etiology such as human papillomavirus-related cancers may be considered histology-agnostic. Another type of trials investigating NMEs can be the so-called n-of-1 trials. In this kind of study, a single patient is studied, and all characteristics of the individual patient, including the molecular profile and the histologic characteristics of the tumor, are taken into consideration.

- Basket trials

Several trials allowing to include different histologies sharing similar genetic alterations have been developed. The ongoing multi-tumor type EORTC trial 90101 CREATE explores the ALK-/MET inhibitor Crizotinib in patients with advanced disease across six heterogeneous malignancies that are (in part) associated with ALK and/or MET alterations. The six cohorts are defined by their histological tumor type, and each cohort is divided into two subgroups defined by the molecular subtype (ALK/MET+ and ALK/MET- patients). Each cohort usually follows traditional methodology, and data are collected and analyzed according to classical methods. The treatment effect will be assessed separately for the different histological tumor types, and also for the whole patient population. The design allows adaptation and expansion of the cohorts if clinical responses or activity are observed while excluding those who do not show an early signal of response (Sleijfer et al., 2013).

The French AcSe program (Accès Sécurisé à des thérapies ciblées innovantes) of Institut National du Cancer could be considered as a basket trial but at a much larger scale, since 21 cohorts of tumors amenable to Crizotinib treatments have been opened to patient entry (Institut National du Cancer). Thus, this unique program implemented and supported at the national level allows several tumor types to be rapidly tested for activity based on target expression. The initiative can be considered as a landmark for new European approaches towards personalized treatments.

Novartis performed a basket trial investigating imatinib in a variety of non-GIST malignancies with kit mutations during the early days of exploration of this prototype kinase inhibitor (Heinrich et al., 2008). A total of 186 patients with 40 different malignancies known to express one or more imatinib-sensitive tyrosine kinases, refractory to standard therapy or without proven therapeutic option, were included in this phase II trial. A confirmed response was seen in 8.9% of solid tumor patients (4 complete, 9 partial) and in 27.5% of hematologic malignancy patients (8 complete, 3 partial). Six malignancies were identified in which imatinib therapy was associated with one or more objective clinical responses and

**Table 1 – Risks and benefits of different types of trials.**

| Trial type | Benefit | Risk |
|---|---|---|
| N-of-1 | • Highly personalized | • Not suitable for drug approval, hypothesis generating<br>• Not appropriate for statistical analysis |
| Basket trials | • Reduction of administrative, regulatory and infra-structural duplication<br>• Cost benefits<br>• Possible in rare cancers<br>• Enhance knowledge for basic research | • Operational challenge (across departments)<br>• Extensive translational research required<br>• Different biology across different tumor types |
| Anatomically based trials | • Current standard<br>• Already established infrastructure | • Single indication approval per trial<br>• No knowledge obtained for other possible clinical situations |

this benefit was confined to diseases with known genomic mechanisms of activation of imatinib target kinases. The drug is currently indicated by EMA in three of these tumor types (myelodysplastic/myeloproliferative diseases, advanced hypereosinophilic syndrome, and dermatofibrosarcoma protuberans). Though this may not necessarily be a breakthrough model, it represents a new approach embracing drug development from other angles.

- Anatomically based trials/Specific clinical situations

Trials focusing on the anatomical location of the metastatic malignancy irrespective of the origin of the primary tumor, such as trials in patients with brain or bone metastases, may also be considered as histology agnostic. These trials focus mostly on treatment strategies aiming at avoiding local complications and investigating local treatments, such as radiotherapy or surgery, or supportive care interventions, such as the administration of bisphosphonates. They do, however, represent important clinical situations for which current treatments offer insufficient relief. In such cases, the clinical research methodology does not differ from that used in traditional trials. However, operational and strategy issues to ensure a cohesive approach from different medical specialties should not be underestimated. Provided the trial's primary objective is sufficiently separate from the histology or tumor type involved, acceptance of broader application of its results should be easier. This may be the case for areas such as (late) toxicity of radiotherapy or chemotherapy, survivorship themes and secondary tumors.

- N-of-1 trials

Whether or not n-of-1 trials should be considered a clinical trial is a matter of debate. N-of-1 trials have not yet been widely used, but the combination of coordinated n-of-1 trials and meta-analyses of their data might become more common in the future, leading to new types of data sets (Lillie et al., 2011). The United Kingdom based stratified medicine program may, to some extent, be considered one of the most innovative partnerships between academia, charity, government, and industry. It is a national service aiming at standardizing high quality, cost-effective genetic testing of tumors. Therefore, when targeted treatments become available, patients will be able to choose to have genetic tests that can help doctors decide the most suitable treatment for them. It represents, possibly, one of the most personalized access to cancer treatment (Cancer research UK) as it allows cancer patients on an individual basis to have rapid access to targeted treatments based on systematic analysis of their tumor profile.

### 3.1. *Advantages and benefits of cross histology trials*

Enrichment of the patient population based on the presence or overexpression of the target is the basis for modern clinical trials investigating NMEs. Selecting a subset of the population in which a positive effect of the tested drug is expected to be more likely or more pronounced, the trial concepts are mostly based on the molecular profile of the tumor. Nevertheless, enrichment strategies carry their own particular challenges. Often, neither a validated test nor an explicit biological rationale are established in early drug development; tumors without the presumed target may also respond to the agent under investigation (at least this needs to be tested, and the absence of an effect demonstrated). Enrichment and subclassification according to molecular characteristics invariably lead to fragmentation of the respective histological tumor type and make adequate recruitment in a traditional clinical trial almost impossible. As many subtypes and targets of interest are present in less than 10% of the tumors, a large number of patients need to be screened in order to identify an occasional "candidate" for the novel compound. Such screening is challenging and expensive, and new forms of clinical trial access are needed.

One way of facing this challenge is the development of Collaborative Molecular Screening Platforms (CMSPs) (Burock et al., 2013a,b). CMSPs facilitate the implementation of molecularly informed clinical trials by integrating molecular profiling and predefining a specific patient population for an individualized treatment.

CMSPs can best be described as academic lead precompetitive paltforms mutualizing efforts of all participating stakeholders including patients, pharmaceuticla industry, diagnostic companies, as well as regulators. CMSPs can sort and direct patients to treatments based on matching drugs to potential genomic targets detected on their tumors. With high and regulatory quality data of the screening phase being made available to participating academic consortia and pharmaceutical companies, it will facilitate patient recruitment into clinical trials. Ultimately, CMSP can bring to the clinician the necessary biomarkers and genomics information for treating patients in a personalised fashion.

An advantage for anatomically based across-histology approaches is their contribution to the understanding of the biology of the disease. For example, the demonstration that brain metastases clonal subtypes can diverge from primaries can raise new hypotheses for therapeutic approaches (Brastianos et al., 2014).

Another field where a histology independent, multi-tumor approach can be useful, is in rare cancers. According to the definition of the Surveillance of Rare Cancers in Europe (RARECARE) rare cancers are those with an incidence of less than six out of 100,000 persons each year. This means that about 22% of all cancers diagnosed per year in the EU can be considered to be rare cancers (Gatta et al., 2011), however the percentage of rare cancers will increase as we continue to molecularly characterize and subgroup the various previously frequent disease entities. Even common cancers may need to be approached as a collection of rare entities. Just 5% of the patients with adenocarcinomas of the lung carry the EML4-ALK fusion gene with a high likelihood (>65%) to benefit from a targeted treatment with Crizotinib (Xalcori®, Pfizer, New York, NY). Despite the low frequency of EML4-ALK mutations over 60,000 lung cancer patients every year may benefit from Crizotinib, enough to make the development commercially interesting (Shaw et al., 2013).

The neologism "nichebuster" rather than blockbuster has been coined for agents primarily developed in highly selected subsets of diseases, and a number of agents have received regulatory approval in recent years in niche indications (U.S.Food

and Drug Administration Center for Drug and Research, 2014; Matthew Perrone, 2014). Looking at "druggable" targets related to a specific molecular profile across different histological tumor-types might make rare molecular subtypes less rare. Patients with extremely rare histological tumor types for which no standard treatment exists may benefit from molecular-profile tailored treatments.

These approaches are of an exploratory nature and could potentially accelerate the translation of science to the clinic by elucidating the differences of the same molecular profile across multiple histological tumor types in early clinical development. However, the histological tumor type is still considered a stratification factor, since underrepresentation of the best responding tumor type might dilute the drug effect (Sleijfer et al., 2013). Another correlative advantage of largely inclusive trials is the reduction of unnecessary administrative, regulatory and infrastructural duplication and that the exploration of efficacy of a treatment can be relatively fast and possibly cost effective, though this remains to be demonstrated.

### 3.2. *Challenges and risks of cross histology trials*

A limitation of cross histology trials is that the clinical development of a new drug, the exploratory biomarker testing done in preclinical models, and the formal validation of the required enrichment methodology do not always go in parallel. Hence, all the required background information may not be available at the time of trial initiation. However, as in the French AcSe program, limiting inclusion to advanced patients where no other therapeutic option exists for signal detection can be a medically valid approach addressing the needs of patients.

The presence of a targeted molecular alteration throughout the natural course of disease and across metastatic sites is not always a given, necessitating the acquisition of multiple biopsies. Potentially repetitive molecular screening of tumor tissue from cancer patients is cost intensive and poses logistic challenges. It can be limited by steps ensuring efficient use of biological material, overcoming legal hurdles, and coordinated access to tissue across research consortia. Indeed, new forms of cooperation such as the CMSPs described above would facilitate the understanding of treatment outcome and patterns of progression by optimizing the longitudinal follow up of patients and their biological material currently secluded in successive silos as the disease of the patient evolves.

It is obvious that N-of-1 trials have no statistical strength or validity for supporting drug development decisions. Nevertheless, they are useful for activity signal detection or highly personalized approaches. Nevertheless, N-of-1 trials should be prospectively coordinated for appropriate follow up of patients and consistent data storage for gathering cases. Building well organized databases of successive cases may lead to critical mass of information which would support decision for wider use and possibly regulatory approval. However, as of today this remains purely speculative and no appropriate consensus or methodology has been prospectively developed and validated to sustain such approach.

Basket trials, while efficient for protocol start up regulatory procedures as described here above, also bear the burden of having to coordinate potentially different expert teams at the same research institutions. Clinical departments are commonly organized according to disease-specific expertise and the represented medical discipline. Clinical trials including several histological tumor types need to involve different specialists of the respective departments. Common standard operating procedures (SOPs) for trial conduct that are followed in the different departments need to be implemented. This holds particularly true for the uniform collection and processing of the necessary human biological material, because poor quality in this crucial aspect of the trial is one of the major bottlenecks hindering successful clinical research. A challenge may also be that response assessment criteria would require cross-tumor harmonization, since these can differ depending on tumor type (e.g. RECIST for solid lesions versus assessment of lymph nodes).

## 4. The path towards histology agnostic trials

Despite all the recent progress in cancer research, we are still just beginning to understand tumor-signaling pathways. One example of the complexity of these pathways is the role of BRAF mutations in different histological tumor types. BRAF mutations activate the BRAF kinase and promote tumor growth and angiogenesis. They are found in approximately 8% of all human cancers. However, the prevalence across tumor types is highly variable, and a higher frequency is observed in melanoma, thyroid carcinoma, and colorectal cancer (Davies et al., 2002). Clinical trials investigating the effects of the BRAF inhibitor vemurafenib in melanoma with V600E BRAF mutations led to drug approval in this indication (Chapman et al., 2011). There is also increasing evidence that BRAF-driven differentiated thyroid carcinomas, which can harbor the same mutational subtype as melanoma, can be very sensitive to this compound (Kim et al., 2013). However, when testing this drug in colorectal cancer patients with V600E BRAF mutations, the results were disappointing and showed only one confirmed partial response out of 21 treated patients (Kopetz et al., 2010). So, a pathway may be relevant (driver) in one malignancy, but in the complex context of another tumor, the mutation or pathway is an unsuitable therapeutic target.

A possible explanation for these findings is a feedback activation of Epidermal Growth Factor Receptor (EGFR) in colorectal cancer patients, and since melanoma cells express low levels of EGFR, they are likely not subject to this activation (Prahallad et al., 2012). This exemplifies how variable the complex cross talk between the pathways is among different histological tumor types and highlights the difficulty in defining the appropriate molecular profile across them. If this compound had been tested in a completely histology agnostic trial based on profiling/enriching only for the V600E BRAF mutation genotype, the effect would possible have been diluted, and the drug would likely have failed. Extensive translational research needs to be an integral part of these trials, even if this increases the overall complexity.

Another hurdle for these trials is the current regulatory landscape. Due to the lack of experience and precedent, neither regulators nor researchers or sponsors know what is

required for approval of new agents based solely on presence and response of a molecular target. This may require further methodological development for regulatory acceptance (Willyard, 2013). The tyrosine kinase inhibitor imatinib previously depicted in this article included several diseases associated with mutations in the genes coding for Abl, Kit, or PDGFR protein tyrosine kinases. The basis for regulatory approval was individual analyses of each malignancy under investigation. The master protocol harbored five separate sub-studies for each indication (McCaughan, 2011). The European Medicines Agency (EMA) states in its "Guideline on the evaluation of anticancer medical products in man" about phase III confirmatory trials:"… in studies investigating the activity of a compound targeting a specific, molecular well-defined structure assumed to be pivotal for the condition(s), it might be possible to enroll patients with formally different histological diagnosis, but expressing this target." (European Medicines Agency) In the same section they state: "… the study should be designed so that it is possible …, to conclude on the benefit-risk in the different subgroups of patients for which a claim is to made."

In addition, the challenges may be bigger than anticipated due to the potential need of inhibiting multiple pathways. This requires combination of NMEs that are not necessarily available from the same company or at the same stage of development, increasing the legal and regulatory complexity of setting up such initiatives.

A nearly perfect understanding of the biology will be required so that a given pathway can be evaluated across histologies. Overcoming administrative hurdles and developing compelling models will require close cooperation among the regulatory bodies, the academic community, and the private sector. Regulators and the pharmaceutical sector are already discussing alternative and more agile approaches to drug registration referred to as adaptive licensing (Eichler et al., 2012). Emerging data indicate that treatment outcome may improve if patients' treatment is based on associated tumor driven alterations. Clinicians are more and more inclined to treat patients based on potential genomic targets. However, the multiplicity of technologies and platforms as well as the absence of cross validated quality assurance programs open huge variability and make a rationale process to decision making complicated. Variability of performance and detection leads to a lack of trust by regulatory competent bodies. Therefore, the move to truly personalized medicine and histology agnostic trials, if feasible, will require centralized qualification and validation processes based on solid quality assurance for assessment of the analytical methods.

A possible solution could be to integrate the models described here and performing them in sequence. Basket studies could give grounds for registration access in larger populations. From there, new ways for drug access could be developed which would allow off label access based on strong quality assurance and quality control (QA/QC). This should feed into more agile drug access or licensing systems which closely involve regulators and payers. Recent scientific advances have led to the development of promising individual cancer therapies, but it is increasingly clear that the current way of testing drugs in clinical trials needs to be re-evaluated. Finding the right trial design for testing NMAs is complex, and there is no one-size-fits-all approach. However, newer and more flexible development models need to be evaluated.

Histology agnostic trials may become more common in the future, particularly to investigate the effectiveness of therapeutics on rare cancers, but the model still needs to prove its feasibility. It is quite apparent that this kind of trials needs to be based on a strong biological rationale and should not be used to complement weak preclinical data. The United States National Cancer Institute (NCI) recently announced plans for the MATCH (Molecular Analysis for Therapy Choice) trial which consists of an umbrella protocol for multiple, single-arm phase II trials (Varmus's remarks at the AACR, 2013). The idea is to test various cancers for their molecular profile and assign patients to clinical trials that are testing drugs targeting a specific abnormality across histological tumor types. Another example is the Winther trial which aims to provide biologically guided therapy to patients whose tumors express alterations that can be targeted by currently available drugs (ESMO, 2013).

There is no question that molecular analyses across different histologies are important to learn more about the disease. These analyses should be done on a global scale, ideally in international initiatives to guarantee robust data by developing international concerted standards and practices for data generation, analysis and interpretation (Taking pan-cancer analysis global, 2013).

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