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“Personalized biomarker-based treatment strategy for patients with squamous cell carcinoma of the head and neck: EORTC position and approach.”

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ABSTRACT
The molecular landscape of squamous cell carcinoma of the head and the neck (SCCHN) has been characterized and actionable or targetable genomic alterations have been identified. However, targeted therapies have very limited activity in unselected SCCHN and the current treatment strategy is still based on tumor location and disease stage and not on tumor biology.

Trying to select upfront the patients who will benefit from a specific treatment might be a way to improve patients’ outcome. With the objective of optimizing the activity of targeted therapies and immunotherapy, we have designed an umbrella biomarker-driven study dedicated to recurrent and/or metastatic SCCHN patients (EORTC-1559-HNCG, NCT03088059).

In this paper, we review the different trial designs for biomarker-driven studies with their respective advantages and opportunities but also the potential pitfalls that led to the design of the EORTC-1559-HNCG protocol. We also discuss the scientific and logistic challenges of biomarker-driven trials.

KEY WORDS
SCCHN, biomarker, personalized, umbrella, EORTC-1559-HNCG

KEY MESSAGE
SCCHN harbors potential therapeutic targets but the use of targeted drugs in an unselected population is disappointing. We review the existing biomarker-driven trials and introduce the EORTC-HNCG-1559 trial, an approach using a common screening platform to guide a personalized, biomarker-based treatment strategy for recurrent/metastatic SCCHN.
Introduction

Squamous cell carcinoma of the head and the neck (SCCHN) is the seventh most common malignancy [1]. The main risk factors are smoking and alcohol consumption, which are responsible for the majority of SCCHN occurring in the oral cavity, pharynx, and larynx. Another risk factor for oropharyngeal cancer (OPC) is the human papillomavirus (HPV). Tobacco and/or alcohol-induced SCCHN and HPV-related OPC are two separate entities with different clinical and molecular features [2-4].

Less than 60% of the patients with locally-advanced SCCHN remain disease-free at 3 years, despite a multimodal treatment combining surgery and/or (chemo)radiation [5]. Patients with recurrent/metastatic disease that are not amenable to radiotherapy or surgery have a median survival of 10-12 months. Platinum-based chemotherapy in combination with cetuximab improves overall survival (OS) in the first-line treatment of incurable disease [6]. Nivolumab increases OS of patients who progress after platinum therapy [7]. Pembrolizumab is also approved in the same indication by the Food and Drug Administration (FDA) [8]. No standard of care exists for patients who progress after platinum-therapy and anti-programmed cell death protein 1 (PD-1) compounds.

The current treatment strategy of patients with SCCHN is still based on tumor location and disease stage and not on tumor biology [4, 9, 10]. Targeted therapies have shown disappointing results [11-13]. Trying to select upfront the patients who will benefit from a specific treatment might improve the outcome. The European Organization for Research and Treatment of Cancer (EORTC) is conducting the EORTC-1559-HNCG trial, the first international biomarker-driven umbrella trial in recurrent SCCHN. In this paper, we will review the different trial designs for biomarker-driven studies with their respective advantages and opportunities but also the potential pitfalls that led to the design of the EORTC 1559 protocol. We will also discuss the scientific and logistic challenges of this trial.
Lessons learned from previous biomarker-driven studies

Study designs

“Master protocol” terminology refers to a framework in which several (sub)studies that investigate multiple therapies are operated in parallel under one ‘overarching’ master protocol [14]. Master protocols include two different study designs: basket and umbrella trials. Table 1 summarizes the opportunities and drawbacks of these designs.

**Basket trials** are biomarker-driven clinical trials that include patients based on pre-defined specific molecular tumor abnormalities, irrespective of tumor origin and histology (Table 2). One of the advantages of this histology agnostic approach is to investigate the activity of targeted drugs across different cancer types, even in rare cancers for which clinical trials do not exist. They also offer the possibility to target low incidence molecular alterations.

**Umbrella trials** are biomarker-driven clinical trials that are histology specific, investigating different therapeutic interventions in a single cancer type (Table 3). A histology specific approach is interesting to avoid the heterogeneity due to different biology across various tumor types.

**Strategy trials** investigate if selecting the treatment based on molecular alterations results in superior outcome compared to standard therapy, independently of the drug, the disease, and the studied biomarker(s).

**Molecular screening programs** have been implemented to facilitate the access to precision medicine trials. These screening initiatives can be histology-agnostic or histology-specific.

Theranostic and molecular screening tools

Different diagnostic tests are routinely used to predict the activity or resistance of some targeted therapies. Most of them are evaluated on tumor biopsies, although liquid biopsies are entering into the clinic (e.g. Epidermal Growth Factor Receptor (EGFR) T790M mutation in non-small cell lung cancers (NSCLC)). Biomarkers can be evaluated at the proteomic level such as the estrogen receptor status assessed by immunohistochemistry (IHC) but also at the
genomic level such as Human Epidermal Receptor-2 (HER2) amplifications or EGFR activating mutations.

The tumor molecular profile has been obtained in 74% to 93% of screened patients in biomarker-driven clinical trials [16, 18-23]. Most of them use DNA sequencing on tumor biopsies. Reproducibility and reliability of the molecular screening tools are important. Most of the trials use certified laboratories, but the analysis is not always centralized. In these cases, some trials performed an inter-laboratory analytical validation before starting the trial [24] or validated the assay [25].

A fresh biopsy is probably more reliable than an archival one. Indeed, the cancer molecular profile can change during disease evolution [26]. IMPACT [18, 21] used archival paraffin-embedded tissue (FFPE). In the LUNG-MAP trial [27] and LUNG-MATRIX trial [23], both archival or fresh-taken tissues are accepted. In the MOSCATO 01 [20], NCI-MPACT [15], NCI-MATCH [15], BATTLE [16], and SHIVA [17] trials, a fresh tumor biopsy has/had to be taken for the trial purpose.

**Actionable genomic alteration frequency and enrolment rate**

According to ESMO glossary [28], targetable genomic alteration encodes an altered protein against which a drug exists or can be synthesized and an actionable genomic alteration includes both targetable alterations and genomic alterations that cannot be directly targeted but that lead to dysregulation of a pathway in which there are possible targets.

The percentage of patients that had an actionable genomic alteration identified through screening programs ranged from 46% to 63% [18, 20, 21, 29]. However, the number of patients who were finally treated with a matched targeted therapy were low: 13%, 16%, and 19% in SAFIR01 [29], IMPACT (first published report [21]), and MOSCATO 01 [20], respectively. This number increased to 27% in the most recent IMPACT publication [18], probably related to the extension of the screening panels. Different reasons may explain these low enrolment rate: tumor tissue issues, decline in the performance status or rapidly progressing disease, the absence of a targetable event, and the access to matched clinical
trials or drugs. As IMPACT and the MOSCATO 01 were screening programs, patients were referred to enrolling clinical trials with obvious limitations in the treatment possibilities.

A way to partially solve these issues is to include the access to drugs into the clinical trial design. The NCI-MATCH basket trial pre-planned the access to some targeted compounds. However, only 12% of the patients were finally enrolled in the trial [22]. This low enrolling rate might be due to the low incidence of the targeted variants since only 18% of the screened tumors were found to have a genomic alteration that matched one of the 30 treatment arms. In contrast, in BATTLE and LUNG-MAP, two umbrella trials for NSCLC, 75% and 37% of the patients were included in one of the sub-studies, respectively [16, 27]. The number of treated patients is higher in these two last trials due to a pre-planned access to matched targeted therapies. In addition, for the Battle trial, the molecular profile strategy was disease-specific and adapted to NSCLC, explaining the high prevalence of some of the investigated biomarkers.

**Treatment efficacy in Master protocols**

Treatment selection based on DNA biomarkers has proven its efficiency: anti-HER2 therapies for HER2 amplified breast cancer [30] and EGFR or pan-HER inhibitors for EGFR mutated NSCLC [31]. Pembrolizumab has been approved, independently of the tumor type, for microsatellite instability-high and mismatch repair deficient cancers [32] as well as for the first-line treatment of metastatic NSCLC with high PD-L1 expression [33].

Different endpoints are used in biomarker-driven trials. In MOSCATO 01 [20], the primary endpoint was the progression-free survival (PFS) ratio calculated for each patient, that must be > 1.3 to define clinical benefit (PFS ratio = PFS on the molecular-profile selected therapy/PFS on prior therapy). The approach is judged efficient if it modifies the natural history of the disease and is associated with a longer PFS than the previous line of treatment. Thirty-three percent of patients treated with a targeted therapy had a PFS ratio > 1.3. However, the number of patients who benefited from the personalized approach represented only 7% of the screened patients.

In IMPACT, the clinical outcomes of patients with molecular aberrations treated with matched therapy were compared with those of consecutive patients who were not treated
with a matched therapy. They reported a better objective response rate (ORR) (11% vs 5%), a longer failure-free survival (3.4 vs 2.9 months), and a longer OS (8.4 vs 7.3 months) in the matched group [18]. The clinical benefit rate in the matched group, defined as the proportion of patients with either a stable disease lasting more than 6 months or a partial response or complete response, was 29% (111/381) as compared to 24% (56/238) in the non-matched group. However, only 8% of the whole population finally experienced a clinical benefit. The use of non-optimal targeted drugs or sub-optimal dosages in phase 1 trials, and sometimes the level of evidence concerning the investigated biomarker(s) may explain the limited treatment efficacy observed.

In MyPathway basket trial [34], the ORR was 23% in 14 different tumor types, a clinically significant result for advanced refractory disease. In the SUMMIT trial [35], a basket trial studying neratinib in patients with a tumor harboring either \textit{HER2} or \textit{HER 3} mutations, the primary endpoint was reached only for breast cancer, and not for lung, bladder, and colorectal cancers, underlining the importance of the histology and the tissue of cancer origin. In BATTLE [16], the 8-week disease control rate and ORR were 46% and 4%, respectively. The first data of the ongoing Lung-MAP trial reported an ORR of 4-7% for the first 3 biomarker-driven cohorts [27].

The SHIVA trial was the first randomized trial comparing a molecularly targeted therapy based on tumor molecular profiling versus conventional therapy for advanced cancer [17]. This study tested the overall strategy of a biomarker-driven treatment approach versus standard therapy. The trial did not meet its primary endpoint (PFS). Several reasons could explain this overall negative result. First, they used drugs that were marketed in France at that time and not necessarily the best in class to target the molecular alteration identified. Second, the experimental arm was also heterogeneous with multiple drugs and various tumor types. This could have blinded the benefit of some drugs in some specific cancer(s). The ongoing NCI-MPACT trial [15] is also a strategy trial. To avoid a negative trial linked with inadequate target modulation by the selected agents, all the targeted agents used in NCI-MPACT have been validated to engage their purported targets and have at least an established phase II dose.
Biomarker-driven studies for SCCHN

Only a few biomarker-driven trials are dedicated to SCCHN (table 4). Some phase II trials are selecting patients upfront based on a rare specific genomic alteration (HRas proto-oncogene (HRAS) mutations or Fibroblast Growth Factor Receptor (FGFR) mutations/amplifications/translocations). However, these trials offer only one potential therapeutic option for the very low percentage of patients harboring these rare genomic events. This results in a high rate of screening failure. There is another ongoing trial in Korea assessing personalized therapy for recurrent/metastatic SCCHN and oesophageal cancer (NCT03292250) where patients are allocated to different treatment arms after first line platinum-based therapy according to molecular characterization.

Actionable or targetable genomic alterations in SCCHN

Next generation sequencing (NGS) technologies have identified potentially actionable/targetable genomic alterations in SCCHN [4, 9, 10]. Targetable genomic alterations in HPV-negative SCCHN include events in genes related to kinase growth factor family receptors or their downstream molecular pathways: EGFR (15%), FGFR 1-3 (14%), HER2 (5%), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) (34%), and HRAS (5%). HPV-negative SCCHN has also potentially actionable cell cycle genomic alterations: TP53 mutation (70%), cyclin D1 (CCND1) amplification (20-30%), and CDKN2A inactivation (80-90%). In HPV-positive OPC, where the oncoprotein E6 and E7 inactivate respectively p53 and Rb, PIK3CA amplifications/mutations are found in 56% whereas the other genomic alterations are rare.

The EORTC-1559-HNCG trial (UPSTREAM: Personalized STrategy for REcurrent And/or Metastatic SCCHN)

Our main objective was to design a biomarker-driven study dedicated to SCCHN patients. Below, we describe the overall study design as well as the different treatment cohorts.
EORTC-1559-HNCG design

The EORTC-1559-HNCG trial is a biomarker-driven umbrella trial that enrolls patients with recurrent/metastatic SCCHN, progressing after first-line platinum-based chemotherapy. Each patient must undergo a fresh tumor biopsy. NGS is performed to identify somatic mutations and copy number alterations with a custom panel that has been designed for the trial. This panel covers 13 oncogenes and tumor suppressor genes: EGFR, HER2, TP53, PIK3CA, CCND1, NRAS, KRAS, HRAS, PTEN, FGFR1, FGFR2, FGFR3, and cMET. The analysis also includes p16 (p16 positive = Histo-score ≥ 210) and PTEN (PTEN High = Histo-score > 150) determined by IHC [36]. mRNA FGFR expression is evaluated by NGS. All these analyses are performed centrally in an ISO 15189 certified laboratory (OncoDNA, Belgium).

Based on the molecular alterations identified, each patient is allocated to one of the cohorts. If the patient is not eligible for one of the biomarker-driven cohorts, he/she is included in one of the immunotherapy cohorts. The global design of the trial as well as the molecular rules for treatment allocation and prioritization are depicted in figures 1 and 2.

The full protocol includes a core protocol and several addenda. The core protocol describes the overall study design, the objectives and endpoints, the inclusion/exclusion criteria, the study flow chart, the statistical hypotheses, the data analysis plan, and the biobanking processes. For each experimental treatment, there is one separate addendum that contains the confidential information related to the drug. The national health regulatory authorities, the ethical committee, and the investigators have access to the core protocol and all the addenda. The pharmaceutical companies have access to the core protocol but they can view and comment only the addendum/addenda concerning the cohort(s) for which they are supporting.

EORTC-1559-HNCG biomarker-driven and immunotherapy cohorts

Each patient cohort is designed as a phase II study with its own statistical hypothesis (Table 5). The primary endpoint is either ORR or PFS rate. Sample sizes vary from 32 to 76 patients across cohorts. The study can be amended to add other cohorts based on drug availabilities or other biomarker hypotheses.
Pan-human epidermal growth factor receptor (HER) inhibitor cohorts

EGFR mutations/amplifications are described in 15% of HPV-negative SCCHN and HER2 is altered (mutation/amplification) in 5%.

The ORR with cetuximab monotherapy is 13% [37]. In contrast to colon cancer where RAS mutations are predictive markers of resistance, RAS alterations are found in only 4% of HPV-negative SCCHN. Although RAS mutations might also play a role in cetuximab resistance in SCCHN [38], other mechanisms including activation of other HERs are involved [39, 40].

Pan-HER inhibitors target all the dimers forms by HER family and have the potential to overcome anti-EGFR therapy resistance caused by cross-talk between EGFR and the other HERs. In unselected SCCHN patients who progress after platinum therapy, afatinib, an irreversible pan-HER inhibitor, improves PFS compared with methotrexate: median PFS 2.7 versus 1.6 months [41]. However, afatinib does not increase OS. Biomarkers analyses were performed within this trial [36]. Median PFS favored afatinib in patients with p16-negative, EGFR-amplified (defined as ≥ 50% of cells with ≥ 4 copies, or ≥1 cell with ≥ 8 copies), HER3-low (defined as H-score ≤ 50), and PTEN-high (defined as H-Score > 150) tumors. In the MCC15780 trial where 38 SCCHN patients were treated with cetuximab [42], PFS was also significantly increased in PTEN-high tumors compared to PTEN-low tumors [43]. The fact that afatinib seemed to be more active in case of HER3-low and PTEN-high disease suggests that pan-HER inhibitors could be more active when the PI3K pathway is not or less activated.

Cetuximab-naïve patients with p16 negative tumor had also a significant benefit from afatinib (ORR: 27%).

We designed two biomarker-driven cohorts in the EORTC-1559 trial where the patients are randomized between afatinib or investigator’s choice. The first cohort includes patients with p16 negative SCCHN harboring either an EGFR mutation/amplification or HER2 mutation/amplification or PTEN high (H-score > 150). We did not include patients with HER3 low disease as this IHC is not always reproducible [44]. The second cohort includes cetuximab-naïve SCCHN patients with p16-negative tumor. SCCHN with any RAS mutations are excluded [38].

Fibroblast growth factor receptor (FGFR) inhibitor cohorts

FGFRs can activate the RAS-MAPK, PI3K, STAT, and PLCγ pathways [45]. FGFR1 mutation/amplification are found in 5-10% of HPV-negative SCCHN, while FGFR 3 mutations
are more frequent in HPV-induced OPC (1-12%). Genetic alterations of FGFR2 are observed in only 2-4%.

Erdafitinib, a pan-FGFR inhibitor, induced ORR in 24-35% of patients with metastatic urothelial cancer harboring FGFR alterations (including activating mutations and translocations) [46]. Twenty-four percent of patients with urothelial cancer overexpressing FGFR1-3 mRNA achieved ORR with Rogaratinib, another pan FGFR inhibitor [47]. Partial responses were also observed in some patients with squamous cell lung cancer, SCCHN, and adenoid cystic carcinoma [48]. Interestingly, some responding patients had elevated tumor FGFR3 mRNA levels without corresponding genomic alterations. The prevalence of FGFR1-3 mRNA positivity among 46 SCCHN patients was 56.5% [49].

We will investigate Rogaratinib in cases of high FGFR mRNA levels assessed by NGS.

**Cell cycle inhibitor cohort**

The vast majority of HPV-negative SCCHN harbors genetic alterations (TP53 mutations, CCND1 amplification, and p16 inactivation) that enable them to circumvent the mitotic checkpoints through aberrant cyclin-dependent kinase (CDK) activation. Since p16 inactivates CDK4/6 whereas cyclin D1 activates CDK4/6, there is a rationale to test CDK4/6 inhibitors in patients with p16 negative and CCND1-amplified SCCHN. Palbociclib in combination with cetuximab has been investigated in recurrent SCCHN with promising preliminary results (ORR: 35%) [50]. However, palbociclib monotherapy has not been investigated in SCCHN.

We will investigate palbociclib in patients with p16 negative tumors harboring CCND1 amplification.

**Poly ADP ribose polymerase (PARP) inhibitor cohorts**

DNA repair deficiency increases sensitivity to platinum-based chemotherapy and PARP inhibitors [51]. A comprehensive analysis for homologous recombination deficiency (HRD) was performed and HRD was associated with ovarian, lung, SCCHN, and bladder cancer. Preclinical studies have shown that HPV-positive SCCHN have DNA double strand repair defects responsible for increased sensitivity to the PARP inhibitor veliparib [52]. These data
support the two patient cohorts that will investigate niraparib, another PARP-inhibitor, in p16-positive OPC and in platinum-sensitive p16 negative SCCHN.

**Immunotherapy cohorts**

PD-1/PD-L1 blockers have activity in SCCHN but the 2-year’s OS rate is still low: 16.9% [53]. Therefore, other immunotherapy approaches have to be investigated.

HLA-E is a non-classical major histocompatibility complex molecule that constitutes a way for cancer cells to escape immune surveillance. HLA-E is highly expressed in 70% of SCCHN [54]. HLA-E binds to NKG2A receptor on NK cells and T-lymphocytes to inhibit the cytotoxic functions of CD8+ T lymphocytes and NK cells. Monalizumab is a human IgG4 antibody targeting the NKG2A receptor. In the first immunotherapy cohort, patients will receive monalizumab monotherapy. In the second immunotherapy cohort, patients will be randomized to receive the combination of durvalumab and monalizumab versus monalizumab monotherapy versus physician’s choice.

**EORTC1559 Feasibility**

The trial is open for inclusion since December 2017. On 19 July 2018, 19 sites are open in 3 countries. 64 patients have been screened, 24 included in one of the biomarkers cohorts and 23 in one of the immunotherapy cohorts. The turnaround time between the biopsy and the molecular diagnosis provided by the central lab is 10 calendar days.

**Discussion**

The EORTC-1559-HNC trial is the first European international umbrella trial assessing a personalized treatment strategy for patients with recurrent/metastatic SCCHN. We hypothesize that this approach can improve patients’ outcome. The trial design has different strong points: one single protocol with pre-planned access to matched targeted therapies, one fresh tumor biopsy to deal with tumor evolution over time, an ISO-certified central laboratory, well-defined biomarker hypotheses, and the possibility to have a never-ending protocol with the opportunity of adding new cohorts.
Besides the inherent complexity of such trials, numerous logistic and scientific challenges were encountered when designing this protocol. Although the pharmaceutical companies accepted the concept of having only one protocol including the different compounds, complex negotiations were crucial to successfully achieve that all stakeholders agreed (i) to standardize the processes, (ii) to accept the pre-defined protocol structure, (iii) to use the central biomarker laboratory, (iv) to match the company interests with the academic wishes, and (v) to align all the companies on the same protocol wording in particular for the inclusion/exclusion criteria. The protocol was submitted in 4 different countries (Belgium, France, Italy, United Kingdom) and will be submitted in Germany to both competent authorities (CA) and applicable ethics committees (EC). Overall, the study was well received by the CA and EC without major comments on the study design. The main question received from EC was concerning the criteria to allocate patients to the different cohorts. Regarding the regulatory strategy, having all those cohorts in only one study simplifies the submission process, as it requires only one initial clinical trial application to each CA and one initial request of opinion to each EC. Also, each amendment can group modifications concerning more than one cohort at the same time. If we had considered each cohort as one trial, different submissions would have been necessary, increasing the regulatory workload and probably time for activation. As separate trials, the advantage would have been that the current cohorts could be opened/closed independently across the countries without the need of a main protocol amendment. In addition, the liaison with the stakeholders would be easier, as the number of stakeholders per trial would be significantly reduced.

The new European clinical trials regulation [55] fully in application next year might bring a novel perspective for studies with a complex design. Multiple member states will participate on the coordinated assessment of some sections of the dossier, ensuring that consolidated communication reaches the applicant. This may reduce the volume of correspondence and facilitate the management of any protocol modifications if they are required. Several challenges remain. Optimal management of country-specific documents adaptation and effective communication with the stakeholders might be the key to ensure fulfillment of adequate deadlines and quick activation of new cohorts to follow the fast advancing head and neck cancer research field.
At the scientific level, the study is still missing some treatment arms that target important genetic aberrations. *PIK3CA* alterations occur in 16 to 34% of HPV-negative patients and in up to 56% of HPV-positive patients. Patient-derived SCCHN tumor xenografts with *PIK3CA* activating mutations are sensitive to mTOR/PI3K inhibitors [56] and, in the BERIL-1 trial, buparlisib improved OS when added to paclitaxel [57]. Among other interesting targets, there is a scientific rationale to test Farnesyl transferase inhibitors in the 5% of SCCHN harboring *HRAS* mutations or WEE1 inhibitors in *TP53* mutated tumors.

In the current design, immunotherapy cohorts are not linked to biomarker(s). Among others, HPV-positivity, PD-L1 overexpression, in-frame or frameshift alterations of specific tumor suppressor genes, and mutational burden are potential biomarkers that have been associated with a higher efficacy of immunotherapy in SCCHN [7, 8, 58]. However, these predictive markers are far to be optimal. Umbrella trials represent an ideal platform to further investigate the predictive value of immune biomarkers.

We cannot deny that tumor heterogeneity that can cause treatment resistance is not addressed by the use of targeted compounds in monotherapy. Therefore, we also collect whole blood, plasma as well as tumor biopsies for translational research. Analyzing these biological samples will give us more insight on the genetic landscape of recurrent/metastatic SCCHN, which may lead to the discovery of new therapeutic targets, and may help to investigate more precisely the utility of liquid biopsy. Translational research will also provide information regarding drug resistance mechanisms and will help us to develop new combination treatments that are able to tackle them.

A finding of biomarker-driven studies is the low number of patients who benefit from this approach. This suggests that for heterogeneous cancers with multiple potential oncogenic drivers, biomarkers assessed only at the DNA level may not predict drug responses reliably. The signification of some genomic alterations can vary from one cancer histology to another. Therefore, for further developments, we will have to take into account several others parameters such as the phenotype (e.g. gene expression/proteomic profiles) and the tissue of cancer origin [59].
In conclusion, precision medicine remains a major challenge for the medical community. Large efforts are needed to optimize the study designs, the theranostic tools, and the trial logistics. Designing biomarker-driven studies requires close collaboration with country competent authorities, ethics committees, and pharmaceutical companies to reduce the administrative burden and facilitate the processes linked with the design and conduct of such clinical trials.
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J-P. Machiels is member of the advisory board of MSD (uncompensated) and INNATE; C.Le Tourneau has been part of advisory boards of MSD, BMS, Merck Serono, Roche, Amgen, Novartis, Nonobiotix; J. Guigay has been part of advisory boards for AstraZeneca, Bristol-Myers Squibb, Innate Pharma, and Merck KGaA and has received grants for research from GSK, Bristol-Myers Squibb, Chugai, and Merck KGaA; L. Licitra has served as consultant/adviser and/or give lectures for AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Debiopharm, Eisai, Merck-Serono, MSD, Novartis, Roche and Sobi. She has received research funds from AstraZeneca, Boehringer Ingelheim, Eisai, Merck-Serono, MSD, Novartis and Roche. She received travel coverage for medical meetings from Bayer, BMS, Debiopharm, Merck-Serono, MSD and Sobi; JF. Laes is an employee of OncoDNA; E. Saada-Bouzid is member of advisory board of BMS; A. Kong has served as an adviser for PUMA Biotechnology and Avvinity/Centuari Therapeutics Limited. He has received research grants from AstraZeneca and PUMA Biotechnology and has also received honoraria from Merck, BMS and MSD as an invited speaker.
All remaining authors have declared no conflicts of interest.
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Figure legends:
Figure 1. General design of the EORTC1559 umbrella trial
Figure 2. Prioritization algorithm for the allocation to different patient cohorts
Table 1. Advantages and pitfalls of “biomarker-driven” clinical trial designs

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<tr>
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<th>ADVANTAGES</th>
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<tbody>
<tr>
<td><strong>MASTER PROTOCOLS</strong></td>
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<tr>
<td>BASKET trials</td>
<td>can include rare cancer types</td>
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<td>can target low incidence</td>
<td>genetic alteration has the same signification across different tumor types</td>
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<td>UMBRELLA trials</td>
<td>targets molecular alterations in one cancer type and avoid heterogeneity</td>
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<td>due to multiple cancer histologies</td>
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<td>if an actionable/targetable alteration is present, the specific drug is not</td>
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<td>have the potential to identify an actionable/targetable genetic alteration</td>
<td>Effect of the strategy can be diluted by less effective target-drug pairs</td>
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<td>Tumor</td>
<td>Study design</td>
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<td>Screening program</td>
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<td>All, refractory advanced cancer</td>
<td>Strategy trial Multicentre, open-label, proof-of-concept, randomized, phase II trial</td>
</tr>
<tr>
<td>----------------------</td>
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</tr>
<tr>
<td><strong>MOSCATO 01 trial [20]</strong></td>
<td>All, advanced cancer</td>
<td>Screening program Single-centre, single-arm, open-label, prospective clinical trial</td>
</tr>
<tr>
<td>CREATE trial [60-63]</td>
<td>Advanced tumours characterized by MET and/or ALK alterations (papillary renal-cell carcinoma type 1, alveolar soft part sarcoma, clear-cell sarcoma, anaplastic large-cell lymphoma, inflammatory myofibroblastic tumour, and alveolar rhabdomyosarcoma)</td>
<td>Multinational, multitumour, prospective phase II clinical trial</td>
</tr>
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<td>-------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>NCI-MPACT [15]</td>
<td>All, advanced solid tumor</td>
<td>Strategy trial Double-blind, randomized trial New biopsy or recent biopsy of &lt; 6 months with no interim therapy sequencing assay for more than 4,000 different</td>
</tr>
<tr>
<td>NCI-MATCH [15]</td>
<td>All, advanced solid tumors</td>
<td>Master protocol Phase II, multicenter, open-label, non-randomized Basket trial New biopsy or recent biopsy of &lt; 6 months with no interim therapy sequencing assay for more than 4,000 different</td>
</tr>
</tbody>
</table>
| **Mypathway**  
[34] | Advanced refractory solid tumor harboring MA in HER2, EGFR, BRAF or Hedgehog pathway |
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>MP</strong></td>
<td>Master protocol Phase Ila, multicenter, non-randomized, multiple basket study</td>
</tr>
<tr>
<td><strong>Pts</strong></td>
<td>Pts are assigned to specific treatment cohorts based on the presence of a relevant target MA</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>Investigator-assessed ORR within each tumor-pathway cohort</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>NA, pts were only included if testing already performed outside the clinical trial</td>
</tr>
<tr>
<td><strong>Efficacy analysis</strong></td>
<td>Efficacy analysis population: 230 pts</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>ORR: 23% within 14 different tumor types</td>
</tr>
</tbody>
</table>

| **SUMMIT**  
[35] | Solid tumors harbouring HER2 and HER3 mutations |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>MP</strong></td>
<td>Master protocol Multi-cohort basket study</td>
</tr>
<tr>
<td><strong>Pts</strong></td>
<td>Pts with HER2-mutant cohorts were enrolled into disease-specific cohorts and HER3 mutants into one cohort</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>Investigator-assessed ORR</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>Total: 125 HER2 mutant pts and 16 HER3 mutant pts</td>
</tr>
<tr>
<td><strong>Observation</strong></td>
<td>For HER2 mutant tumors, primary endpoint was met only for breast cancer (ORR 32%) and not for lung, colorectal or bladder. No responses were observed in the HER3 mutant cohort</td>
</tr>
</tbody>
</table>

**Abbreviations**
<table>
<thead>
<tr>
<th>Study</th>
<th>Tumor</th>
<th>Study design</th>
<th>Biomarker</th>
<th>Methodology</th>
<th>Endpoint</th>
<th>Identification of target and number of treated patients</th>
<th>Results and impact on outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The BATTLE trial [16]</strong></td>
<td>Non-small cell lung cancer</td>
<td>Master protocol</td>
<td>Fresh biopsy (FFPE)</td>
<td>Multiples arms: 5 biomarker groups with different targeted therapies equal random assignment for 97 first pts, and adaptive randomization for next 158</td>
<td>DCR at 8 weeks</td>
<td>341 pts enrolled: 299 with adequate tissue for analysis (88%) 255 pts were randomized (75%)</td>
<td>Overall 8w DCR: 46% Biomarker groups less predictive than individual biomarkers</td>
</tr>
<tr>
<td><strong>SAFIR01 [29]</strong></td>
<td>Metastatic breast cancer</td>
<td>Screening program</td>
<td>Fresh biopsy aCGH for preselected genes and Sanger sequencing for mutational hotspots on PIK3CA and AKT1</td>
<td>Screening: Based on the identified genomic alteration, pts were treated with targeted therapy if possible (within clinical trial or not)</td>
<td>Proportion of patients for whom a targeted therapy could be offered</td>
<td>423 pts included, biopsy obtained for 407 pts Targetable alteration in 195 (46%)</td>
<td>Therapy could be personalized in 55/423 pts (13%)</td>
</tr>
<tr>
<td><strong>LUNG-MAP master protocol [27]</strong></td>
<td>Advanced lung squamous cell carcinoma</td>
<td>Master protocol</td>
<td>Archival FFPE or fresh tumor biopsies</td>
<td>Mutliple arms: Based on the molecular profile, each pt is enrolled in a sub-study with matched targeted therapy or in non-match sub-study</td>
<td>ORR</td>
<td>1392 pts registered to the screening component 523 pts registered to a sub-study (37%)</td>
<td>First results for 3 biomarker driven cohorts (S1400B, S1400C and S1400D): ORR 4-7% Cohorts closed due to futility at interim analysis S1400A (immunotherapy): 16% ORR Other sub-studies ongoing</td>
</tr>
<tr>
<td><strong>The National Lung Matrix [23]</strong></td>
<td>Advanced NSCLC</td>
<td>Master protocol Phase II umbrella trial</td>
<td>Pre-screening of tumor biopsies through the Stratified Medicine Programme 2 (take place in parallel with the patient receiving first line treatment): adaptable 28-gene NGS sequencing platform designed by Illumina covering the range of molecular abnormalities being targeted</td>
<td>Multiples arms (8 investigational medicinal products, within 21 distinct cohorts) Patients are allocated to the appropriate targeted therapy according to the molecular genotype of their cancer Bayesian adaptive design “No actionable mutation arm” for patients without specific eligibility for one of the targeted genomic aberrations</td>
<td>ORR or PFS</td>
<td>As of July 2016: - 1664 pts tested - 1229 passed QC step (74%), 1098 pts with NGS results (66%) - 731 pts with aberration for MATRIX (44%) - 458 pts (28%) with MA and eligible (not registered) for MATRIX</td>
<td>As at 9 June 2017, 151 patients have been registered, 125 of these patients have received targeted treatments within the Lung Matrix trial. No results available per cohort. The Osimertinib cohort has been closed for recruitment.</td>
</tr>
<tr>
<td><strong>FOCUS4 [64]</strong></td>
<td>Advanced colorectal cancer</td>
<td>Master protocol Phase II-III umbrella trial</td>
<td>FFPE block taken prior to commencement of standard chemotherapy Mutations of some preselected genes + some IHC, mRNA EREG</td>
<td>Multiple arms After induction chemotherapy, pts are enrolled in different cohorts on the basis of MA in the tumor, to test different targeted agents versus placebo or in a no-biomarker cohort testing standard capecitabine vs placebo as maintenance</td>
<td>PFS</td>
<td>NA</td>
<td>First results for 1 patient cohort (FOCUSD): Median PFS 3.48 mo with placebo and 2.96 mo with AZD8931: closed for futility</td>
</tr>
</tbody>
</table>

**Abbreviations**

Table 4. Ongoing biomarker-driven trials in squamous cell carcinoma of the head and neck

<table>
<thead>
<tr>
<th>Study title</th>
<th>ClinicalTrials.gov identifier and status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan FGFR kinase inhibitor BGI398 in treating patients with FGFR1-3 translocated, mutated, or amplified recurrent head and neck cancer</td>
<td>NCT02706691 Not yet recruiting</td>
</tr>
<tr>
<td>Phase II study of tipifarnib in squamous head and neck cancer with HRAS mutations</td>
<td>NCT02383927 Recruiting</td>
</tr>
<tr>
<td>Copanlisib in Association with Cetuximab in Patients with Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinomas Harboring a PI3KCA Mutation/Amplification and/or a PTEN Loss</td>
<td>NCT02822482 Recruiting</td>
</tr>
<tr>
<td>SF1126 in Recurrent or Progressive SCCHN and Mutations in PI3CA Gene and/or PI-3 Kinase Pathway Genes</td>
<td>NCT02644122 Terminated (Slow enrollment)</td>
</tr>
<tr>
<td>Korean Cancer Study Group: Translational biomarker Driven UMBrella Project for Head and Neck (TRIUMPH), Esophageal Squamous Cell Carcinoma- Part 1 (HNSCC)</td>
<td>NCT03292250 Recruiting</td>
</tr>
</tbody>
</table>
Table 5. Different patient cohorts of EORTC HNCG 1559 trial

<table>
<thead>
<tr>
<th>Patient Cohort</th>
<th>Biomarker(s)</th>
<th>Targeted drug/IO</th>
<th>Design</th>
<th>Sample size (max)</th>
<th>Statistical hypothesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B1</strong>*</td>
<td>p16 negative and <em>EGFR</em> amplification/mutation or <em>PTEN</em> high or <em>HER2</em> amplification/mutation</td>
<td>Afatinib</td>
<td>Phase II, randomized, open-label, multi-center study</td>
<td>55</td>
<td>H0: PFSR at 16 weeks = 20% H1: PFSR at 16 weeks = 40%</td>
</tr>
<tr>
<td><strong>B2</strong>*</td>
<td>p16 negative and cetuximab naïve</td>
<td>Afatinib</td>
<td>Phase II, randomized, open-label, multi-center study</td>
<td>55</td>
<td>H0: PFSR at 16 weeks = 20% H1: PFSR at 16 weeks = 40%</td>
</tr>
<tr>
<td><strong>B3</strong></td>
<td>p16 negative and <em>CCND1</em> amplification</td>
<td>Palbociclib</td>
<td>Phase II, randomized, open-label, multi-center study</td>
<td>55</td>
<td>H0: PFSR at 16 weeks = 20% H1: PFSR at 16 weeks = 40%</td>
</tr>
<tr>
<td><strong>B4</strong></td>
<td>p16 negative and 'platinum-sensitive'</td>
<td>Niraparib</td>
<td>Phase II, single arm, proof-of-concept, multi-center study</td>
<td>32</td>
<td>H0: ORR over first 16 weeks = 5% H1: ORR over first 16 weeks = 20%</td>
</tr>
<tr>
<td><strong>B5</strong></td>
<td>p16 positive oropharyngeal cancer</td>
<td>Niraparib</td>
<td>Phase II, single arm, proof-of-concept, multi-center study</td>
<td>32</td>
<td>H0: ORR over first 16 weeks = 5% H1: ORR over first 16 weeks = 20%</td>
</tr>
<tr>
<td><strong>B6</strong>*</td>
<td>FGFR1/2/3 mRNA overexpression</td>
<td>Rogaratinib</td>
<td>Phase II, single arm, proof-of-concept, multi-center study</td>
<td>20</td>
<td>H0: ORR over first 16 weeks = 5% H1: ORR over first 16 weeks = 25%</td>
</tr>
<tr>
<td><strong>Immunotherapy cohorts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>I1</strong></td>
<td>NA</td>
<td>Monalizumab</td>
<td>Phase II, single arm, proof-of-concept, multi-center study</td>
<td>40</td>
<td>H0: ORR over first 16 weeks = 3% H1: ORR over first 16 weeks = 15%</td>
</tr>
<tr>
<td><strong>I2</strong></td>
<td>NA</td>
<td>Monalizumab + Durvalumab</td>
<td>Phase II, randomized, open-label, multi-center study</td>
<td>76</td>
<td>H0: ORR over first 16 weeks = 3% H1: ORR over first 16 weeks = 15%</td>
</tr>
</tbody>
</table>

*Patients included in the afatinib arms should not have activating mutation in RAS
** Patients included in the rogaratininb arm should not have activating mutation in RAS or PIK3CA

Abbreviations
ORR: overall response rate, PFSR: progression-free survival rate
Figure 1. General design of the EORTC1559 umbrella trial

159x136mm (72 x 72 DPI)
Figure 2. Prioritization algorithm for the allocation to different patient cohorts