Regulatory requirements for histology independent indications in oncology

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Abbreviations

MP	medicinal product
CNS	central nervous system
MSI-H	microsatellite instability high
dMMR	deficient mismatch repair system
TMB	tumor mutational burden
NTRK	neurotrophic receptor kinase
FDA	Food and Drug Administration
EMA	European Medicines Agency
CHMP	Committee for Medicinal Products for Human Use
GIST	gastrointestinal stromal tumor
NSCLC	non-small cell lung cancer
HCC	hepato-cellular carcinoma
CML	chronic myologenous leukemia
AML	acute promyelocytic leukemia
PAC	pancreatic adenocarcinoma
NCCN	National Comprehensive Cancer Network
ESMO	European Society for Medical Oncology
EPAR	European Public Assessment Report
SmPC	summary of product characteristics
Her-2	human epidermal growth factor 2
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-ligand 1
ERK	extracellular signal-regulated kinase
EGFR	epidermal growth factor receptor
CD	companion diagnostic
IVD	in vitro diagnostic
CRC	colorectal cancer
BRAF	v-Raf murine sarcoma viral oncogene homolog B1

NGS	next-generation sequencing
FISH	fluorescence in situ hybridisation
IHC	immunohistochemistry
RCT	randomized controlled trial
MAH	marketing authorization holder
HTA	health technology assessment
IRC	independent review committee
INV	Investigator
SAT	single arm trial
RCT	randomized controlled trial
PFS	progression free survival
OS	overall survival
ORR	overall response rate
DOR	duration of response
HRQoL	health related quality of life questionnaire
EORTC	European Organisation for Research and Treatment of Cancer

1. Introduction

Traditionally, classification of cancers is based on their histology and anatomical location, e.g., small-cell lung cancer, pancreatic adenocarcinoma, gastrointestinal stromal tumor (GIST). In consequence, the development of cancer treatments has also followed a histology and anatomy specific pathway.

Evolving knowledge on gene expression, (epi)genomics and mechanisms of cancer genesis or progression has resulted in the description of various oncologic driver mechanisms. These milestones in cancer research lead imperatively to the development of novel strategies in cancer drug development triggered by the understanding of the underlying biology through sophisticated, biomarker driven clinical trials (Park et al. 2019; Lacombe et al. 2014). Targeting specific biological pathways has raised the expectation of more focused and personalized treatments in the oncologic field.

To date, plenty of targeted oncologic medicinal products have been developed in combination with an adequate biomarker assay (Companion Diagnostic) (US FDA 2019.) Nonetheless, these drugs have been still approved within a conventional cancer indication, based on tumor histology. In 2017, the Food and Drug Administration (FDA) approved the monoclonal antibody pembrolizumab (Keytruda, MSD) for the treatment of microsatellite instability-high (MSI-H) and mismatch-repair-deficient (dMMR) positive patients (Lemery 2017). Subsequently, the kinase-inhibitor larotrectinib (Vitrakvi, Loxo Oncology/Bayer), a small molecule, for patients with neurotrophic receptor tyrosine kinase (NTRK) fusion was approved by the FDA and the European Medicines Agency (EMA) (Drilon et al. 2018; CHMP 2019). This regulatory decision made by the FDA and the EMA should be classified as a paradigm shift in biomarker guided cancer drug development. In contrast to oncologic drugs developed traditionally, at least larotrectinib was not developed for conventional cancer indications defined by their histology and anatomical location, but based on its effect related to specific molecular aberrations or mutations.

Considering this milestone in cancer drug development, the objective of this master thesis is to describe the regulatory view on this paradigm shift. After providing some fundamental definitions, the thesis will analyze the two histology independent applications. The differences

in the requirements and challenges between both approvals will be highlighted and the differences in the US and EU regulatory environments will be identified. After a discussion on the imperative nature of this paradigm shift, conclusions and a detailed outlook on further histology independent drug developments in the pipeline will be provided.

2. Drug development in oncology: the traditional paradigm and the global revolution of classical concepts

2.1. What defines disease and population in oncology

In the past years, cancer therapy has been rapidly changing from the "one fits all" cytotoxic therapies to specific approaches, which are designed to precisely target molecular alterations (Coyle et al. 2017). Starting with the introduction of chemotherapeutics at the beginning of the 20th century (DeVita and Chu 2008), oncologic drugs were developed and approved based on conventionally defined cancer indications. Conventionally defined cancer indications use tumor histological classifications related to a specific anatomic location (Jørgensen 2019). In consequence, the indication was always defined by tumor type and line of therapy, e.g., first-line advanced and metastatic non-small cell lung cancer (NSCLC) or hepato-cellular carcinoma (HCC) after previous sorafenib treatment.

Classifying cancers according to the organ they grow in is owed to the hypothesis that the origin of the tumor is what causes its biological behavior and can therefore guide us in understanding its pathophysiology and treating it properly (Raez and Santos 2018). A consequence of this traditional drug development paradigm is that there exist approximately 150 types of cancer categorized primarily according to organ-specificity. These are sometimes subgrouped according to patient age or the cell types affected (NCI 2019). This is also reflected in the current treatment guidelines, such as by the National Comprehensive Cancer Network (NCCN) or the European Society of Medical Oncology (ESMO), which are primarily organized along the affected organ systems (e.g., lung cancer, breast cancer, or colorectal cancer) (NCCN Guildelines; ESMO Guidelines)

2.2. A new era : personalized medicines - identification of biomarkers and correlation with diseases and progression

A biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Strimbu and Tavel 2010). Biomarkers in oncology can be classified as prognostic or predictive. A prognostic biomarker is associated with disease outcome. Prognostic biomarker expression on cancer cells can predict either a better or a worse overall survival of the patient. A predictive biomarker is used to identify patients who are more likely than patients without this biomarker to experience a favorable or unfavorable effect under treatment with a special medical product (FDA Biomarker Working Group) (Figure 1). In general, biomarkers can be both predictive and prognostic, but predictive and prognostic are not necessarily associated.

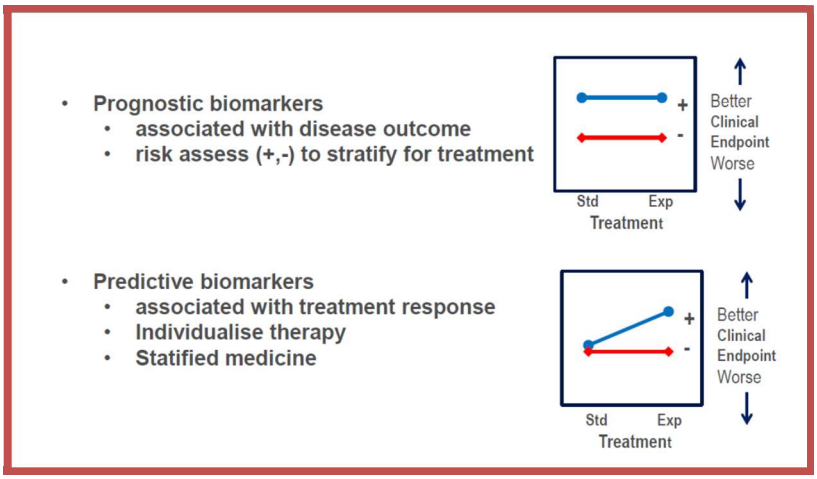

Figure 1 The role of biomarkers in oncologic drug development

The implementation of biomarkers into cancer drug development has helped to focus on subpopulations of cancers that are predicted to be more responsive to the pharmacodynamic modulation by the medicinal products, especially those targeting molecular biomarkers (Yan and Zhang 2018). As a consequence, the clinical benefit for populations expressing those molecular targets or biomarkers is enhanced. Over the past two decades the FDA and the EMA have approved more than 50 molecularly targeted oncology drugs. These therapies include both small molecules and biologics (generally antibodies) targeting cancer specific pathways. The different mechanisms of action are inducing programmed cell death

(apoptosis), blocking specific enzymes and growth factor receptors involved in cell proliferation, or modifying the function of proteins that regulate gene expression and other cellular functions (Hanahan, Douglas and Weinberg, Robert A. 2000) (Figure 2). The success of treatments directed against molecular targets started with drugs against hematological cancers, such as imatinib against the BCR-ABL fusion gene in chronic myologenous leukemia (CML), rituximab (anti-CD-20) against B-cell lymphomas and retinoic acid against PML/RAR fusion in acute promyelocytic leukemia (AML). The first landmark in the solid tumor area was the development of trastuzumab against human epidermal growth factor 2 (HER2)-positive breast cancer, which dramatically improved the outcome of patients with this type of cancer (Vogel et al. 2002). This illustrated the potential of targeted therapies in tumors sustaining special genetic aberrations or differential protein expression, predicted to mediate therapy sensitivity (predictive biomarker; Figure 1). More recently, checkpoint inhibiting programmed cell death protein-1/programmed cell death-ligand 1 (PD-1/PD-L1)-antibodies have been approved in various cancer types (Gong et al. 2018). The PD-1/PD-L1 interaction is a key factor for the immune evasion mechanisms exploited by tumor cells (please refer to Chapter 3.1). Responses to PD-1/PD-L1 antibodies in advanced cancers like melanoma or NSCLC can be regarded as outstanding. In consequence, drug development entered a new era where predictive biomarkers are the decisive factor in the drug development process (Jørgensen 2019).

In the US, targeted therapies are generally approved with companion diagnostic tests (CDT). The FDA definition for companion diagnostic is that it is a medical device, often an in vitro diagnostic (IVD), which provides information that is essential for the safe and effective use of a corresponding drug or biological product. CDTs are developed in order to decide which targeted therapy strategies should be utilized for specific patients. In the European regulatory framework, legislations covering the development and marketing of medicinal products (MPs) and assays (IVDs) are not directly linked. Nevertheless, in the past years regulatory guidances concerning biomarker assay development (EMA/CHMP/800914/2016 2016) have been revised or are under revision. In addition, the new IVD Regulation 2017/746 (applies in May 2022) states that assays (including potential CDTs) are principally IVDs falling under the regulation. All these efforts to improve the performance of biomarker assay development reflect the importance of biomarker and targeted therapies in the past 20 years.

Nevertheless, one has to point out that for most of these MPs, defined as targeted therapies for subpopulations of cancers, the therapeutic benefit was received by targeting genetic

alterations that, retrospectively evaluated, were only restricted to very few cancer types. This has been the case for EGFR inhibitors (e.g. Gefitinib, Erlotinib, Lapatinib) for EGFR activating mutations, Alk inhibitors (e.g.crizotinib, encretinib) for ALK fusions and for the HER2-overexpression. For HER2-amplified and BRAF mutant tumors, it turned out that the efficacy observed in one tumor type can differ substantially from the treatment effect in various others with the same genetic alteration (Flaherty et al. 2010; Kopetz et al. 2015; CHMP 2005). One of the most illustrative cases is the development of the v-Raf murine sarcoma viral oncogene homolog B1 (BRAF). The BRAF inhibitor vemurafenib showed promising efficacy in patients with melanoma enrolled in a phase I trial (ORR=81%) (Flaherty et al. 2010). However, only 5% of BRAFmut patients with colon cancer responded to verumafenib monotherapy, reflecting the heterogeneous pattern of BRAF activation within this histology (Kopetz et al. 2015). Retrospectively gained preclinical insights showed that, especially in colon cancer, the verumafenib effect could be rapidly bypassed by an escape mechanism (ERK reactivation through an EGFR-mediated activation of RAS and C-RAF). (Prahallad et al. 2012). This special mechanism is not activated in melanoma patients, therefore the difference could be explained, but the BRAF case was a throwback for the histology independent drug development.

Programmed cell death protein-1/programmed cell death-ligand 1 (PD-1/PD-L1) was also expected to be a “pan-tumor” biomarker. The target PD-1 or PD-L1 is overexpressed in various different tumor types, but it was demonstrated that the predictive accuracy for the treatment varies significantly across cancer types (EPAR-Keytruda). Therefore, one has to take into consideration that drug development even in this early personalized era was still based on the original tumor type/histology. It was predicated on a biomarker within a tumor type, e.g., HER-2 positive breast cancer or RAS-wild type colorectal cancer.

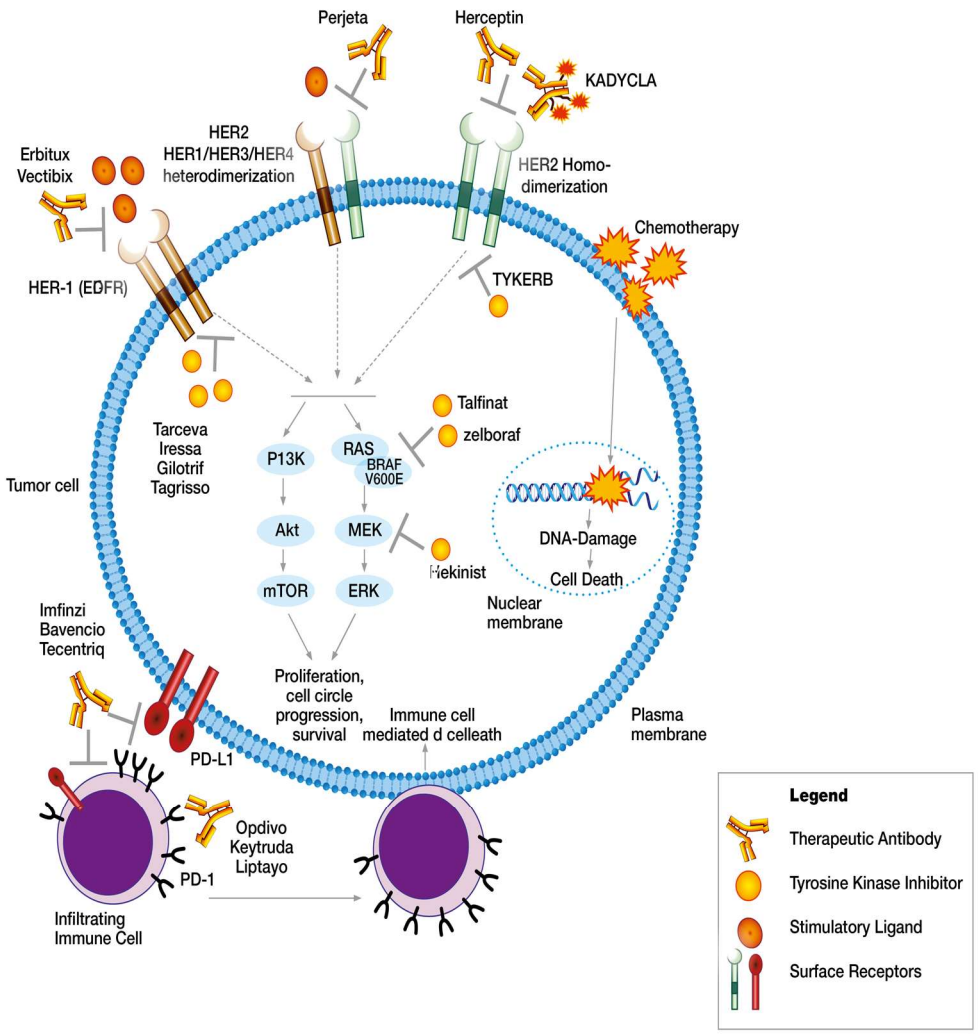

Figure 2 Systemic view of therapeutics selectively targeting HER2, EGFR, PD-1/PD-L1 or cell circle signaling adapted from Twomey et al. 2017. Herceptin (trastuzumab), Kadcyla (trastuzumab emtansin),Tykerb (lapatinib) target at HER2; Peretja (pertuzumab) HER3; Erbitux (cetuximab), Vectitbix (panitumumab), Tarceva (erlotinib), Iressa (gefitinib), Gilotrif (afatinib), Targisso (osimertinib) target at EGFR; Mekinist (trametinib) is a MEK-inhibitor and Tafinar (darafenif), Zelobraf (verumafenib) are two of the BRAFmut inhibitors. A variety of PD-1/PD-L1 inhibitors are approved Tecentriq (atezolizumab), Bavencio (avelumab), Imfinzi (durvalumab) targeting PD-L1 and Opdivo (nivolumab), Libtayo (cemplicimab) and Keytruda (pembrolizumab) targeting PD-1.

2.3. Paradigm shift to histology independent indications

Nonetheless, the recent advances in human genome sequencing and the subsequent availability of comprehensive, clinical grade molecular profiling platforms have increased not only the number of predictive biomarkers, but also the quality of the biomarkers serving to predict the effectiveness of MPs in various cancers. Targeting tumor-specific pathways raises hopes of a focused medicine, which could lead to the development of more efficient and adjusted treatments for patients. Consequentially, drug development paradigms have had to adapt to a number of challenges. These challenges include in particular the decreasing frequencies of molecular alterations/biomarkers (resulting in rare subpopulations) and the identification of biomarkers across multiple tumor histologies (Weinstein and Joe 2006; Akbani et al. 2014; Overman et al. 2017). Clinical trials including patients based on molecular aberrations instead of pure pathology criteria are on the rise. They have evolved to incorporate a strong focus on histology independent drug development. Examples of standard clinical trials types that, although not completely histology independent, do already provide insights into the risks and benefits beyond a single histology are shown in Table 1.

Type of trial	Advantages	Problems
Standard anatomically based trial	• **Current standard**	• **Single indication**
N-of-1	• **Highly personalized**	• **Not designed for marketing authorization (Kauselmann, 2017)** • **Not frequently used in oncology**
Basket trials	• **Pragmatic: many in one** • **Cost benefits** • **Possible in rare cancers** • **Enhance knowledge for basic research**	• **Operational challenges (across departments)** • **Extensive translational research required** • **Different biology across different tumor types**

Table 1 Risk and benefits of different types of trials adapted from Lacombe et al. 2014

An N-of-1 trial (not designed for marketing authorization) is a clinical trial that uses repeated cycles of treatments, with different medicinal products (test MP and control), in a single patient. The N-of-1 trial is rather deigned for chronic disease the for cancer indications and the use in oncologic trials required some modifications (Collette and Tombal 2015). The trial concept of choice to date for studying efficacy across different tumor indications is the basket trial. In contrast to the classical trial concept, in basket trials, patients with a range of histologies are grouped under the same treatment protocol (Figure 3). Basket trials include parallel cohorts with a separate statistical design for each cohort. In general, no randomized control arm is included for each cohort.

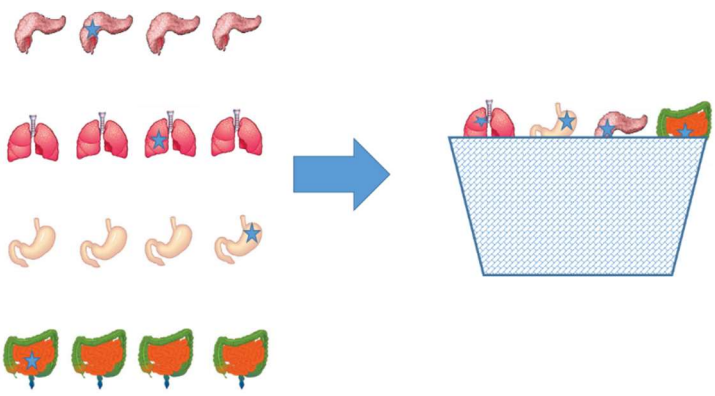

Figure 3 Principle of basket trials

In the past years, an increasing amount of basket trials were initiated. A comprehensive search in the EudraCT database was performed (please refer to the Annex). Out of 2500 oncological trials, 81 trials were classified as basket trials, excluding trials that evaluate pharmakokinetiks and safety alone. One has to take into consideration that most basket trials are still designed to evaluate safety and preliminary efficacy in different indications and are mostly of exploratory nature, but 24 trials could be defined as potential pivotal for a histology independent indication. There are to date two basket studies, served as pivotal trial for a histology independent approval: KEYNOTE-16, evaluating the efficacy of pembrolizumab in MSI-H patients with colorectal carcinoma (CRC) and other tumors, and the LOXO-TRK-15002 study, evaluating larotrectinib in patients with neurotrophic receptor kinase (NTRK)

fusions. Both medicinal products were approved in the US in 2017 and 2019. Larotrectinib was also approved with a histology independent indication in the EU in September 2019.

With the two drug approvals mentioned above, precision medicine just witnessed a breakthrough in oncology. Histology independent (or tumor agnostic therapy[1]) has become a reality. This must be considered a paradigm shift in the cancer drug development. The next two chapters focus on these approvals, their differences and the regulatory conclusions one can draw from both cases.

3. Histology independent indications – case studies

3.1. The first histology independent indication approved by the FDA - Keytruda in MSI-H solid tumors.

PD-1 inhibition and cancer therapy

Binding of the PD-1/PD-L1 ligand-receptor activates a signaling pathway that downregulates the inflammation response and therefore controls T-cell responses, to prevent exceeding immunereactions (Kythreotou et al. 2018; Wei et al. 2018). PD-1 regulates the activation of T-Lymphocytes through interaction with its ligands PD-L1 and PD-L2 (Freeman et al. 2000). PD-1 is expressed on T and B lymphocytes upon activation (Agata et al. 1996). The ligands (PD-L1 and PD-L2) are broadly expressed in non-lymphoid tissues, and therefore PD-1 reduces mainly the T-cell activation in the periphery (Keir et al. 2006). After binding of its ligands, PD-1 transmits a negative costimulatory signal via the tyrosine phosphatase SHP2 in order to suppress T-cell activation (Sun et al. 2018; Wei et al. 2018). Thus, the PD-1/PD-L1

[1] *The term "histology or tumor agnostic" was and is still often used for description. 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. Currently, pure histology agnostic trials do not exist, although there are clinical trials that have been opened across tumor types (Lacombe et al. 2014). Therefore, the term tumor agnostic is not used in this master thesis and the term histology independent is used instead.*

axis is a central pathway to maintain immune tolerance and for the prevention of autoimmune reactions, but additionally the PD-1/PD-L1 interaction is also responsible for the balance between tumor immune surveillance and immune resistance (Hirano et al. 2005; Ribas 2015) . Chapter 2.2 already shortly introduced the discovery of cancer therapy by inhibition of negative immune regulation as a milestone in the therapeutic approach to cancer treatment. The EMA approved the first PD-1/PD-L1 inhibitors (Nivolumab, Opdivo and Pembrolizumab, Keytruda) in 2015 for the treatment of advanced melanoma. Multiple type-II variations for other indications have followed, and to date the European Commission has already approved six different PD-1 or PD-L1 inhibitors (Nivolumab, Pembrolizumab , Atezolizumab, Durvalumab, Avelumab, Cemiplimab). The pioneering research on PD-1 and PD-L1, which marks the beginning of the new era of cancer immunotherapy, was awarded with the Nobel Prize in Physiology or Medicine in 2018 to James P. Allison and Tasuku Honjo.

Based on the mechanism described above, PD-1/PD-L1 inhibitors block the negative immune-regulatory signal pathways (Figure 4). PD-1/PD-L1 inhibitors have been tested in a variety of tumor indications and demonstrate potent and exceptionally durable anti-tumor effects in refractory tumors (SmPC Imfinzi; SmPC Keytruda; SmPC Tecentriq; SmPC Opdivo; SmPC Bavencio)

Biomarkers

Despite exceptionally durable responses observed in patients treated with PD-1/PD-L1 inhibitors, the primary problem for the clinical practice with PD-1/PD-1 inhibitors are the low response rates in unselected (overall) populations. To achieve higher overall response and overall survival (OS) rates, PD-L1 expression on tumor cells and/or immune cells in the tumor microenvironment is commonly used as biomarker. But the results in different indications with different antibodies do not show a homogeneous picture (SmPC Imfinzi; SmPC Bavencio; SmPC Tecentriq; SmPC Keytruda; SmPC Opdivo). In some indications, PD-L1, as a predictive biomarker, has not been established at all (MCC, Bavencio; SCLC Tecentriq). In some indications, survival benefit was observed regardless of whether patients had tumors that were tested PD-L1 negative or PD-L1 positive (Melanoma, Opdivo: NSCLC (second-line), Keytruda). In some indications (NSCLC (first line), for example), the efficacy of anti PD-1/PD-L1 inhibitors in patients with PD-L1 negative tumors has not been established and, as a consequence, the antibodies were approved for the treatment of tumors with moderate or high PD-L1 expression. In general, PD-L1 as biomarker helps to maximize

the treatment effect of PD-1/PD-L1 inhibitors, but effects do not seem very consistent across indications, therefore PD-L1 cannot be used as biomarker to be providing a basis for histology independent indications (Camarero 2017).

Tumor mutational burden (TMB) was another promising biomarker for a histology independent approach. TMB leads to a high amount of mutations with increased potentiality of neo-antigen expression. This neo-antigen expression could lead to elevated immunogenicity with activated immune cells in the tumor microenvironment (Figure 4) (Yi et al. 2018). In the context of anti-PD-1/PD-L1 treatment , an activated microenvironment was shown to be a favorable prognostic factor (Jiang et al. 2019). Using Next-Generation Sequencing (NGS), it is possible to profile nonsynonymous somatic mutations of tumor cells (Goodman et al. 2017; Yi et al. 2018). The level of (TMB is expressed as mutations per megabase. A meta-analysis with 27 tumor types demonstrated a significant correlation between TMB and objective response rate (ORR; correlation coefficient: 0.74) in patients treated with PD-1/PD-L1 inhibitors (Yarchoan et al. 2017; Yi et al. 2018). However, the adequacy of TMB as biomarker is not confirmed by prospective data from clinical trials so far. TMB failed to be effective as a predictive biomarker to chemotherapy plus checkpoint inhibitor (Keytruda) or chemotherapy alone as first-line treatment for nonsquamous non–small cell lung cancer (NSCLC) in two different exploratory analyses of KEYNOTE trials, KEYNOTE 21 and 189 (Garassino 2019; Langer 2019). In addition, Bristol-Myers Squibb recently withdrew their supplemental biologics license application to the FDA for the combination of nivolumab and ipilimumab for the treatment of patients with advanced NSCLC with high TMB (BMS 2018, 2019).

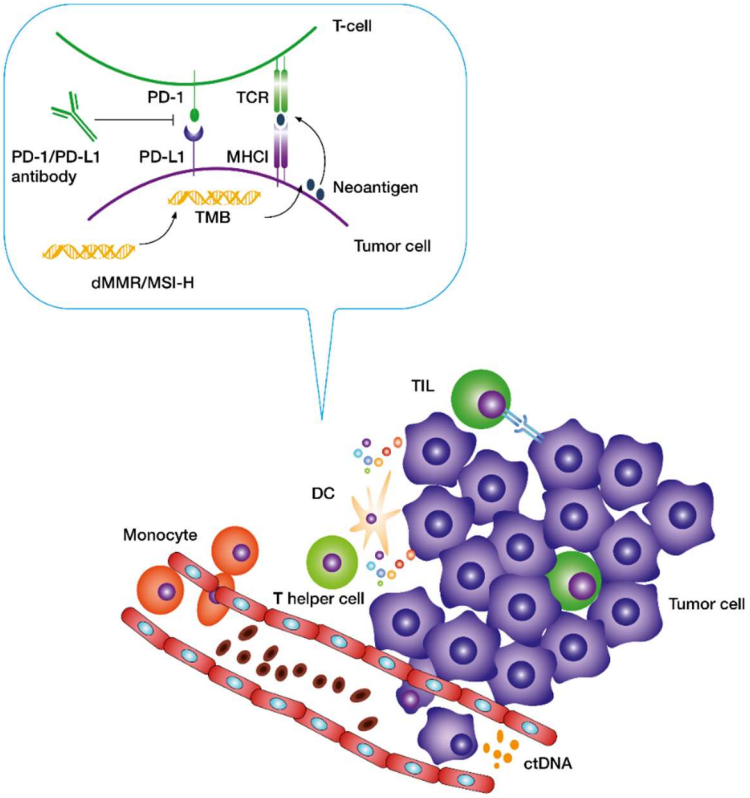

Figure 4 Mechanisms of main biomarkers predicting efficacy of PD-1/PD-L1 inhibitors from (Yi et al. 2018). PD-L1 status reflects the level of adaptive immune resistance. PD-1/PD-L1 receptors are targeted by the PD-1/PD-L1 inhibitors. Mismatch repair deficiency (dMMR) and high microsatellite instability (MSI-H) correlates strongly with high tumor mutational burden (TMB) .TMB enhances the immunogenicity via neo-antigen expression.

MSI-H cancer and Immunotherapy

One mechanism leading to high TMB is the microsatellite instability (MSI-H) phenotype. As consequence, MSI-H correlates strongly with high TMB (Figure 4).

Tumors with the MSI-high phenotype normally have a deficient mismatch repair system (dMMR). The mismatch repair system is involved in fixing base-base mismatch, insertion, and deletion defects during DNA replication. Members belonging to the MMR system, including MutL homolog 1 (MLH1), MutS protein homolog 2 (MSH2), MutS homolog 6 (MSH6), and PMS1 homolog 2 (PMS2), contribute to maintaining genomic stability (Yi et al. 2018). dMMR refers to deficiency in proteins MSH2, MSH6, MLH1, PMS2, whose depletion leads to oncogenesis, especially in gastrointestinal cancers (Yuza et al. 2017). dMMR promotes the accumulation of mutations, which promotes the production of potential neo-

antigens. A high concordance between dMMR and the MSI–H phenotype could be demonstrated (Yamashita et al. 2018). In fact, the primary reason of MSI-H in colorectal cancer is the epigenetic or genetic variation of the MMR system (Puccini et al. 2017). The MSI-H/dMMR tumors genome comprises thousands of mutations (i.e., high TMB; hypermutated phenotype).

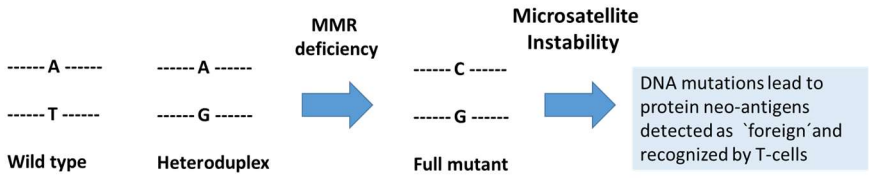

Figure 5 Schematic figure of the mismatch repair pathway. A base mismatch is recognized by mismatch repair proteins (MSH2/MSH6 and PMS2/MLH1). The mismatch on the newly synthesized strand is excised and the correct nucleotides are synthesized. Finally, the DNA strands are ligated.

The underlying hypothesis for the studies in MSI-H/dMMR cancer was that anti PD-1/PD-L1 antibodies are effective in the treatment of MSI-H cancers, regardless of tumor histology, because MSI-H/dMMR cancer is associated with a high TMB (hypermutated phenotype) leading to high neo-antigen expression (Figure 6). Subsequently, the high neo-antigen expression leads to autologous immune recognition of the cancer cells. As described in Chapter 2, this autologous immune recognition is inhibited by PD-1. Therefore, blockingthe PD-1 signal pathway on tumor neo-antigen-specific T cells with anti PD-1/PD-L1 antibodies can reactivate immune responses of these T-cells.

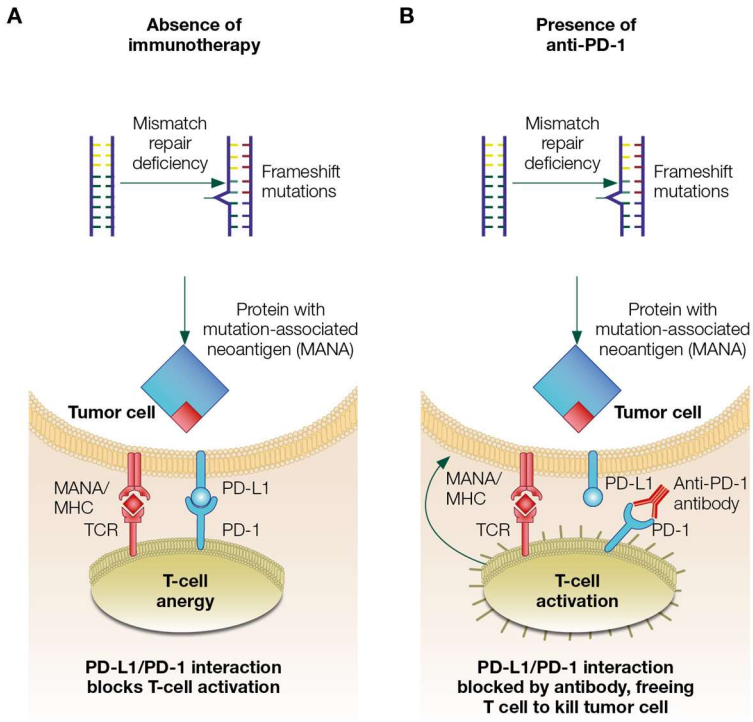

Figure 6 Activation of immune response depending on elevated levels of mutation-associated neo-antigens (from (Dudley et al. 2016)

Clinical detection of MSI-H

MSI-H identifies a common genetic abnormality across different tumor types, nevertheless cancers that are more likely to be MSI-H (i.e., prevalence ~5% or higher) include those of the gastrointestinal and gynecological organ systems (Figure 7).

A deficient mismatch repair system is associated with a favorable prognosis in early stage colorectal cancer (CRC); however, patients with advanced or metastatic MSI-H/dMMR disease tend to have a poor prognosis, but data are still limited (Venderbosch et al. 2014). These observations have led to the recommendation for a universal screening of all newly diagnosed colorectal cancers for dMMR and MSI status, and increasing evidence supports the evaluation of MSI in all human tumors regardless of the cancer tissue of origin (Eriksson et al. 2019).

Multiple laboratory tests are available to evaluate the status of the mismatch repair pathway. These tests include immunohistochemistry (IHC) staining for 4 mismatch repair proteins (MLH1, PMS2, MSH2 and MSH6), PCR-based microsatellite instability analysis, MLH1 promoter methylation analysis, and BRAF sequencing. In addition, several reliable NGS methods are published (Nowak et al. 2017). These tests are performed directly on tumor samples and have prognostic and therapeutic implications for nearly all patients with colorectal carcinoma (Setaffy und Langner 2015).

Patients with advanced MSI-H/dMMR cancers were usually treated with general standard-of-care therapies. Poor clinical outcomes include low overall response rates (ORRs) and brief duration of responses (DORs), and significant toxicity in the second-line and later settings (high unmet medical need).

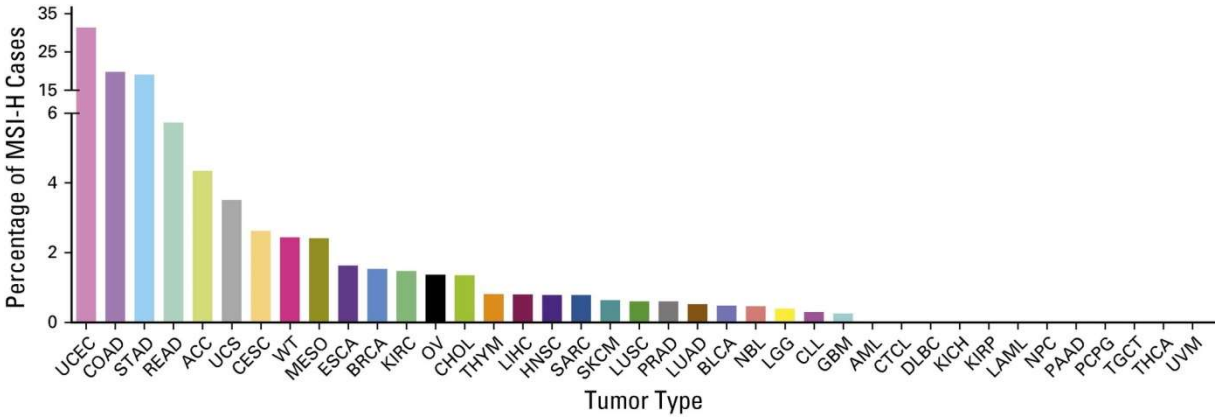

Figure 7 Prevalence of MSI-H in different cancer types (from (Bonneville et al. 2017) *ACC, adrenocortical carcinoma; AML, pediatric acute myeloid leukemia (TARGET); BLCA, bladder carcinoma; BRCA, breast carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; CTCL, cutaneous T-cell lymphoma; DLBC, diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia (TCGA); LGG, lower-grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; NBL, pediatric neuroblastoma; NPC, nasopharyngeal carcinoma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectal adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TCGT, testicular germ cell tumor; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma; WT, Wilms tumor*

Data supporting pembrolizumab approval

The first approval of a histology independent indication was based on data from 149 patients with MSI-H/dMMR solid tumor generated in altogether five multicenter, single-group clinical trials. The majority of patients (84% for colorectal cancer and 53% for other tumors) had received two or more therapies for advanced/metastatic disease. Table 1 lists the different trials.

One has to consider that also data from retrospectively identified patients from KEYNOTE-12 and KEYNOTE-28, two exploratory basket trials, were included.

Study	Design	Number	Prior treatments
KEYNOTE-016	• prospective, investigator-initiated • patients with CRC and other tumors (basket)	28 CRC 30 non-CRC	• CRC: ≥ 2 prior regimens • Non-CRC: ≥1 prior regimen
KEYNOTE-164	• prospective, international • CRC	61	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR
KEYNOTE-012	retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer	6	≥1 prior regimen
KEYNOTE-028	retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC	5	≥1 prior regimen
KEYNOTE-158	• prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC • retrospectively identified patients *who were enrolled in specific rare tumor non-CRC cohorts*	19	1 prior regimen

Table 1 Data supporting pembrolizumab approval in MSI-H

The pivotal study for this histology independent indication was Keynote-16: a Phase II basket study in patients with MSI-H/dMMR solid tumors. Keynote-16 was a three-basket study with two cohorts of colorectal cancer: Cohort A MSI-H/dMMR n=40 and Cohort B MSS/pMMR n= 25. Cohort C consists of MSI-H/dMMR non-colorectal cancers (n=40). The analysis approach was to pool across the trials and across histologies(indications) to examine consistency of effect. The primary efficacy endpoint across all trials was ORR and the key secondary efficacy endpoint DOR. The efficacy results are summarized in Table 2. :

	N=149
ORR (95% CI)	39.6% (31.7, 47.9)
Complete response rate CR	7.4%
Partial response rate PR	32,2%
DOR Median in months (range)	NR (1.6+, 22.7+)
% with duration ≥6 months	78%

. NR=not reached

Table 2 Efficacy results for patients with MSI-H/dMMR cancer (Keytruda prescribing information USFDA)

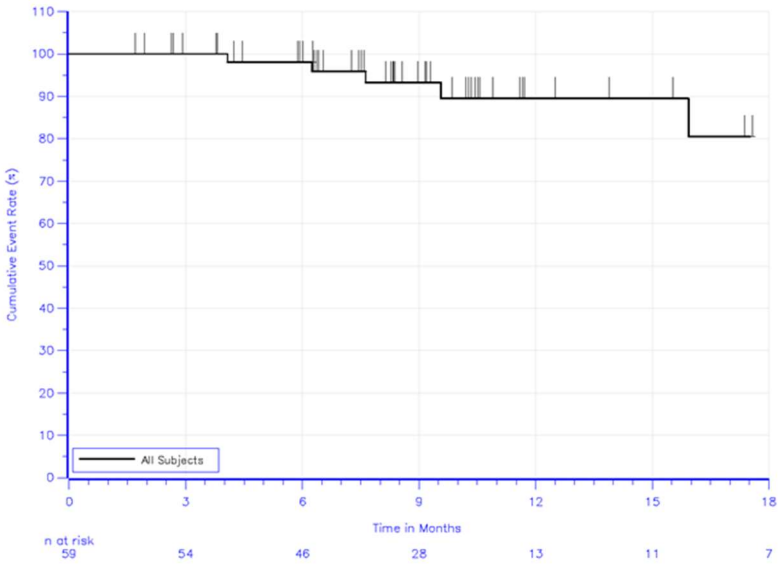

Figure 8 Kaplan-Meier estimates of response duration in subjects with confirmed response based on IRC assessment per RECIST 1.1 / (MK3475 200mg Q3W) (ASaT population)

Looking at the responses by tumor type in 15 different (Table 3), one could conclude that the responses are generally consistent across the different indications, however, nine of these tumor types are only represented by 1 or 2 patients. ORR was similar regardless of the origin (36% in colorectal cancer vs. 46% in 14 other cancer types). Almost 40% responders had a durable response (Figure 8).

	N	Objective response rate n (%) 95% CI
CRC	90	32(36%) (26%, 46%)
Non-CRC	59	27 (46%) (33%, 59%)
Endometrial cancer	14	5 (36%) (13%, 65%)
Biliary cancer	11	3 (27%) (6%, 61%)
Gastric or Gejunction cancer	9	5 (56%) (21%, 86%)
Pancreatic cancer	6	5 (83%) (36%, 100%)
Small intestinal cancer	8	3 (38%) (9%, 76%)
Breast cancer	2	PR,PR
Prostate cancer	2	PR,SD
Bladder cancer	1	NE
Esophageal cancer	1	PR
Sarcoma	1	PD
Thyrioid cancer	1	NE
Retroperitoneal adenocarcinoma	1	PR
Small cell lung cancer	1	CR
Renal cell cancer	1	PD

Table 3 Pembrolizumab in MSI-H/dMMR solid tumors: response by tumor type; PR=partial response; SD=stable disease; CR=complete response; NE=not evaluable

Finally, the FDA considered the data sufficient for an approval. In May 2017, the FDA granted accelerated approval of pembrolizumab for *MSI-H or dMMR Patients Whose Disease Has Progressed Following Prior Treatment and Who Have No Satisfactory Alternative Treatment Options, Which Includes Patients with Colorectal Cancer That Has Progressed Following Treatment with Fluoropyrimidine, Oxaliplatin, and Irinotecan.*

This paradigm change was justified by the following arguments. First, the FDA considered the scientific and biological rationale as strong. Second, the clinical data were classified as compelling. Third, it was approved for patients without available therapies, therefore a high unmet medical need existed. In addition, there is an extensive history of clinical use for pembrolizumab and the safety profile is well established and manageable.

So far, this histology independent indication was not submitted as a type II variation to the EMA. The potential reasons for this will be listed and discussed in Chapter 4.

Post-approval challenges

To put it bluntly, the histology independent development strategy pembrolizumab was settled by chance. The indication pembrolizumab for MSI-H or dMMR patients has two major advantages. As already mentioned, the first advantage is that pembrolizumab was already approved for different indications and the safety profile could be regarded as established and manageable compared to 2nd or 3rd line chemotherapy regimens (Boutros et al. 2016). The second advantage is the biomarker. Multiple validated laboratory tests are available and are being routinely used in clinical practice. In addition, already pediatric formulations were developed.

Nevertheless, there remain some challenges. The biological rationale was built on the theory that MSI-H cancer is associated with a high TMB (hypermutated phenotype) that leads to high neo-antigen expression. Thus, TMB was for a time the biomarker of choice in several pivotal trials ((Roche 2018)B-F1RST (NCT02848651, Keynote-021). Nevertheless, as described above, to date the utility of TMB as biomarker could not be verified by prospective data from clinical trials.

The indication was approved via accelerated approval; therefore, continued approval of pembrolizumab for this indication will rely on the final results of clinical benefit in the ongoing confirmatory trials. Updated phase II data from Keynote 164 (CRC, Table 1) showed that the ORR was 33% (95% Confidence Interval [CI], 21%–46%) in cohort A, whose patients had received two or more previous lines of therapy (3rd line +). The ORR in cohort B (2nd line + patients)was 33% (95% CI, 22%–46%). The median DOR was not reached in both cohorts (Le et al. 2020) . A phase III study (KEYNOTE-177; ClinicalTrials.gov identifier: NCT02563002), which is evaluating the antitumor activity of first-line pembrolizumab compared with standard chemotherapy for patients with MSI-H/dMMR metastatic CRC, is ongoing. In addition, some promising data from Nivolumab/Opdivo advanced CRC/MSI-H/dMMR were recently published (Overman et al. 2017). In short, for metastatic CRC there are good prospects that final results will support an indication. However, updated data from the tumor-agnostic phase II basket trials (KEYNOTE-158) could be discussed controversially. In KEYNOTE-158, a total of 233 patients with one of 27 different advanced-stage MSI-H/dMMR nonCRC solid tumor types were included. At a median follow-up duration of 13.4 months, 33.4% of patients had an objective response; however, ORRs varied substantially when stratified by primary tumor histology. Among tumor types for which >10 patients were included, those with endometrial cancer had an ORR of 57.1%, compared with 18.2% for

pancreatic cancer and 0% for CNS cancers. These lower ORRs were reflected in median overall survival (OS) durations of 4.0 months and 5.6 months among patients with pancreatic cancer or glioblastoma, respectively. By contrast, median OS was not reached in the endometrial, gastric, ovarian, or small intestine cancer subgroups and was 24.3 months among patients with cholangiocarcinoma (Marabelle et al. 2020; Sidaway 2019). These data indeed challenge the idea that MSI-H dMMR can be applied to all solid tumor types regardless of primary histology.

3.2. The first histology independent indication approved by the EMA - Vitrakvi in NTRK fusion solid tumors

NTRK gene fusion and cancer development

Chromosomal translocations (e.g. gene fusions) are familiar oncogenic drivers. Therefore, targeting gene fusions has become an extensively studies treatment strategy in the last years (Takeuchi et al. 2012; Dupain et al. 2017; Paratala et al. 2018; Stransky et al. 2014). In general, the neurotrophic receptor kinase (NTRK) family act in the nervous system where NTRK regulate pain, proprioception, appetite, and memory (Kaplan et al. 1991). The NTRK genes NTRK1, NTRK2, and NTRK3 encode for the tropomyosin receptor kinase (TRK) proteins TRKA, TRKB, and TRKC, respectively. These kinases are single-pass transmembrane proteins binding with high affinity to the neurotrophins NGF, BDNF, and NT3 (Ricciuti et al. 2019). In normal signaling processes, neurotrophin ligand binding to the extracellular TRK domain leads to receptor dimerization and subsequent activation of various downstream pathways, including Ras–Raf–MAPK, PI3K–Akt–mTOR and PLCc–PKC (Ricciuti et al. 2019). TRK activation therefore strongly depends on ligand-binding.

The first report of an NTRK gene fusion was described in colorectal cancer in 1986 (Martin-Zanca et al. 1986; Martin-Zanca et al. 1989). Subsequently, somatic fusion events involving the NTRK1, NTRK2 or NTRK3 genes (NTRK gene fusions) could be identified across multiple cancers in children and adults (Vaishnavi et al. 2015). Typically, the 5′ region of a gene that is expressed by the tumor cell progenitor is joined with the 3′ region of one of the NTRK genes. The majority of characterized NTRK fusions contain the 5′ partner gene sequence encoding for one or more dimerization domains, which is predicted to result in constitutively active, ligand independent downstream signaling (Vaishnavi et al. 2015). In

addition to gene fusion events, somatic point mutations of NTRK genes have also been identified in human tumors (Ding et al. 2008; Kummar and Lassen 2018).

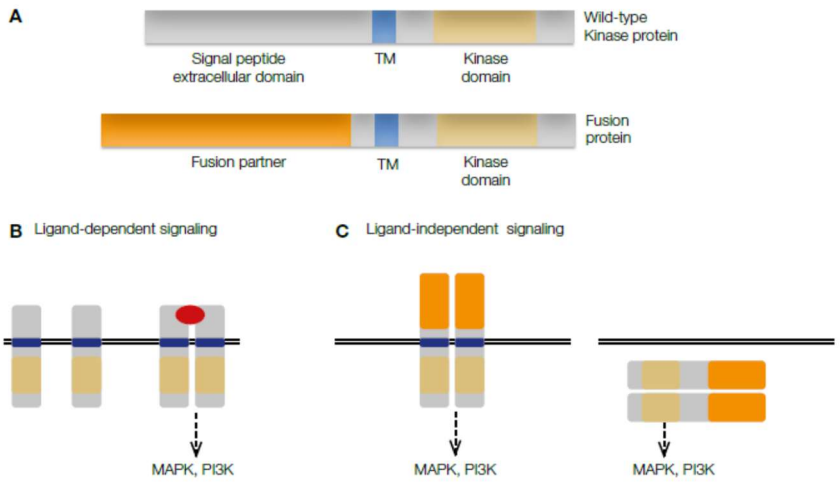

Figure 9 Mechanism of NTRK fusion (from (Farago 2017)

Clinical detection of NTRK gene fusion

No clinical (prognostic) characteristics have been associated with NTRK alterations so far. As a result, there is no routine laboratory test available and the FDA has granted approval without companion diagnostic test. A wide array of different techniques can be employed in the detection of NTRK1/2/3 fusions (Marchiò et al. 2019). Gene fusions have been assayed historically by fluorescence in situ hybridization (FISH). Reverse transcriptase (RT)-PCR, and FISH assays for the detection of the ETV6–NTRK3 fusion gene are commercially available. In the study protocols involving larotrectinib and other TRK inhibitors the use of either NGS or FISH was allowed and generally, NGS-based RNA and DNA approaches have used (CHMP 2019; Drilon et al. 2018). Using NGS has advantage that multiple genes can be tested simultaneously with a limited amount of tissue, which is extremely valuable in tumors where NTRK alterations are very rare and other molecular therapeutic targets might be present (eg .NSCLC) (Ricciuti et al. 2019). However, one should consider that often NGS

platforms are not designed to detect NTRK fusions, and it has been observed that, due to large intronic regions in the NTRK2 and NTRK3 genes, DNA-based NGS assays might be unable to detect some fusions (Ricciuti et al. 2019).

FISH and RT PCR are faster and are less expensive, compared to NGS. In addition, IHC is potentially able to detect TRK protein overexpression, an indirect proof of NTRK fusions. Two different case series employing IHC with a pan-TRK antibody in different solid tumors showed excellent concordance with NTRK fusions, with high sensitivity (95%–97%) and specificity (97%–100%) (Hechtman et al. 2017).

Prevalence of NTRK gene fusion

NTRK fusions promoting oncogene addiction and occur in estimated 1% of all solid tumors (Ricciuti et al. 2019; Vaishnavi et al. 2015). The concept of oncogene addiction postulates that some tumors rely on one single dominant oncogene for growth and survival, so that inhibition of this specific oncogene is sufficient to stop cancer growth (Torti and Trusolino 2011). NTRK gene fusions have been detected in many prevalent tumors, e.g., lung cancer, breast cancer, colorectal cancer, thyroid cancer, sarcoma. Nevertheless, they occur in these indications at very low frequencies. In very rare tumors, like infantile fibrosarcoma (IFS), secretory/juvenile breast cancer, and mammary analogue secretory cancer of the salivary glands, NTRK gene fusions are the defining genetic feature of these tumor types, occurring in 93% to 100% of tumors ((Kummar and Lassen 2018; Vaishnavi et al. 2015) (Figure 10).

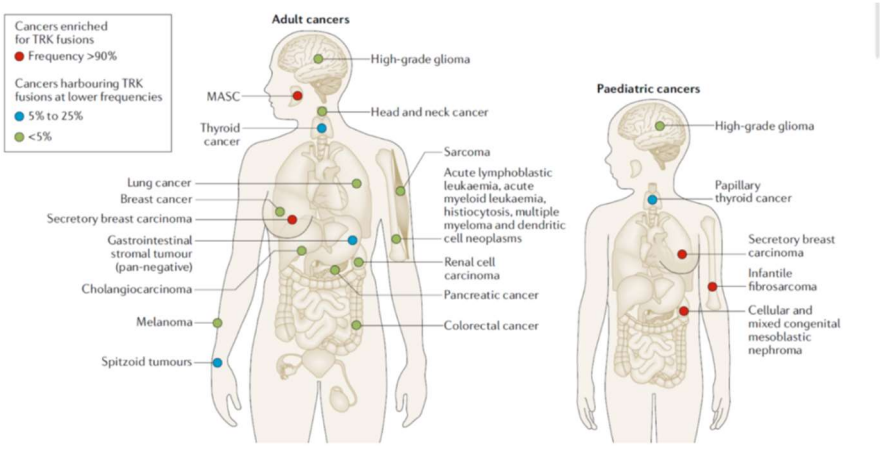

Figure 10: TRK fusions in different cancer types from (Cocco et al. 2018)

Data supporting larotrectinib approval in the US and in the EU

The first approval of larotrectinib was based on pooled interim data from three currently ongoing trials: one dose-finding phase I/II study in adults with or without NTRK gene fusions (LOXO-TRK-14001), a phase II basket trial in adolescent and adult patients with NTRK fusions (LOXO-TRK-15002), and a dose-finding phase I/II study in paediatric patients with NTRK fusions (LOXO-TRK-15003) were included in the pooled dataset. All studies are open-label without parallel comparator (Table 4).

Study	Design	Number	Endpoints
LOXO-TRK-14001 8 sites US	Phase 1, open-label, 3 + 3 dose escalation study with expansion phase in patients with NTRK gene fusions only	8	Primary : Safety, MTD, RP2D. Secondary: ORR (CR + PR) Duration of response
LOXO-TRK-15002 21 sites US, EU, Asia	Phase 2, open-label "basket" study	63 Non-small cell lung cancer 6 Thyroid 9 Sarcoma 12 Colorectal 6 Salivary gland14 Biliary 2 Primary CNS 3 Others 11	Primary :ORR (CR + PR) Secondary: BOR, DOR, PFS, OS, Quality of life Safety
LOXO-TRK-15003 17 sites US, EU, Australia	Phase 1, open-label, dose escalation study Phase 2, single arm open-label study in IFS, other extracranial solid tumours, and primary CNS tumours	43	Phase 1 Primary: Safety, DLT Secondary: BOR, DOR Quality of life Safety Phase 2 Primary: ORR Secondary: DOR, Safety

Table 4 List of studies supporting larotrectinib approval in patients with NTRK fusion tumors

The FDA approval (November 2018) was based on the first 55 patients enrolled across the three trials (PAS). The European approval (September 2019) was based on an extended efficacy primary analysis set (ePAS2), which consists of 93 patients from the studies 14001, 15002 and 15003.

The ORR by IRC was 72% (n=67/93, 95% CI: 62, 81%), and ORR by investigator assessment (INV) was 80%. The single-arm, open-label setting allowing for potential investigator bias is noted. The agreement rate between IRC and INV assessments was 90% (Table 5).

	N=55 (PAS)	N=93 (ePAS2)
ORR (95% CI)	75% (61, 85)	72% (62, 81)
Complete response rate CR	22%	16%
Partial response rate PR	53%	55%
DOR Median in months (range)	NR (1.6+, 33,2+)	NR (0.9+,33,2+)
% with duration ≥6 months	73%	88%

Table 5 Efficacy results for patients with NTRK fusion genes (CHMP 2019)

The ORRs per NTRK fusion type were 63% (95% CI: 47, 78%) for NTRK1 (n=41), 33% (95% CI: 1, 91%) for NTRK2 (n=3), and 82% (95% CI: 68, 91%) for NTRK3 (n=49).

Figure 11 provides an overview of the ORRSacross the different tumor types studied. The ORR was highly variable across the studied tumor types, from 0% in single patients with breast cancer, cholangiocarcinoma and pancreatic cancer to 100% in the 4 patients with GIST. Tumor types where NTRK gene fusions are characteristic (or even considered pathognomonic) of the disease, such as IFS 9n=13), Salivary gland/MASC (n=10), and congenital mesoblastic nephroma (n=1), tended to have higher ORR (92%, 80%, and 100%, respectively).

	N	Objective response rate (%)	95% CI
Soft tissue sarcoma	21	81	(58, 95)
Salivary gland	17	88	(64, 99)
Infantile fibrosarcoma	13	92	(64, 100)
Thyroid	10	70	(35, 93)
Lung cancer	7	71	(29, 96)
Melanoma	7	43	(10, 82)
Colon cancer	6	33	(4, 78)
GIST	4	100	(40, 100)
Bone sarcoma	2	50	(1, 99)
Cholangiocarcinoma	2	NE,SD	
Congenital mesoblastic nephroma	1	100	
Appendix	1	SD	
Breast cancer	1	PD	
Pancreas	1	SD	

Figure 11 ORR rates by tumor type

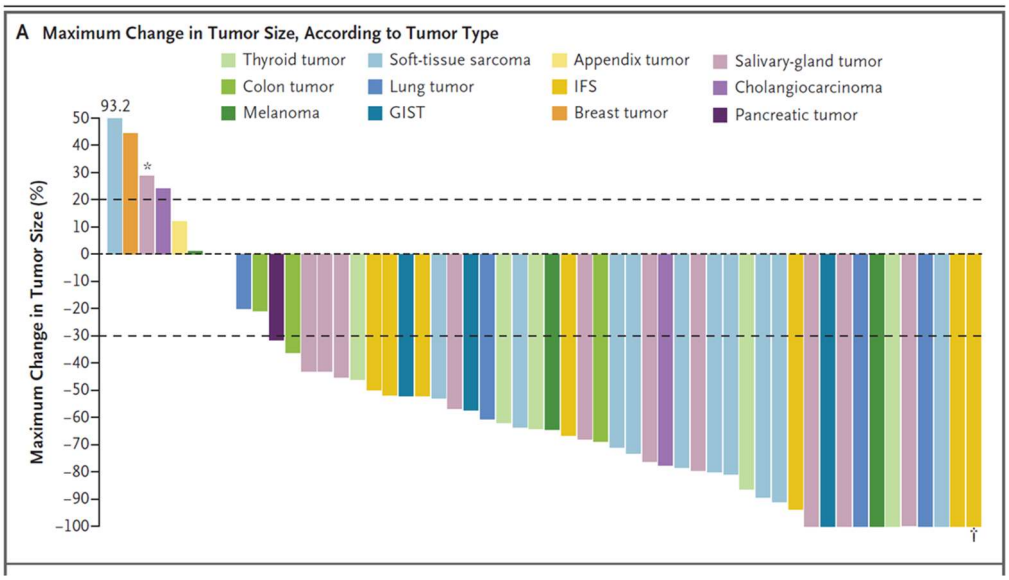

Figure 12 Maximum change in tumor size, according to tumor type from (Drilon et al. 2018)

In Study 14001; 62 patients without any NTRK fusion were included, only 1 (2%) PR (seen in a patient with a total tumor burden of 11 mm); and no CR were observed in patients with TRK fusion-negative tumors (n=62). No responses in NTRK fusion-negative patients provide clinical support of the proposed mechanism of action and the selectivity of the effect to patients harboring the drug target.

In comparison with conventional chemotherapies, and considering that larotrectinib is given in a later line where lower efficacy is generally expected, the larotrectinib ORR and PFS range seem overall favorable or at least comparable, although the data are far from comprehensive.

Regarding the overall safety perspective (adult patients and pediatric patients), larotrectinib appears reasonably tolerable and the toxicity is considered to be manageable with appropriate risk minimization measures, as evidenced by the low treatment discontinuation rate.

The FDA approved VITRAKVI with the following indication statement:

"VITRAKVI is a kinase inhibitor indicated for the treatment of ***adult and pediatric*** patients with **solid tumors** that:

- **have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion** without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- **have no satisfactory alternative treatments** or that have progressed following treatment".

The indication statement in the European SmPC differs only slightly:

"VITRAKVI as monotherapy is indicated for the treatment of **adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion**,

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
- **who have no satisfactory treatment options** (see sections 4.4 and 5.1)".

The Summary of product characteristics (SmPC) does not mention the necessity of the absence of a known acquired resistance mutation, because secondary NTRK mutations altering the kinase domain of TRK thus appear to be the major acquired resistance mechanism to larotrectinib (CHMP 2019). Information has been included in the SmPC. Primary and secondary resistance mechanism have to be investigated post-approval.

Larotrectinib is the second new cancer therapy that can be used for treatment of any kind of tumor that has a specific characteristic, as opposed to where in the body the tumor originated.

The Committee for Medicinal Products for Human Use (CHMP) justified this paradigm change with the following conclusion: "*Overall, the efficacy estimates available today may be considered outstanding in this generally late stage disease setting. The main issue regarding the efficacy is the robustness and generalizability of these estimates. While it is likely that the estimates may change, possibly in a negative direction, the present outstanding estimates provide some reassurance as to the presence of a large treatment benefit. Important quantitative interactions between treatment and tumor type will be further explored"* (CHMP 2019).

Nonetheless, available data were considered as non-comprehensive and a conditional approval was recommended.

Post-approval challenges

The approval of larotrectinib was a conditional marketing authorization and pursuant to Article 14-a of Regulation (EC) No 726/2004, the Marketing Authorization Holder (MAH) should submit, in order to fulfil a comprehensive data package, a pooled analysis for the increased sample size (additional 200 patients) including the final report of study LOXO-TRK-15002 (NAVIGATE) and LOXO-TRK-15003 (SCOUT) with 5 year follow-up data. The CHMP claimed the need to provide a more precise estimate of efficacy in the common cancers where NTRK fusions are rare (lung cancer, colorectal cancer, melanoma and non-secretory breast cancer), based on lower available efficacy estimates in such patients compared to those seen in rare cancers where NTRK-fusions are common or pathognomonic.

The CHMP also expressed his concerns regarding that the relationship between biomarker and response may be abolished by tissue-specific bypass mechanisms and, as a consequence, the presence of NTRK fusions in a given histology is not necessarily a predictor for larotrectinib activity. Resistance mechanisms should be further investigated.

In order to further confirm the appropriate dose recommended in pediatric patients, the MAH should submit an updated pop PK model based on additional PK sampling in patients aged 1 month to 6 years from study LOXO-TRK-15003 (SCOUT).

The landmark approval of larotrectinib has prompted an urgent need to define the routine diagnostic testing to identify gene fusions as a companion diagnostic method to support

clinical decision in this context. The different techniques were described above. In a few specific histologies, namely secretory carcinoma of the breast and of the salivary glands, congenital fibrosarcoma and cellular mesoblastic nephroma, NTRK fusions can be detected at a very high frequency, and for those patients it should be recommended that NTRK1/2/3 fusion genes should be routinely tested with optimal approaches for the identification (FISH, RT-PCR and RNA- and DNA-based NGS assays).

Nevertheless, for the other indications where NTRK fusions are extremely rare there remain many pitfalls to discuss. Efficiency and cost challenges should be considered with regards to the definition of the population that should be tested and with regards to the method which should be applied (please refer to Chapter 4.4)

4. Regulatory considerations

4.1. Basic requirements for a histology independent approval

Taken the scientific rationale and all relevant clinical data for both histology independent indications into consideration, one can extract the following main criteria, which could be considered as basis for the decision-making of the regulatory authority (Figure 13):

- An unmet medical need is indispensable.
- The biomarker of interest must be validated.
- The Mode of Action (MoA) must be established (preclinical data, proof of principle), and this MoA must be tumor tissue independent.
- There must be a clinical proof of principle (is a pivotal randomized study feasible?).
- The activity across different tumor types must be demonstrated.
- The clinical safety profile must be established and manageable.

The most important precondition for a histology independent indication is a real unmet medical need. In situations where the benefit/risk of a MP can be evaluated in large (or large enough) populations with standard (curative) treatment options, MPs have to be tested in RCTs. In the case of histology independent indications, clinical data are generated in basket

trials (Chapter 2). In general, basket trials are “baskets“ of multiple single arm trials (SAT). Thus, the crucial limitation of such studies is that clinical benefit is inferred from anti-tumoral activity in combination with a non-comparative assessment of safety and limited information on long-term efficacy. Consequently, in the general case, approvals based on SATs may be appropriate in settings where available treatment options provide limited documented clinical benefit in the target population; e.g., in late lines of treatment. Conversely, if there are established treatment options providing clinical benefit in the target population, a demonstration of relative efficacy and safety is anticipated in order to determine the impact of the test agent on PFS and OS and, at least, exclude a detrimental effect on the latter. Shortly, in contexts where available therapies have demonstrated a clinically meaningful OS gain, approvals based on SATs would generally not be appropriate.

The biomarker (target) detection must be established. For these biomarker assays, analytical, clinical and statistical validity must be sufficiently assured. The validation has to be in compliance with legal requirements for biomarkers and assays and the validation process should be finished before the initiation of the trial. (EMA/CHMP/641298/2008; EMA/CHMP/SAWP/72894/2008rev.3; EMA/CHMP/718998/2016; EMA/CHMP/800914/2016 2016).

In addition, the established MoA is extremely important. The targeted pathways must be oncogenic “drivers”, and its biological significance must be well described in the literature and by preclinical models. The MoA must be independent of tumor type/histology and other disease characteristics. As highlighted in Chapter 2, the histological context is presumably of importance, and intratumoral heterogeneity (Ciriello et al. 2013) adds to the complexity in evaluating the value of novel targeted treatments.

Regarding the proof of principle, the efficacy is generally evaluated through ORR and DoR, whereas the impact of treatment on PFS, OS and quality of life (HRQoL) cannot be isolated because of the lack of comparator arms. The lack of a randomized comparator arm also hampers the assessment of safety. In conclusion, the activity must be “outstanding” compared to available treatment options in order to demonstrate clinical benefit. The treatment benefit should be consistent across the different indications.

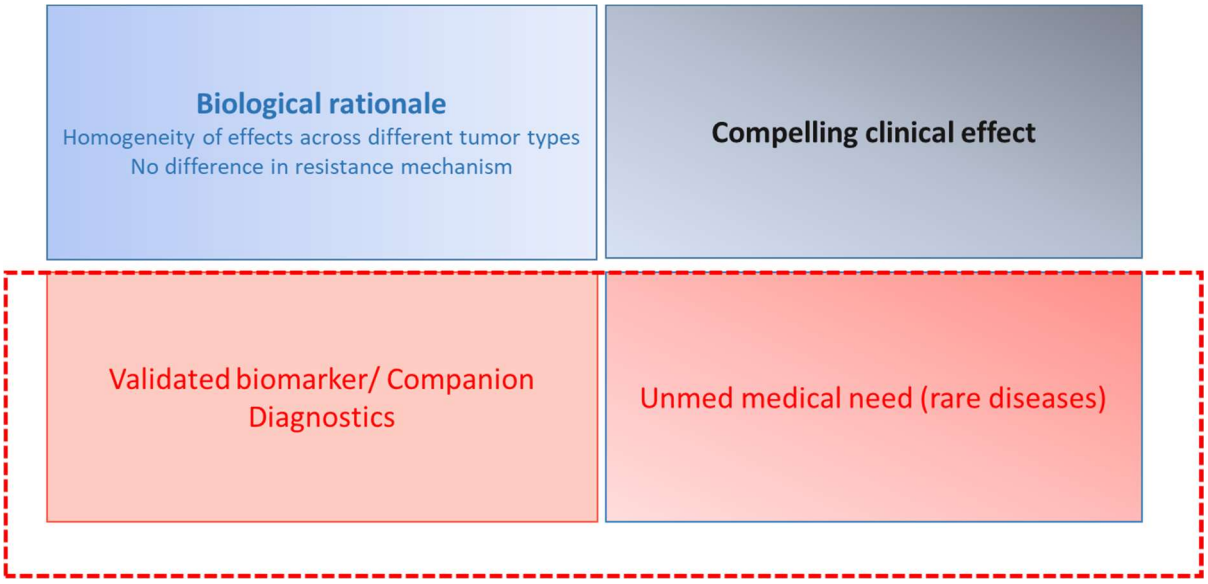

Figure 13 Considerations for histology independent development of new drugs in oncology. The basis for a histology independent indication must be the unmed medical need and the availability of a validated biomarker.

4.2. Pembrolizumab/MSI-H from a regulatory (EU) perspective

The FDA accelerated approvals of pembrolizumab for patients with microsatellite instability-high (MSI-H)/ deficient DNA mismatch repair (dMMR) metastatic or unresectable solid tumors and of nivolumab provide potentially curative options for such patients. Remarkably, this histology independent indication was not submitted as a type II variation to the EMA. The reasons could be anticipated by reviewing the available data (please refer to 3.1. and considering the discussion of the CHMP and the SAG Oncology position regarding the larotrectinib approval (CHMP 2019). It should be recognized that two of the "must" criteria for a histology independent indication are surely fulfilled, namely the unmet medical need and the validated biomarker. However, the biological rationale and the clinical data available to date should be further discussed.

It was assumed that MSI-H/dMMR is a predictive histology independent biomarker. The biological rationale was built on the theory that MSI-H/dMMR cancer is associated with a high mutational burden (hypermutated phenotype). The rationale is predicated on an indirect mechanism. Tumor mutational burden (TMB) leads to neo-antigen expression, leading to higher cancer-directed immune response, which is consequently down-regulated via PD-1/PD-L1 interaction. There are several publications either describing the role of neo-antigens

in cancer immunity (Giannakis et al. 2016) or the role of MSI-H/dMMR as a surrogate for TMB (Goodman et al. 2017). Nevertheless, the rationale for the anti-PD-1-treatment in patients with MSI-H/dMMR solid tumors was developed after findings of previous studies with PD-1 inhibitors in metastatic CRC were disappointing. Responses in the all-comer population were only rarely seen (Brahmer et al. 2012), and further interpretation of these studies revealed a high TMB as a predictive marker for response. This was the starting point for the clinical development of anti-PD-1 treatment in MSI-H/dMMR solid tumors. Unfortunately, TMB failed to prove effective as a biomarker for response to two different exploratory analyses of KEYNOTE trials (KEYNOTE 21 and 189) (Garassino 2019; Langer 2019). In addition, Bristol-Myers Squibb recently withdrew their supplemental biologics license application to the FDA for the combination of nivolumab and ipilimumab for the treatment of patients with advanced NSCLC with high TMB (BMS 2018, 2019). For NSCLC, TMB is not a predictive marker, and this is a major drawback for the theory of MSI-H/dMMR as a surrogate for TMB and as a predictive histology independent marker.

Clinical data as presented in Chapter 3.1 should be regarded as borderline for a histology independent indication. On the one hand, the safety profile is well established, and missing data from rare indications could be generated in a post-marketing setting,. On the other hand, EU regulators could indeed consider that the current dataset is too limited to support a histology independent indication. Most of the data were generated in metastatic CRC, and the relatively high amount of CRC patients included in this trial (N=90) suggests that a randomized trial is feasible in this indication. Indeed, a randomized Phase III trial (Keynote-177) on first-line pembrolizumab (Pembro) versus investigator-choice chemotherapy for MSI-H/ dMMR mCRC is currently ongoing (Diaz et al. 2018).

One additional problem is the prognostic value of MSI-H/dMMR in patients with advanced or metastatic disease. A deficient mismatch repair system is associated with a favorable prognosis in early stage CRC disease (Sinicrope and Yang 2011); however, data on patients with advanced or metastatic MSI-H/dMMR disease are still limited. Reviewing the literature, available data could not be considered sufficient to inform on the prognosis of patients with MSI-H/dMMR mCRC or define MSI-H/dMMR status as an independent prognostic factor (Venderbosch et al. 2014; Aasebø et al. 2019; Innocenti et al. 2019). For other tumor indications with MSI-H/dMMR, the prognostic relevance of MSI-H differs widely between the indications (Li et al. 2020). Therefore, ORRs generated from SAT should be regarded with caution.

	Data supporting the histology independent indication	Data arguing against the histology independent indication
Biological rationale	MSI-H/dMMR identifies a common abnormality across different tumor types	
	Hypothetical rationale: MSI-H cancer is associated with TMB and subsequently leads to high neo-antigen expression and, as a consequence, the tumor is more accessible for the immune system (Jiang et al. 2019; Dudley et al. 2016).	Indirect treatment mechanism No prospective data could be generated with TMB as biomarker so far (BMS 2018, 2019; Garassino 2019; Langer 2019).
	MSI-H is a negative prognostic marker	Data on prognostic relevance are still limited (Aasebø et al. 2019; Innocenti et al. 2019; Venderbosch et al. 2014).
Clinical data	The approval was based on 149 patients with MSI-H/dMMR tumors across the five uncontrolled, single-arm trials. ORR was similar irrespective of the origin (36% in colorectal cancer vs. 46% in 14 other cancer types). The responses were durable. Well established safety profile	RCT feasible in mCRC Data from other indications are limited (n=59) Updated data from the KEYNOTE-158 Pooled across indications ORR was 33.4%; however, ORRs varied substantially by primary tumor histology (ORR=57.1% in EC, 18.2% in PAC and 0% in CNS-tumors) (Marabelle et al. 2020; Sidaway 2019)

Table 6 Critical reflection of data regarding histology -independent indication (MSI-H/dMMR) RCT=randomized controlled trial

After the critical reflection of the data provided as a basis for this histology independent indication, it is important to reconsider one important difference between the European and the US regulations. In the EU, the conditional marketing authorization (CMA) scheme is currently limited to initial marketing authorization applications and therefore not applicable to Type II variations (e.g., for new indications). CMA in the EU is an early-access pathway for medicines that show promising therapeutic effects, but for which comprehensive data are not available (EMA/CHMP/509951/2006). A CMA must be justified and is only applicable in case of seriously debilitating or life-threatening diseases, medicinal products to be used in emergency situations or orphan medicinal products. The risk-benefit balance of the product must be positive, it must be likely that the applicant will be able to provide comprehensive data and an unmet medical need must be fulfilled (EMA/CHMP/509951/2006). In contrast, the FDA offers breakthrough designation/accelerated approval for new indications of existing products in case of high unmet medical need and/or orphan indications. As pembrolizumab was initially approved in 2015 for melanoma, a conditional approval is excluded for the MSI-H/dMMR indication. In consequence, the comprehensive data should be submitted for approval. The exploitation of comprehensive data is a major drawback in this setting.

4.3. The EMA position on larotrectinib in solid NTRK fusion cancers

Larotrectinib (Vitrakvi) is the first 'histology independent' cancer treatment recommended for approval in the EU.

The primary reasons for granting this exceptional indication are discussed in this paragraph. Considering the basic regulatory requirements for this type of indication as described in Chapter 4.1, one of the main criteria (the unmet medical need) is clearly fulfilled. All cancer types enrolled in the 3 trials supporting larotrectinib approval (Table 4) can be classified as advanced cancer that have exhausted therapeutic options. NTRK gene fusions have been identified in a wide range of prevalent tumors, but either they occur at very low frequencies in common tumors or they have high prevalence in very rare tumors. To perform randomized controlled trials (RCTs) in this setting is challenging.

The other main criterion (the validated biomarker) could be discussed. The correct detection of NTRK fusion is paramount. No companion diagnostic is available and no clear test was recommended for the clinical larotrectinib studies 14001, 15002 and 15003, which fulfilled the criteria for data pooling. Most of the tests performed were NGS-based (N = 98), while the minority were FISH-based (N = 6) and RT-PCR-based (N=1).

The biological rationale is strong. NTRK gene fusion mechanism has been extensively studied in the literature since 1986 (Martin-Zanca et al. 1986; Martin-Zanca et al. 1989), and somatic fusion events involving the NTRK1, NTRK2 or NTRK3 genes (NTRK gene fusions) have been identified across diverse cancers that occur in children and adults (Vaishnavi et al. 2015). Although NTRK fusions mechanism and the pharmacodynamics of larotrectinib are well understood, the Scientific Advisory Group (SAG) in Oncology (consulted by the CHMP during this procedure) pointed out that data do not support the hypothesis that NTRK gene fusions are universally oncogenic "drivers", independently of tumor type/histology and other disease characteristics (CHMP 2019). In addition, the association between the NTRK-fusions or the fused NTRK genes and prognosis in terms of long-term clinical outcomes is generally not well understood.

The main efficacy analysis set is the pooled ePAS2, which consists of 93 patients. The ORR by IRC was 72% (n=67/93, 95% CI: 62, 81%), and ORR by investigator assessment (INV) was 80%. The agreement rate between IRC and INV assessments was 90%. The median change in target tumor lesions sizes was a decrease of 66%. This level of pharmacodynamic activity seen was regarded as impressive (CHMP 2019). Mechanisms for primary and secondary resistance mechanisms to larotrectinib have been addressed in the SmPC, and will be further investigated in the post-authorization setting as part of the CMA conditions.

The overall toxicity of larotrectinib appears manageable with appropriate risk minimization measures as recommended in the SmPC. The safety profile is thus not considered to negatively impact the B/R balance of larotrectinib.

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	Data supporting the histology independent indication	Data arguing against the histology independent indication
Biological rationale	NTRK gene fusion mechanism has been extensively studied in literature	Association between the NTRK-fusions or the fused NTRK genes and prognosis in terms of long-term clinical outcomes is not well understood.
	NTRK gene fusion mechanism has been extensively studied in literature	For some indications, the role of NTRK fusions as oncogenic "drivers" is not properly studied and well established.
Clinical data	The approval was based on 93 patients with NTRK fusions across the three uncontrolled, single-arm trials. The ORR by IRC was 72% (n=67/93, 95% CI: 62, 81%), and ORR by investigator assessment (INV) was 80%. The agreement rate between IRC and INV assessments was 90%. The overall toxicity of larotrectinib appears manageable.	The observed objective responses rates were highly variable across the studied tumour types, from 0% ORR in single patients with breast cancer, cholangiocarcinoma and pancreatic cancer to 100% in the 4 patients with GIST tumors. Limited data set Mechanisms for primary and secondary resistance

Table 7 Critical reflection of data regarding histology independent indication (NTRK fusion)

4.4. Discussion of this paradigm shift

The biological relevance of molecular aberrations and the response to target agents can substantially differ depending on tumor type (Hierro et al. 2019). This is not only due to the difference in the prevalence of a specific target. Target expression or molecular status alone is not sufficient to predict response. The signaling pathway might play different roles in each specific histologic context and different mechanistic explanations could mediate resistances (please refer to Chapter 2). One major drawback in tumor-agnostic treatment development was the result from the VE-BASKET trial *A histology-independent, flexible, early phase II study of vemurafenib in patients with non-melanoma cancers harboring BRAF V600 mutations*. It was clearly demonstrated that although it is scientifically evident that BRAF V600 mutations are driver mutations in many cancers and effective BRAF inhibition leads to significant improvement in long-term survival in some indications, the histologic context is an important determinant of response in BRAF V600–mutated cancers. With these data in mind, the decided change operated by the FDA and the EMA seems to be remarkable.

In order to understand the motivation of the CHMP to go forward with this histology independent indication despite the fairly negative opinion expressed by the SAG Oncology, the data from both histology independent indications, Keytruda in MSI-H/dMMR tumors and Vitrakvi in NTRK-fusion tumors, should be considered. As already mentioned, the regulatory obstacle for the Keytruda approval was surely the missing CMA pathway for extensions of indications in the centralized European procedure. Nevertheless, critical reflection of data submitted to the FDA (EPAR-Keytruda; Lemery 2017) highlighted another drawback for the histology bindependent approval: the biological rationale. Compared to the strong rationale for the inhibition of NTRK fusion constant signaling, the hypothetical rationale for the PD-1/PD-L1 indirect effect in MSI-H dMMR remains borderline, and much more preclinical science is required. This is also true for larotrectinib in NTRK-fusion tumors and is underlined by the request of the CHMP to further investigate primary and secondary resistance mechanisms to larotrectinib in the post-authorization setting as part of the CMA conditions. Nevertheless, the belief in the mode of action and its independency of tumor histology was strong enough to initiate this paradigm shift. In short, the less clinical data are available, the more data gained from preclinical studies and peer reviewed literature should be submitted (Figure 14)

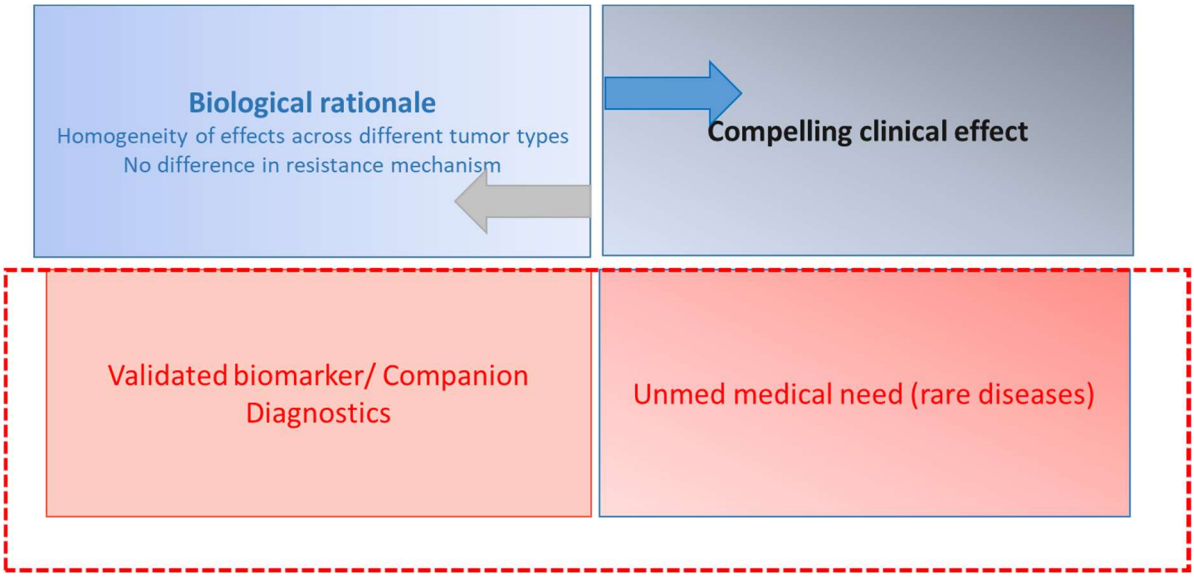

Figure 14 Considerations for histology independent development of new drugs in oncology. The stronger the biological rationale, the less could be the clinical evidence.

At the workshop on site and histology independent indications in oncology that was held in December 2017 by the EMA, the scientific director of the European Organisation for Research and Treatment of Cancer (EORTC) summarized:

“In the preparation of a histology-independent indication there is a very high need of upfront science to address the credible pathway essential to the tumor and alternative pathways and resistance mechanisms?” (Bogaerts 2017).

5. Outlook and final conclusions

5.1. Consequences on Regulatory Guidance

General considerations (the industry perspective)

After analyzing the first histology independent indications approved, the key question remains: Should a sponsor develop a medicinal product irrespective of histology? The answer is complex and it will rely on several preclinical and clinical factors. One factor is the amount and the reliability of data supporting the scientific rationale and the context of treatment in patients with different tumor types. As discussed in Chapter 3.3, the scientific rationale is strongly dependent on the target and the mechanism of action, which should be agrred by the scientific community to be independent of tumor type. This applies also to the resistance mechanisms, which should be well understood. Regarding the clinical context, all types of tumors intended to be included in the indication should be rare. In case one of the indications is not rare enough and an RCT is feasible, the european regulatory agencies (e.g. EMA) will almost certainly request data from a pivotal RCT. The FDA seems to be more flexible, as the agency approved pembrolizumab in the MSI-H/dMMR-indication despite including the CRC MSI-H/dMMR tumors. Another aspect the sponsor should consider is the large variety of standard therapies across different indications. If a medicinal product is most effective in combination regimens, histology independent development may not be appropriate. This applies mostly to earlier lines of cancer treatments. As a consequence, those histology independent therapies will be limited to patients with no alternative treatment options in later lines of treatment. In addition, for highly toxic medicinal products or in case of a poor understanding of toxicity, limited clinical data will not be acceptable for approval. Given the single-arm designs of basket trials, a tissue-agnostic development is only appropriate to be considered in situations where it is expected or likely that the drug-target interaction will demonstrate very high (outstanding!) activity across different tumor types. The majority of approved medicinal products based on ORR are “breakthrough” therapies, i.e. transformative (CHMP 2019).

The clinical data package will be most likely evaluated as non-comprehensive by the regulators and the agencies will raise conditions with the approval. Nevertheless, the postponing of efficacy data generation to the post-marketing setting (CMA) is usually not preferable. The Regulation (EC 658/2007) defines financial penalties for infringement of

certain obligations in connection with marketing authorizations granted under Regulation (EU 726/2004). In the case of infringement of specific obligations, the commission can apply a financial penalty to the marketing authorization holder, which could amount to a total of 0.5% of the turnover of the MAH in the EU in the preceding business year.

A truly histology independent indication would allow for the treatment of adult patients and children. In consequence, sponsors who are assessing the effects of a medicinal product across tumor types have to consider how they will address the needs for children with tumors possessing the respective biomarker. American regulators explicitly recommended the inclusion of adolescents (age 12-17) in disease- and target-appropriate adult oncology trials (Chuk et al. 2017). The perception of the EMA is in all likelihood similar. Considering the specific obligations (SOB) linked to the conditional approval of larotrectinib in Europe (to provide further PK data in small children and to provide long-term safety outcomes particularly in children), it is quite evident that one main focus of the regulatory agencies is to get comprehensive efficacy and safety data from children (Josephson 2019).

The last aspect and surely one of the most important to consider is that histology independent trials often start with a molecular screening phase (basket trials), and positivity to a given biomarker is often the common denominator between the different sub-studies. Accuracy of the biomarkers is the cornerstone of these design. Otherwise, false positive patients will be enrolled. As shortly addressed in Chapter 2, the companion diagnostic or, in Europe, the in vitro diagnostic (IVD) must have been fully validated before the initiation of the respective trials. As the IVD is intended to select patients and has clearly a medical purpose, it will be regulated under the scope of the new Regulation 746/2017 of the European commission (EU 746/2017). The regulation will therefore apply before Marketing Authorization and should be taken into account before clinical trial application.

To summarize, tumor type-independent development may only be applicable to drugs with high clinical response rate, in rare tumor types, with pediatric formulations available and, in addition, this should go together with a reliable assay development for the biomarker. A high risk remains with the MA-Applicant if any of the points, described above, is not sufficiently addressed.

General considerations (the regulatory perspective)

In general, with the approval of larotrectinib, the CHMP clearly stated that it is willing to prioritize cancer drugs that target tumors according to their genetic makeup rather than where

they originate in the body. The decision for approval was controversially discussed and, remarkably, the SAG Oncology explicitly indicated by consensus source that available data do not support the hypothesis that NTRK gene fusions are universally oncogenic “drivers”, independently of tumor type/histology and other disease characteristics. According to the SAG oncology statement (which was understood to be also the view of several members of the CHMP) the indication should have been restricted to several tumor indications as studied in the pivotal trial. However, the CHMP decided to move forward and granted the first histology independent indication. With this paradigm change, the CHMP has set a precedent with other novel therapies. The CHMP also clearly stated that it is willing to fast-track these histology independent drugs (in the same way as it has CAR-T cell therapies for cancer) (NHS 2019).

Thus, it appears that in case of promising targeted therapies addressing a specifically high unmet medical need (e.g. rare cancer), the clinical development will move away from strict exploratory and confirmatory phases to more seamless adaptive trial designs with conditional approval and market entry early after clinical proof-of-concept based on surrogate endpoints, such as ORR in oncology (Wegener)(Figure 15).

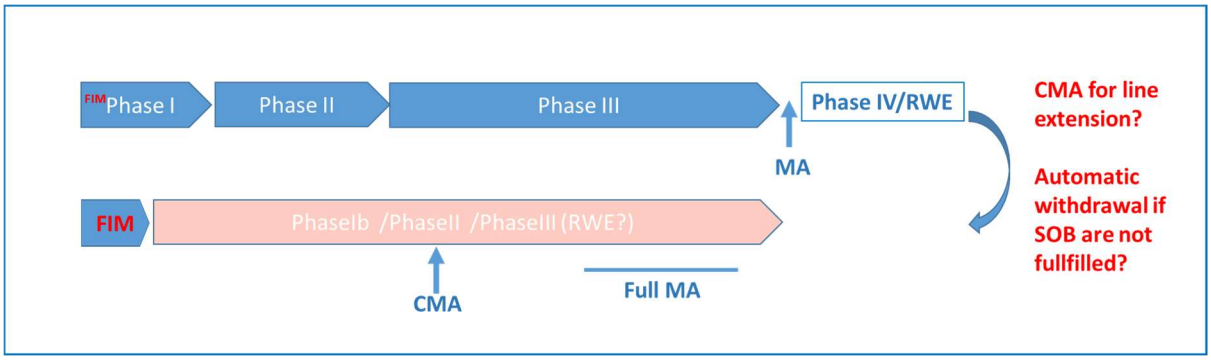

Figure 15 Schematic overview comparing classical clinical development with the adaptive scheme.

In this sense, regulatory agencies may have to consider changes in drug approval conditions, to deal with the inevitable degree of uncertainty associated with the evidence of efficacy provided from trials lacking randomization, pooling across heterogeneous populations where sometimes there is no standard-of-care or limited data on prognosis. Conditional approval translates the judgement that the magnitude of benefit-risk assessment performed by regulatory agencies is positive, but clinical evidence is incomplete. Nevertheless, there are

some challenges in EU regulatory environment, and one major drawback in Europe is the legal construction of the CMA. As already discussed above, the CMA is currently limited to initial marketing authorization applications and it is not applicable to Type II variations (EMA 2020a). For the latter, only Annex-II conditions could be applied. The legal problem for both (and particularly for the Annex-II condition) is that there is no possibility of an automatic withdrawal of the marketing authorization, if the specific obligations (ongoing or new studies, additional activities) are not fulfilled in the post-approval setting. Although the fulfilment of specific obligations is legally binding, no medicinal product can be withdrawn from the market purely because the obligation was not fulfilled (Hoekman et al. 2016) (EC 507/2006). Withdrawal of marketing authorization is a time consuming procedure, in general an article 20 pharmacovigilance procedure, and has to be initiated by the EMA (EU 726/2004).

Feasible regulatory strategies to support histology independent approvals should include temporal approvals or approvals at risk, that can be continuously reviewed once more data from post-authorization studies become available, reflecting the "real-world" data (Gellad and Kesselheim 2017). Those regulatory procedures have to be set in place by the European Commission to allow easier withdrawal of an MP, but yet no initiative with this regard is noticed.

Indeed, post-marketing data will be crucial for verifying the real clinical benefit of a new drug, especially when conditional approvals are based on surrogate or intermediate endpoints, such as ORR instead of OS. After the approval in various tumor types, randomized studies in these rare patient populations may not be feasible. Such indications might even increase the need for better real-life data (real world evidence, RWE), real-life follow-up (for safety data generation, RWE is inadequate for the proof of efficacy).

Nevertheless, after exemplifying the restrictions in the present regulatory system, one has to point out one of the major advantages of a histology independent development program from a regulatory point of view. Histology independent indication could be a real opportunity for rare cancers in the future. In addition, a truly histology independent indication would allow for the treatment of adult patients and children at the same time, which really could be a chance that medicinal products for the treatment of oncologic adolescent patients would be tested and approved more expeditiously.

Gerneral considerations (the Health Technology Assessment (HTA) perspective)

The recent tumour-agnostic approval by the European Commission is the first indication that the pipeline of tumor-agnostic therapies will be growing. To date, it is not clear how the HTA agencies may evaluate the value of these therapies. For larotrectinib, statements of the Gemeinsamen Bundesausschusses (GBA) and the National Institute for Health and Care Excellence (NICE) are already published (GBA 2020; IQWIQ 2020; NICE 2020). Of course, the published statements are no official finals decisions (the expected publication date will be beginning of April 2020 (GBA) and 27 May 2020 (NICE)), but the both statements clearly show that clinical data provided so far will not be sufficient for generating enough evidence. The existing process for HTA evaluation will need to evolve further; in a tumor-agnostic scenario, new "rare" diseases are essentially created out of many individual conditions by combining biomarker or genomic subsets into one larger population (eg, TRK fusion cancer for larotrectinib). Given the complexity of the trial design used for histology independent therapies, early scientific advice from regulatory agencies combined with the HTA advices (parallel scientific advice procedures) is highly recommended (EMA 2020b).

General considerations (health care professionals and patients)

Targeting oncologic driver mutations could indeed lead to the development of breakthrough therapies, which are expected to have remarkable efficacy across multiple tumor types (CHMP 2019). This allows earlier access of the medicinal product to patients with high unmet medical need tumors and rare tumor types.

Larotrectinib (and all potential histology independent approvals) will soon face another challenge: identifying cancer patients who would benefit from it. It should be discussed if all patients with advanced cancer really need to be screened, looking for these oncogenic drivers, even though it may be very rare, in a given type of cancer. When using a diagnostic test to identify patient populations with low prevalence molecular alterations, efficiency and cost challenges should be considered (Murphy et al. 2017). For the detection of NTRK fusions in daily practice and clinical research, ESMO recommendations have already been published (Marchiò et al. 2019). In brief, for patients with tumors in which NTRK fusion are known to be highly prevalent, any technique is applicable in principle. Nevertheless, the best options as confirmatory techniques are FISH, RT-PCR or RNA-based targeted panels. In the other case, were NTRK fusions are really rare and the challenge is the identification of NTRK fusions in an unselected population, it would be recommended to use NGS targeted panel (DNA- or RNA-based) that reliably detects NTRK fusions. If an NTRK fusion is identified, then IHC should be used to confirm protein expression of the detected NTRK fusions. Alternatively, a

‘two-step approach’ could be considered, which includes IHC first and confirmation of any positivity detected with IHC by NGS. The question of whether advanced cancer patients will be routinely tested for NTRK fusions depends on the implementation of NGS techniques in the clinical routine molecular diagnostics of cancer. The simultaneous screening of a large number of genes should be more effective than a gene-by-gene approach (Marino et al. 2018). Indeed, NGS has become more widespread. Many oncologists have begun to use commercial tests, such as FoundationOne CDx (Foundation Medicine), but the development is far from be denominated as clinical routine (Avila, M. and Meric-Bernstam, F. 2018). It is obvious that the diagnostic pathway is uncertain until the different EU states establish NGS whole genome testing of all solid tumors will be implemented in the clinical routine service.

5.2. Overview on future development in cancer therapies

The regulatory approvals analyzed in this master thesis are a precedent for histology-independent therapy for various medicinal products, intended to be at present in different stages of clinical development (Figure 16).

Figure 16 demonstrates that the industry believes that the principle of histology -independent treatment works case of tyrosine-kinase mutations, rspecially NTRK and receptor-tyrosine kinase (RET) alterations (fusions or rearrangements). Encretinib was the second medicinal product targeting NTRK fusions, which was approved by the FDA in August 2019 for last-line patients with NTRK fusions. In October 2017. Encretinib obtained PRIME-status from the EMA, but the approval is still pending. Loxo-195 (Selecretinib) is a next-generation inhibitor targeting NTRK-fusion, and its intended-use is the treatment of patients developing restistance while treated with larotrectinib.

An analysis of the oncology clinical trial pipeline according to EudraCT was conducted to determine the extent of (basket) trials which could potentially be utilized as data basis for histology independent indications (Annex A). This analysis was repeated on ClinicalTrials.gov.

According to the databases TRX-0005 (repotrectinib) and meresetinib, both targeting NTRK rearrangements, are still tested in basket studies with multiple indications. Nevertheless, at

least the approval strategy for merestinib seems not to apply for a histology independent indication.

Targeting receptor-tyrosine kinase (RET) seems to be another promising histology independent target. RXDX-105 (targeting RET fusions), Loxo-292 and BLU-664 (targeting RET rearrangements are being tested in various basket trials. This applies also for PLX9486,targeting the Tyrosinkinase KIT . Her2 and Her3 are still valuable targets for a pan-tumor application. Zenocutuzumab targeting HER3, TAS0728 targeting HER3 and MCLA-128 tageting the HER2 and HER3 are being tested in basket trials including multiple tumor indications.

According to EudraCT, a variety of basket trials are ongoing in solid tumors harbouring FGF/FGFR aberations, fusions and mutations. These basket trials are evaluating the efficacy of the MPs Pemigatinib, the pan-FGFR inhibitor Debio 1347 and TAS-120.

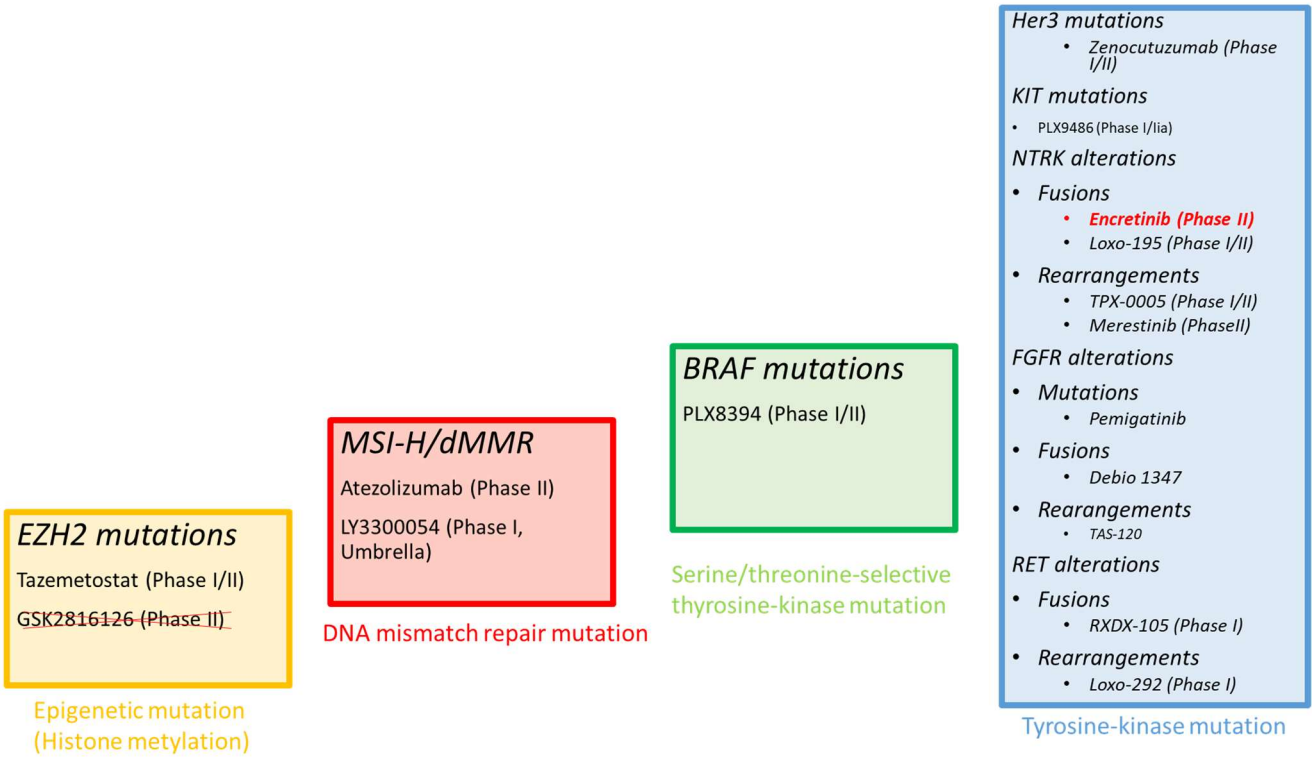

Figure 16 The biomarker targets of histology independent therapies.

Medicinal products targeting BRAF mutations are generally not tested histology independent, with exemption of combination study, but an histology independent approval for combination

therapies might be an unrealistic strategy (please refer to chaper 5.1). Nevertheless, PLX8394 (Yao et al. 2019) and LGX818 (Array Biopharma) is tested in a basket study.

Interestingly, only two PD-1/PD-L1 inhibitors are still under evaluation in basket studies of MSI-H/dMMR tumors: atezolizumab and LY3300054 and LY3300054 are tested in several combinations (Umbrella study). In contrast, several studies are active in mCRC with MSI-H/dMMR reflecting the doubts raised by critical reflection of the FDA Keytruda approval (please refer to Chapter 3.1).

For completeness, one has to mention the efforts to target epigenetic histone methylation, but from the two drugs tested in a tumour-agnostic manner (Tazomeostat and GSK2816126), GSK2816126 has already failed to show sufficient efficacy.

5.3. Summary and Conclusion

With the approvals of pembrolizumab for patients with MSI-H and dMMR tumors and larotrectinib for patients with NTRK fusion tumors, the FDA was the first agency prioritizing histology independent cancer drug development. Although the paradigm change was heavily discussed, the EMA (CHMP) followed the lead and approved larotrectinib finally in September 2019.

Critical reflection of clinical data demonstrates that the database is borderline for both indications. Pembrolizumab in patients with MSI-/H dMMR tumors was never submitted for approval in Europe. This fact suggests that the clinical evidence with OR rates of roughly 40% in the context of a Mode of Action, based on the rather theoretical assumption that a high mutational load would indirectly lead to better sensitivity for immunotherapy, was not sufficient for the European agencies to enforce a paradigm change in oncology. This paradigm change was executed two year later, when the CHMP expressed a positive opinion for the approval of larotrectinib. As with pembrolizumab the clinical evidence for the treatment of larotrectinib in patients NTRK fusion tumors could be regarded as limited. Besides ORR of roughly 70%, a high ORR variability across studied tumor types and possibly unknown resistance mechanism were a matter of concern in the assessment. Nevertheless, the scientifically sound rationale for the target (NTRK-fusion), supposed to be a major

oncological driver across indications, should have been the key factor for this paradigm change in 2019.

To date, histology independent indications could indeed be a realistic way forward for cancer drug development. In particular, the necessity of such histology independent paths in developing medicinal products for rare tumor types and pediatric indications should be acknowledged. However, looking closely at both approvals and the related discussions, it should be noted that the tumor-agnostic development path is far from being established.

Beside the fact that, in the European regulatory framework, histology independent indication are only conceivable in rare cancer indications, the scientific rationale must be extraordinary strong. This means a well-established and oncologic driver and, ideally, the resistance pathways should have been explored, with no difference between indications. In addition, a fully validated biomarker in companion with a detection method, well established in clinical practice, must be available. In brief, basic requirements for histology independent indications are an unmet medical need, an established tumor tissue independent Mode of Action, a validated biomarker, a clinical proof of principle with demonstrated activity across tumor types, and a manageable safety profile. Histology-independent therapies challenge not only the existing market entry pathways and regulatory frameworks. It is not yet foreseeable, how the HTAs will evaluate the clinical benefit of these indications. First statements on larotrectinib indicate that clinical data are considered to be uncomprehensive. Another obstacle is the patient screening as universal testing in the clinical routine for rare biomarkers may not be covered through insurance due to high costs. Nevertheless, the recent development of multiplex NGS platforms will further facilitate the adaptation of medicinal products targeted to rare oncologic driver mutations in clinical practice.

A comprehensive literature and EudraCT database search was conducted and demonstrated that only a minority of MPs are being tested in basket trials with multiple baskets of different tumor types, which could be hypothetically used for an histology independent marketing authorization (1/100 of oncologic trials n=24) . Looking closely at the targeted MPs, studied in a histology independent manner, on can notice that at least the tyrosine kinase mutations, rearrangements and fusions are suspected to driver mutations and ubiquitously important enough to serve as a target in multiple tumor indications.

To recapitulate, the histology independent drug pathway is an innovative possibility to develop medicinal products effectively target rare cancer populations (including paediatric populations) and with the expansion of multiplex NGS platforms, it will become more and

more important. Nevertheless, histology independent development should still be viewed and applied with great caution. The tumor histology context must still considered. The historical experience with the BRAFV600E inhibitors demonstrated that the same level of antitumor activity might not occur across different malignancies and this also applies for MPs targeting oncologic driver mutations. In addition, there are practical challenges, as testing of histology-independent medicinal products in a basket trial may be a long process due to recruitment hurdles owing to small sample sizes. Therefore, histology independent indications will remain exceptional cases in the near future.

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References

Aasebø, Kristine Ø.; Dragomir, Anca; Sundström, Magnus; Mezheyeuski, Artur; Edqvist, Per-Henrik; Eide, Geir Egil et al. (2019): Consequences of a high incidence of microsatellite instability and BRAF-mutated tumors: A population-based cohort of metastatic colorectal cancer patients. In *Cancer medicine* 8 (7), pp. 3623–3635. DOI: 10.1002/cam4.2205.

Agata, Y.; Kawasaki, A.; Nishimura, H.; Ishida, Y.; Tsubata, T.; Yagita, H.; Honjo, T. (1996): Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes. In *International immunology* 8 (5), pp. 765–772. DOI: 10.1093/intimm/8.5.765.

Akbani, Rehan; Ng, Patrick Kwok Shing; Werner, Henrica M. J.; Shahmoradgoli, Maria; Zhang, Fan; Ju, Zhenlin et al. (2014): A pan-cancer proteomic perspective on The Cancer Genome Atlas. In *Nature communications* 5, p. 3887. DOI: 10.1038/ncomms4887.

Avila, M. and Meric-Bernstam, F. (2018): Next-Generation Sequencing for the General Cancer Patient. In *Clinical Advances in Hematology & Oncology* 17 (8).

BMS (2018): Bristol-Myers Squibb Provides Update on the Ongoing Regulatory Review of Opdivo Plus Low-Dose Yervoy in First-Line Lung Cancer Patients with Tumor Mutational Burden ≥10 mut/Mb. Bristol-Myers Squibb. Available online at https://bit.ly/2ySdgOC., updated on 10/19/2018.

BMS (2019): Bristol-Myers Squibb Reports Fourth Quarter and Full Year Financial Results., updated on January 24, 2ß19.

Bogaerts, Jan (2017): What defines the disease and populations? How to deal with large subgroups within an indication?, 2017. Available online at https://www.ema.europa.eu/en/events/workshop-site-histology-independent-indications-oncology.

Bonneville, Russell; Krook, Melanie A.; Kautto, Esko A.; Miya, Jharna; Wing, Michele R.; Chen, Hui-Zi et al. (2017): Landscape of Microsatellite Instability Across 39 Cancer Types. In *JCO precision oncology* 2017. DOI: 10.1200/PO.17.00073.

Boutros, Celine; Tarhini, Ahmad; Routier, Emilie; Lambotte, Olivier; Ladurie, Francois Leroy; Carbonnel, Franck et al. (2016): Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. In *Nature reviews. Clinical oncology* 13 (8), pp. 473–486. DOI: 10.1038/nrclinonc.2016.58.

Brahmer, Julie R.; Tykodi, Scott S.; Chow, Laura Q. M.; Hwu, Wen-Jen; Topalian, Suzanne L.; Hwu, Patrick et al. (2012): Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. In *The New England journal of medicine* 366 (26), pp. 2455–2465. DOI: 10.1056/NEJMoa1200694.

Camarero, Jorge (2017): Histology – independent indications in Oncology, 2017. Available online at https://www.ema.europa.eu/en/events/workshop-site-histology-independent-indications-oncology.

CHMP (2005): EPAR-Herceptin, Trastuzumab, 2005. Available online at https://www.ema.europa.eu/en/medicines/human/EPAR/herceptin.

CHMP (2019): EPAR-Vitrakvi; larotrectinib. In *Assessment report EMA/CHMP/469135/2019*. Available online at https://www.ema.europa.eu/en/medicines/human/EPAR/vitrakvi#assessment-history-section.

Chuk, Meredith K.; Mulugeta, Yeruk; Roth-Cline, Michelle; Mehrotra, Nitin; Reaman, Gregory H. (2017): Enrolling Adolescents in Disease/Target-Appropriate Adult Oncology Clinical Trials of Investigational Agents. In *Clinical cancer research : an official journal of the American Association for Cancer Research* 23 (1), pp. 9–12. DOI: 10.1158/1078-0432.CCR-16-1367.

Cocco, Emiliano; Scaltriti, Maurizio; Drilon, Alexander (2018): NTRK fusion-positive cancers and TRK inhibitor therapy. In *Nature reviews. Clinical oncology* 15 (12), pp. 731–747. DOI: 10.1038/s41571-018-0113-0.

Collette, Laurence; Tombal, Bertrand (2015): N-of-1 trials in oncology. In *The Lancet Oncology* 16 (8), pp. 885–886. DOI: 10.1016/S1470-2045(15)00062-5.

Coyle, Krysta Mila; Boudreau Jeanette E.; Marcato, Paola (2017): Genetic Mutations and Epigenetic Modifications Driving Cancer and Informing Precision Medicine. In *Hindawi BioMed Research International* (Volume 2017).

DeVita, Vincent T.; Chu, Edward (2008): A history of cancer chemotherapy. In *Cancer research* 68 (21), pp. 8643–8653. DOI: 10.1158/0008-5472.CAN-07-6611.

Diaz, Luis A.; Le, Dung T.; Yoshino, Takayuki; André, Thierry; Bendell, Johanna C.; Rosales, Minori et al. (2018): KEYNOTE-177: Phase 3, open-label, randomized study of first-line pembrolizumab (Pembro) versus investigator-choice chemotherapy for mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal carcinoma (mCRC). In *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 36 (4_suppl), TPS877-TPS877. DOI: 10.1200/JCO.2018.36.4_suppl.TPS877.

Ding, Li; Getz, Gad; Wheeler, David A.; Mardis, Elaine R.; McLellan, Michael D.; Cibulskis, Kristian et al. (2008): Somatic mutations affect key pathways in lung adenocarcinoma. In *Nature* 455 (7216), pp. 1069–1075. DOI: 10.1038/nature07423.

Drilon, Alexander; Laetsch, Theodore W.; Kummar, Shivaani; DuBois, Steven G.; Lassen, Ulrik N.; Demetri, George D. et al. (2018): Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. In *The New England journal of medicine* 378 (8), pp. 731–739. DOI: 10.1056/NEJMoa1714448.

Dudley, Jonathan C.; Lin, Ming-Tseh; Le, Dung T.; Eshleman, James R. (2016): Microsatellite Instability as a Biomarker for PD-1 Blockade. In *Clinical cancer research : an official journal of the American Association for Cancer Research* 22 (4), pp. 813–820. DOI: 10.1158/1078-0432.CCR-15-1678.

Dupain, Célia; Harttrampf, Anne Catherine; Urbinati, Giorgia; Geoerger, Birgit; Massaad-Massade, Liliane (2017): Relevance of Fusion Genes in Pediatric Cancers: Toward Precision Medicine. In *Molecular therapy. Nucleic acids* 6, pp. 315–326. DOI: 10.1016/j.omtn.2017.01.005.

EC 507/2006: COMMISSION REGULATION (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council.

EC 658/2007: COMMISSION REGULATION (EC) No 658/2007. concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No 726/2004 of the European Parliament and of the Council.

EMA (2020a): Conditional marketing authorisation. Available online at https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation, checked on 2/20/2020.

EMA (2020b): Parallel consultation with regulators and health technology assessment bodies. Available online at https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/parallel-consultation-regulators-health-technology-assessment-bodies.

EMA/CHMP/509951/2006, Rev.1: GUIDELINE ON THE SCIENTIFIC APPLICATION AND THE PRACTICAL ARRANGEMENTS NECESSARY TO IMPLEMENT COMMISSION REGULATION (EC) No 507/2006 ON THE CONDITIONAL MARKETING AUTHORISATION FOR MEDICINAL PRODUCTS FOR HUMAN USE FALLING WITHIN THE SCOPE OF REGULATION (EC) No 726/2004.

EMA/CHMP/800914/2016 (2016): Predictive biomarker-based assay developement in the context of drug development and lifecycle.

EPAR-Keytruda. Available online at https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda.

Eriksson, Jennifer; Amonkar, Mayur; Al-Jassar, Gemma; Lambert, Jeremy; Malmenäs, Mia; Chase, Monica et al. (2019): Mismatch Repair/Microsatellite Instability Testing Practices among US Physicians Treating Patients with Advanced/Metastatic Colorectal Cancer. In *Journal of Clinical Medicine* 8 (4). DOI: 10.3390/jcm8040558.

ESMO Guidelines. Available online at https://www.esmo.org/Guidelines.

EU 746/2017: REGULATION (EU) 2017/ 746 on in vitro diagnostic medical devices and repealing Directive 98/ 79/ EC and Commission Decision 2010/ 227/ EU. REGULATION (EU) 2017/ 746.

EU 726/2004: Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agenc.

Farago, Anna F. (2017): The TRK to Tumor-Agnostic Care in Solid Tumors, 2017.

Flaherty, Keith T.; Puzanov, Igor; Kim, Kevin B.; Ribas, Antoni; McArthur, Grant A.; Sosman, Jeffrey A. et al. (2010): Inhibition of mutated, activated BRAF in metastatic melanoma. In *The New England journal of medicine* 363 (9), pp. 809–819. DOI: 10.1056/NEJMoa1002011.

Freeman, G. J.; Long, A. J.; Iwai, Y.; Bourque, K.; Chernova, T.; Nishimura, H. et al. (2000): Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. In *The Journal of experimental medicine* 192 (7), pp. 1027–1034. DOI: 10.1084/jem.192.7.1027.

Garassino, M. (2019): EVALUATION OF TMB IN KEYNOTE-189: PEMBROLIZUMAB PLUS CHEMOTHERAPY VS PLACEBO PLUS CHEMOTHERAPY FOR NONSQUAMOUS NSCLC, 2019. Available online at https://wclc2019.iaslc.org/wp-content/uploads/2019/08/WCLC2019-Abstract-Book_web-friendly.pdf.

GBA (2020): Nutzenbewertung nach § 35a SGB V Nutzenbewertungsverfahren zum Wirkstoff Larotrectinib (Solide Tumore, histologieunabhängig). Available online at https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/502/, updated on 1/15/2020.

Gellad, Walid F.; Kesselheim, Aaron S. (2017): Accelerated Approval and Expensive Drugs - A Challenging Combination. In *The New England journal of medicine* 376 (21), pp. 2001–2004. DOI: 10.1056/NEJMp1700446.

Giannakis, Marios; Mu, Xinmeng Jasmine; Shukla, Sachet A.; Qian, Zhi Rong; Cohen, Ofir; Nishihara, Reiko et al. (2016): Genomic Correlates of Immune-Cell Infiltrates in Colorectal Carcinoma. In *Cell reports* 15 (4), pp. 857–865. DOI: 10.1016/j.celrep.2016.03.075.

Gong, Jun; Chehrazi-Raffle, Alexander; Reddi, Srikanth; Salgia, Ravi (2018): Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: a comprehensive review of registration trials and future considerations. In *Journal for immunotherapy of cancer* 6 (1), p. 8. DOI: 10.1186/s40425-018-0316-z.

Goodman, Aaron M.; Kato, Shumei; Bazhenova, Lyudmila; Patel, Sandip P.; Frampton, Garrett M.; Miller, Vincent et al. (2017): Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers. In *Molecular cancer therapeutics* 16 (11), pp. 2598–2608. DOI: 10.1158/1535-7163.MCT-17-0386.

Hanahan, Douglas and Weinberg, Robert A. (2000): The Hallmarks of cancer. In *Cell* (100), pp. 57–70.

Hechtman, Jaclyn F.; Benayed, Ryma; Hyman, David M.; Drilon, Alexander; Zehir, Ahmet; Frosina, Denise et al. (2017): Pan-Trk Immunohistochemistry Is an Efficient and Reliable Screen for the Detection of NTRK Fusions. In *The American journal of surgical pathology* 41 (11), pp. 1547–1551. DOI: 10.1097/PAS.0000000000000911.

Hierro, Cinta; Matos, Ignacio; Martin-Liberal, Juan; Ochoa de Olza, Maria; Garralda, Elena (2019): Agnostic-Histology Approval of New Drugs in Oncology: Are We Already There? In *Clinical cancer research : an official journal of the American Association for Cancer Research* 25 (11), pp. 3210–3219. DOI: 10.1158/1078-0432.CCR-18-3694.

Hirano, Fumiya; Kaneko, Katsumi; Tamura, Hideto; Dong, Haidong; Wang, Shengdian; Ichikawa, Masao et al. (2005): Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. In *Cancer research* 65 (3), pp. 1089–1096.

Hoekman, Jarno; Klamer, Thea T.; Mantel-Teeuwisse, Aukje K.; Leufkens, Hubert G. M.; Bruin, Marie L. de (2016): Characteristics and follow-up of postmarketing studies of conditionally authorized medicines in the EU. In *British journal of clinical pharmacology* 82 (1), pp. 213–226. DOI: 10.1111/bcp.12940.

Innocenti, Federico; Ou, Fang-Shu; Qu, Xueping; Zemla, Tyler J.; Niedzwiecki, Donna; Tam, Rachel et al. (2019): Mutational Analysis of Patients With Colorectal Cancer in CALGB/SWOG 80405 Identifies New Roles of Microsatellite Instability and Tumor Mutational Burden for Patient Outcome. In *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 37 (14), pp. 1217–1227. DOI: 10.1200/JCO.18.01798.

IQWIQ (2020): Larotrectinib bei Tumoren mit NTRK-Genfusion: Daten reichen noch nicht für Zusatznutzen-Ableitung. Available online at https://www.iqwig.de/de/presse/pressemitteilungen/2020/larotrectinib-bei-tumoren-mit-ntrk-genfusion-daten-reichen-noch-nicht-fuer-zusatznutzen-ableitung.12768.html, updated on 1/15/2020.

Jiang, Xianjie; Wang, Jie; Deng, Xiangying; Xiong, Fang; Ge, Junshang; Xiang, Bo et al. (2019): Role of the tumor microenvironment in PD-L1/PD-1-mediated tumor immune escape. In *Molecular cancer* 18 (1), p. 10. DOI: 10.1186/s12943-018-0928-4.

Jørgensen, Jan Trøst (2019): A paradigm shift in biomarker guided oncology drug development. In *Annals of translational medicine* 7 (7), p. 148. DOI: 10.21037/atm.2019.03.36.

Josephson, Filip (2019): A regulatory view on the role of registries for generating data on cancer therapies, 2019. Available online at https://www.ema.europa.eu/en/documents/presentation/presentation-regulatory-view-role-registries-generating-data-cancer-therapies-filip-josephson_en.pdf.

Kaplan, D. R.; Martin-Zanca, D.; Parada, L. F. (1991): Tyrosine phosphorylation and tyrosine kinase activity of the trk proto-oncogene product induced by NGF. In *Nature* 350 (6314), pp. 158–160. DOI: 10.1038/350158a0.

Keir, Mary E.; Liang, Spencer C.; Guleria, Indira; Latchman, Yvette E.; Qipo, Andi; Albacker, Lee A. et al. (2006): Tissue expression of PD-L1 mediates peripheral T cell tolerance. In *The Journal of experimental medicine* 203 (4), pp. 883–895. DOI: 10.1084/jem.20051776.

Keytruda prescribing information USFDA. Available online at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s014lbl.pdf.

Kopetz, Scott; Desai, Jayesh; Chan, Emily; Hecht, Joel Randolph; O'Dwyer, Peter J.; Maru, Dipen et al. (2015): Phase II Pilot Study of Vemurafenib in Patients With Metastatic BRAF-Mutated Colorectal Cancer. In *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 33 (34), pp. 4032–4038. DOI: 10.1200/JCO.2015.63.2497.

Kummar, Shivaani; Lassen, Ulrik N. (2018): TRK Inhibition: A New Tumor-Agnostic Treatment Strategy. In *Targeted oncology* 13 (5), pp. 545–556. DOI: 10.1007/s11523-018-0590-1.

Kythreotou, Anthousa; Siddique, Abdul; Mauri, Francesco A.; Bower, Mark; Pinato, David J. (2018): PD-L1. In *Journal of clinical pathology* 71 (3), pp. 189–194. DOI: 10.1136/jclinpath-2017-204853.

Lacombe, Denis; Burock, Susen; Bogaerts, Jan; Schoeffski, Patrick; Golfinopoulos, Vassilis; Stupp, Roger (2014): The dream and reality of histology agnostic cancer clinical trials. In *Molecular oncology* 8 (6), pp. 1057–1063. DOI: 10.1016/j.molonc.2014.06.002.

Langer, C. (2019): TMB AND OUTCOMES FOR CARBOPLATIN AND PEMETREXED WITH OR WITHOUT PEMBROLIZUMAB FOR NONSQUAMOUS NSCLC, 2019. Available online at https://wclc2019.iaslc.org/wp-content/uploads/2019/08/WCLC2019-Abstract-Book_web-friendly.pdf.

Le, Dung T.; Kim, Tae Won; van Cutsem, Eric; Geva, Ravit; Jäger, Dirk; Hara, Hiroki et al. (2020): Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: KEYNOTE-164. In *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 38 (1), pp. 11–19. DOI: 10.1200/JCO.19.02107.

Lemery, Steven (2017): Approval of pembrolizumab (MSI-H/dMMR) and considerations for site-agnostic development of drugs in oncology, 2017.

Li, Kai; Luo, Haiqing; Huang, Lianfang; Luo, Hui; Zhu, Xiao (2020): Microsatellite instability: a review of what the oncologist should know. In *Cancer cell international* 20, p. 16. DOI: 10.1186/s12935-019-1091-8.

Marabelle, Aurelien; Le, Dung T.; Ascierto, Paolo A.; Di Giacomo, Anna Maria; Jesus-Acosta, Ana de; Delord, Jean-Pierre et al. (2020): Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. In *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 38 (1), pp. 1–10. DOI: 10.1200/JCO.19.02105.

Marchiò, C.; Scaltriti, M.; Ladanyi, M.; Iafrate, A. J.; Bibeau, F.; Dietel, M. et al. (2019): ESMO recommendations on the standard methods to detect NTRK fusions in daily practice and clinical research. In *Annals of oncology : official journal of the European Society for Medical Oncology* 30 (9), pp. 1417–1427. DOI: 10.1093/annonc/mdz204.

Marino, Patricia; Touzani, Rajae; Perrier, Lionel; Rouleau, Etienne; Kossi, Dede Sika; Zhaomin, Zou et al. (2018): Cost of cancer diagnosis using next-generation sequencing targeted gene panels in routine practice: a nationwide French study. Nature Publishing Group. Available online at https://www.nature.com/articles/s41431-017-0081-3, updated on 2/29/2020, checked on 2/29/2020.

Martin-Zanca, D.; Hughes, S. H.; Barbacid, M. (1986): A human oncogene formed by the fusion of truncated tropomyosin and protein tyrosine kinase sequences. In *Nature* 319 (6056), pp. 743–748. DOI: 10.1038/319743a0.

Martin-Zanca, D.; Oskam, R.; Mitra, G.; Copeland, T.; Barbacid, M. (1989): Molecular and biochemical characterization of the human trk proto-oncogene. In *Molecular and cellular biology* 9 (1), pp. 24–33. DOI: 10.1128/mcb.9.1.24.

Murphy, Danielle A.; Ely, Heather A.; Shoemaker, Robert; Boomer, Aaron; Culver, Brady P.; Hoskins, Ian et al. (2017): Detecting Gene Rearrangements in Patient Populations Through a 2-Step Diagnostic Test Comprised of Rapid IHC Enrichment Followed by Sensitive Next-Generation Sequencing. In *Applied immunohistochemistry & molecular morphology : AIMM* 25 (7), pp. 513–523. DOI: 10.1097/PAI.0000000000000360.

NCCN Guildelines. Available online at https://www.nccn.org/professionals/physician_gls/default.aspx.

NCI (2019): Cancer Types. National Cancer Institute. Available online at https://www.cancer.gov/types.

NHS (2019): NHS prepares to fast-track ‘game changing’ cancer drugs that target genetic mutations. Available online at https://www.england.nhs.uk/2019/06/fast-track-game-changing-cancer-drugs/, updated on 6/19/2019.

NICE (2020): Larotrectinib for treating NTRK fusion-positive solid tumours. Available online at https://www.nice.org.uk/consultations/829/1/proposed-date-for-review-of-guidance, updated on 2/7/2020.

Overman, Michael J.; McDermott, Ray; Leach, Joseph L.; Lonardi, Sara; Lenz, Heinz-Josef; Morse, Michael A. et al. (2017): Nivolumab in patients with metastatic DNA mismatch

repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. In *The Lancet Oncology* 18 (9), pp. 1182–1191. DOI: 10.1016/s1470-2045(17)30422-9.

Paratala, Bhavna S.; Chung, Jon H.; Williams, Casey B.; Yilmazel, Bahar; Petrosky, Whitney; Williams, Kirstin et al. (2018): RET rearrangements are actionable alterations in breast cancer. In *Nature communications* 9 (1), p. 4821. DOI: 10.1038/s41467-018-07341-4.

Park, Jay J. H.; Siden, Ellie; Zoratti, Michael J.; Dron, Louis; Harari, Ofir; Singer, Joel et al. (2019): Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. In *Trials* 20 (1), p. 572. DOI: 10.1186/s13063-019-3664-1.

Prahallad, Anirudh; Sun, Chong; Huang, Sidong; Di Nicolantonio, Federica; Salazar, Ramon; Zecchin, Davide et al. (2012): Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. In *Nature* 483 (7387), pp. 100–103. DOI: 10.1038/nature10868.

Puccini, Alberto; Berger, Martin D.; Naseem, Madiha; Tokunaga, Ryuma; Battaglin, Francesca; Cao, Shu et al. (2017): Colorectal cancer: epigenetic alterations and their clinical implications. In *Biochimica et biophysica acta. Reviews on cancer* 1868 (2), pp. 439–448. DOI: 10.1016/j.bbcan.2017.09.003.

Raez, Luis E.; Santos, Edgardo S. (2018): Tumor Type-Agnostic Treatment and the Future of Cancer Therapy. In *Targeted oncology* 13 (5), pp. 541–544. DOI: 10.1007/s11523-018-0593-y.

Ribas, Antoni (2015): Adaptive Immune Resistance: How Cancer Protects from Immune Attack. In *Cancer discovery* 5 (9), pp. 915–919. DOI: 10.1158/2159-8290.CD-15-0563.

Ricciuti, Biagio; Genova, Carlo; Crinò, Lucio; Libra, Massimo; Leonardi, Giulia Costanza (2019): Antitumor activity of larotrectinib in tumors harboring NTRK gene fusions: a short review on the current evidence. In *OncoTargets and therapy* 12, pp. 3171–3179. DOI: 10.2147/OTT.S177051.

Roche (2018): ASCO 2018: Roche discusses TMB as a predictive biomarker for NSCLC. Available online at https://www.pharmaceutical-technology.com/comment/asco-2018-roche-discusses-tmb-predictive-biomarker-nsclc/, updated on 8.June.2018.

Sidaway, Peter (2019): MSI-H: a truly agnostic biomarker? In *Nature reviews. Clinical oncology*. DOI: 10.1038/s41571-019-0310-5.

Sinicrope, Frank A.; Yang, Zhineng Jayson (2011): Prognostic and predictive impact of DNA mismatch repair in the management of colorectal cancer. In *Future oncology (London, England)* 7 (3), pp. 467–474. DOI: 10.2217/fon.11.5.

SmPC Keytruda. Available online at https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda, checked on 2020.

SmPC Bavencio. Available online at https://www.ema.europa.eu/en/medicines/human/EPAR/bavencio, checked on 2020.

SmPC Imfinzi. Available online at https://www.ema.europa.eu/en/medicines/human/EPAR/imfinzi, checked on 2020.

SmPC Opdivo. Available online at https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo, checked on 2020.

SmPC Tecentriq. Available online at https://www.ema.europa.eu/en/medicines/human/EPAR/tecentriq, checked on 2020.

Stransky, Nicolas; Cerami, Ethan; Schalm, Stefanie; Kim, Joseph L.; Lengauer, Christoph (2014): The landscape of kinase fusions in cancer. In *Nature communications* 5, p. 4846. DOI: 10.1038/ncomms5846.

Strimbu, Kyle; Tavel, Jorge A. (2010): What are biomarkers? In *Current opinion in HIV and AIDS* 5 (6), pp. 463–466. DOI: 10.1097/COH.0b013e32833ed177.

Sun, Chong; Mezzadra, Riccardo; Schumacher, Ton N. (2018): Regulation and Function of the PD-L1 Checkpoint. In *Immunity* 48 (3), pp. 434–452. DOI: 10.1016/j.immuni.2018.03.014.

Takeuchi, Kengo; Soda, Manabu; Togashi, Yuki; Suzuki, Ritsuro; Sakata, Seiji; Hatano, Satoko et al. (2012): RET, ROS1 and ALK fusions in lung cancer. In *Nature medicine* 18 (3), pp. 378–381. DOI: 10.1038/nm.2658.

Torti, Davide; Trusolino, Livio (2011): Oncogene addiction as a foundational rationale for targeted anti-cancer therapy: promises and perils. In *EMBO molecular medicine* 3 (11), pp. 623–636. DOI: 10.1002/emmm.201100176.

Twomey, Julianne D.; Brahme, Nina N.; Zhang, Baolin (2017): Drug-biomarker co-development in oncology - 20 years and counting. In *Drug resistance updates : reviews and commentaries in antimicrobial and anticancer chemotherapy* 30, pp. 48–62. DOI: 10.1016/j.drup.2017.02.002.

US FDA (2019.): List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). Available online at https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm, updated on 9/29/2019., checked on 11/12/2019.

Vaishnavi, Aria; Le, Anh T.; Doebele, Robert C. (2015): TRKing down an old oncogene in a new era of targeted therapy. In *Cancer discovery* 5 (1), pp. 25–34. DOI: 10.1158/2159-8290.CD-14-0765.

Venderbosch, Sabine; Nagtegaal, Iris D.; Maughan, Tim S.; Smith, Christopher G.; Cheadle, Jeremy P.; Fisher, David et al. (2014): Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and

FOCUS studies. In *Clinical cancer research : an official journal of the American Association for Cancer Research* 20 (20), pp. 5322–5330. DOI: 10.1158/1078-0432.CCR-14-0332.

Vogel, Charles L.; Cobleigh, Melody A.; Tripathy, Debu; Gutheil, John C.; Harris, Lyndsay N.; Fehrenbacher, Louis et al. (2002): Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. In *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 20 (3), pp. 719–726. DOI: 10.1200/JCO.2002.20.3.719.

Wegener, Elmar: Real World Evidence Real World Evidence-Impact on Regulatory Decision Making.

Wei, Spencer C.; Duffy, Colm R.; Allison, James P. (2018): Fundamental Mechanisms of Immune Checkpoint Blockade Therapy. In *Cancer discovery* 8 (9), pp. 1069–1086. DOI: 10.1158/2159-8290.CD-18-0367.

Weinstein, I. Bernard; Joe, Andrew K. (2006): Mechanisms of disease: Oncogene addiction--a rationale for molecular targeting in cancer therapy. In *Nature clinical practice. Oncology* 3 (8), pp. 448–457. DOI: 10.1038/ncponc0558.

Yamashita, Hitomi; Nakayama, Kentaro; Ishikawa, Masako; Nakamura, Kohei; Ishibashi, Tomoka; Sanuki, Kaori et al. (2018): Microsatellite instability is a biomarker for immune checkpoint inhibitors in endometrial cancer. In *Oncotarget* 9 (5), pp. 5652–5664. DOI: 10.18632/oncotarget.23790.

Yan, Li; Zhang, Wei (2018): Precision medicine becomes reality-tumor type-agnostic therapy. In *Cancer communications (London, England)* 38 (1), p. 6. DOI: 10.1186/s40880-018-0274-3.

Yao, Zhan; Gao, Yijun; Su, Wenjing; Yaeger, Rona; Tao, Jessica; Na, Na et al. (2019): RAF inhibitor PLX8394 selectively disrupts BRAF dimers and RAS-independent BRAF-mutant-driven signaling. In *Nature medicine* 25 (2), pp. 284–291. DOI: 10.1038/s41591-018-0274-5.

Yarchoan, Mark; Hopkins, Alexander; Jaffee, Elizabeth M. (2017): Tumor Mutational Burden and Response Rate to PD-1 Inhibition. In *The New England journal of medicine* 377 (25), pp. 2500–2501. DOI: 10.1056/NEJMc1713444.

Yi, Ming; Jiao, Dechao; Xu, Hanxiao; Liu, Qian; Zhao, Weiheng; Han, Xinwei; Wu, Kongming (2018): Biomarkers for predicting efficacy of PD-1/PD-L1 inhibitors. In *Molecular cancer* 17 (1), p. 129. DOI: 10.1186/s12943-018-0864-3.

Yuza, Kizuki; Nagahashi, Masayuki; Watanabe, Satoshi; Takabe, Kazuaki; Wakai, Toshifumi (2017): Hypermutation and microsatellite instability in gastrointestinal cancers. In *Oncotarget* 8 (67), pp. 112103–112115. DOI: 10.18632/oncotarget.22783.

ANNEX A: EudaCT search (09.03.2020)

- Search cancer or tumor or tumour or neoplasm or carcinoma
- Ongoing trials
- Phase II/IIII

(Results: 2500 trials; only triels with >3 indications were selected; FIM, dose.selection/escalation trials, T-Cell and DC.cell-therapy trials, pediatric trials were excluded)

1. **2019-002071-34** Vejle Hospital (Investigator)
   Allocation of patients with pre-treated solid tumors to anti-cancer therapy based on gene expression drug response prediction - a phase II basket trial
   Medical condition: Breast cancer Ovarian cancer Lung cancer Colorectal cancer Prostate
2. **2018-003546-16** Debiopharm International SA SMARTPLUS-106:
   Debio 1143 a SMAC Mimetic In Combination With Nivolumab In Patients Failing Prior PD-1/PD-L1 Treatment: A Basket Trial A dose-optimization, exploratory phase Ib/II study to assess...
3. 2017-005108-89 Vall d'Hebron Institute of Oncology (VHIO); Basket of Baskets: A Modular, Open-label, Phase II, Multicentre Study To Evaluate Targeted Agents in Molecularly Selected Populations With Advanced Solid Tumors.
4. **2018-004623-36 :**Uppsala University Hospil; A MolEcularly Guided Anti-Cancer Drug Off-Label Trial – a multicenter, basket and umbrella explorative trial on the efficacy and safety of molecular profile selected commercially available target...
5. **2017-001857-14** UNICANCER; A phase I/II basket trial evaluating a combination of Metronomic Oral Vinorelbine plus anti-PD-L1/anti-CTLA4 ImmunothErapy in patients with advanced solid tumours....
6. **2018-003115-21** Gustave Roussy; A phase II whole exoMe sequencing-bAsed baskeT trIal for combination therapy with durvaLumab (anti-PDL1) (MEDI4736) anD tremelimumAb (anti-CTLA4) in patients with metastatic solid tumors
7. **2015-000269-30** Hoffmann-La Roche Lt AN OPEN-LABEL, MULTICOHORT, PHASE II STUDY OF ATEZOLIZUMAB IN ADVANCED SOLID TUMORS
8. **2018-001744-62** Gustave Roussy A multicenter, open label, phase II basket trial exploring the efficacy and safety of the combination of rucaparib (PARP inhibitor) and atezolizumab (anti-PD-L1 antibody) in patients with DNA repair deficiency
9. **2015-004062-29** University Hospital Southampton NHS Trust;SGI-110 to potentiate platinum response: A phase Ib/randomised IIa open label clinical trial combining SGI-110 with cisplatin and gemcitabine chemotherapy
10. 2013-004398-28; Medical Research Council Clinical Trials Unit at UC ; A phase III double-blind placebo-controlled randomised trial assessing the effects of aspirin on disease recurrence and survival after primary therapy in common non-metastatic solid tumours.
11. 2019-002113-19 Janssen-Cilag International NV; A Phase 2 Study of Erdafitinib in Subjects with Advanced Solid Tumors and FGFR Gene Alterations
12. **2016-004989-25** Incyte Biosciences; A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of INCAGN01876 in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies.
13. **2017-005076-26** Seattle Genetics, Inc.; Open Label Phase 2 Study of Tisotumab Vedotin for Locally Advanced or Metastatic Disease in Solid Tumors

14. 2013-002844-10 Bristol-Myers Squibb; A Phase 1/2, Open-label Study of Nivolumab Monotherapy or Nivolumab combined with Ipilimumab in Subjects with Advanced or Metastatic Solid Tumors
15. **2017-001743-12** Incyte Corporation Full Title: A Phase 1/2, Open-Label, Dose-Escalation, Safety, Tolerability, and Efficacy Study of Epacadostat and Nivolumab in Combination With Immune Therapies in Subjects With Advanced or Metastatic Maligna...
16. **2016-004743-37** Genmab A/S; A multi-center, open-label trial investigating the efficacy and safety of continued treatment with tisotumab vedotin in patients with solid tumors known to express tissue factor
17. **2016-001860-12** Novartis Pharma Services AG A phase I/II, multicenter, open-label study of MAK683 in adult patients with advanced malignancies
18. **2015-002067-41** Merck Sharp & Dohme Corp.; A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects with Advanced Solid Tumors (KEYNOTE 158)
19. **2015-005464-42** Gustave Roussy ; A phase II study to assess the efficacy of the anti-PD-L1 antibody atezolizumab (MPDL3280A) administered with stereotactic ablative radiotherapy (SABR) in patients with metastatic tumours
20. **2017-000300-26** Eisai Ltd.; A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors
21. **2016-000461-23** :Bristol-Myers Squibb ; An Open-label Phase 2 Multi-cohort Trial of Nivolumab in Advanced or Metastatic Malignancies
22. **2014-003773-42** Pharma Mar S.A. Sociedad Unipersonal; A Multicenter Phase II Clinical Trial of Lurbinectedin (PM01183) in Selected Advanced Solid Tumors.
23. **2018-000124-34** Pfizer Inc; A Phase 1b/2, study to evaluate safety and clinical activity of avelumab in combination with binimetinib with or without talazoparib in patients with locally advanced or metastatic RAS-Mutant Solidid tumors.
24. **2016-003312-12** Celyad SA; A multinational, open-label, dose escalation Phase I/II study to assess the safety and clinical activity of multiple administrations of NKR-2 in patients with different metastatic tumor types
25. **2018-002108-15** Bristol-Myers Squibb ; Phase 1/2 Study of BMS-986310 Administered Alone and in Combination with Nivolumab in Participants with Advanced Solid Tumors Medical condition: Advanced Solid Tumors
26. **2016-002260-14** UNICANCER; Secured access to pembrolizumab for adult patients with selected rare cancer types.
27. **2016-003543-11** Nektar Therapeutics; A Phase 1/2, Open-label, Multicenter Study of the Combination of NKTR-214 and Nivolumab or the Combination of NKTR-214, Nivolumab, and Other Anti-Cancer Therapies in Patients with Select Locally Ad...
28. **2016-000210-29** Novartis Pharma Services ; A Phase Ib/II, open label, multicenter study of MCS110 in combination with PDR001 in patients with advanced malignancies
29. **2018-002966-37** Belgian Society of Medical Oncology Efficacy of Olaparib in advanced cancers occurring in patients with germline mutations or somatic tumor mutations in homologous recombination genes.
30. **2016-003411-34** BSMO; Precision 2: an open explorative phase II, open label study of afatinib in the treatment of advanced cancer carrying an EGFR, a HER2 or a HER3 mutation.
31. **2017-002243-15** Immunocore Ltd.; A Phase I/II Open-Label, Multi-center Study of the Safety and Efficacy of IMCnyeso, an HLA-A* 0201-Restricted, NY-ESO-1 and LAGE-1A-specific soluble T Cell Receptor and Anti-CD3 Bi-specific Molecul...
32. 2018-003172-12 Kymab Ltd ; A Phase 1/2, open-label, multi-center study of the safety and efficacy of KY1044 as single agent and in combination with anti-PD-L1 (atezolizumab) in adult patients with selected advanced malignancies.
33. 2015-005019-34 Novartis Pharma ; A phase I/II study of safety and efficacy of ribociclib (LEE011) in combination with trametinib (TMT212) in patients with metastatic or advanced solid tumors
34. **2017-003182-** 94 Hoffmann-La Roche Ltd, AN OPEN-LABEL, MULTICENTER, PHASE II STUDY TO EVALUATE THE THERAPEUTIC ACTIVITY OF RO6874281, AN

IMMUNOCYTOKINE, CONSISTING OF INTERLEUKIN-2 VARIANT (IL-2V) TARGETING FIBROBLAST ACTIVATION PROTEIN-...

35. **2019-002013-20** Alkermes, Inc.; A Phase 1/2 Study of ALKS 4230 Administered Subcutaneously as Monotherapy and in Combination With Pembrolizumab in Subjects With Advanced Solid Tumors (ARTISTRY-2)
36. **2017-002904-29** Incyte Corporation; A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Efficacy of INCB001158 in Combination With Chemotherapy, in Subjects With Advanced or Metastatic Solid Tumors.
37. **2014-003929-17** Novartis Pharma Services AG Open label multicenter Phase I/II study of the safety and efficacy of PDR001 administered to patients with advanced malignancies
38. **2013-000445-39** GlaxoSmithKline; A phase I/II open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK525762 in subjects with relapsed, refractory haematological malignancies
39. **2015-002552-27** Pfizer Inc,; A PHASE 1B/2 OPEN-LABEL STUDY TO EVALUATE SAFETY, CLINICAL ACTIVITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF AVELUMAB* (MSB0010718C) IN COMBINATION WITH OTHER CANCER IMMUNOTHERAPIES IN PATIENTS WI...
40. **2019-001946-17** Seattle Genetics, Inc.; Open-Label Phase 2 Study of Ladiratuzumab Vedotin (LV) for Unresectable Locally Advanced or Metastatic Solid Tumors
41. **2016-004289-25** Incyte Corporation; A Phase 1/2 Study Exploring the Safety, Tolerability, Effect on the Tumor Microenvironment, and Efficacy of Azacitidine in Combination With Pembrolizumab and Epacadostat in Subjects With Advanced Solid Tumors
42. **2018-003747-37** Merck Sharp & Dohme Corp., A Multicenter; Open-label Phase 2 Study of Lenvatinib (E7080/MK-7902) Plus Pembrolizumab (MK-3475) in Previously Treated Subjects with Selected Solid Tumors (LEAP-005)
43. **2017-000241-49** Novartis Pharma AG; A Phase 2, multi-center, open label study of NIR178 in combination with PDR001 in patients with selected advanced solid tumors and non-Hodgkin lymphoma
44. **2019-001998-90** Alkermes, Inc.; A Phase 1/2 Study of ALKS 4230 Administered Intravenously as Monotherapy and in Combination with Pembrolizumab in Subjects with Advanced Solid Tumors- ARTISTRY-1
45. **2018-002941-12** :Incyte Corporation A Phase 2 Study of INCMGA00012 (PD-1 Inhibitor) in Participants With Selected Solid Tumors (POD1UM-203)
46. **2015-004005-16** Astra Zeneca AB, A Phase I/II Study of MEDI4736 (Anti-PD-L1 Antibody) in Combination with Olaparib (PARP inhibitor) in Patients with Advanced Solid Tumors
47. **2017-001725-40** Bristol-Myers Squibb; A Phase 1b/2 Study of BMS-813160 in Combination with Chemotherapy or Nivolumab in Patients with Advanced Solid Tumors.
48. **2015-003656-40** Pharmacyclics LLC A Phase 1b/2 Study of Ibrutinib Combination Therapy in Selected Advanced Gastrointestinal And Genitourinary Tumors
49. **2018-001796-21** :FORMA Therapeutics, Inc. A Phase 1b/2 Study of FT-2102 in Patients with Advanced Solid Tumors and Gliomas with an IDH1 Mutation
50. **2019-000999-42** CytomX Therapeutics, Inc.; A Phase 2, Open-Label, Multi-cohort Study of PD-L1 Probody™ Therapeutic CX-072 in Combination With Other Anticancer Therapy in Adults With Solid Tumors (PROCLAIM-CX-072-002)
51. **2018-000058-22** Bristol-Myers Squibb; A Phase 1/2 Study of Relatlimab (anti-LAG-3 Monoclonal Antibody) Administered in Combination with Both Nivolumab (anti-PD-1 Monoclonal Antibody) and BMS- 986205 (IDO1 inhibitor) or in Combination w...
52. **2013-004482-14** Novartis Pharma Services AG; A phase I/II, multicenter, open-label study of EGFRmut–TKI EGF816,administered orally in adult patients with EGFRmut solid malignancies
53. **2017-000794-37** Hoffman-La Roche Ltd.; A PHASE II, OPEN-LABEL, MULTICENTER, MULTI-COHORT STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF COBIMETINIB PLUS ATEZOLIZUMAB IN PATIENTS WITH SOLID TUMORS
54. **2015-002934-32** AstraZenenca; A Phase II, Multi-Center, Open-Label Study of Tremelimumab Monotherapy in Patients with Advanced Solid Tumors

55. **2015-000449-21** Novartis Pharma Services AG; A Phase I/II, open label, multicenter study of the safety and efficacy of LAG525 single agent and in combination with PDR001 administered to patients with advanced malignancies
56. **2018-001400-11** Amgen Inc.; A Phase 1/2, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 510 Monotherapy in Subjects With Advanced Solid Tumors With KRAS p.G12C Mutant..
57. **2012-004083-21** Epizyme, Inc.; An Open-Label, Multicenter, Phase 1/2 Study of Tazemetostat **(EZH2 Histone Methyl Transferase [HMT] Inhibitor**) as a Single Agent in Subjects With Advanced Solid Tumors or With B Cell Lymphomas
58. **2017-004246-20** Bayer Consumer Care AG; Bayer 20810 - A Phase 1/2 Study of the TRK Inhibitor Selitrectinib (BAY 2731954) in Adult and Pediatric Subjects with Previously Treated **NTRK Fusion** Cancers
59. **2016-003616-13** Turning Point Therapeutics, Inc.; A Phase 1/2, Open-Label, Multi-Center, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity of TPX-0005 in Patients with Advanced Solid Tumors Harboring **ALK-gene rearrangements,** ...
60. **2015-003385-84** F. Hoffman-La Roche Ltd Full AN OPEN-LABEL, MULTICENTER, GLOBAL PHASE 2 BASKET STUDY OF ENTRECTINIB FOR THE TREATMENT OF PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS THAT HARBOR **NTRK1/2/3, ROS1, OR ALK GENE REARRANGEMENTS**...
61. **2011-005875-17** :Array Biopharma Inc; A Phase Ib/II, multicenter, open-label, dose escalation study of LGX818 in combination with MEK162 in adult patients with **BRAF V600 - dependent advanced solid tumors**
62. **2016-004390-41** Blueprint Medicine; A Phase 1/2 Study of the Highly-selective **RET Inhibitor**, BLU-667, in Patients with Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC) and Other Advanced Solid Tumors
63. **2018-004768-69** Incyte Corporation; A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Previously Treated Locally Advanced/Metastatic or Surgically Unresectable Solid Tumor Malignancies **Harboring Activating FGFR Mutations** or Translocations (FIGHT-207)
64. **2019-001745-40** Start Date*: 2019-11-24 Sponsor Name:Merck Sharp & Dohme Corp., A Phase 2 Study of Olaparib in Combination with Pembrolizumab in Participants with Previously Treated, **Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency**
65. **2017-004415-39** Taiho Oncology, Inc.; A PHASE 1/2, OPEN-LABEL, MULTICENTER STUDY TO INVESTIGATE THE SAFETY, PHARMACOKINETICS, AND EFFICACY OF TAS0728, AN ORAL COVALENT BINDING INHIBITOR OF HER2, IN SUBJECTS WITH ADVANCED SOLID TUMORS with **HER2 or HER3 mutation ...**
66. **2016-002596-10** Incyte Corporation A Phase 2, Open-Label, Monotherapy, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects With Myeloid/Lymphoid Neoplasms With FGFR1 Rearrangement
67. **2014-003277-42** Merus B.V.; A Phase I/II Study of MCLA-128, a full length IgG1 Bispecific Antibody T**argeting HER2 and HER3**, in Patients with Solid Tumors
68. **2018-000345-39** Pfizer Inc.; A Phase 2 Study to Evaluate Safety and Anti-tumor Activity of Avelumab in Combination with Talazoparib In Patients with **BRCA or ATM Mutant Tumors**
69. **2018-003007-19** Merck Sharp & Dohme Corp.; A Phase 2 Study of Olaparib Monotherapy in Participants with Previously Treated, **Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD**) Positive Advanced Cancer
70. **2019-001155-39** Hoffmann-La Roche Ltd; A PHASE 1/2, OPEN-LABEL, DOSE-ESCALATION AND EXPANSION STUDY OF ENTRECTINIB (RXDX-101) IN PEDIATRICS AND YOUNG ADULTS WITH NO CURATIVE FIRST-LINE TREATMENT OPTION OR RECURRENT/REFRACTORY SOLID TUMORS.
71. **2016-003616-13** Turning Point Therapeutics; A Phase 1/2, Open-Label, Multi-Center, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics, and Anti-Tumor

Activity of TPX-0005 in Patients with Advanced Solid Tumors Harboring **ALK gene rearrangements** .....

72. **2015-004535-12** Kura Oncology, Inc. An Open Label Phase II Study of Tipifarnib in Advanced Non-Hematological Malignancies **with HRAS Mutations**
73. **2015-000230-29** Bristol-Myers Squibb Inc Non-Comparative, Open-Label, Multiple Cohort, Phase 1/2 Study of Nivolumab and Nivolumab plus Ipilimumab in Subjects with **Virus-Positive and Virus-Negative Solid Tumors**
74. **2015-003582-28** Loxo Oncology Inc ; A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects with **NTRK Fusion-**Positive Tumors
75. **2016-003498-16** Loxo Oncology Inc.; A Phase 1/2 Study of the Oral TRK Inhibitor LOXO-101 in Pediatric Patients with Advanced Solid or Primary Central Nervous System
76. **2013-002872-42** Puma Biotechnology, Incm: An Open-Label, Phase 2 Study of Neratinib in Patients With Solid Tumors With **Somatic Human Epidermal Growth Factor Receptor (EGFR, HER2, HER3) Mutations or EGFR gene amplification**
77. 2017-000800-59 Loxo Oncology, Inc.; A Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumors, **Including RET Fusion-Positive Solid Tumors**, Medullary Thyroid Cancer, and Other Tumors with RET Activation (LIBRETTO-001)
78. **2016-002898-35:** Bristol-Myers Squibb: A Randomized, Open-Label, Phase 2 Study of Nivolumab in Combination with Ipilimumab or Nivolumab Monotherapy in Participants with Advanced or **Metastatic Solid Tumors of High Tumor Mutational Burden**...
79. **2018-003584-53** :Debiopharm International SA A Phase II basket study of the oral selective pan-FGFR inhibitor Debio 1347 in subjects with solid tumors **harboring a fusion of FGFR1, FGFR2 or FGFR3**.
80. 2013-004810-16 Sponsor Protocol Number: TPU-TAS-120-101 Start Date*: 2014-04-10 Sponsor Name:Taiho Oncology Inc.; PHASE 1/2 STUDY OF TAS-120 IN PATIENTS WITH ADVANCED SOLID TUMORS **HARBORING FGF/FGFR ABERRATIONS**
81. **2015-003582-28** Loxo Oncology Inc A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects with **NTRK Fusion**-Positive Tumors

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

(Hilke Zander)