FRIENDS of CANCER RESEARCH

A Friends of Cancer Research White Paper

CAPITALIZING ON THE TOTALITY OF EVIDENCE TO STREAMLINE APPROVALS FOR SUPPLEMENTAL INDICATIONS

INTRODUCTION

The FDA approves new drugs for sale and marketing in the U.S. after careful review of new drug applications (NDA). Every NDA contains a large amount of data about the new therapy; from discovery in a laboratory, to drug metabolism and toxicology in nonclinical studies, to safety and efficacy in the clinic, to chemistry and manufacturing processes. Only after a drug has demonstrated significant evidence of safety and efficacy in the form of clinical benefit through well-powered and appropriately-controlled studies, it is approved and made available to patients.

As our understanding of drug mechanisms and the natural history of disease increases, we are witnessing a greater number of drugs being used for multiple cancer types and patient populations, which are also known as treatment settings or indications. This is especially true for targeted therapies, which block specific proteins or receptors that participate in cancer growth and progression. As we become more aware of the mechanisms by which cancer forms, more precise therapies are created that modulate targets and pathways that are relevant in the formation of cancer arising in several different tissues and patient populations. Targeted therapies, therefore, are prime examples of drugs that can be used in different indications. The use of therapies in combination will also increase the number of indications for which each drug is used.

Every time a drug manufacturer, or sponsor seeks regulatory approval for a drug in a new indication, whether that refers to a different patient age group, cancer type, or molecular tumor subgroup, the FDA requires a supplemental NDA (sNDA), consisting of the same quality and content as the drug's first or original NDA. The review and assessment of sNDAs is very similar to that of the original NDA, which consume considerable time and

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Friends of Cancer Research drives collaboration among partners from every healthcare sector to power advances in science, policy, and regulation that speed life-saving treatments to patients.

resources and may not always add much value to the regulatory determination of safety and efficacy of a drug for which previous submissions have established a well-characterized profile. Indeed, approved drugs are backed up by a wealth of high-quality data collected from previous submissions, along with post-marketing experience and published literature, which should also be considered when seeking approval for a new indication. These robust data could provide an additional level of confidence on the drug's efficacy and safety, and expedite its regulatory approval process for a new indication.

In the past, approvals were hastened when enough evidence was presented to provide confidence that a drug's efficacy could be based on reliable and well-established intermediate endpoints. Under some circumstances, an intermediate endpoint—an early measure of treatment effect on patients in a clinical trial—may be used as a reliable surrogate marker of clinical benefit, which refers to a patient's ability to survive, feel, or function. Usually, clinical benefit is evaluated after a long period of time and when comparing drug response between patients in the treatment and control arms in the context of a randomized clinical trial (RCT). However, there are cases in which a RCT with conventional clinical endpoints such as progression-free survival (PFS) or overall survival (OS) is not feasible, possible, or ethical, and clinical benefit needs to be assessed in different ways, such as by single-arm studies determining objective response rate (ORR)—a direct measure of tumor shrinkage using standard criteria, or duration of response (DoR). In these rare cases, especially when new therapies are needed for patient populations with large unmet clinical needs and who face no other treatment options, an intermediate endpoint such as ORR, or DoR is considered the most appropriate way, or sufficient to assess clinical benefit. The FDA has recently addressed the need for expedited approvals in these cases. The Accelerated Approval pathway bases approval decisions on intermediate endpoints of clinical benefit, but full approval is contingent on sponsors demonstrating clinical benefit using more conventional clinical endpoints through additional confirmatory trials that commonly occur in a slightly different indication and which may take several years to culminate.

As fully approved drugs start to be evaluated in multiple indications, sNDAs may be submitted to meet an urgent clinical need for which clinical benefit is measured using an intermediate endpoint. In these cases, historical data for the drug's original NDA are available and may be taken into consideration in the decision to fully approve this drug, knowing that conventional clinical endpoints have already been evaluated for the first indication. Currently, the FDA grants full approval to sNDAs based on an intermediate endpoint on a case-by-case scenario, but there are no available or standardized guidelines that could help (1) weigh the urgency in a scenario of unmet clinical need, and (2) assess the type and quality of evidence necessary to provide sufficient confidence in the decision to grant full approval to drugs used for a supplemental indication.

The objective of this white paper is to provide a framework that will aid in examining the unmet clinical need of a patient population and leveraging the totality of evidence available for an approved drug to determine whether there is sufficient data to support full approval in a new indication based on an intermediate endpoint.

LEARNING FROM THE PAST: WHAT CHARACTERISTICS HAVE LED TO THE FULL APPROVAL OF DRUGS BASED ON AN INTERMEDIATE ENDPOINT IN A NEW INDICATION?

Unmet clinical need

Gauging the urgency for a new indication by taking into consideration the unmet clinical need of the population is crucial in determining whether a drug's supplemental indication should be approved based on an intermediate endpoint. Evidence generated during clinical trials, post-market studies and investigator-initiated studies contributes to the totality of evidence that may support the decision to grant full approval for a supplemental indication; however, it is the urgency for filling a medical gap that prompts the evaluation of whether the potential benefit could outweigh the known and unknown risks to expedite the approval of these indications.

How serious or life-threatening is the disease? How rare is the disease? What are the current treatment options available to these patients? These are all factors to assess when considering the benefits and risks that will inform the decision-making process. These factors should contribute to the discussion of whether it is reasonable and feasible to grant full approval to a drug for a novel indication based on an intermediate endpoint (Table 1). Previous scenarios where an earlier measure of efficacy has been used as basis for full approval of supplemental indications have all demonstrated a high degree of unmet clinical need. For example, the combination treatment of daratumumab with pomalidomide and dexamethasone was approved for patients with refractory multiple myeloma (MM) who had received at least two prior therapies including lenalidomide and a proteasome inhibitor such as bortezomib. Eighty-nine percent of patients in the study were refractory to lenalidomide and 71% to bortezomib, with 64% refractory to the combination of lenalidomide and bortezomib. Therefore, limited to no further treatment options were available for these patients. A response rate was observed in 59.2% of patients in the open-label single armed trial, with a median DoR of 13.6 months. These efficacy outcomes were considered substantial in this unique population and supported the full approval of this combination therapy in the absence of further therapies for patients with relapsed or refractory disease.[1]

Table 1. What need-based factors should be taken into consideration?

UNMET CLINICAL NEED
Rarity of disease
Availability of treatment options
RANDOMIZED CONTROLLED TRIAL IS NOT FEASIBLE
Length of time for patient accrual
Ethical considerations

Patients with metastatic non-small cell lung cancer (NSCLC) that have failed or progressed on standard therapies have very poor prognosis and limited treatment options. Targeted therapies are becoming more common for the treatment of NSCLC patients with tumors harboring unique molecular or genetic alterations. The large unmet need of these patients is driving research and clinical trials that test the efficacy of targeted therapies in subsets of patients selected based on a diagnostic test. Mutations in the proto-oncogene, BRAF, are very rare in NSCLC, accounting for about 1% of all NSCLC cases and have been associated with a particularly poor prognosis, with a low proportion of patients achieving a response to platinum-based chemotherapy. The combination of dabrafenib—an inhibitor of BRAF—and trametinib—an inhibitor of MEK, a protein downstream of BRAF—was granted full approval based on a durable ORR for patients with metastatic BRAF V600 positive NSCLC as an alternative to, or in patients that failed to respond to platinum chemotherapy.[2] Likewise, ROS Proto-Oncogene 1 (ROS1) rearrangements in NSCLC are also very rare, accounting for another 1% of NSCLC cases. Crizotinib, a kinase inhibitor that targets aberrant ROS1, was given full approval based on ORR, possibly because patients with metastatic ROS1+ NSCLC had no further therapeutic options. The original indication approvals for the combination of dabrafenib and trametinib, and crizotinib tested these drugs in more common tumors (BRAF V600 mutated melanoma, and ALK+ NSCLC, respectively), where the larger population sizes enabled the appropriate benefit: risk comparisons from well-conducted randomized Phase III studies.
Since the supplemental indications were seeking to help a rare subset of patients with large unmet medical needs, urgency may have played an important role in the decision to approve the use of these drugs in the new indication without demonstrating definitive survival benefit with a RCT, but still demonstrating substantial early efficacy outcomes in these rare lung cancer subpopulations.

Optimal understanding of natural history of disease:
Having a thorough understanding of the natural history of disease is imperative when seeking to expand the use of a well-characterized drug in a new cancer subtype. This includes a greater awareness of the mechanisms by which cancer arises, and its evolution in a patient over time.

The advent of powerful molecular technologies has enabled the study and characterization of a tumor's genome, epigenome, and transcriptome, which can be unique to a single tumor type or shared across several tumors with similar etiologic pathways. For example, leading research in lung cancer has identified multiple oncogenic driver mutations and rearrangements that are currently targeted through different therapies.[3] In NSCLC, some targeted agents, such as kinase inhibitors have demonstrated a greater clinical benefit than cytotoxic platinum-based chemotherapy. Crizotinib inhibits several receptor tyrosine kinases, that when altered, drive the development of NSCLC. This product was first approved for the treatment of patients with metastatic NSCLC whose tumors were positive for the anaplastic lymphoma kinase (ALK). A supplemental indication was sought for use in patients with NSCLC whose tumors were positive for ROS1, a receptor tyrosine kinase with a similar structure to ALK. Because these two tyrosine kinases are related and have been shown to drive the growth and progression of NSCLC, it could be expected that this well-characterized targeted agent would have similar

effects on these tumors harboring different genomic aberrations. Since Crizotinib had already demonstrated substantial evidence of safety and efficacy in the same tissue type and stage (metastatic NSCLC), and there were no treatment options available for this small and unique group of patients, the FDA fully approved this drug for the treatment of patients with metastatic ROS1+ NSCLC using ORR and DoR as the efficacy outcomes, which were measured in a single-arm trial with 50 patients.[4] Due to a clear understanding of the role of receptor tyrosine kinases in the growth and metastatic progression of NSCLC, there was increased confidence that crizotinib would have a similar therapeutic effect on both indications. Thus, when the safety profile and intermediate endpoint for the drug in the new indication were consistent with the original indication, it was reasonable to conclude that the drug would demonstrate substantial clinical benefit.

Well-understood drug's mechanism of action and performance in different disease settings: Understanding a drug's mechanism of action, including its pharmacokinetics, pharmacodynamics, and drug interactions, as well as how well it performs in different cancer settings is critical when seeking to expand its use. For example, daratumumab is an anti-CD38 monoclonal antibody approved for the treatment of patients with MM. Daratumumab binds CD38, which is a receptor commonly found on the surface of hematopoietic cells. MM cells express CD38 on their cell surface, therefore the binding ability of this drug is unique to these cancerous cells. Daratumumab demonstrated clinical benefit as a monotherapy in patients with MM who had received at least three prior lines of therapy. Because daratumumab's mechanism of action was well-known, it was then tested in combination with the current standard of care for MM patients: lenalidomide and dexamethasone, or bortezomib and dexamethasone, in patients with MM who had received at least one prior therapy. The supplemental approval of daratumumab in combination with pomalidomide and dexamethasone for the treatment of patients with MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (such as bortezomib) was based on an open-label single arm trial where ORR was the efficacy outcome.[1] For the supplemental indication, daratumumab was studied in combination with a second thalidomide analogue (pomalidomide), which is in the same family as lenalidomide, a drug combination for which daratumumab had already received approval; therefore, efficacy had already been demonstrated in combination of daratumumab and a thalidomide analogue.

In addition to understanding how the drug works as a single agent and in the context of combination therapies, it is important to evaluate whether the efficacy benefit translates into other diseases. Dabrafenib and trametinib are kinase inhibitors that modulate two independent targets in the Mitogen Activated Protein kinase (MAP kinase) pathway. Together, they have been successfully used in the treatment of patients with BRAF V600-mutant metastatic melanoma, and metastatic NSCLC. However, when the combination therapy was used in BRAF-mutant metastatic colorectal cancer, which is typically refractory to standard treatments and confers a poor prognosis, the response rate observed was modest and the impact of this treatment on disease was much lower than the robust clinical response observed in BRAF mutated metastatic melanoma.[5] Even though the mechanism of action for these kinase inhibitors were well-understood and efficacy had been previously demonstrated in controlled trials, a more detailed pre-clinical investigation on critical factors such as the drug's pharmacodynamics and potential heterogeneity of tissue-unique mechanisms of resistance, was necessary to validate and understand the performance of these drugs in a new indication.

Robust and well-established safety database

Relying on a well-established and robust safety database for a product, that includes drug interactions, adverse reactions, warnings and precautions, and dosage, is essential when seeking approval for new indications. Supplemental NDAs require sponsors to submit the safety profile of a drug in a new patient population and provide relative indirect summary comparisons to previously approved indications. Further support for the effectiveness of a drug in the new indication is obtained when the safety profile in the new indication resembles that of the original indication, demonstrating that the drug behaves similarly in both settings. Dabrafenib and trametinib were granted full approval as monotherapies and in combination for the treatment of patients with metastatic melanoma carrying BRAF V600 mutations. These two drugs demonstrated substantial evidence both as monotherapies and combination therapy, to support their safety in a large number of patients with metastatic melanoma. When a new indication of the combination of these two small molecule inhibitors was sought for a smaller cohort of patients with metastatic NSCLC carrying BRAF V600 mutations, a similar safety profile was observed that was considered manageable and did not substantially differ despite different tumor type. The consistent safety profile observed in the new indication may have contributed to increased confidence to approve the combination therapy in patients with metastatic BRAF V600 mutation-positive NSCLC based on ORR in a three-cohort, non-randomized trial.[2] Similarly, daratumumab's safety profile had been characterized when used as a monotherapy and combination therapy for the treatment of a large number of patients with melanoma during different lines of treatment before it was approved for the new indication of treatment with pomalidomide and dexamethasone in a smaller cohort of patients who had received at least two prior therapies.[1] Lastly, the safety profile of crizotinib for its new indication in patients with ROS1+ NSCLC was consistent with the profile in ALK+ NSCLC, which provided confidence to approve the drug's new indication based on an earlier measure of efficacy.[4]

Reliable study endpoint that has consistently demonstrated clinical benefit

The reliability of an intermediate endpoint as a surrogate marker of clinical benefit is very important in determining whether a drug should receive full approval. In all the examples described so far, ORR per the Response Evaluation Criteria In Solid Tumors (RECIST) as assessed by independent review committee and DoR were the study endpoints measured to predict clinical benefit, and because previous trials had demonstrated these to be reliable surrogates, they were considered sufficient to grant full approval. In all original indications for daratumumab, crizotinib, and the combination of dabrafenib and trametinib, ORR was an intermediate endpoint that was later confirmed to demonstrate clinical benefit through randomized, appropriately-controlled clinical trials. Considering the totality of evidence, including the fact that ORR translated into robust and durable clinical responses and increased survival in the original indications, approvals were granted for additional indications in which response rate, a well-characterized and objectively determined intermediate endpoint, was high.

Accurate and well-instituted companion diagnostics

Targeted therapies rely on diagnostics that consistently and accurately identify a group of patients whose tumors carry the alterations being targeted. When sponsors seek supplemental indications for targeted therapies, sensitive, specific, and reproducible companion diagnostics provide greater confidence that the therapies will have a substantial effect on disease because the patient group is well-characterized. For

example, the combination of dabrafenib and trametinib used for treatment of patients with BRAF V600 mutation positive NSCLC and melanoma, and crizotinib for treatment in patients with ROS1+ NSCLC rely on tests that reliably and consistently identifies single nucleotide variants and rearrangements in tumor tissue, such as the FDA-approved companion diagnostic (Oncomine™ Dx Target Test) that identifies alterations in several genes including BRAF and ROS1.[6] Having a reliable diagnostic test, that performs consistently regardless of the laboratory in which it is performed, is necessary to properly identify patients who would benefit from targeted therapies and provide greater confidence that a substantial effect will be observed in the selected population.

DEVELOPMENT OF FRAMEWORK OUTLINING FACTORS TO CONSIDER WHEN SEEKING APPROVAL FOR A NEW INDICATION

The above examples illustrate different factors that contributed to the decision-making process that ultimately led to the full approval of supplemental indications. Although each case is unique, two general themes have emerged from these examples: consideration of the clinical need of the new indication and the available data. Table 2 outlines a list of these factors and questions that will help facilitate the clinical trial development, curation of available data, and decision-making process to inform approvals of a supplemental indication.

Table 2. Framework to help inform the decision-making process for the approval of a drug seeking a supplemental indication based on an intermediate endpoint

Category	Factors	Questions
Need	Unmet clinical need	Is there an unmet medical need for the patient population? What are the limitations or availability of existing therapies?
	Rare disease	What is the epidemiology of the patient population and how feasible is it to accrue enough patients in a reasonable amount of time to run a randomized control trial?
	Equipoise	Is there early data or strong scientific justification suggesting that a randomized control trial for the supplemental indication may lack equipoise?
Data	Natural history of disease	Are the disease etiology, epidemiology, molecular profile, evolution, and mechanisms of resistance known?
	Relatedness	How closely related is the disease in the supplemental indication to that of the original indication?
	Drug mechanism & pharmacology	Is the drug's mechanism of action, pharmacokinetics, and pharmacodynamics, well understood, and does it perform similarly in different cancer types?
	Dose & regimen	Is the dose and regimen of the drug well supported for the new disease setting?
	Drug's safety profile	Is there an adequate understanding of the drug's adverse event profile and safety management guidelines from randomized trials?
	Efficacy	Are efficacy outcomes significantly greater than those observed with the current standard of care?
	Benefit: risk ratio	Is the magnitude of the benefit significantly high and does it outweigh any known, or unknown, potential risks?
	Contribution of components	For combination therapies, is the contribution of each component to efficacy, or safety, outcomes known?
	Study endpoint	Is the intermediate endpoint a reliable proxy or is it sufficient proof of clinical benefit?
	Diagnostics	For targeted therapies, are well-established and reliable diagnostics available to identify defined population?

LOOKING AHEAD: UTILITY OF FRAMEWORK IN APPROVAL OF SUPPLEMENTAL INDICATIONS

A streamlined approach that guides the evaluation of the confidence and consistency of the totality of evidence available for a drug's new indication is necessary to expedite the approval process while maintaining strict standards of safety. This working group proposes the use of the framework outlined above, to identify whether a supplemental indication has sufficient grounds based on need and previously generated data, to seek full approval based on intermediate endpoints measuring efficacy.

How could this framework be used to guide future cases?

Entrectinib (RXDX-101)[7] and Larotrectinib (LOXO-101)[8] are tyrosine kinase inhibitors that are currently being tested in tissue-agnostic open-label, multicenter, global Phase 2 basket studies for the treatment of patients with solid tumors that harbor a fusion affecting tropomyosin receptor kinase fusions (NTRK1/2/3), ROS1, or ALK. These drugs may potentially work across multiple indications, therefore using the proposed framework outlined in Table 2 would be helpful in guiding the decision-making process that may grant full approval to the supplemental indications based on intermediate endpoints. The factors suggested could be taken into consideration to provide confidence on the expected clinical benefit in the new indication. Master protocols, which refer to one overarching protocol designed to answer multiple questions by investigating efficacy on a single disease after treatment with multiple therapies (umbrella trial), or multiple diseases after one therapy (basket trials)[9] are changing the face of clinical trials. These comprehensive studies will require innovative ways to capitalize on the totality of evidence established for drugs seeking several indications. Likewise, with the increasing number of drug combinations, new indications will arise for the use of approved drugs in new therapeutic permutations. For example, indoleamine (2,3)-dioxygenase (IDO) inhibitors are immunomodulatory drugs that could be used in combination with immune checkpoint inhibitors. There are currently many clinical studies that are investigating the efficacy of these drug combinations in several tumor subtypes,[10, 11] and as these, and other combination therapies become more common, especially in the nascent field of immuno-oncology (see Appendix Table 1), a streamlined approach that relies on the use of historical data and takes into consideration the medical need to expedite the approval of drug combinations will be necessary.

DISCUSSION

In the scenarios described in this white paper, full approval was given to drugs seeking a supplemental indication based on the degree of medical urgency in the affected population and the type and level of evidence available. In these scenarios, after assessing the lack of available options for patients and the drug's historical data, the agency determined that the magnitude of benefit observed when measuring an intermediate endpoint was a substantial improvement over what could be expected with the standard of care, and considering the context of the new indication, sufficient confidence existed to believe that the drug would be efficacious and safe in the new indication.

However, as we better understand the limitations and capabilities of data collected outside of traditional clinical trials to assess the long-term efficacy and safety of approved drugs on the market, it may be inter-

esting to determine whether approvals for supplemental indications based on an intermediate endpoint actually derive clinical benefit in the long term. Programs that use electronic health records and claims data to track safety of regulated medical products, such as the Sentinel system, are already being set into place and may be the key to answer questions about not only a drug's long-term safety, but also efficacy. These surveillance programs could be utilized to examine how well intermediate endpoints are able to predict clinical benefit in order to further improve our confidence on the reliability and accuracy of these surrogates.

Moreover, as the future of cancer research moves from treating to preventing disease, the field will have to more heavily rely on earlier markers of response that predict a prolonged benefit to patients. For example, studies in disease interception, which focus on the development of medicines that stop or delay disease progression for patients with premalignant disease, will require a refined understanding of surrogate endpoints early within the disease continuum that demonstrate elevated predictive power.

Demonstrating clinical benefit outside of the traditional overall survival estimates will require innovative thinking from multiple stakeholder groups working together to assure a fine balance between the most optimal level of efficacy and safety that matches the urgency patients have for life-saving therapies.

QUESTIONS

- **How do we define efficacy and how can different intermediate endpoints predict efficacy in patients?**
- **Would simplified mechanisms of approval for supplemental indications incentivize sponsors to submit sNDAs? What role would these mechanisms play in helping to keep product labels updated?**
- **Is there a need to confirm clinical benefit for drugs approved based on an intermediate endpoint?**

APPENDIX

Additional Examples:

Pembrolizumab

The advent of precision medicine has been a catalyst in the development of molecular targeted drugs and immunotherapies, which work in very specific populations. As we learn more about how these drugs work and what other populations it may help, we will see an increase in the number of their indications. Pembrolizumab is a good example of this phenomenon. In 2014, Pembrolizumab was first approved under accelerated approval for the treatment of patients with unresectable or metastatic melanoma[12] (Appendix Table 1). In under three years, the sponsor of this PD-1 inhibitor has submitted applications for 10 other indications, some of which were approved under accelerated approval and some of which were fully approved after the confirmation of clinical benefit based on overall survival. None of these supplemental applications have been granted full approval based on an intermediate endpoint; however, this may be due to how new the field of immuno-oncology is and the lack of long-term efficacy and safety data available for immunotherapies. As our understanding of this nascent field increases, more indications will be identified and a streamlined approach to expedite the submission of supplemental applications will be a largely beneficial tool.

Ibrutinib

This kinase inhibitor was initially granted accelerated approval for the treatment of patients with mantle cell lymphoma (MCL) who had received at least one prior therapy in an open-label, multi-center, single-arm trial based on ORR as the efficacy outcome. Additional indications for treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with or without 17p deletion were fully approved after various randomized multicentered, open-label trials based on progression free and overall survival as their efficacy outcomes.

Additional indications for treatment of adult patients with Waldenström's macroglobulinemia (WM), marginal zone lymphoma (MZL), and chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy, were given approval after open-label, multicentered, single arm trials based on a surrogate endpoint (ORR) as the efficacy outcome.[13] Factors that may have supported the decision to grant full approval of supplemental indications based on ORR include: great efficacy as demonstrated by very high response rates (90.5%) observed in adult patients with WM who had received a median of 2 prior therapies, and unmet clinical need (for example, WM is very rare and although this is a slow-growing B-cell lymphoma, eventually patients progress and require therapy. Current therapies are limited for patients with WM).

Appendix Table 1: Summary of Indications for Pembrolizumab in Chronological Order By Date of Submission

Action Date	Submission	Supplement Category	Tumor Type	Indication	Type of approval
09/04/2014 12/18/2015	ORIG-1 SUPPL-4 SUPPL-6	Original Approval	Metastatic melanoma	patients with unresectable or metastatic melanoma	Accelerated approval (9/14), full approval (12/15)
10/02/2015 10/24/2016	SUPPL-5 SUPPL-8	Efficacy-New Indication	Metastatic NSCLC	treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 [Tumor Proportion Score (TPS) ≥ 1%] as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy	Accelerated approval (10/15), full approval (10/16)
08/05/2016	SUPPL-9	Efficacy-New Indication	Metastatic HNSC	treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (metastatic HNSC) with disease progression on or after platinum-containing chemotherapy	Approved under accelerated approval
10/24/2016	SUPPL-12	Efficacy-New Indication	Metastatic NSCLC	expansion of the metastatic NSCLC indication to include first-line treatment of patients whose tumors have high PD-L1 expression (TPS ≥ 50%) as determined by an FDA approved test, with no EGFR or ALK genomic tumor aberrations.	Full approval
03/14/2017	SUPPL-15	Efficacy-New Indication	Refractory classical Hodgkin Lymphoma	treatment of adult and pediatric patients with refractory classical Hodgkin Lymphoma, or who have relapsed after 3 or more prior lines of therapy	Approved under accelerated approval
05/10/2017	SUPPL-16	Efficacy-New Indication	Metastatic non-squamous NSCLC	in combination with pemetrexed and carboplatin, for the first-line treatment of patients with metastatic non-squamous, NSCLC.	Approved under accelerated approval
05/18/2017	SUPPL-17	Efficacy-New Indication	Metastatic urothelial carcinoma	for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy	Approved under accelerated approval
05/18/2017	SUPPL-18	Efficacy-New Indication	Metastatic urothelial carcinoma	for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy	Full approval
05/23/2017	SUPPL-14	Efficacy-New Indication	MSI-H, dMMR solid tumors	unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Approved under accelerated approval
05/23/2017	SUPPL-14	Efficacy-New Indication	MSI-H, dMMR CRC	metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.	Approved under accelerated approval
09/22/2017	SUPPL-24	Efficacy-New Indication	Metastatic gastric cancer	for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu targeted therapy	Approved under accelerated approval

REFERENCES

[1] Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood 2017;130(8):974–81.

[2] Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAFV600E mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. Lancet Oncol [Internet] 2016;17: 984-93. Available from: http://dx.doi.org/10.1016/ S1470-2045(16)30146-2

[3] Swanton C, Govindan R. Clinical Implications of Genomic Discoveries in Lung Cancer. N Engl J Med 2016;374(19):1864–73. Available from: http://www.nejm.org/doi/10.1056/NEJMra1504688

[4] Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1 -Rearranged Non–Small-Cell Lung Cancer. N Engl J Med 2014;371(21):1963–71. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1406766

[5] Corcoran RB, Atreya CE, Falchook GS, et al. Combined BRAF and MEK inhibition with dabrafenib and trametinib in BRAF V600-Mutant colorectal cancer. J Clin Oncol 2015;33(34):4023–31.

[6] Center for Devices and Radiological Health. Approval Order for PMA: P160045, Oncomine Dx Target Test. Accessed October 2017 https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160045A.pdf

[7] ClinicalTrials.gov, 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. Accessed September 2017 https://www.clinicaltrials.gov/ct2/show/NCT02568267

[8] ClinicalTrials.gov, Study of LOXO-101 (Larotrectinib) in Subjects With NTRK Fusion Positive Solid Tumors (NAVIGATE). Accessed October 2017 https://www.clinicaltrials.gov/ct2/show/NCT02576431

[9] Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med 2017;377:62–70.

[10] ClinicalTrials.gov, A Phase 1/2 Study of the Concomitant Administration of Indoximod Plus Immune Checkpoint Inhibitors for Adult Patients With Advanced or Metastatic Melanoma. Accessed September 2017 https://clinicaltrials.gov/ct2/show/NCT02073123

[11] ClinicalTrials.gov, A Phase I Study of GDC-0919 for Adult Patients With Recurrent Advanced Solid Tumors. Accessed September 2017 https://clinicaltrials.gov/ct2/show/NCT02048709

[12] Drugs @FDA: FDA Approved Drug Products. Biologic License Application (BLA): 125514 Accessed October 2017 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s024lbl.pdf

[13] Drugs @FDA: FDA Approved Drug Products. New Drug Application (NDA): 205552 Accessed October 2017 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205552s017lbl.pdf