



## Cost of Cancer Care: Evaluating Financial Toxicity

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It's no secret: the cost of cancer care is rising. Over the last few years, a plethora of reports have surfaced examining the seemingly outrageous cost of new cancer therapies in relation to their effectiveness. A 2010 analysis estimated the national cost of cancer care will increase from \$125 billion in 2010 to \$158 billion in 2020.<sup>1</sup> Why are expenses increasing? Reported contributing factors include an aging population with an increasing prevalence of cancer, the advent of new drugs and new techniques in radiation therapy and surgery, the increasing use of more expensive diagnostic techniques, and the availability of health care to a larger population.<sup>2,3</sup>

An oft-cited cost from “bench to bedside” for anticancer medications is \$1 billion, which is too often used as justification for the high price of drugs.<sup>4</sup> Unfortunately, the principle of “just price or fair price” does not apply to cancer medications, which are priced by their own market rules and do not follow the idiom of being priced at “what the market will bear.”<sup>5</sup> The hope is that the price reflects the benefits and value of the treatment, as well as the cost of research and development. However, this not always the case. National headlines were made in 2012 when Bach and colleagues submitted an editorial in *The New York Times* that drew attention to the price of ziv-aflibercept, which was twice that of bevacizumab despite producing similar efficacy results in patients with metastatic colorectal cancer.<sup>6</sup> Imatinib, a tyrosine kinase inhibitor (TKI), cost \$30,000 per year in 2001 when it was approved for chronic myeloid leukemia, and had inflated to \$80,000–\$92,000 in 2012. This was even though newer TKIs have since been approved in imatinib-resistant disease and have even shown improvements in early surrogate end points when compared head-to-head with imatinib.<sup>4</sup> So what actually determines the cost of a drug? The lead contributor may be reimbursement. The majority of cancer medications are dispensed within the confines of a physician’s office or ambulatory infusion clinic and are therefore covered by the patient’s medical benefits (versus pharmacy benefits). Manufacturers may competitively increase the prices of drugs to provide the dispensing physician a larger margin of financial benefit while ignoring the harmful effect on the patient’s financial situation.<sup>7</sup>

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Throughout the continuum of cancer treatment, patients undergo various procedures and systemic therapies. Numerous risks and adverse events of these treatments are well documented, but all these interventions share one toxicity in common that has gained a new official name: “financial toxicity.” Doctors Yousuf Zafar and Amy Abernethy highlighted the life-altering effect of financial toxicity in a two-part series published in the journal *Oncology* describing one patient and her family.<sup>3,8</sup> The 67-year-old breast cancer patient, nicknamed “Janet,” admitted to her physician that her family doesn’t travel anymore, nor do they “do anything” due to her “\$100,000 illness.” “It sucks,” she admitted, “but what are you going to do?”<sup>3</sup> Patients who are uninsured may trigger concerns about cost at the forefront of their care. However, with increasing medical expenses across the board, even patients with adequate insurance are feeling the sting of medical debt. Third-party payers have shifted costs to patients, increasing their out-of-pocket costs. Not only have we seen more high-deductible plans, but insurance premiums have also had a huge impact on patients’ bank accounts. Between 1999 and 2011, premiums increased 170%, while worker earnings increased only 50%.<sup>5</sup>

Cancer patients have an especially daunting problem. Nationally, 9.7% of adults with chronic conditions report a high objective financial burden. This is compared to 13% of cancer patients in the same age range.<sup>3</sup> Cancer care is one of the fastest growing components of U.S. healthcare costs, and patients are feeling the growing pains. Patients who experience high out-of-pocket costs report reduced spending on food and clothing, poor adherence to costly medications, and avoidance of recommended procedures and appointments.<sup>2</sup> It has unfortunately been accepted as “the norm” by many patients, cancelling vacations, using life savings, and working overtime just to pay for their treatments.<sup>3</sup> Out of a surveyed group of insured patients applying for financial assistance, 68% reported they cut back on leisure activities, 46% reduced spending on food and clothes, 46% used their savings, and 17% sold possessions or property just to pay for cancer-related costs.<sup>9</sup>

So, what can be done about this? The first step has already been taken. Transitioning cancer cost from the elephant in the room to a public conversation has already had an effect. Within a week of Bach and colleagues’ *New York Times* editorial, the manufacturer of ziv-aflibercept reduced the price by half.<sup>4</sup> Last year, *60 Minutes* aired a special on the cost of cancer drugs in which the term “financial toxicity” was broadcast to the masses. In the special, Leonard Saltz, MD, blamed pharmaceutical companies for taking advantage of people’s fear and anxiety about their cancer diagnosis. Hagop Kantarjian, MD, very bluntly admitted, “The only drug that works is a drug that the patient can afford.”<sup>10</sup> Dr. Saltz has continued his quest to draw attention to the unsustainable costs of cancer care. This year, in the plenary session at the American Society of Clinical Oncology (ASCO) annual meeting, he highlighted concerns with the new immunotherapy drugs reporting annual costs potentially reaching \$1 million per patient.<sup>11</sup>

There are a variety of factors that allow this extraordinary cost of medications. One of the biggest barriers is the prohibition of the Centers for Medicare and Medicaid Services (CMS) to negotiate the price of drugs coming to market, which Dr. Saltz addressed as a start to the high-cost solution. Another barrier that needs to be ameliorated is the allowance of pharmaceutical companies to pay fees to delay the introduction of competing generics.<sup>12</sup> Dr. Saltz also reinforced that the U.S. Food and Drug Administration (FDA) should be allowed to consider price in the approval process as other nations do.<sup>11</sup> The United Kingdom’s National Institute for Health and Care Excellence has a formalized process involving clinical and econometric analyses to determine the value of a new therapeutic option. Canada, Australia, France, and Germany all have similar processes that consider efficacy, toxicity, and cost in the context of disease prevalence, medical need, and prevailing alternatives. Despite the United States far exceeding these other countries in healthcare spending, improvements in health outcomes have failed to match that growth. Adults in the United States, more than any of these other countries, had access issues to health care because of treatment cost.<sup>13</sup> Patients in the United States are paying two-three times more for the same drug than patients in Canada, Australia, and other European countries.<sup>10</sup>

We are aware of the overarching issues that need to be addressed, but until they are, we have to focus on each individual patient. The question that needs to be answered first is: When is the appropriate time, if any, to talk about cost with patients? Cancer patients may be more sensitive to a discussion regarding cost in relation to value. Patients may be hesitant to broach the subject of cost on their own due to embarrassment about financial distress or inflated beliefs in benefit from therapy.<sup>8</sup> If patients are not coming forward on their own, is there a way to identify patients who may be more susceptible to financial toxicity? Singling out patients by age, ethnicity, education level, income, or employment status will not necessarily identify all patients at risk. Insured patients may be falling under the radar of who we typically think will suffer from financial toxicity. Stump and colleagues reported almost half of insured cancer patients they surveyed report concerns about costs, and 22.3% report personal and family sacrifices just to pay for their cancer care.<sup>14</sup> One recommendation is to monitor for financial toxicity the same way we would for any other toxicity from treatment: at each visit, patients would be screened for adverse events as they normally are, but with the inclusion of financial distress or concerns.<sup>8</sup> The COST (comprehensive score for financial toxicity) measure was developed for exactly this purpose. The 11-item questionnaire assesses patients' concerns about their current financial situation, future financial issues, and direct and indirect financial barriers. The final COST measure score can be used to assess the severity of an individual patient's financial toxicity.<sup>15</sup>

ASCO formed the Task Force on the Cost of Cancer Care in 2007 to address how to help providers deliver the highest-quality care without compromising for cost. In 2013, the ASCO Board of Directors charged the Task Force to develop a system to compare relative clinical benefit, toxicity, and the cost of treatment in the medical oncology setting. This framework was published in June 2015.<sup>2</sup> This framework is guided by the core principles of the physician-patient relationship to ensure informed decision-making and to encourage the provider to be a good steward of healthcare resources. The task force defined value in cancer care by emphasizing clinical benefit (efficacy), toxicity (safety), and cost (efficiency). Value was then assessed using quality-adjusted life-years and incremental cost-effectiveness ratios. Two frameworks were then developed: one for advanced cancer and another for potentially curative cancer. In the advanced disease framework, clinical benefit is given a categorical score based on the fractional improvement in median overall survival (OS) when comparing a new therapy with the standard-of-care therapy. If OS was not reported or assessed, progression-free survival (PFS) is used. If neither OS nor PFS is available, overall response rate (ORR) is used. In the curative framework, the hazard ratio (HR) between OS of the new and standard of care regimens is used. If the HR for OS is not available, then the HR for disease-free survival (DFS) is used. OS, PFS/DFS, and ORR are all weighted differently, with OS being weighted the highest as it represents the most important component of the value assessment. In both frameworks, toxicity is given a categorical score (-20 to +20) based on the relative toxicity of the new therapy versus the standard of care. Bonus points can also be awarded for statistically significant improvement of cancer-related symptoms or improvement in treatment-free interval. Once the points are combined, it results in the net health benefit (NHB) score. Two types of cost estimates

are included: drug acquisition cost and patient cost. The NHB is then compared to cost to facilitate the assessment of value.<sup>2</sup>

There are weaknesses with these frameworks. First, their comparisons are extremely narrow in scope. They can only compare therapies within the context of the study and not to other regimens. Second, the information provided by these frameworks must be able to be presented in an understandable way to patients to ensure their participation in treatment-related decisions.<sup>2</sup> As the task force continues to strengthen these frameworks for general use, they are still useful conversation-starters about the value of care.

Pharmacists are primed to help patients handle financial toxicity—not only on an individual basis, but also as a whole organization. Kantarjian and colleagues recommended that professional societies representing cancer specialists should reduce the hype around new antineoplastics that have no major effects on patient outcomes.<sup>5</sup> Pharmacists can provide information through pharmacy technicians specifically trained to handle prior authorization requests and well-versed in the various patient assistance programs. Pharmacy technicians specially dedicated to these programs can greatly reduce the stress on patients who may not be familiar with the particular avenues available. When a patient is set to start a new, possibly cost-prohibitive treatment, the pharmacy technician would be immediately involved to search out and summarize the financial assistance programs for which the patient may be eligible.

Pharmacists can also be more involved with economic analyses research. This is especially impactful to show how cost affects patient adherence, and therefore outcomes. If the discussion of cost is brought to the forefront of prescribing, pharmacists and prescribers can have open conversations about what is in the patient's best interest. This may not always be appropriate when considering chemotherapy. However, when discussing supportive care options, there may be a variety of medications to choose from that are similar in effectiveness yet vastly different in cost.

The evaluation of cost in relation to benefit is not a new concept. Aristotle was the first to examine cost in relation to worth in the *Nicomachean Ethics*. More than 2,000 years later, we are still striving for Aristotle's *justum pretium*: the just price. Determining the just price for cancer care is a conflict the oncology community is not quite prepared to handle. However, the first steps towards curing financial toxicity are being taken with increased conversation and development of cost-conscious practice guidelines. 

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# Reliability of PD-L1 as a Predictive Biomarker in NSCLC

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Even through numerous developments in treatment, lung cancer remains the leading cause of cancer death in the United States.<sup>1</sup> Many avenues have been attempted to prolong overall survival of this disease. The most recent has been immunotherapy, specifically immune-checkpoint inhibitors targeted at the programmed death 1 (PD-1) receptor. Nivolumab and pembrolizumab are the two immunotherapies currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of progressive non-small cell lung cancer (NSCLC). Although these agents may be similar in target, their respective journeys to approval revealed we have much to learn about the impact of these therapies.

Nivolumab was approved first for squamous NSCLC in March 2015 based on the CheckMate-017 phase 3 trial. This compared nivolumab to docetaxel in patients with advanced squamous NSCLC who had progressed on or after receiving a platinum-based chemotherapy regimen. Nivolumab provided an improved median overall survival (9.2 versus 6.0 months), response rate (20% versus 9%), and progression-free survival (3.5 versus 2.8 months) over docetaxel. Nivolumab also produced fewer grade 3 or 4 adverse events at 7%, compared with the 55% in the docetaxel group.<sup>2</sup> In October 2015, the FDA extended the approval to non-squamous NSCLC based on the results of the CheckMate-057 phase 3 trial. CheckMate-057 compared nivolumab to docetaxel in patients with non-squamous NSCLC after progression during or after platinum-based chemotherapy. Again, nivolumab proved superior to docetaxel, with improved overall survival (12.2 versus 9.4 months) and response rates (19% versus 12%). The data for median progression-free survival did not actually favor nivolumab (2.3 versus 4.2 months). However, at 1 year, a higher percentage of patients treated with nivolumab were alive than those treated with docetaxel (19% versus 8%), representing a delay in response to therapy known to occur with immunotherapy. Nivolumab still proved to be better tolerated, with only 10% reporting grade 3 or 4 adverse events compared to the 54% in the docetaxel group.<sup>3</sup>

Pembrolizumab was approved for NSCLC in October 2015 based on the data from the phase I KEYNOTE-001 trial. The objectives of KEYNOTE-001 were to evaluate the side effects, safety, and anti-tumor activity of pembrolizumab in NSCLC patients, as well as define and validate a tumor PD-L1 expression level associated with an increased likelihood of benefit from pembrolizumab. Pembrolizumab was given at a dose of 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, or 10 mg/kg every 2 weeks. PD-L1 positivity was determined by an immunohistochemical (IHC) assay and defined as at least 1% of cells showing membranous staining (proportion score). The investigators determined  $\geq 50\%$  proportion score as the cutoff for validation of

PD-L1 as a predictive biomarker. The most common adverse events reported were fatigue, pruritus, and decreased appetite. The overall response rate was 19.4% across untreated and previously treated patients. Median overall survival was 12 months and progression-free survival was 3.7 months. No differences in response rates or toxicities were seen between the varying doses and schedules; therefore, the investigators recommend the 2 mg/kg every 3 week schedule. Patients with  $\geq 50\%$  proportion score per the validation assay had longer progression-free survival than patients with 1% to 49% or  $< 1\%$  proportion scores (6.3 versus 4.1 versus 4.0 months, respectively) and longer overall survival (not reached versus 10.6 versus 10.4 months, respectively). The FDA approval for pembrolizumab in NSCLC dictates patients must test positive for PD-L1 with the companion diagnostic assay.<sup>4</sup>

KEYNOTE-001 suggests that PD-L1 expression (at  $\geq 50\%$  proportion score) may represent a predictive biomarker for the treatment of NSCLC with pembrolizumab.<sup>4</sup> However, the CheckMate trials provide conflicting reports on whether PD-L1 expression is a valid biomarker. CheckMate-017 defined samples as PD-L1 positive at predefined levels of 1%, 5%, and 10% and found no difference in predictive benefit of nivolumab activity.<sup>2</sup> CheckMate-057 used the same IHC assay as CheckMate-017 and the same predefined positivity levels. At the interim analysis, an association between PD-L1 expression and clinical outcome was described. Expression above the predefined levels all correlated with better survival outcomes than docetaxel; however, in patients whose tumors had negative expression, the survival outcomes were similar to docetaxel. The authors concluded that because the safety profile of nivolumab out-performed docetaxel, nivolumab should still be considered an option regardless of PD-L1 expression.<sup>3</sup>

The question these three trials raise is whether PD-L1 is a reliable biomarker for predictive response to immunotherapy, particularly in NSCLC.

In the CheckMate trials assessing nivolumab in NSCLC, PD-L1 expression was relatively consistent at 83% in CheckMate-017 and 78% in CheckMate-057.<sup>2,3</sup> In KEYNOTE-001, 23.2% of patients had a proportion score of at least 50% and 37.6% had 1%-49%.<sup>4</sup> Other trials exploring immunotherapies in NSCLC describe positivity for PD-L1 expression ranging from 21% to 95%. PD-L1 expression varies with disease state, with reports for melanoma patients ranging from 38% to 100% and reports for renal cell carcinoma ranging from 14% to 54%, depending on which site of disease was tested (primary versus metastasis).<sup>5</sup> The wide range of positivity could be explained by each disease state's heterogeneity; however, trials have not been consistent

in which IHC assay has been used to determine PD-L1 positive expression.

As of this time, there is no standard IHC assay used to calculate expression of PD-L1, nor is there a standard definition of “positive” expression. There are about two dozen anti-human PD-L1 antibodies currently being used in IHC assays, including 28-8, 5H1, MIH1, and 20C3. In addition, manufacturers of PD-1 and PD-L1 inhibitors concurrently develop their own proprietary companion test when seeking FDA approval. All these different assays complicate the ability to possibly standardize PD-L1 positive quantification. Cutoff points for positive PD-L1 expression range from >1% to >50%, which would explain the incidence of patients who are considered PD-L1 “positive” yet do not respond to immunotherapy as expected, and conversely, the patients considered PD-L1 “negative” who do respond to therapy.<sup>6</sup> Although PD-L1 expression may not be the best biomarker to include or exclude patients to receive immunotherapy, levels of expression could possibly be used to guide which regimens of immunotherapy may benefit the patient the most. It is clear that patients who have higher

rates of PD-L1 expression do respond better to single-agent immunotherapy, and patients who have lower or negative rates of PD-L1 expression may be better suited to receive combination immunotherapy. Differing levels of expression could also be used to stratify patients in clinical trials exploring new combinations of immunotherapy.<sup>7</sup>

Although PD-L1 presents as a tempting predictive biomarker for immunotherapy in NSCLC, there are a few barriers before relying on PD-L1 as a definitive biomarker to choose which patients should or should not receive immunotherapy. Standardization must occur across assays as to which anti-PD-L1 antibody is used for expression description. The cut-offs for what constitute positivity must also be addressed, and may be dependent on tumor type, biopsy site, and assay used to determine positivity. As immunotherapy becomes an option for more patients with oncologic diseases, these issues will hopefully be addressed through future clinical trials.

For more information, see the article “Nivolumab for Non-Small Cell Lung Cancer” on page 18. 

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## Board Update: New Beginnings at HOPA

Scott Soefje, PharmD MBA BCOP FCCP, HOPA President

It is just after New Year's Day as I write this and I am thinking of new beginnings.

HOPA starts a major new beginning this year as a provider of recertification education for the Board Certified Oncology Pharmacy (BCOP) program. While HOPA has been providing BCOP programming at our Annual Meeting for several years, that programming was in collaboration with the American College of Clinical Pharmacy, and was offered as a convenience to our members. We did organize and develop the programming and gain valuable insight into what the oncology pharmacist wanted, but we were not the official providers. This year we move into official-provider status and I want to spend time outlining what this means for oncology pharmacists.

To understand how HOPA became a provider, you need to know a little history. The 2015 response to a request for proposal (RFP) was not the first time that HOPA had planned to respond to the Board of Pharmaceutical Specialties (BPS) call for new programs. Several years ago, the HOPA board authorized a group to develop a proposal in anticipation of BPS putting out an RFP. This proposal was never submitted, because BPS put a freeze on new program development while it conducted a self-study to determine the effectiveness of board certification for pharmacists. HOPA participated in BPS task forces to provide feedback on the benefits and needs of the certification process. In 2015, the call went out again for providers for BPS programming. HOPA submitted to become a BCOP provider and heard from BPS in mid June 2015 that we had been accepted as one of two providers.

Then the real work started. Our proposal was that we would start the offering in January 2016. We had to develop the infrastructure, the committees, the process, and, finally, the content to offer our first webinar by February 2016. A daunting task for any organization, but I can say, HOPA pulled it off exceptionally well. We also listened to our membership and designed a BCOP recertification program that meets the current needs of the oncology pharmacist. We are offering 38 hours per year of qualified recertification education credits. These are broken down into four different offerings. Let us take a closer look at each offering.

First are the **Emerging Issues in Oncology Pharmacy webinars**. Five webinars, 1 hour each, will recap the best of and most important information needed by oncology pharmacists from five of the top oncology meetings including ASH, San Antonio Breast Cancer Symposium, ASCO, ASPHO, and ASBMT Tandem Meetings. These webinars will be live and enduring allowing you to view them on your own schedule. We then have the **programming at the Annual Meeting in Atlanta**. This programming will be 8 hours and will be repeated at the Practice Management Symposium in Chicago and eventually made an enduring program online. We listened to members and no longer do you have to get all 8 hours at one venue. You can mix and match as it suits your needs.

New this year, HOPA is beginning our third live annual program with the **Oncology Pharmacy Updates Course**. This course will focus on BCOP-level content that, over a 3-year period, will cover all of the core elements required for BCOP recertification. This is not an entry level course. We heard from members that there was a need to “ramp up the content” to reflect the level of practice a BCOP pharmacist provides. Held in July every year, this course provides that higher level of learning and will be a live session offering 10 hours of credit. This content will ultimately be put online as well. Lastly is the **Self-Study Online Program**. This 15-hour program is a mix of case-based learning and literature review focusing on new advances that will affect oncology pharmacy practice. This program will be entirely online and will allow self-paced learning.

This programming provides an exciting new start to the BCOP offerings for HOPA. We feel we have developed a diverse set of programs that will meet the educational needs of our members, but we still want your feedback. As you can see, many of the ideas and programming are based directly on feedback from the members, so it is extremely important that you continue to provide that feedback.

Our Annual Meeting offers another opportunity for beginnings—our first off-site preconference symposium. Emory University has opened up its campus to offer the preconference “Phase I Clinical Trials: Establishing a Culture and Infrastructure for Conducting Drug Development Studies.” We have other preconference offerings in bone marrow transplantation and immuno-oncology, so we hope there is something for everyone.

Every year we struggle to bring in a keynote speaker that excites, interests, and provides relevant information to the oncology pharmacist. I hinted in an earlier address that we would have a special speaker, and I am very pleased that this year we were able to get one of the most popular requests on the member feedback to be our speaker. We are pleased to welcome Siddhartha Mukherjee, MD PhD, a leading cancer physician and researcher, as our John G. Kuhn Keynote lecturer. You may know Dr. Mukherjee as the author of *The Laws of Medicine* and *The Emperor of All Maladies: A Biography of Cancer*, which won the Pulitzer Prize for general nonfiction in 2011. The latter book was converted into a 6-hour Public Broadcasting Service (PBS) offering by Ken Burns and Barak Goodman, which aired on PBS in March 2015. We look forward to Dr. Mukherjee's insights and views on cancer care.

While 2015 was an exceptional year for HOPA—our accomplishments are numerous, our external connections grew, and we see a strong and healthy organization—I can only imagine what 2016 will bring us. We are definitely off to a great start. New beginnings bring great new opportunities. So make sure you take advantage of the BCOP offerings and I hope to see every one of you at the Annual Meeting in Atlanta.

Happy New Year! 

## Highlights from the JADPRO Live at APSHO 2015 Conference

Megan Brafford May, PharmD BCOP

Clinical Oncology Pharmacy Specialist

Baptist Health Lexington

Lexington, KY

The third annual *Journal of the Advanced Practitioner in Oncology* (JADPRO) Live conference was held in Phoenix, AZ, on November 5–8, 2015. This conference was held in conjunction with the second annual Advanced Practitioner Society for Hematology and Oncology (APSHO) meeting. The focused theme of this year's meeting was "Collaborate, Learn, Care, and Lead" and concentrated on advanced practitioners and physicians coming together to discuss current treatment options and advances in the care of cancer patients. The first day of the conference consisted of multiple workshop options: grant writing advice, an immunotherapy primer, everyday applications to be used as tools and technology, primary care considerations for the patient with cancer, and a hands-on skills workshop reviewing bone marrow aspiration, lumbar puncture, Ommaya reservoir placement, punch biopsy, and suturing.

The remaining three days consisted of more than 20 educational sessions comprising didactic, interactive, patient case-based and evidence-based content targeted to advanced practitioners in oncology, including nurse practitioners, physician assistants, clinical nurse specialists, other advanced-degree nurses, hematology/oncology nurses, pharmacists, and physicians. Each presentation reviewed best practices involving a multidisciplinary setting. One of the unique characteristics of the JADPRO Live conference is that the majority of presentations included at least two speakers with different roles from the multidisciplinary team.

One of the panel discussions on "Revolution at the Corner Drugstore" addressed the importance of the collaborative practice team in order to manage multiple issues regarding the increased use of oral chemotherapies such as drug payment assistance, monitoring for drug adherence, dosing issues, proper patient education, and managing toxicities. The panel stated, "with approximately 800 oncology drugs in the pipeline and 40% of these being oral medications and 80% of those being first-in-class medications, the need for increased awareness of oral chemotherapies is imperative." Each year, approximately \$100 billion to \$300 billion dollars are spent on health care due to non-adherence. The panel discussed the benefit of providing calendars

to patients on oral agents to increase adherence. Matthew Farber (senior director of oncology for Walgreens) noted that pharmacists can and should play a larger role in assisting patients with reimbursement and other critical issues related to oral therapy. Other major topics discussed included herbals and supplements and their interaction with oral chemotherapies, as well as the need for accurate medication reconciliation.

An additional program directly related to pharmacy topics included "Review of Newly Approved Oncologic Therapies." This was a great review of pharmacology and indications of every new oncology/hematology drug approved in late 2014 and the first half of 2015. Recommendations for monitoring and management of treatment-related toxicities were also addressed. Lastly, this presentation emphasized the impact of each of these medications on advanced practitioners and how to utilize each medication in clinical practice.

Another highlight was the keynote presentation by Laura Adams, titled "There's a Patient on the Care Team: The New Design for Health and Healing." The resonating statement throughout the presentation was the confirmation that what we do as healthcare professionals matters and that we touch our patients' lives with everything we do. Laura shared her concerns regarding the lack of patient record sharing throughout our entire healthcare system and addressed the many issues this creates for our patients. She also shared her personal story regarding coping with and surviving breast cancer. Utilizing her personal experiences, she is educating providers to ensure the patient is a part of each medical team. Collaboration may be the most important survival strategy for every organization and the patient. She left the audience with the quote "We can only connect the dots we collect."

JADPRO Live at APSHO 2015 gave practitioners the opportunity to network with providers from various specialties and work together to better serve our patients. More information about joining APSHO and attending JADPRO Live can be found at the website [www.apsho.org](http://www.apsho.org). Save the date for the 2016 meeting at the Gaylord National Hotel in Washington, DC, November 3–6, 2016. 

# Survey of Interest in Future HOPA Standards/White Papers: Summary of Results

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In February 2015, a survey was submitted to the HOPA membership to identify topics for future standards or white papers. This survey was prepared and reviewed by members of the Standards Committee. The survey asked participants about practice setting, time in clinical practice, and their interest in a list of topics for future standard or white paper development. Survey participants also had the opportunity to identify additional topics of interest not listed in the survey.

**Results:** There were a total of 225 responses to this survey, capturing 10% of HOPA's membership. The majority of respondents (65%) classified themselves as clinical oncology pharmacists; 31% had been in practice for less than 5 years and 23% for 5–10 years. Approximately 29% of survey participants listed their primary practice setting as hospital inpatient, while an additional 27% listed it as an ambulatory infusion center.

Given a list of potential topics for standard or white paper development, survey participants rated development of chemotherapy template standards/decision-making tools and dose rounding of chemotherapy/targeted therapy (average score of 4.08 and 3.89 out of 5, respectively). When asked to rate the two top priority projects for potential standard or white paper development, development of chemotherapy template standards and decision-making tools, as well as dose rounding of chemotherapy/targeted therapy, scored highest (47% and 38%, respectively). Additional lower-priority topics were considered, including pharmacist involvement in personalized medicine (36%), clinically relevant drug interactions between chemotherapy and complementary and alternative medicine (29%), oncology residency training clinical experiences (16%), drug triage in shortage situations (17%), pharmacy involvement in survivorship programs (13%), and fertility preservation and the involvement of pharmacists (3%).

When asked to provide additional potential topics, there were 31 suggestions that could be further categorized: oral chemotherapy (six responses), chemotherapy dosing (five responses), training/education (seven responses), administrative (six responses), and miscellaneous suggestions (seven responses). Requested topics included additional published guidance for dosing chemotherapy in special populations (e.g., obesity, organ dysfunction, age), benchmarking data for justification of additional pharmacist positions, and pharmacist involvement/training in outpatient oral chemotherapy management.

**Conclusions:** This survey indicated that HOPA membership would prioritize standards or white paper creation for dose rounding of chemotherapy/targeted therapy and development of chemotherapy template standards and decision-making tools. After further review of currently available publications and standards, the Standards Committee and the HOPA Board of Directors recommended pursuing a white paper on dose rounding of chemotherapy and targeted agents since there is minimal published guidance. This paper would offer the greatest impact for the HOPA membership. The Standards Committee will be meeting to further discuss this project.

Available resources for chemotherapy template standard and decision-making tools include the National Comprehensive Cancer Network ([www.nccn.org](http://www.nccn.org)) with disease-specific order set templates for purchase, the American Society of Clinical Oncology ([www.asco.org](http://www.asco.org)) with staging guidelines for specific cancers, and the Institute for Safe Medication Practices ([www.ismp.org](http://www.ismp.org)) with guidelines for standard order sets.

We thank the membership for your responses to this survey, as well as the individuals who developed, reviewed, and summarized the survey.



## HOPA Central

## UPDATES

HOPA Central is approaching its first anniversary! We are always looking at ways to improve the member community, and with the help of member feedback, we have made a couple of small changes to improve the user experience:

- HOPA members can now reply to a thread directly from their Daily Digest without having to log into HOPA Central. If you have logged in within the past 21 days, you can use the Reply to Group Online option without logging in again. This auto login will last for 21 days, after which you will be required to log in again. Please note: With this change, it is important to know that if you forward digest messages to colleagues, and he or she replies to the thread, the reply will appear from you as it will still be under your profile.
- HOPA has increased the number of allowable poll questions in the Code of Conduct to **no more than 5 questions**. This means that you can now post up to five questions per discussion post.



# Recalls and Safety Alerts from the FDA

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## Recalls

### Fluorouracil Injection (Adrucil)

Teva Parenteral Medicines issued a voluntary recall of six lots of fluorouracil injection (5 g/100 mL) because of the potential presence of silicone rubber pieces from a filter diaphragm and fluorouracil crystals. There have been no adverse events reported. For a full list of recalled products, visit, <http://www.fda.gov/Safety/Recalls/ucm456093.htm>.

### Gemcitabine and Methotrexate

Mylan has issued a voluntary recall of select lots of injectable products, including gemcitabine and methotrexate, because of the presence of visible particles observed during a routine quality test. Lots of gemcitabine for injection were distributed in the United States between January 8, 2014, and February 10, 2015. Methotrexate lots were distributed in the United States between December 8, 2014, and December 19, 2014. There have been no adverse events reported related to this recall.

<http://www.fda.gov/Safety/Recalls/ucm450140.htm>

### Moses Lake Professional Pharmacy Recall in Washington

Moses Lake Professional Pharmacy of Moses Lake, WA, voluntarily recalled certain unexpired human and veterinary sterile compounded drugs. This recall was a result of the lack of sterility assurance. These products were made from July 21, 2014, through July 21, 2015, and dispensed to patients or distributed to physicians in Arizona, Idaho, Florida, Oregon, Texas, and Washington. There have been no adverse events reported from the recalled products. For a complete listing of affected drugs, visit:

<http://www.fda.gov/Safety/Recalls/ucm455925.htm>

## Safety Alerts

### Anagrelide (Agrylin)

The clinical trial subsection under the adverse reactions section has been edited to list other less frequent adverse reactions (<1%) in both cardiac disorders (ventricular tachycardia, supraventricular tachycardia) and nervous system disorders (hypoesthesia).

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm175918.htm>

### Brentuximab (Adcetris)

Due to reports of fatal outcomes related to respiratory issues with brentuximab use, updates have been made in the warning and precautions section along with the adverse reactions section to address pulmonary toxicity. Pneumonitis, interstitial lung disease, and acute respiratory distress syndrome can occur and patients receiving brentuximab should be closely monitored for signs and symptoms of pulmonary toxicity. The medication should be held in the event of new or worsening pulmonary symptoms.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm426241.htm>

### Cabazitaxel (Jevtana)

Cabazitaxel is now contraindicated for use in patients with severe hepatic impairment (total bilirubin  $>3$  ULN). Recommendations for use in patients with mild and moderate hepatic impairment have been added to the warning and precautions section of the prescribing information. Dose reductions should be made in the setting of mild (total bilirubin  $>1$  to  $\leq 1.5$  x ULN or AST  $>1.5$  x ULN) and moderate (total bilirubin  $>1.5$  to  $\leq 3.0$  x ULN and any AST) hepatic impairment. The updated warnings and precautions section includes bone marrow suppression, specifically neutropenia and its clinical consequences. Blood counts should be monitored carefully to determine if dose modifications or G-CSF is needed. Patients with high-risk clinical features should be considered to receive prophylaxis with G-CSF. The use of cabazitaxel should also be used with caution in patients with hemoglobin  $<10$  g/dL.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm392358.htm>

### Ceritinib (Zykadia)

Updates have been made to the warnings and precautions section of the package insert for ceritinib. The update includes the risk of hepatotoxicity, QT interval prolongation, hyperglycemia, and pancreatitis. The clinical trials had less than 1% of patients having concurrent elevations in ALT greater than three times the ULN and total bilirubin greater than two times the ULN with normal alkaline phosphatase. QTc interval prolongation occurred in patients receiving ceritinib in clinical trials and should be monitored throughout treatment as it can lead to cardiac arrhythmia and sudden death. Serum glucose levels should be routinely monitored before and throughout treatment with ceritinib since hyperglycemia can occur. The clinical trials also showed pancreatitis occurring in less than 1% of patients on ceritinib, but there has been one report of a pancreatitis-related fatality. There are recommendations to monitor lipase and amylase prior to starting treatment with ceritinib and periodically during treatment. Depending on the severity of laboratory abnormalities, the medication should be held and dose reduction recommendations can be found in Table 1 of the package insert. Due to the potential seriousness of pancreatitis, the patient counseling information recommends that patients starting therapy with ceritinib be counseled on the signs and symptoms of pancreatitis.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm458065.htm>

### Darbepoetin alfa (Aranesp)

The increased possibility of mortality, myocardial infarction, stroke, and thromboembolism has been edited in the warnings and precautions section to specify "adult patients" in Table 2 of the package labeling.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm458055.htm>

## Dasatinib (Sprycel)

The updated warnings and precautions section of the prescribing information includes myelosuppression, fluid retention, and severe dermatologic reactions. Patients with chronic phase CML should have complete blood counts (CBCs) drawn every 2 weeks for 12 weeks, then every 3 months thereafter or as clinically indicated. CBCs should be performed weekly for the first 2 months of therapy and then monthly thereafter or as clinically indicated in patients with advanced phase CML or Ph+ ALL. The clinical trials with dasatinib use in patients with chronic phase CML and advanced phase CML or Ph+ ALL showed grade 3 or 4 fluid retention in the reported 5%–8% range. Patients developing symptoms of pleural effusion or other fluid retention should be evaluated promptly. Fluid retention events can typically be managed by supportive care measures such as diuretics or short courses of steroids. Dose reductions or treatment interruption should be considered in those patients that experience fluid retention while on dasatinib therapy.

There have been reports of severe mucocutaneous dermatologic reactions, including Stevens-Johnson syndrome and erythema multiforme, in patients receiving dasatinib. These skin and subcutaneous tissue disorders have been added to the postmarketing experience of the package labeling. Dasatinib should be permanently discontinued in patients who experience severe mucocutaneous reactions during therapy when no other causes can be identified.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm223728.htm>

## Deferasirox (Exjade)

Renal tubular necrosis and gastrointestinal perforation has been added to the postmarketing experience under the adverse reactions section of the package labeling. The warnings and precautions now address reports of ulcers and gastrointestinal perforations, including those with fatal outcomes. Severe skin reactions have also been included in this section. If Stevens-Johnson syndrome or erythema multiforme is suspected, deferasirox should be discontinued permanently. For patients who experience skin rash while on deferasirox, the medication should not be resumed until the rash is completely resolved.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm200643.htm>

## Denosumab (Xgeva)

The prescribing information for denosumab has been revised to update information on hypocalcemia and osteonecrosis of the jaw (ONJ) in the warnings and precautions section. Fatal cases of severe hypocalcemia while using denosumab have been reported. Pre-existing hypocalcemia should be corrected prior to initiating therapy with denosumab and frequent monitoring of calcium levels needs to be performed throughout treatment. Supplementation of calcium, magnesium, and vitamin D should be administered when necessary. In clinical trials, there was an increased risk of hypocalcemia seen in patients with severe renal dysfunction (creatinine clearance less than 30 mL/minute or on dialysis), and with inadequate/no calcium supplementation. In patients who developed ONJ while on denosumab, 79% had a

history of tooth extraction, poor oral hygiene, or use of a dental appliance as a predisposing factor. Other risk factors for developing ONJ include immunosuppressive therapy, treatment with angiogenesis inhibitors, systemic corticosteroids, diabetes, and gingival infections. Patients should have an oral examination and preventive dentistry prior to starting denosumab and periodically throughout therapy. Invasive dental procedures should be avoided while on denosumab therapy.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm303740.htm>

## Enzalutamide (Xtandi)

The warnings and precautions section of the package labeling for enzalutamide has been revised to include the reports of posterior reversible encephalopathy syndrome (PRES). Symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances that can present rapidly with PRES. Brain imaging is required to diagnose PRES and enzalutamide therapy should be discontinued in patients that develop PRES.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm460724.htm>

## Etoposide Injection (Etopophos)

The package labeling has a new infertility subsection under the warnings section to give information about contraception precautions and the potential loss of fertility. The drug interactions have been updated to take precaution when using antiepileptic medications concurrently with etoposide.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm250461.htm>

## Filgrastim (Neupogen)

The updated warning and precautions section includes glomerulonephritis, which has been added to the postmarketing experience. Glomerulonephritis has occurred in patients on filgrastim. The diagnoses were made with a renal biopsy and presence of azotemia, hematuria (microscopic and macroscopic) and proteinuria. Reductions in dose or discontinuation of the medication should be made if glomerulonephritis occurs. The patient counseling information section addresses this issue of glomerulonephritis and recommends educating patients on the symptoms such as swelling of the face or ankles, dark colored urine or blood in the urine, or a decrease in urine production.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm219032.htm>

## Hydroxyurea

The boxed warning for hydroxyurea now includes myelosuppression and malignancies. Blood counts should be monitored at baseline and throughout treatment as hydroxyurea may cause severe myelosuppression. Treatment should be interrupted and dose reductions performed as necessary. Since hydroxyurea is carcinogenic, patients on therapy should be monitored for malignancies and counseled on sun protective measures.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm458082.htm>

### **Ipilimumab (Yervoy)**

Skin disorders, specifically drugs with eosinophilia and systemic symptoms (DRESS syndrome), have been reported during the postapproval use of ipilimumab and is included in the postmarketing section of the labeling information. These reactions are voluntarily reported from a population of unknown size and it is not always possible to estimate their frequency or establish a causal relationship to ipilimumab exposure.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm328023.htm>

### **Pembrolizumab (Keytruda)**

The warnings and precautions section of the prescribing information for pembrolizumab has been updated to include immune-mediated endocrinopathies (hypophysitis, thyroid disorders, and type 1 diabetes mellitus), other immune-mediated adverse reactions, and infusion-related reactions. For patients receiving pembrolizumab, signs and symptoms for hypophysitis, including hypopituitarism and adrenal insufficiency, should be monitored carefully. The drug should be held for moderate (Grade 2) hypophysitis, held or discontinued for severe (Grade 3) hypophysitis, and permanently discontinued for life-threatening (Grade 4) hypophysitis. Corticosteroids should be administered for Grade 2 or greater hypophysitis. Thyroid disorders can occur at any time during treatment with pembrolizumab, as both hyperthyroidism (1.2%) and hypothyroidism (8.3%) occurred in the clinical trial. Corticosteroids should be administered for Grade 3 or greater hyperthyroidism, hold treatment for severe (Grade 3) hyperthyroidism, and permanently discontinue the drug for life-threatening (Grade 4) hyperthyroidism. Isolated incidents of hypothyroidism can be managed with replacement therapy alone. Type 1 diabetes mellitus and even diabetic ketoacidosis have occurred in patients on therapy with pembrolizumab. Insulin should be given for type 1 diabetes and treatment should be held in cases of severe hyperglycemia. Patients should be monitored for signs and symptoms of diabetes while receiving pembrolizumab.

Significant immune-mediated adverse reactions have occurred across clinical studies with pembrolizumab such as severe dermatitis, myasthenic syndrome, optic neuritis, and rhabdomyolysis. Pembrolizumab should be held based on the severity of the reaction and corticosteroids should be administered. If the adverse reaction improves to Grade 1 or less, corticosteroids may be tapered over at least one month, and pembrolizumab may be resumed if the reaction stays at Grade 1 or less. The drug should permanently be discontinued for any severe or Grade 3 immune-mediated reaction that recurs and for any life-threatening adverse reaction.

Infusion-related reactions (e.g., fevers, chills, rigors, flushing, rash, hypotension), including severe and life-threatening reactions, have been reported in patients on therapy with pembrolizumab. Discontinue the drug if there are any severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm454354.htm>

### **Thalidomide (Thalomid)**

The risk of thrombocytopenia has been added to the warnings and precautions section of the package labeling for thalidomide. Blood counts, platelet counts, and signs and symptoms of bleeding should be carefully monitored as dose reductions, treatment delays, or discontinuation of therapy may be required.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm402899.htm>

### **Topotecan Injection (Hycamtin)**

The boxed warning has been revised to include the risk of severe bone marrow suppression. Topotecan injection should only be administered to patients with baseline neutrophil counts greater than or equal to 1,500 cells/mm<sup>3</sup> and platelet counts greater than or equal to 100,000 cells/mm<sup>3</sup>.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm208464.htm>

### **Vemurafenib (Zelboraf)**

The drug interactions section of the prescribing information has been revised to include the effect of vemurafenib on P-glycoprotein (P-gp) substrates. There was a 1.8-fold increase in systemic exposure of digoxin, a P-gp substrate, when given concurrently with vemurafenib. Concurrent use of P-gp substrates known to have narrow therapeutic indices should be avoided. If these medications are unavoidable, then dose reductions should be considered in the P-gp substrates.

The updated warnings and precautions section for vemurafenib addresses the reported cases of radiation sensitization and recall. Some cases were severe and involved cutaneous and visceral organs in patients treated with radiation prior to, during, or subsequent to vemurafenib treatment. Patients should be monitored closely if they are receiving concurrent treatment with vemurafenib and radiation. Radiation sensitization and recall has also been included in the postmarketing experience under the adverse reactions section. Gastrointestinal disorders, specifically pancreatitis, have been added to the postmarketing experience as well.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm364374.htm>

### **Zoledronic Acid (Zometa)**

The new labeling for zoledronic acid includes the risk of osteonecrosis of the jaw (ONJ) in the warnings and precautions section, along with reports of Stevens-Johnson syndrome in the adverse reactions section. The duration of exposure to bisphosphonates increases the risk of ONJ. Case reports have been made of Stevens-Johnson syndrome and toxic epidermal necrolysis in patients receiving zoledronic acid.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm244411.htm>

## Gefitinib (Iressa®)

**Class:** Epidermal Growth Factor Receptor (EGFR) Inhibitor, Tyrosine Kinase Inhibitor

**Indication:** Non-small cell lung cancer (NSCLC), metastatic, with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations

**Dose:** 250 mg by mouth once daily

**Dose modifications:** Increase gefitinib to 500 mg once daily when given with strong CYP3A4 inducers (in the absence of severe adverse drug reactions); reduce gefitinib dose back to 250 mg once daily 7 days after discontinuing the strong CYP3A4 inducer.

**Common adverse effects:** Diarrhea and skin reactions (including rash, acne, dry skin, pruritus, or itching)

**Serious adverse effects:** Interstitial lung disease, hepatotoxicity, gastrointestinal perforation, severe diarrhea, and ocular disorders

**Drug interactions:** Gefitinib is primarily metabolized via CYP 3A4 and 2D6. Dose of gefitinib should be temporarily increased when given with strong CYP3A4 inducers. Elevated gastric pH may also reduce gefitinib plasma concentrations. Avoid concomitant use of proton pump inhibitors, if possible.

## Gefitinib for Non-Small Cell Lung Cancer

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Lung cancer currently ranks second among cancer diagnosis and first among causes of cancer death in the United States.<sup>1</sup> Approximately 221,000 new cases of lung and bronchus cancer were diagnosed in 2015. Of those with a lung cancer diagnosis, approximately 158,000 died in 2015.<sup>1</sup>

The World Health Organization classifies lung cancer into two main types: small cell lung cancer and non-small cell lung cancer (NSCLC).<sup>2</sup> NSCLC comprises approximately 85% of all lung cancers and can be further classified into two major types: adenocarcinoma and squamous cell carcinoma.<sup>3</sup> Several predictive biomarkers may also be found in NSCLC. These include epidermal growth factor receptor (EGFR) mutations and ALK mutations, both of which can be targeted with medications.<sup>2-4</sup> EGFR mutations, in particular, occur in approximately 10% of NSCLC tumors.<sup>2</sup>

In July 2015, the FDA granted gefitinib orphan product designation for the treatment of EGFR mutation-positive metastatic NSCLC.<sup>5</sup> The National Comprehensive Cancer Network (NCCN) guidelines now list gefitinib—along with erlotinib and afatinib—as a category 1

recommendation for first-line therapy in patients with NSCLC and a sensitizing EGFR mutation.<sup>4</sup> The drug originally received FDA approval in 2003 specifically for the treatment of patients with advanced NSCLC after progression on platinum doublet chemotherapy and docetaxel. When subsequent studies failed to show clinical benefit, however, gefitinib was voluntarily withdrawn from the market.

Gefitinib's new designation was primarily based on a multicenter, phase IV, single-arm study.<sup>6</sup> The trial, published in the *British Journal of Cancer* in 2014, included 106 Caucasian patients with sensitizing EGFR mutations.<sup>6</sup> All patients received 250 mg of gefitinib daily until progression.<sup>6</sup> Primary end point was objective response rate (ORR), which was defined as a composite of complete response plus partial response based on the Response Evaluation Criteria In Solid Tumors.<sup>6</sup> Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety.<sup>6</sup> Authors reported an ORR of 69.8% (95% Clinical Interval: 60.5–77.7).<sup>6</sup> Secondary endpoints included a DCR of 90.6% median PFS 9.7 months (95% CI: 8.5–11.0), median OS 19.2 months (95% CI: 17.0–NR).<sup>6</sup> Most common adverse events included rashes (44.9%) and diarrhea (30.8%).<sup>6</sup>

The FDA briefing also cited confirmatory results of a subset analysis of a randomized, multicenter, open-label trial of patients with metastatic NSCLC receiving first-line treatment. Study participants received gefitinib 250 mg once daily or up to six cycles of combination chemotherapy with carboplatin and paclitaxel.<sup>8</sup> Of the trial's 1,217 patients, 186 who were EGFR-positive were included in the subset analysis—88 treated with gefitinib and 98 with chemo. Median duration of gefitinib treatment was 9.8 months.<sup>8</sup>

Median PFS was 10.9 months in the gefitinib group and 7.4 months in the chemo arm Hazard Ratio-0.54; 95% CI: 0.38, 0.79. ORR was 67% (95% CI: 56–77) with gefitinib at 41% (95% CI: 31–51) for carboplatin/paclitaxel.<sup>8</sup> Median duration of response was 9.6 months in the gefitinib arm and 5.5 months for carboplatin/paclitaxel patients.<sup>8</sup> There was no significant difference in overall survival between groups.<sup>8</sup>

Serious adverse events observed in trials include skin reactions, gastrointestinal events (including grade 3 or 4 diarrhea), hepatotoxicity, ocular toxicity, and interstitial lung disease (ILD).<sup>5</sup> Patients should be observed for the presence of serious adverse effects and treatment should be interrupted or discontinued.<sup>5</sup> Manufacturer's labeling suggests withholding gefitinib for severe or persistent (up to 14 days) diarrhea.<sup>5</sup> An increase in mortality was observed in patients who developed pulmonary toxicity if they were smokers, had CT evidence of reduced lung function, preexisting ILD, age greater than or equal to 65, and extensive areas adherent to pleura.<sup>5</sup>

Gefitinib has been observed to cause adverse events in animal reproduction studies and may cause fetal harm.<sup>5</sup> Women who are of reproductive age should use effective contraception during and for at least 2 weeks following gefitinib treatment.<sup>5</sup> Excretion in breast milk of gefitinib is unknown.<sup>5</sup> Breastfeeding while using gefitinib is not recommended.<sup>5</sup>

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Gefitinib is extensively hepatically metabolized via CYP3A4 and CYP2D6.<sup>5</sup> Excretion is primarily through feces (86%), with less than 4% renal elimination.<sup>5</sup> No initial dosage adjustments for renal or hepatic impairment are provided in the manufacturer's labeling.<sup>5</sup> Gefitinib has not been studied in patients with a creatinine clearance less than 20 mL/min.<sup>5</sup> If grade 2 or higher hepatic impairment occurs during treatment, hold therapy until fully resolved.<sup>5</sup> Permanently discontinue for severe hepatic impairment.<sup>5</sup>

Due to its metabolism by the CYP system, the dose of gefitinib should be temporarily increased when given with strong CYP3A4 inducers.<sup>5</sup> Elevated gastric pH may also reduce gefitinib plasma concentrations. Avoid concomitant use of proton pump inhibitors, if possible.<sup>5</sup> Gefitinib may be taken without regard to food.<sup>5</sup>

Gefitinib is available in 250 mg oral tablets. Instruct patients to store at room temperature.<sup>6</sup> Patients should also inform their physician if any severe adverse events occur.

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## Irinotecan Liposome Injection (Onivyde™)

**Class:** Topoisomerase I inhibitor

**Indication:** In combination with fluorouracil and leucovorin for the treatment of metastatic adenocarcinoma of the pancreas with disease progression following a gemcitabine-based initial regimen. Liposomal irinotecan is not approved as a single agent for the treatment of metastatic pancreatic cancer.

**Dose:** 70 mg/m<sup>2</sup> infused over 90 minutes every 2 weeks. If genetic testing reveals UGT1A1\*28 homozygosity, the recommended starting dose is 50 mg/m<sup>2</sup>. Premedication with a corticosteroid and an antiemetic administered 30 minutes prior to liposomal irinotecan initiation is recommended.

**Dose modifications:** See Table 1 on page 19.

**Common adverse effects:** Diarrhea, fatigue/asthenia, nausea, vomiting, decreased appetite, stomatitis, pyrexia, lymphopenia, and neutropenia

**Serious adverse effects:** Severe neutropenia or neutropenic fever, pyrexia, sepsis, septic shock, pneumonia, interstitial lung disease, hypersensitivity reaction, diarrhea, dehydration, nausea, vomiting, acute renal failure, and thrombocytopenia

**Black box warnings:** Severe neutropenia and severe diarrhea. Therapy should be held for absolute neutrophil count (ANC)  $\leq$  1500/mm<sup>3</sup>, neutropenic fever, diarrhea of Grade 2-4 severity, and in cases of bowel obstruction.

**Drug interactions:** Strong CYP3A4 inducers should be avoided; substitute nonenzyme inducing agents at least 2 weeks before initiating therapy with liposomal irinotecan. Strong CYP3A4 and UGT1A1 inhibitors should also be avoided; strong CYP3A4 inhibitors should be discontinued at least 1 week before initiating therapy with liposomal irinotecan.

The National Cancer Institute estimates about 50,000 new cases of pancreatic cancer in the United States in 2015 and approximately the same number of deaths (~40,000).<sup>3</sup> Because pancreatic cancer is difficult to diagnose, it is often detected in advanced stages for which treatment options are limited and palliative care measures are commonly used.

Conventional irinotecan has been used for the treatment of pancreatic cancer as part of the FOLFIRINOX regimen.<sup>4-5</sup> The new liposomal formulation of this chemotherapeutic agent shows promising results as a second-line therapy for metastatic pancreatic cancer. Liposomal irinotecan is encapsulated in a lipid bilayer vesicle and interrupts DNA replication by inducing its unique single-strand break in the DNA helix, causing DNA damage and cell death.<sup>1-2,6</sup> The indication for use in metastatic pancreatic cancer was based on the NAPOLI-1 trial, an open-label, three-arm, randomized, phase III trial of 417 patients with metastatic pancreatic cancer whose disease had progressed after receiving gemcitabine-based therapy. Patients were eligible for the study if they met the following criteria: prior gemcitabine therapy, albumin  $\geq$  3.0 g/dL, serum bilirubin within normal limits, and Karnofsky Performance Status (KPS)  $\geq$  70. Patients were randomized to receive: (a) liposomal irinotecan 70 mg/m<sup>2</sup> as an intravenous (IV) infusion over 90 minutes given prior to leucovorin 400 mg/m<sup>2</sup> IV over 30 minutes and fluorouracil 2400 mg/m<sup>2</sup> IV over 46 hours, every 2 weeks; (b) leucovorin 200 mg/m<sup>2</sup> IV over 30 minutes, followed by fluorouracil 2000 mg/m<sup>2</sup> IV over 24 hours administered on days 1, 8, 15, and 22 of a 6-week cycle; or (c) liposomal irinotecan 100 mg/m<sup>2</sup> IV over 90 minutes every 3 weeks. Patients who were homozygous for UGT1A1\*28 received reduced liposomal irinotecan doses of 50 mg/m<sup>2</sup> in arm a and 70 mg/m<sup>2</sup> in arm c. The primary endpoint was overall survival (OS), comparing two pairs of regimens, liposomal irinotecan versus fluorouracil/leucovorin and the combination of liposomal irinotecan/fluorouracil/leucovorin versus fluorouracil/leucovorin.

Four hundred and seventeen patients were included in the trial: 117 to arm a, 149 to arm b, and 151 to arm c.<sup>1-2,6</sup> The liposomal irinotecan combination regimen (arm a) demonstrated a significant improvement in OS (unstratified hazard ratio [HR] = 0.68; 95% confidence interval [CI]: 0.50–0.93;  $p = .014$ ) with an increase in median OS of 1.9 months when compared with fluorouracil/leucovorin (arm b) alone (6.1 months versus 4.2 months). Improvement in OS was not seen for patients receiving single-agent liposomal irinotecan compared to patients on the fluorouracil/leucovorin arm. Therefore, monotherapy with liposomal irinotecan is not recommended for the treatment of metastatic pancreatic cancer. The study also evaluated progression-free survival to further assess the efficacy of liposomal irinotecan. When compared to fluorouracil/leucovorin alone, the liposomal irinotecan combination arm had a significant delay in the time to tumor progression (1.5 versus 3.1 months, respectively; HR = 0.55; 95% CI: 0.41–0.75), reinforcing its benefit as a treatment option for this aggressive disease.

## Irinotecan Liposome Injection in the Treatment of Metastatic Pancreatic Cancer

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Liposomal irinotecan (Onivyde™, Merrimack Pharmaceuticals) is a topoisomerase I inhibitor that was approved on October 22, 2015, by the U.S. Food and Drug Administration (FDA) for use in the treatment of metastatic adenocarcinoma of the pancreas in combination with fluorouracil and leucovorin after disease progression following gemcitabine-based therapy.<sup>1,2</sup> Based on its potential to positively impact the course and survival of pancreatic cancer patients, the FDA granted priority review and orphan drug designation.<sup>2</sup> Pancreatic cancer is a relatively rare malignancy compared to other types of cancers.

Safety outcomes were also assessed and the side effects were reported by the NAPOLI-1 investigators.<sup>1,2</sup> The most common adverse events, which occurred in more than 20% of the patients, include diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. Additionally, the most common serious adverse reactions ( $\geq 2\%$ ) were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia. Permanent discontinuation of therapy was seen in 11% of the patients in the liposomal irinotecan combination arm due to diarrhea, vomiting, or sepsis. In this same treatment arm, 33% of the patients required dose reductions attributed to neutropenia, diarrhea, nausea, or anemia. The most common laboratory abnormalities of Grade 3 or 4 in severity seen in more than 10% of the patients included lymphopenia (27%) and neutropenia (20%). The reported incidences of these life-threatening complications contributed to the required black box warnings for severe neutropenia and severe diarrhea.

Liposomal irinotecan is not a benign therapy, and thus, certain safety measures are recommended. Complete blood cell counts with differential should be monitored on Days 1 and 8 of every treatment cycle, and therapy is to be held if ANC falls below 1500/mm<sup>3</sup> or if neutropenic sepsis ensues.<sup>1</sup> Atropine can be used in patients who experience early-onset diarrhea while loperamide can be given if late-onset diarrhea occurs. If diarrhea is categorized as Grade 2-4 in severity, liposomal irinotecan therapy should be held until episodes of diarrhea decrease to less than or equal to Grade 1 in severity. At this point, liposomal irinotecan can be resumed at a reduced dose as described on the dose modifications table. Furthermore, precautions should be taken when administering liposomal irinotecan to patients with progressive dyspnea, cough, and fever, or with signs/symptoms of anaphylactic reactions due to the risk of interstitial lung disease and severe hypersensitivity reactions, respectively.

Based on previously observed drug interactions with conventional irinotecan, similar provisions are warranted when administering liposomal irinotecan with enzyme inhibitors or inducers. Concentrations of conventional irinotecan and its active metabolite, SN-38, are significantly reduced when CYP3A4 inducers are simultaneously administered.<sup>1,4</sup> Strong CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort) should be avoided, and substitution with non-enzyme inducing agents is suggested at least 2 weeks before administering liposomal irinotecan. In addition, exposure to CYP3A4 or UGT1A1 inhibitors substantially increases the concentrations of conventional irinotecan and its active metabolite SN-38. If possible, discontinue strong CYP3A4 inhibitors (i.e., clarithromycin, lopinavir, ritonavir, voriconazole, etc.) and/or strong UGT1A1 inhibitors (i.e., atazanavir, gemfibrozil, indinavir, etc.) at least 1 week before starting therapy with liposomal irinotecan is recommended.

Several observations in the NAPOLI-1 trial provide helpful treatment principles in specific populations. Differences in irinotecan exposure were found in respect to individuals who are homozygous for the UGT1A1\*28 allele.<sup>1</sup> The presence of this gene was associated with an increased risk of severe neutropenia (Grade 3 or 4), and thus, the

starting dose of liposomal irinotecan should be reduced to 50 mg/m<sup>2</sup>. Furthermore, pharmacokinetic analysis revealed that mild-to-moderate renal and hepatic impairment had no significant effect on the concentrations of irinotecan or SN-38. However, no data are available for patients with CrCL <30 mL/min or bilirubin concentrations >2 mg/dL. In addition, a subgroup analysis on ethnicity demonstrated that Asians have 56% lower total irinotecan concentrations and 8% higher total SN-38 concentrations when compared to Caucasians. These differences in concentrations correlated with higher incidences of Grade 3 or 4 neutropenia in the Asian patients (55%) when compared to the Caucasian patients (18%), indicating that subsequent cycles of liposomal irinotecan in Asian patients may warrant reduced doses to lower the risk of neutropenia.

Liposomal irinotecan is supplied as a 43 mg/10 mL single-dose vial.<sup>1</sup> For preparation, an accurate calculated volume should be withdrawn from the vial and diluted in 500 mL 5% dextrose or 0.9% sodium chloride with gentle inversion. The diluted solution must be protected from light and should not be frozen. It is recommended that the solution be administered within 4 hours of dilution if the preparation is kept at room temperature or within 24 hours of preparation if the solution is refrigerated [2°C to 8°C]. Premedication with a corticosteroid and an antiemetic 30 minutes prior to infusion is suggested, and the liposomal irinotecan solution should be administered intravenously over 90 minutes.

The approval of liposomal irinotecan is an important addition to the arsenal of agents for metastatic pancreatic cancer. The successful response rates for OS and delay to tumor progression, coupled with an acceptable side effect profile, establishes this therapy as a promising alternative for patients with advanced disease. Further research, clinical trials, and experience will serve as key indicators in the incorporation of liposomal irinotecan in treatment algorithms for metastatic adenocarcinoma of the pancreas.

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**Table 1. Dose Modifications for Irinotecan Liposome Injection (Onivyde)**

Toxicity	Occurrence	Adjustment in patients receiving 70mg/m <sup>2</sup>	Adjustment in patients homozygous for UGT1A1*28 without previous increase to 70 mg/m <sup>2</sup>
Grade 3-4 adverse reactions	Withhold therapy - Initiate loperamide for late-onset diarrhea - Initiate atropine 0.25-1 mg (IV or SubQ) for early-onset diarrhea Upon recovery and evidence of ≤ Grade 1 adverse reactions, resume therapy with dosing regimens as described below:		
	First	50 mg/m <sup>2</sup>	43 mg/m <sup>2</sup>
	Second	43 mg/m <sup>2</sup>	35 mg/m <sup>2</sup>
	Third	Discontinue therapy	
Interstitial Lung Disease	First	Discontinue therapy	
Anaphylactic Reaction	First	Discontinue therapy	

## Nivolumab (Opdivo®)

**Class:** Human programmed death receptor-1 (PD-1)-blocking monoclonal antibody

**Indications:** Unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

Metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy

**Dose:** 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity

**Dose modifications:** Hold dose for grade 2 pneumonitis, grade 2 or 3 colitis, aspartate aminotransferase/alanine transaminase (AST/ALT) 3–5 x upper limit of normal (ULN) or total bilirubin > 1.5–3 x ULN, creatinine > 1.5–6 x ULN or > 1.5 x baseline, or any other severe or grade 3 treatment-related adverse reactions. Nivolumab can be resumed in patients whose adverse reactions recover to grade 0 to 1. Permanently discontinue for any life-threatening grade 4 adverse reaction, grade 3 or 4 pneumonitis, grade 4 colitis, AST/ALT > 5 x ULN or total bilirubin > 3 x ULN, creatinine > 6 x ULN, any severe or grade 3 treatment-related adverse reaction that recurs, inability to reduce corticosteroid dose to ≤10 mg of prednisone or equivalent per day within 12 weeks, or persistent grade 2 or 3 treatment-related adverse reactions that do not recover to grade 1 or resolve within 12 weeks after last dose.

**Common adverse effects:** Rash, fatigue, dyspnea, musculoskeletal pain, decreased appetite, cough, nausea, constipation

**Serious adverse effects:** Immune-mediated reactions such as pneumonitis, colitis, hepatitis, nephritis, and hypothyroidism/hyperthyroidism

**Drug interactions:** No formal pharmacokinetic drug-drug interaction studies have been conducted.

## Nivolumab for Non-Small Cell Lung Cancer

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Lung cancer is the leading cause of cancer death in the United States, claiming more than 158,000 lives each year. The prognosis remains poor, with only 16.8% of patients alive 5 years or more after diagnosis. More than 85% of all lung cancers are categorized as non-small cell lung cancer (NSCLC), which is further specified into the histologic types of nonsquamous (adenocarcinoma, large cell, and NSCLC not otherwise specified) and squamous cell carcinoma. The nonsquamous histologies can present with an activating mutation in EGFR or rearrangement in the EML4-ALK genes, which are both targetable with oral medications.<sup>1</sup> Unfortunately, pure squamous cell NSCLC patients

rarely present with these targetable mutations, therefore conventional chemotherapy, specifically a platinum doublet, remains the standard of care.

For patients with squamous NSCLC, a platinum doublet regimen containing gemcitabine, paclitaxel, or vinorelbine is recommended as first-line treatment. Previous data have shown the benefit of cisplatin plus gemcitabine over cisplatin plus pemetrexed in squamous NSCLC. Cisplatin plus gemcitabine demonstrated an increase in overall survival (OS), although not statistically significant, compared with cisplatin plus pemetrexed for squamous histology (10.8 versus 9.4 months, respectively; [hazard ratio {HR} = 1.23; 95% confidence interval {CI}: 1.00–1.51;  $p = .05$ ]).<sup>2</sup> Despite thorough research, treatment options for squamous NSCLC are limited when compared with options for nonsquamous histology. After a patient progresses on or after a platinum-based therapy, options include single-agent systemic therapy, best supportive care, or clinical trials. Docetaxel was approved as second-line therapy in 1999 based on superior overall response rates to vinorelbine or ifosfamide (6.7%–10.8% with docetaxel versus 0.8% for both vinorelbine and ifosfamide;  $p = .001$  and  $p = .036$  respectively). OS did not differ between the groups, ranging from 5.5 to 5.7 months.<sup>3</sup> Due to the paucity of highly effective agents in the subsequent-line setting for squamous cell NSCLC, the search for novel agents has expanded past conventional chemotherapy.

Nivolumab is a fully human IgG4 antibody second in the class of immune agents targeting the programmed death receptor-1 (PD-1). The PD-1 receptor is expressed on activated T cells and engaged by the ligands PD-L1 and PD-L2, which are expressed by tumor cells and infiltrating immune cells. Activation of PD-1 via the ligands results in inhibition of T-cell activation, allowing tumor cells to escape recognition and elimination by the immune system. Nivolumab disrupts PD-1-mediated signaling to restore antitumor immunity.<sup>4</sup> Nivolumab was first approved by the U.S. Food and Drug Administration (FDA) in December 2014 for unresectable or metastatic melanoma. In March 2015, nivolumab gained approval for metastatic squamous NSCLC with progression on or after platinum-based chemotherapy based on the CheckMate-017 trial.

The CheckMate-017 trial was a randomized, open-label, international, phase 3 study that compared nivolumab with docetaxel as subsequent therapy following failure on a platinum-containing regimen in patients with advanced squamous NSCLC. Nivolumab was given at a dose of 3 mg/kg intravenously every 2 weeks and docetaxel was given at a dose of 75 mg/m<sup>2</sup> intravenously every 3 weeks. A total of 260 patients (131 in nivolumab group, 129 in docetaxel group) were assessed for efficacy and safety. The primary endpoint of OS was superior for nivolumab at 9.2 months compared with docetaxel at 6 months (HR = 0.59; 95% CI: 0.44–0.79;  $p < .001$ ). Nivolumab was also superior for progression-free survival at 3.5 months versus 2.8 months for docetaxel (HR = 0.62; 95% CI: 0.47–0.81;  $p < .001$ ). The median time to response did not differ between the two groups (2.2 versus 2.1 months for nivolumab and docetaxel, respectively).<sup>4</sup>

Nivolumab proved to be better tolerated than docetaxel. Events of any grade occurred in 58% of patients in the nivolumab group and the most frequently reported events were fatigue (16%), decreased appetite (11%), and asthenia (10%). Events of any grade occurred in 86% of patients in the docetaxel group and the most frequently reported events were neutropenia (33%), fatigue (33%), alopecia (22%), and nausea (23%). In addition, grade 3 or 4 events were reported in fewer patients in the nivolumab group (7% versus 55% in docetaxel group). Discontinuation of treatment due to treatment-related adverse events occurred less frequently with nivolumab versus docetaxel (3% versus 10%, respectively) and no deaths were attributed to nivolumab compared with three deaths attributed to docetaxel.<sup>4</sup>

Although rare, immune-related adverse events have been reported in trials of patients receiving nivolumab for solid tumor malignancies. Rates of immune-mediated events have been reported as follows: pneumonitis 2.2%–6%, colitis 0.9%–2.2%, hepatitis 1.1%, nephritis 0.7%–0.9%, hypothyroidism 4.3%–8%, and hyperthyroidism 1.7%–3%. There are specific recommendations on when to withhold treatment and initiate corticosteroids or permanently withhold treatment based on the severity of the suspected immune-related adverse event. If corticosteroids need to be administered, initiate at a dose of 0.5–2 mg/kg/day prednisone equivalents based on adverse event and severity with adjustments in dose based on patient response. For immune-mediated hypothyroidism, initiate hormone replacement. For immune-related hyperthyroidism, initiate appropriate medical management.<sup>5</sup>

Although nivolumab is only FDA-approved for squamous NSCLC, data presented at the American Society of Clinical Oncology annual meeting in June 2015 showed benefit in nonsquamous NSCLC. The CheckMate-057 randomized, phase 3 trial compared nivolumab with docetaxel in patients with nonsquamous NSCLC who had progressed on or after platinum-based chemotherapy. Median OS for nivolumab and docetaxel was 12.2 months and 9.4 months, respectively (HR = 0.73; 95% CI: 0.59–0.89;  $p = .0015$ ). As well as improved efficacy, grade 3 to 5 adverse events occurred less often in the nivolumab group (10%) compared with the docetaxel group (54%).<sup>6</sup> Based on these data, the National Comprehensive Cancer Network panel recommends nivolumab as subsequent therapy for patients with nonsquamous NSCLC who have progressed on or after platinum-based therapy.<sup>1</sup>

Both CheckMate-017 and CheckMate-057 trials evaluated PD-L1 expression in patients to determine a relationship to prognosis or predict a response to nivolumab.<sup>4,6</sup> CheckMate-017 reported that PD-L1 expression was neither prognostic nor predictive of any of the efficacy endpoints.<sup>4</sup> CheckMate-057 reported PD-L1 expression to be associated with treatment benefit with nivolumab.<sup>6</sup> More expansive data on the subject of PD-L1 expression effects on nivolumab efficacy are expected to be reported in the future.

The mean elimination half-life of nivolumab is 26.7 days. No clinically important differences in clearance have been noted in patients with mild to severe renal impairment or those with mild hepatic impairment; therefore, there are no dose adjustments recommended for patients with renal or hepatic impairment. However, nivolumab has not been studied in patients with moderate to severe hepatic impairment. There have been no formal drug interaction studies conducted at this time. Animal reproduction studies have shown increased abortion and premature infant death, therefore nivolumab should be avoided in pregnant women. Females of reproductive potential should continue to use effective contraception for at least 5 months after the last dose of nivolumab.<sup>5</sup>

Nivolumab is supplied as a solution in 40 mg/4 mL and 100 mg/10 mL single-use vials. The required volume should be withdrawn from the vial and transferred into an intravenous container containing either 0.9% sodium chloride injection, USP or dextrose injection, or USP to a final concentration of 1 to 10 mg/mL. The prepared product for infusion should be stored at room temperature for no more than 4 hours, or under refrigeration at 2°C–8°C (36°F–46°F) for no more than 24 hours. Nivolumab should be administered as an infusion over 60 minutes through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding in-line filter (pore size of 0.2–1.2  $\mu$ m). No other medication should be administered through the same line.<sup>5</sup>

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## Nivolumab (Opdivo®)

**Class:** Human-programmed death receptor-1 (PD-1) blocking monoclonal antibody

**Indication:** In combination with ipilimumab for unresectable or metastatic BRAF V600 wild-type melanoma

**Dose:** Nivolumab 1 mg/kg administered as an intravenous infusion over 60 minutes, followed by ipilimumab 3 mg/kg on the same day, every 3 weeks for four doses. The subsequent dose of nivolumab as a single agent is 3 mg/kg given over 60 minutes as an intravenous infusion every 2 weeks until disease progression or unacceptable toxicity.

**Dose modifications:** Hold dose for grade 2 colitis and pneumonitis, grade 2 or 3 hypophysitis, grade 2 adrenal insufficiency, grade 3 rash, aspartate aminotransferase /alanine aminotransferase (AST)/(ALT) > 3-5 x upper limit of normal (ULN) or total bilirubin > 1.5-3 x ULN, creatinine > 1.5-6 x ULN or > 1.5 x baseline, or any other severe or grade 3 treatment-related adverse reactions. Nivolumab can be resumed in patients whose adverse reactions return to grade 0 to 1. Permanently discontinue for any life-threatening grade 4 adverse reaction; grade 4 rash and hypophysitis; grade 3 or 4 colitis, pneumonitis, and adrenal insufficiency; AST/ALT > 5 x ULN or total bilirubin > 3 x ULN; creatinine > 6 x ULN; any severe or grade 3 treatment-related adverse reaction that recurs; inability to reduce corticosteroid dose to ≤ 10 mg of prednisone or equivalent per day within 12 weeks; or persistent grade 2 or 3 treatment-related adverse reactions that do not recover to grade 1 or resolve within 12 weeks after the last dose. If nivolumab is held for any adverse reaction, ipilimumab should also be withheld.

**Common adverse effects:** Rash, pruritus, headache, vomiting, and colitis

**Serious adverse effects:** Immune-mediated reactions including pneumonitis, colitis, hepatitis, endocrinopathies (hypophysitis and thyroid dysfunction), nephritis, and rash

**Drug interactions:** No formal pharmacokinetic drug-drug interaction studies have been conducted.

## Nivolumab in Combination with Ipilimumab for Unresectable or Metastatic Melanoma

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Melanoma is the most aggressive and deadly skin cancer in the United States, with an estimated 9,900 related deaths in 2015. Unfortunately, the incidence of melanoma continues to rise and the mortality associated with advanced or metastatic melanoma remains high.<sup>1</sup> The

survival rate of melanoma largely depends on the stage at presentation with the potential for cure in the adjuvant setting for localized disease. Long-term survival for patients with metastatic melanoma is less than 10% and this disease at advanced stages continues to be a challenge to treat.<sup>2</sup> Surgery and radiation therapy have limited roles in the treatment of metastatic disease and systemic therapy is the mainstay of treatment for most patients. Single-agent chemotherapy is well tolerated, but response rates remain low with ranges in the 5% to 20%.<sup>3</sup> Although combination chemotherapy has been shown to improve response rates, there are no improvements in survival benefit and they are associated with more toxicity.<sup>3</sup>

With the recent development of novel agents, both targeted therapy and immunotherapeutic approach, the treatment paradigm for metastatic melanoma has changed rapidly with better efficacy than cytotoxic chemotherapy. Advances in immunotherapy have led to durable remissions and prolonged survival rates. One of the earlier immunologic approaches to fight malignancies was to block the cytotoxic T-lymphocyte antigen-4 (CTLA-4) receptors using monoclonal antibodies. The CTLA-4 molecule acts as a “checkpoint” in the immune system down-regulating the pathways of T-cell activation.<sup>5</sup> Ipilimumab, a fully-human monoclonal antibody (IgG1), blocks CTLA-4, allowing unrestrained T-cell proliferation to promote antitumor immunity.<sup>6</sup> In March 2011, ipilimumab (Yervoy®) received approval by the U.S. Food and Drug Administration (FDA) for the treatment of unresectable or malignant melanoma. In several phase 3 trials, ipilimumab significantly improved overall survival in previously treated and untreated patients with unresectable or metastatic melanoma.<sup>6-8</sup>

The success of ipilimumab has generated interest to identify other targets in the area of immunotherapies that also have antitumor activity in advanced melanoma. Another important immune checkpoint is the pathway between programmed cell death protein 1 (PD-1) and its ligand, PD-L1. Activated T-lymphocytes and B-lymphocytes express PD-1 receptors and antigen-presenting cells express PD-L1 on their surfaces. This interaction between PD-1 and PD-L1 deactivates the T cells. Many tumor types, including up to 40% of melanomas, inhibit the active T-cell immune surveillance by expressing the PD-L1. Blocking this interaction between PD-1 and PD-L1 may restore antitumor activity.<sup>9</sup> Nivolumab is a fully humanized (IgG4) PD-1 antibody that selectively blocks the PD-L1 and PD-L2 from binding to the PD-1 receptor. It received FDA approval in December 2014 for the treatment of patients with unresectable or metastatic melanoma in the second-line setting after ipilimumab use and a BRAF inhibitor, if BRAF V600 is mutation positive. In the phase 3 study, CheckMate 037, nivolumab showed improved objective response rate (ORR) compared to standard chemotherapy.<sup>10</sup>

The independent successes of ipilimumab and nivolumab in clinical trials showing superiority over other standard regimens led to studies using both immunotherapeutic agents concurrently. Many believed the nonoverlapping mechanisms of action of CTLA-4 inhibitors and

PD-1 inhibitors could result in further improved survival data in patients with advanced melanoma. Additionally, early phase 1 data combining both ipilimumab and nivolumab achieved an ORR of 40% and up to 80% reduction in tumor volume, which provided more support to pursue further studies in combining these immunotherapy agents.<sup>11</sup>

Nivolumab in combination with ipilimumab received accelerated approval by the FDA on September 30, 2015.<sup>12</sup> This approval was based on data from 142 treatment-naïve patients with unresectable or metastatic melanoma in a multicenter, double-blind, phase 2 clinical trial (CheckMate-069 study). The study randomized (2:1) patients to receive either nivolumab in combination with ipilimumab (n= 95) or single-agent ipilimumab (n=47). Randomization was stratified by BRAF V600 mutation status based on an FDA-approved test. The combination arm was given nivolumab at a dose of 1 mg/kg and ipilimumab at 3 mg/kg intravenously every 3 weeks for four doses, then nivolumab 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Patients in the ipilimumab arm received ipilimumab 3 mg/kg and nivolumab-matched placebo intravenously every 3 weeks for four doses followed by placebo. The primary endpoint was objective response rate (ORR), including both complete response and partial response. Secondary endpoints included duration of response and progression free survival (PFS).<sup>13,14</sup>

A total of 109 patients with BRAF V600 wild-type melanoma were included in the efficacy analysis. The ORR in the nivolumab plus ipilimumab group was 60% compared to the 11% in the single-agent ipilimumab group ( $p < .001$ ). The combination group had significant improvement in PFS, with 8.9 months compared with the 4.7 months seen with ipilimumab group (HR = 0.40; CI: 0.22–0.71;  $p < .002$ ).<sup>13,14</sup>

Nivolumab in combination with ipilimumab proved to have more adverse effects than single-agent ipilimumab. Serious adverse reactions (62% versus 39%), adverse reactions leading to permanent discontinuation (43% vs 11%) or dose delays (47% versus 22%), and Grade 3 or 4 adverse reactions (69% versus 43%) all occurred more frequently in patients receiving both nivolumab and ipilimumab compared to those receiving ipilimumab alone.<sup>13,14</sup> The first occurrence of any Grade 3 or 4 adverse reaction was reported in more patients in the combination nivolumab plus ipilimumab group (59% versus 10% in the nivolumab single agent group). The most common adverse reactions leading to discontinuation of nivolumab, as compared to single-agent ipilimumab, were colitis (16% versus 2%), increased ALT levels (4% versus 0), increased AST levels (3% versus 0), and pneumonitis (3% versus 0). The most frequently reported events in the combination group, as compared with single-agent ipilimumab, were colitis (17% versus 9%), diarrhea (9% versus 7%), pyrexia (6% versus 7%), and pneumonitis (5% versus 0).<sup>15</sup>

Higher incidences of immune-related adverse events have been reported in the trials of patients receiving combination nivolumab plus ipilimumab for melanoma. Rates of immune-mediated events have been reported as follows: interstitial lung disease 10%, pneumonitis 6%, colitis 57%, hepatitis 15%, hypophysitis 13%, adrenal insufficiency 9%,

hypothyroidism 19%, hyperthyroidism and nephritis 2.1%, and rash 37%. There are specific recommendations on when to withhold treatment and initiate corticosteroids or permanently discontinue treatment based on the severity of the immune-related adverse event. If corticosteroids need to be administered, prednisone equivalents at a dose of 1–2 mg/kg/day should be initiated based on the adverse event and severity. For immune-mediated hypothyroidism, hormone replacement should be initiated. For immune-mediated hyperthyroidism, appropriate medical management should be provided. If nivolumab is held for any adverse reaction, then ipilimumab should be withheld as well.<sup>15</sup>

Based on animal reproduction studies, nivolumab can cause fetal harm and administration in pregnant women should be avoided. Females of reproductive potential should be counseled on using effective contraception while receiving nivolumab and for at least 5 months following the last dose of nivolumab. The safety of nivolumab in combination with ipilimumab has not been established in geriatric patients.<sup>15</sup>

The mean elimination half-life of nivolumab is 24.8 days. The clearance of nivolumab is increased by 24% when given in combination with ipilimumab with no effect on the clearance of ipilimumab. Renal impairment did not have any clinically significant differences in the clearance of nivolumab and no dose adjustments are recommended in patients with renal impairment. Clinically important differences in clearance were not seen in patients with mild hepatic impairment, but nivolumab has not been studied in patients with moderate to severe hepatic impairment. There have been no formal drug interaction studies conducted at this time.<sup>15</sup>

Nivolumab is supplied as a solution in 40 mg/4 mL and 100 mg/10 mL single-use vials. The required volume of nivolumab should be drawn up from the vial and transferred into an intravenous container diluted with either 0.9% sodium chloride injection USP or 5% dextrose injection USP to a final concentration of 1 to 10 mg/mL. The prepared product for infusion should be stored at room temperature for no more than 4 hours or under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours. Nivolumab should be administered as an infusion over 60 minutes using an intravenous line containing sterile, nonpyrogenic, low protein-binding in-line filter (pore size of 0.2  $\mu$ m–1.2  $\mu$ m). Nivolumab should be administered first, followed by ipilimumab on the same day using separate infusion bags and filters for each infusion. Patients should be educated on the potential of serious immune-mediated reactions such as pneumonitis, colitis, hepatitis, and endocrinopathies. Patient should notify their healthcare provider if they experience new or worsening cough, shortness of breath, diarrhea, blood in the stool, severe nausea or vomiting, yellowing of the skin or the whites of the eyes, dizziness, headaches, extreme tiredness, changes in mood or behavior, or rashes.<sup>15</sup>

Metastatic melanoma continues to be a challenging malignancy to treat, but with better understanding of the disease, many promising therapeutic treatments have emerged over the last decade. Immunotherapy appears to be the superior approach in treating this aggressive disease compared to other standard chemotherapy agents.

Combined PD-1 and CTLA-4 inhibition demonstrated improved antitumor responses than either agent alone, but this enhanced T-cell function came with increased adverse reactions, especially immune-mediated reactions. The future treatment options will likely include other combined approaches. However, the new challenge will be combining and sequencing these novel agents with the best toxicity profile for the patients.

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## Trifluridine/tipiracil (Lonsurf®)

**Class:** Trifluridine is a thymidine-based nucleoside analogue and metabolic inhibitor; tipiracil is a thymidine phosphorylase inhibitor.

**Indication:** Metastatic colorectal cancer (mCRC) in patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, antivascular endothelial growth factor (VEGF) biological therapy, and, if RAS wild-type, anti-epidermal growth factor receptor (EGFR) therapy.

**Dose:** 35 mg/m<sup>2</sup>/dose (based on the trifluridine component) orally twice daily within 1 hour of completion of meals in the morning and evening on Days 1 to 5 and Days 8 to 12 of a 28-day cycle (maximum per dose: trifluridine 80 mg). Continue until disease progresses or toxicity becomes unacceptable. Doses should be rounded to the nearest 5 mg increment, per the manufacturer.

**Dose modifications:** For creatinine clearance (CrCl) > 30 ml/min, no initial dosage adjustment is required. Careful monitoring of patients with moderate renal impairment (CrCl 30–59 ml/min) is recommended, as is the incidence of Common Terminology Criteria for Adverse Events (CTCAE). Grade 3 or greater adverse events, serious adverse events, and dose delays and reductions may be increased; dose reduction may be required. Trifluridine/tipiracil has not been studied in patients with CrCl <30 ml/min or End Stage Renal Disease (ESRD). In addition, no dose adjustments are recommended in patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin <1 to 1.5 times ULN and any AST). Trifluridine/tipiracil has not been studied in moderate hepatic impairment (total bilirubin >1.5 to 3 times ULN and any AST) or severe hepatic impairment (total bilirubin >3 times ULN and any AST). Complete blood counts (CBCs) should be drawn prior to and on Day 15 of each cycle, and more frequently if clinically warranted. Therapy with trifluridine/tipiracil should not be initiated until absolute neutrophil count (ANC) is > 1,500/mm<sup>3</sup> or neutropenic fever has resolved, platelet count is > 75,000/mm<sup>3</sup>, and Grade 3 or 4 non-hematological adverse reactions have improved to Grade 0 or 1. Dose modifications are indicated in cases of hematological and nonhematological toxicities. During a treatment cycle, trifluridine/tipiracil dose(s) should be held in the following instances: ANC is <500/mm<sup>3</sup>, neutropenic fever, platelet count is <50,000/mm<sup>3</sup>, Grade 3 or 4 nonhematological adverse reactions. Trifluridine/tipiracil may be restarted at a dose decreased by 5 mg/m<sup>2</sup>/dose from the previous dose once the following conditions have resolved: neutropenic fever; uncomplicated Grade 4 neutropenia (resolution defined as ANC > 1500/mm<sup>3</sup>) or thrombocytopenia (resolution defined as platelet count > 75,000/mm<sup>3</sup>) that causes more than a 1-week delay in the initiation of the next cycle; nonhematological Grade 3 or Grade 4 adverse reaction, except for Grade 3 nausea and/or vomiting controlled by anti-

emetic medication or Grade 3 diarrhea resolved with anti-diarrheal therapy. Of note, a maximum of three dose reductions are permissible (minimum dose of trifluridine 20mg/m<sup>2</sup> twice daily). Once the dose of trifluridine/tipiracil has been reduced, it should not be escalated for future therapy.

**Common adverse effects (>10%):** Abdominal pain, anemia, asthenia/fatigue, decreased appetite, diarrhea, emesis, nausea, neutropenia, pyrexia, thrombocytopenia

**Serious adverse effects:** Grade 3 or 4 myelosuppression (potentially life-threatening), embryo-fetal toxicity

**Drug interactions:** No studies currently available.

## Trifluridine/tipiracil for Metastatic Colorectal Cancer (mCRC)

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In the United States, colorectal cancer is the third most common cause of cancer. The American Cancer Society estimates 93,090 new cases of colon cancer and 39,610 new cases of rectal cancer for 2015.<sup>1</sup> Approximately 20% of patients present with metastatic disease, and 50%–60% of patients eventually develop colorectal metastases.<sup>2</sup> Five-year relative survival in metastatic disease is estimated to be 13.1%.<sup>3</sup> Current National Comprehensive Cancer Network (NCCN) guidelines recommend a fluoropyrimidine-based regimen, typically in combination with irinotecan or oxaliplatin and biologic therapy (specifically, either a vascular endothelial growth factor inhibitor or, if KRAS wild-type, an epidermal growth factor inhibitor) as initial treatment for patients who are candidates for intensive therapy.<sup>2</sup>

Trifluridine/tipiracil (referred to as TAS-102 in clinical studies) was approved by the U.S. Food and Drug Administration (FDA) on September 22, 2015, for treatment of metastatic colorectal cancer in patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an antivascular endothelial growth factor biological therapy, and, if RAS wild-type, anti-epidermal growth factor receptor therapy. Trifluridine is the cytotoxic component of TAS-102 and a nucleoside metabolic inhibitor. Like fluorouracil, trifluridine is a pyrimidine analogue. The triphosphate form of trifluridine is incorporated into DNA and subsequently inhibits DNA synthesis and cellular proliferation.<sup>4</sup> Originally developed in the mid-1960s, trifluridine was abandoned as a potential antineoplastic agent due to the considerable toxicities seen with the dosing regimen used at that time.<sup>5,6</sup> Tipiracil hydrochloride comprises the other component of TAS-102. As a thymidine phosphorylase inhibitor, tipiracil prevents the degradation of trifluridine and thereby promotes therapeutic, constant plasma concentrations of trifluridine and improves the safety profile of that cytotoxic agent.<sup>4,7</sup>

Trifluridine/tipiracil was approved by the FDA based on the results of the double-blind, randomized, international, multicenter, phase III RECOURSE trial conducted by Mayer and colleagues.<sup>8</sup> This trial was prompted after TAS-102 demonstrated antitumor properties against cell lines resistant to fluorouracil in preclinical xenograft studies conducted in mice.<sup>9,10</sup> Additionally, the dosing regimen of 35 mg/m<sup>2</sup>/dose (based on the trifluridine component) orally twice daily on days 1 to 5 and days 8 to 12 of a 28-day cycle for trifluridine/tipiracil was used in the RECOURSE trial stems from phase I studies and other clinical trials involving study subjects from Japan and the United States.<sup>11-16</sup> A phase II double-blind, randomized, placebo-controlled study conducted in Japanese patients diagnosed with metastatic colorectal cancer refractory to fluorouracil, irinotecan, and oxaliplatin demonstrated a median overall survival of 9 months in the trifluridine/tipiracil group versus 6.6 months in the placebo group (HR for death 0.56; P=0.001).<sup>17</sup> Based on this cumulative data, the RECOURSE trial was conducted to determine safety and efficacy of TAS-102 in patients with metastatic colorectal cancer who were no longer candidates for standard therapy due to unacceptable toxicities from those medications or who were refractory to standard therapy.

Inclusion criteria for the RECOURSE trial were as follows: patients must have been at least 18 years old; had biopsy-proven adenocarcinoma of the colon or rectum; received at least two prior standard chemotherapy regimens, which must have included each of the following: a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and, if KRAS wild-type disease, cetuximab or panitumumab; been diagnosed with disease progression within 3 months after last administration of chemotherapy, or clinically significant adverse events secondary to standard chemotherapy that rendered patients ineligible for continuation of that therapy; had KRAS status determined (either wild-type or mutant); had adequate bone marrow, renal, and hepatic function; and were classified with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Exclusion criteria included surgery, radiation therapy, or investigational therapy within the past 4 weeks; anti-neoplastic therapy within the previous 3 weeks; prior treatment with TAS-102; current pregnancy or lactation; Grade 2 or higher unresolved toxicities secondary to prior therapy; brain metastases; or a serious medical illness or condition. Patients who met study inclusion criteria were randomized in a 2:1 fashion to receive either TAS-102 or a placebo. In addition, patients were stratified on the basis of tumor status (e.g., wild-type versus mutant KRAS tumor), time from first diagnosis of metastatic disease and randomization (less than 18 months versus 18 months or more), and geographic location (Japan versus United States, Australia, and Europe). One 28-day treatment cycle consisted of a TAS-102 35 mg/m<sup>2</sup>/dose or a placebo administered orally twice daily after meals for 5 days per week, followed by a 2-day rest period for 2 weeks, then a 14-day rest period. Patients continued treatment until disease progression or development of unacceptable toxicities. A maximum of three reductions in dose, each by 5 mg/m<sup>2</sup>, was permitted. During treatment, patients were assessed every 2 weeks; in addition, patients were evaluated every 8 weeks from the time they discontinued therapy until death or data collection was

no longer being conducted. Best supportive care was received by all study participants, but hormonal therapies, immunotherapies, and other investigational chemotherapy were not permitted. Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was utilized to assess tumor response to therapy based on radiologic images. Patients continued therapy until disease progression per RECIST, clinical progression, severe toxicities, study withdrawal, mortality, or investigator recommendation to stop trial participation.

Overall survival (OS) was the primary end point of the RECOURSE trial. Progression-free survival (PFS), response rate, rate of disease control, and safety compromised secondary end points. A total of 800 patients were randomized: 534 patients to the TAS-102 arm and 266 patients to the placebo group; 760 patients were assessed for tumor response. Baseline characteristics of study participants were similar between the study groups. Median OS was significantly better in the TAS-102 group, at 7.1 months (95% CI 6.5-7.8) versus 5.3 months (95% CI 4.6-6) in the placebo group. This benefit in OS was demonstrated in all subgroups of patients, including those who had been stratified according to tumor status, time from first diagnosis of metastases and randomization, and geographic location. The hazard ratio for death was 0.68 (95% confidence interval 0.58-0.81; P<0.001), demonstrating a 32% reduction in the risk of death in patients receiving TAS-102 as compared to placebo. Median PFS was 2 months versus 1.7 months in the TAS-102 group versus the placebo group, respectively. The hazard ratio for disease progression was 0.48 (95% CI 0.41-0.57; P<0.001), and this benefit was demonstrated in all subgroups of patients. The response rate was not significantly different between the two study arms, with 1.6% of patients in the TAS-102 group and 0.4% of patients in the placebo group achieving response (P=0.29). However, disease control was significantly improved with TAS-102; 44% of patients in that group achieved disease control as compared with 16% of patients who received placebo (P<0.001). Of note, 17% of patients in the TAS-102 arm and 20% of patients in the placebo arm had received prior therapy with the multikinase inhibitor regorafenib; survival benefits of TAS-102 were demonstrated in this patient subset, as well. Moreover, therapy with TAS-102 resulted in a longer time to decline in ECOG performance status, with median time to ECOG performance status of 2 or greater 5.7 months versus 4 months in the placebo group (HR-0.66; p < 0.001). However, a quality of life assessment was not conducted.

Safety analyses revealed that the most common clinically significant toxicities in the TAS-102 group were neutropenia (38% experienced Grade 3 or higher versus 0% in the placebo group); leukopenia (21% experienced Grade 3 or higher versus 0% in the placebo arm), and anemia (18% with Grade 3 or higher versus 3% in the placebo arm). Nausea, vomiting, and diarrhea of any grade were also common in the TAS-102 arm, with 48%, 28%, and 32% of patients experiencing those adverse effects, respectively. One death, related to septic shock, occurred in the TAS-102 group. No significant differences were seen between the study groups in terms of serious renal or hepatic impairment.

The primary mechanism by which trifluridine is metabolized is via thymidine phosphorylase, which converts trifluridine to its inactive metabolite, 5-trifluoromethyluracil. Approximately 19% of this inactive metabolite is excreted in the urine, while <2% of trifluridine (as unchanged drug) undergoes excretion via this pathway. Neither trifluridine nor tipiracil undergo CYP450 metabolism. More than 96% of trifluridine is protein-bound, predominantly to serum albumin. Less than 8% of tipiracil is protein-bound. The half-life of trifluridine and tipiracil, once those compounds have reached steady state concentrations in the body, are 2.1 hours and 2.4 hours, respectively. The mean time to peak plasma concentration is approximately 2 hours.

Trifluridine/tipiracil has demonstrated embryo-fetal toxicity and fatality in studies conducted in pregnant rats at doses that resulted in exposures similar to or lower than those seen with recommended doses in humans. No data is available in pregnant women. Pregnant women should be counseled on the possible harm to a fetus; women of reproductive potential should use appropriate contraception during therapy with trifluridine/tipiracil. Lactating women should be advised not to breastfeed during therapy with trifluridine/tipiracil and for 24 hours following the final dose. In addition, men with female partners of reproductive potential should use condoms during treatment with trifluridine/tipiracil and for 3 months after the completion of therapy.<sup>4</sup>

In the geriatric population receiving trifluridine/tipiracil in clinical studies, patients 65 years of age and older were more likely to develop hematological toxicities as compared to their younger counterparts, specifically Grade 3 or 4 neutropenia (48% versus 30%), Grade 3 anemia (26% versus 12%), and Grade 3 or 4 thrombocytopenia (9% versus 2%).

Trifluridine/tipiracil is available in tablet formulation in two different strengths: 15 mg trifluridine/6.14 mg tipiracil, and 20 mg trifluridine/8.19 mg tipiracil. The tablets are to be stored at 20°C to 25°C (68°F to 77°F), with permissible excursions to 15°C to 30°C (59°F to 86°F). As a cytotoxic medication, trifluridine/tipiracil should be handled and disposed of appropriately. If the tablets are stored outside of the original bottle, they should be disposed of after 30 days.<sup>4</sup>

The results of the RECURSE trial demonstrate that trifluridine/tipiracil significantly improved overall survival in patients from Japan, the United States, Europe, and Australia with metastatic colorectal cancer who had failed standard treatment with fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and, when indicated, cetuximab or panitumumab, irrespective of KRAS tumor status. While the study results are statistically significant in terms of improving median OS by approximately 1.8 months and delaying decline in ECOG performance status by approximately 1.7 months in comparison to placebo, providers must assess whether these results are also clinically significant and outweigh drug-related adverse effects. Regarding place in therapy, trifluridine/tipiracil is, similar to regorafenib, a last-line treatment option for patients whose metastatic disease has progressed through standard regimens. Because of the risk of cytopenias, complete blood counts should be obtained prior to each treatment cycle and periodically throughout treatment. Based on the current version of the NCCN colon cancer guidelines, trifluridine/tipiracil is included as a

treatment option for patients who have progressed through standard therapies.<sup>18</sup> Trifluridine/tipiracil is currently commercially available. A comprehensive access support program designed to assist patients in obtaining the medication is available through the manufacturer.

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