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NCOA ONCOLOGY DRUG NEWSLETTER

NORTH CAROLINA Oncology Association

FDA APPROVALS

Pembrolizumab (Keytruda)

The FDA has approved perioperative **pembrolizumab (Keytruda)** in combination with platinum-containing chemotherapy as neoadjuvant treatment and continued as a single agent in the adjuvant setting for the treatment of patients with resectable stage II, IIIA, or IIIB (T3-4N2) non–small cell lung cancer.[1,2] Findings from the randomized, double-blind, phase 3 KEYNOTE-671 clinical trial (NCT03425643) support this approval because investigators reported a statistically significant and clinically meaningful improvement in event-free survival (EFS).[3,4]

At 24 months, the EFS rate was 62.4% with pembrolizumab plus chemotherapy and adjuvant pembrolizumab versus 40.6% for placebo plus chemotherapy (HR, 0.58; 95% CI, 0.46-0.72; P < .00001). With pembrolizumab, the major pathologic response rate was 30.2% (95% CI, 25.7%-35.0%) compared with 11% (95% CI, 8.1%-14.5%) with placebo (Δ, 19.2%; 13.9%-24.7%; P < .00001). The pathological complete response rate was 18.1% (95% CI, 14.5%-22.3%) with pembrolizumab versus 4% (95% CI, 2.3%-6.4%) for placebo (Δ, 14.2%; 95% CI, 10.1%-18.7%; P < .00001). Moreover, the overall survival (OS) data were immature at the time of the analysis; however, the 24-month OS rate was 80.9% in the pembrolizumab arm compared with 77.6% in the placebo arm (HR, 0.73; 95% CI, 0.54-0.99; P = .02124).

In KEYNOTE-671, 786 patients were randomly assigned to receive chemotherapy plus pembrolizumab (n = 397) or placebo (n = 399). In the perioperative pembrolizumab arm, patients were given intravenous (IV) pembrolizumab 200 mg every 3 weeks for up to

4 cycles plus cisplatin 75 mg/m^2 IV on day 1 of each cycle and either gemcitabine 1000 mg/m^2 IV on days 1 and 8 of each cycle or pemetrexed 500 mg/m^2 IV on day 1 of each cycle. In this arm, treatment was given as neoadjuvant therapy followed by pembrolizumab 200 mg IV every 3 weeks for up to 13 cycles as adjuvant therapy post surgery. Patients in the control arm were given matching placebo plus chemotherapy.

Nivolumab (Opdivo)

The FDA has granted approval to **nivolumab (Opdivo)** as monotherapy for the adjuvant treatment of patients with resected stage IIB or IIC melanoma, according to Bristol Myers Squibb.[6] The approval is supported by results from the pivotal phase 3 CheckMate76K clinical trial (NCT04099251), which showed a statistically significant and clinically meaningful reduction in risk of recurrence or death in patients with resected stage IIB or IIC melanoma who were treated with adjuvant nivolumab monotherapy compared with those who received placebo.

CheckMate76K included 790 patients with completed resected disease and a negative sentinel lymph node biopsy result. Patients were randomly assigned 2:1 to receive 480 mg every 4 weeks for up to 12 months or matching placebo. The prospective period of

treatment was 12 months. Recurrence-free survival (RFS) was the primary end point of the study. The secondary end points explored were overall survival, safety, and distant metastasis-free survival (DMFS). Secondary end points were objective response rate, duration of next-line treatment, progression-free survival (PFS), and end of next-line treatment.[7]

The median follow-up was 15.8 months in the nivolumab arm and 15.9 months in the placebo arm. The mean duration of treatment was 8.8 months (range, 0-12.1) in the nivolumab arm and 9.9 months (range, 0-12.7) in the placebo arm. Adjuvant treatment with nivolumab monotherapy specifically achieved a 58% reduction in the risk of recurrence or death compared with placebo (HR, 0.42; 95% CI, 0.30-0.59; P < .0001). Results for the primary end point of RFS also showed the 12-month RFS rates with nivolumab versus placebo to be 89% (95% CI, 86%-93%) versus 79% (95% CI, 74%-84%), respectively.

FoundationOne CDx and FoundationOne Liquid CDx

The FDA has granted approval to **FoundationOne CDx** and **FoundationOne Liquid CDx** for use as companion diagnostics to aid in the identification of patients with metastatic non–small cell lung cancer (NSCLC) harboring a BRAF V600E mutation who may benefit from treatment with the combination of encorafenib (Braftovi) plus binimetinib (Mektovi).[8]

This regulatory decision quickly follows the FDA approval of the combination of encorafenib plus binimetinib on October 11, 2023, for the treatment of adult patients with metastatic NSCLC harboring a BRAF V600E mutation as detected by an FDA-approved test.[9] FoundationOne CDx uses tumor tissue samples and tests over 300 cancer-related genes for genomic alterations, and the FoundationOne Liquid CDx uses a blood sample to analyze more than 300 cancer-related genes. Encorafenib combined with binimetinib was recently approved based on data from the phase 2 PHAROS trial (NCT03915951). The open-label, multicenter, single-arm study enrolled patients with histologically confirmed metastatic NSCLC harboring a BRAF V600E mutation and measurable disease by RECIST v1.1 criteria.[10]

Once enrolled, patients were given 450 mg of encorafenib orally once daily in addition to 45 mg of oral binimetinib twice daily. Treatment continued until progressive disease or unacceptable toxicity. The study assessed overall response rate by RECIST v1.1 criteria as the primary end point, and the secondary end points were duration of response (DOR), disease control rate (DCR), PFS, overall survival (OS), and safety.

In the study, 59 treatment-naive patients were given the combination, which elicited an overall response rate of 75% (95% CI, 62%-85%).[9] The complete response (CR) and partial response (PR) rates were 15% and 59%, respectively. The median DOR had not yet been reached (95% CI, 23.1-not evaluable [NE]). In the study, 75% of patients achieved a DOR of at least 6 months and 59% had a DOR of at least 12 months. Patients who were previously treated (n = 39) had an overall response rate of 46% (95% CI, 30%-63%). This included a CR rate of 10% and a PR rate of 36%. The median DOR was 16.7 months (95% CI, 7.4-NE), and the 6- and 12-month DOR rates were 67% and 33%, respectively.

Encorafenib (Braftovi)/Binimetinib (Mektovi)

The FDA has approved **encorafenib (Braftovi)** and **binimetinib (Mektovi)** for patients with metastatic NSCLC harboring a BRAF V600E mutation as detected by an FDA-approved test.[11] Findings from the phase 2 PHAROS trial (NCT03915951) support this regulatory decision because the primary end point of objective response rate was met. Among the 59 patients included in the treatment-naive cohort and 39 in the previously treated cohort, the objective response rates were 75% (95% CI, 62%-85%) versus 46% (95% CI, 30%-63%), respectively, and the

median DOR was not estimable (NE; 95% CI, 23.1-NE) versus 16.7 months (95% CI, 7.4-NE).[12]

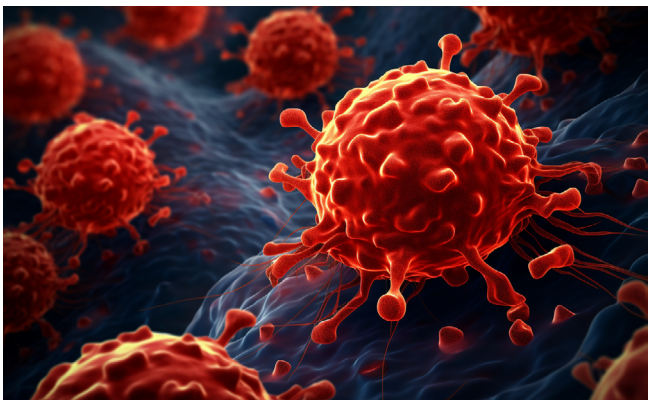
The DCR after 24 weeks in the treatment-naive cohort was 64% compared with 41% in patients who were previously treated. The median PFS was not evaluable (95% CI, 15.7-NE) in the treatment-naive arm and 9.3 months (95% CI, 6.2-NE) in the previously treated cohorts.

In the phase 2 study, the tyrosine kinase inhibitor combination of encorafenib plus binimetinib was evaluated for patients with BRAF-V600–mutated NSCLC to determine the safety, tolerability, and efficacy of the combination. Patients received 450 mg of encorafenib once daily with 45 mg of binimetinib twice daily in a 28-day cycle.

Regarding eligibility, the enrolled patients were those 18 years or older who had received a diagnosis of histologically confirmed stage IV NSCLC exhibiting a BRAF V600E mutation. These patients could be either treatment naive or have previously undergone first-line treatment, including platinum-based chemotherapy or a combination of an anti–PD-1/PD-L1 inhibitor with platinum-based chemotherapy.13 Patients needed to have the presence of measurable disease, an ECOG performance status (PS) of 0 or 1, and adequate bone marrow, hepatic, and renal function.

FoundationOne CDx

The FDA has granted approval to the **FoundationOne CDx** for use as a companion diagnostic for selpercatinib (Retevmo) for the treatment of adult patients with locally advanced or metastatic solid tumors harboring a RET gene fusion whose disease has progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options, according to Foundation Medicine, Inc.[14]



FoundationOne CDx is a next-generation, sequencing-based in vitro diagnostic device that detects substitutions, insertion alterations, deletion alterations, and copy number alterations in 324 genes and select gene rearrangements. The CDx can also detect genomic signatures, including microsatellite instability and tumor mutational burden, through DNA by using formalin-fixed, paraffin-embedded tumor tissue specimens.

In September 2022, the FDA approved selpercatinib for the treatment of adult patients with locally advanced or metastatic solid tumors harboring a RET gene fusion whose disease has progressed on or after previous systemic treatment or who have no satisfactory alternative treatment options, based on findings from the LIBRETTO-001 trial (NCT03157128).[15] In the study, selpercatinib yielded robust and durable responses after more than 20 months of follow-up. Simultaneously, the FDA granted a traditional approval to selpercatinib for the treatment of adults with locally advanced or metastatic non–small cell lung cancer with a RET gene fusion as detected by an FDA-approved test.

NEW DRUG APPLICATION

TERN-701

The FDA has cleared the investigational new drug application and the design of the phase 1 CARDINAL trial (NCT03019185), evaluating the safety, tolerability, pharmacokinetics, and efficacy of **TERN-701** in patients with chronic myelogenous leukemia (CML), according to Terns Pharmaceuticals, Inc.[16]

TERN-701 is an allosteric BCR-ABL tyrosine kinase inhibitor (TKI) that targets the BCR-ABL myristoyl pocket. The potent oral TKI is designed to address the challenges and limitations of active-site TKIs with the goal of achieving improved tumor suppression through a combination of potent activity against BCR-ABL. This includes a broad range of mutations and improved

safety and tolerability profiles.17 The design that has been cleared by the FDA uses insights from an ongoing phase 1 trial in China, which supports using a starting dose that appears to be safe and clinically active based on emerging early clinical data.[16]

In the global, multicenter, open-label, 2-part, phase 1 CARDINAL trial, investigators will evaluate the safety, pharmacokinetics, and efficacy of TERN-701 in patients with previously managed CML across the United States, Europe, and other Terns global territories. The overall goal of the study is to determine the optimal dose of TERN-701 to move forward to a potential pivotal trial for patients with chronic phase CML. The study will consist of 2 parts, with part 1 as the dose-escalation portion of the trial assessing once-daily TERN-701 monotherapy and part 2 as the dose-expansion portion, which will randomly assign patients to once-daily treatment with 1 of 2 doses of TERN-701 to be selected based on findings from part 1.

BIOLOGICS LICENSE APPLICATION

Pegfilgrastim-cbqv (Udenyca OnBody)

The biologics license application (BLA) for the on-body injector (OBI) presentation of **pegfilgrastim-cbqv (Udenyca OnBody)** has been resubmitted to the FDA. The resubmission follows the FDA's completion of its inspection of a third-party filler. The FDA issued a complete response letter (CRL) on September 21, 2023, because of an ongoing review of inspection findings at the third-party filler. The CRL did not identify any issues with the efficacy, safety, trial design, labeling, or manufacturing of pegfilgrastim-cbqv. Moreover, the FDA has not requested any additional data or trials from Coherus BioSciences, the manufacturer.[18]

The OBI delivery system for which this BLA seeks approval would eliminate the need for a patient to return to the hospital the day after chemotherapy. Pegfilgrastim (Neulasta Onpro) is currently the only FDA-approved OBI presentation of pegfilgrastim or its biosimilar. Pegfilgrastim-cbqv is administered the day after chemotherapy to decrease the incidence of chemotherapy-associated febrile neutropenia.[18] The risk of febrile neutropenia is statistically equivalent between patients receiving pegfilgrastim or a biosimilar of pegfilgrastim.[19]

The FDA approved pegfilgrastim-cbqv in March 2023 in its single-dose prefilled autoinjector presentation. The original version launched in the United States in January 2019.

ORPHAN DRUG DESIGNATION

SLS009

The FDA has granted an orphan drug designation (ODD) to **SLS009** for the treatment of patients with acute myeloid leukemia (AML), according to SELLAS Life Sciences Group, Inc.[20] SLS009 is a novel, highly selective CDK9 inhibitor currently under investigation in an open-label, single-arm, multicenter, phase 2a study (NCT04588922) for patients with relapsed or refractory AML.

The basis of this ODD is supported by findings from the phase 1 study evaluating SLS009 that showed all key end points of the study were met, including antitumor activity of up to 77.3% bone marrow blast reduction and durable complete remission with no minimal residual disease. Findings showed desired 24-hour inhibition concentrations greater than 90% (IC90) in peripheral blood concentrations after the first infusion, with IC90 concentrations resulting in up to 97% of cancer cells killed. Desired levels of myeloid cell leukemia 1 (MCL1) and MYC suppression in peripheral blood were achieved, and a decrease in MCL1 or MYC was seen in 97% of the patients evaluated.

The primary end points being evaluated in the trial are safety, tolerability, and efficacy at 2 dose levels of SLS009. The first dose level is SLS009 once weekly at 45 mg, and the second is the recommended phase 2 dose, determined to be 60 mg in combination with azacytidine (Vidaza or Onureg) and venetoclax (Venclexta).[21]

CHANGES IN LABELED INDICATIONS

Bosutinib Monohydrate (Bosulif)

The new drug label indication for bosutinib monohydrate in pediatric patients, 1 year of age or older, with chronic myeloid leukemia (CML) bearing the Philadelphia chromosome (CP Ph+ CML) is supported by the BCHILD trial (NCT04258943) involving 49 patients.[22,23] Among these, the onset of all grade diarrhea occurred within a median time of 2 days after initiation of treatment, with an average duration of 2 days.[24]

Moreover, it was observed that 59% of patients experienced an elevation in alanine aminotransferase (ALT), and 51% saw an increase in aspartate aminotransferase (AST) compared to their baseline levels. A significant majority, comprising 76% of the patients, encountered an increase in either ALT or AST. Significantly, most instances of heightened transaminase levels occurred early in the treatment regimen, with 84% of patients experiencing their initial elevations within the first 3 months. The median onset time was 22 and 15 days, respectively. Furthermore, for grade 3 or 4 adverse events, the median duration for increased ALT was 26 days; for AST, it was 12 days.[22]

A subset of individuals (8%) experienced grade 1 or 2 cardiac events. These included tachycardia in 2 cases, as well as isolated incidents of angina pectoris (1), right bundle branch block (1), and sinus tachycardia (1). Grade 1 or 2 pericardial effusion, peripheral edema, and face edema were also experienced by 1 patient for each event type.

Overall, regarding renal toxicity, 45% of patients who initially exhibited a normal glomerular filtration rate (eGFR) experienced a shift, reaching mild renal toxicity. In parallel, 40% of pediatric patients who initially presented with a mild eGFR shifted to moderate renal toxicity.

The label wording changes include: "bosutinib is a CYP3A substrate [and]…displays pH dependent aqueous solubility." It is advised to swallow capsules whole; however, if the patient is unable to swallow whole capsules, the heath care provider should be informed, and the capsule contents can be poured into yogurt or applesauce. Physicians will adjust dose as the pediatric patient grows. The main adverse event for both child and adult patients is constipation. Bosulif capsules and tablets are available in a child-proof closure and contain a desiccant that should not be eaten. Always store capsules in the original bottle. Ingredients include microcrystalline cellulose, mannitol, croscarmellose sodium, gelatin, poloxamer, magnesium stearate, povidone, red iron oxide, titanium dioxide, and yellow iron oxide. The printing ink used for labeling contains black iron oxide, shellac, potassium hydroxide, propylene glycol, and strong ammonia solution.

It is not yet known if Bosulif is safe for pediatric patients who no longer respond to or who cannot tolerate other treatments or for pediatric patients with AP Ph+ CML or BP Ph+ CML or for patients less than 1 year of age who have been newly diagnosed with CP Ph+ CML.

Encorafenib (Braftovi)

Encorafenib strongly stimulates the CYP3A2 enzyme and as a result it can lead to reduced plasma concentrations of other drugs that are metabolized by this enzyme (CYP3A2 substrates). This includes hormonal contraceptives, and it makes them less effective. It is advised not to take CYP3A2 substrates with encorafenib; however, if unavoidable, refer to the product labeling of the CYP3A2 substrate for recommendations.[25]

The PHAROS trial (NCT03915951) evaluated the safety of encorafenib in combination with binimetinib

for patients with BRAF V600E mutation-positive metastatic NSCLC. The trial included 98 patients who received encorafenib (450 mg once daily) with binimetinib (45 mg twice daily) in an open-label, single-arm study. Sixty-two patients were 65 to 75 years of age, and 20 patients were 75 years of age or older.[26]

In the trial, 2% percent of patients developed cutaneous squamous cell carcinoma (cuSCC) and skin papilloma. In 12% of patients, hemorrhage occurred including fatal intracranial hemorrhage (1%) and grade 3 or 4 hemorrhages (4.1%). The most common types experienced were anal (2%) and hemothorax (2%) hemorrhage. In 1% of patients there was an occurrence of uveitis. In 2.1% of patients there was an increase of the measure of time it takes for the heart's electrical system to recharge (QTcF); the time increased to more than 500 ms.

Patients who are either pregnant or who have the potential to become pregnant should be advised of the potential fetal harm encorafenib could cause.

Patients who have certain cardiac conditions or a history of retinal vein occlusion were excluded from the study. The median duration of treatment with encorafenib and binimetinib was 9.2 and 8.4 months, respectively.

The most common adverse events (AEs), which were reported in more than 25% of patients who received encorafenib, included fatigue, nausea, diarrhea, musculoskeletal pain, vomiting, abdominal pain, visual impairment, constipation, dyspnea, rash, and cough.

In terms of dose management, AEs led to dose interruptions in 59% of patients, with diarrhea (17%) and nausea (13%) being the most frequent causes. Dose reductions were necessary for 30% of patients, with diarrhea and nausea (8% each) being the primary reasons. Notably, 16% of patients experienced AEs that led to discontinuation of encorafenib. The most common causes were diarrhea and musculoskeletal pain (3.1% each), followed by fatigue, rash, nausea, visual impairment, and vomiting (2% each).

Serious AEs were observed in 38% of patients receiving encorafenib in combination with binimetinib. Hemorrhage (6%), diarrhea (4.1%), anemia, dyspnea, pneumonia (3.1% each), and various cardiac events (2% each) were the most frequently reported serious adverse reactions.

Fatal AEs occurred in 2% of patients receiving the combination treatment, including instances of intracranial hemorrhage and myocardial infarction (1% each). Other clinically significant AEs, occurring in less than 10% of patients, included peripheral neuropathy, dysgeusia, facial paresis, pancreatitis, hyperkeratosis, erythema, and drug hypersensitivity.[25]

Encorafenib may elevate the risk of developing both new primary cutaneous and noncutaneous malignancies. Therefore, it is crucial to emphasize that it is important for patients to notify their health care providers in the event of any changes or the emergence of new skin lesions. Additionally, the presence of a BRAF V600E or V600K mutation prior to initiating treatment should be confirmed. Patients also should be educated about recognizing and reporting any symptoms of heart failure. Regular monitoring of serum liver tests, including ALT, AST, and bilirubin, is advised throughout the course of treatment. Patients should be instructed to promptly report any symptoms indicative of liver dysfunction, such as jaundice, dark urine, nausea, vomiting, loss of appetite, fatigue, bruising, or bleeding.[25]

Pembrolizumab (Keytruda)

In regard to the KEYNOTE-913 trial (NCT03783078), which is evaluating first-line pembrolizumab for patients with advanced Merkel cell carcinoma, an

update states that the median duration of exposure was 6.3 months (range 1 day to 28 months). Of the grade 3 and 4 abnormalities, increased lipase occurred in 17% of patients with melanoma or non–small cell lung cancer. These patients were given pembrolizumab as a single agent.[27,28]

Regarding neoadjuvant and adjuvant treatment for resectable NSCLC, the safety and effectiveness of pembrolizumab combined with neoadjuvant platinum-containing chemotherapy followed by surgery, and then continued as adjuvant treatment with pembrolizumab alone, were assessed in the KEYNOTE-671 study (NCT03425643). This was a double-blind, placebo-controlled, multicenter trial involving patients with previously untreated and resectable stage II, IIIA, or IIIB (N2) NSCLC. Patients with active autoimmune disease necessitating systemic therapy within 2 years or a medical condition requiring immunosuppression were not eligible.[28,29]

Binimetinib (Mektovi)

The combination of binimetinib with encorafenib may lead to the development of new primary malignancies, both cutaneous and noncutaneous, as shown in the PHAROS study (NCT03915951).[30] In this study, 2% of patients experienced cutaneous squamous cell carcinoma, and 2% developed skin papilloma. The recommendation is to monitor patients for the emergence of new malignancies before starting treatment, during the course of treatment, and after treatment cessation.[31]

Also reported in the PHAROS study, for cohorts receiving the binimetinib and encorafenib combination, cardiomyopathy occurred in 11% of patients and 1% of patients experienced grade 3 left ventricular dysfunction. However, in 82% of the patients who experienced cardiomyopathy, the condition resolved. Venous thromboembolism (VTE) was found in 7% of patients and 1% of those patients developed pulmonary embolism.[30]

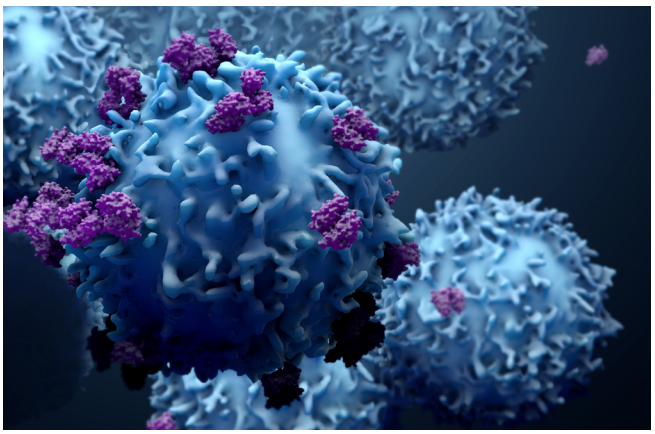
The PHAROS trial results also indicated serious retinopathy in 2% of patients; this did not lead to treatment discontinuation; however, it did result in dose interruption for 1% of patients. Uveitis and pneumonitis each occurred in 1% of patients. Laboratory tests showed an increase in liver dysfunction (grades 3 or 4): 10% AST, 9% ALT, and 3.2% phosphatase. Extensive drug label changes continue. Refer to the original drug label for further prescribing updates.[30]

Darolutamide (Nubeqa)

Additions to prescribing information are based on the ARASENS trial (NCT02799602),[32] which showed that 3.2% of patients who received darolutamide with docetaxel and 0.3% who received placebo with docetaxel developed ischemic heart disease of grade 3 (1.3%) and grade 4 (1.1%), respectively. Of these patients, 0.3% who received darolutamide with docetaxel died, compared to 0 deaths for patients who received placebo with docetaxel.[33]

Nivolumab (Opdivo)

According to the results of the CheckMate76K trial (NCT04099251),[34] which compared nivolumab versus placebo, 18% of patients with resected stage IIB/C melanoma experienced serious adverse events (AEs) while receiving nivolumab. One patient (0.2%) had a fatal AE caused by heart failure and acute kidney injury. The other AEs experienced were diarrhea (1.1%), arthralgia (1.7), and rash (1.7%); these all led to permanent discontinuation. Dose interruptions due to AEs were reported in 25% of patients and included COVID-19, infusion, infusion-related reaction, diarrhea, arthralgia, and increased ALT. The most common AEs experienced were fatigue, musculoskeletal pain, rash, diarrhea, and pruritus.[35]



Nivolumab can be used as a single agent to prevent reoccurrence after complete surgical removal for stage IIB, stage IIC, stage III, or stage IV disease.

Pegfilgrastim-fpgk (Stimufend)

Updated prescribing information explains that the use of pegfilgrastim-fpgk to increase survival for pediatric patients who have been exposed to high doses of radiation is based on the approval of pegfilgrastim-fpgk as a biosimilar to pegfilgrastim. Due to ethical and feasible considerations, efficacy could not be tested on humans; instead, models and simulations were used. The study showed that for pediatric patients who weigh less than 45 kg, 2 weight-based doses of pegfilgrastim given 1 week apart results in comparable outcomes to those seen in adult patients who receive 2 doses of 6 mg each, given 1 week apart. This approach is expected to provide similar benefits in terms of survival and protection against myelosuppression.[36] Patients should be advised that this study was not able to be conducted on humans and, therefore, efficacy was achieved using animal testing.

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