A Review on FDA Approval of Lymphoma Drug Ukoniq (Umbralisib) And Its Withdrwal Due to Safety Concerns

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Abstract

Present study focuses on Ukoniq also known as Umbralisib. The drug approved in June 2020 for treatment of 2 types of lymphoma cancer-MZL & FL. Later on, FDA withdrawn this specific drug approval for umbralisib (Ukoniq), an oral inhibitor of PI3K-δ and CK1-ε which is manufactured by TG Therapeutics. The agency began investigating the drug in February 2022 after findings from the phase 3 UNITY-CLL trial (NCT026112311) suggested that umbralisib might be associated with an increased risk of death. There are many drugs that have been withdrawn from the market because of ADR's. Trends and Reasons for withdrawal of Umbralisib was identified by FDA & has been withdrawn from the market, and communicated as well.

Keywords: Umbrasib,FDA,lymphomaDissorder,

INTRODUCTION

Cancer is the leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, or nearly one in every six deaths. Breast, lung, colon, and rectal cancers are the most common. Tobacco use, a high BMI, alcohol consumption, a lack of fruits and vegetables, and a lack of physical activity account for approximately one-third of cancer deaths. Cancer-causing infections, such as human papillomavirus (HPV) and hepatitis, account for approximately 30% of cancer cases in low- and lower-middle-income countries. Many cancers can be cured if they are detected early and treated effectively1-2. Cancer is a broad term that refers to a wide range of diseasesthat can affect any part of the body.

Malignant tumors and neoplasms are other terms used.One distinguishingfeature of canceris the rapid formationof abnormal cells that grow beyond their normal boundaries and can then invade neighboring parts of the body and spread to other organs; this process is known as metastasis. The primary cause of cancer death is widespread metastasis.

Cancer is a disease that occurs when cells in your body divide at a faster rate than normal. These abnormal cellscombine to form a lump — or tumor. There are various tests through which the extent and severity of cancer can be determined and diagnosed. Basically, there are 4 stages of cancer, the specific stage is determined by a fewdifferent factors including the size, location of tumor.Though stages I through IV are the most common, there is also stage zero this stage describes cancer that is still localized to the area where it began.

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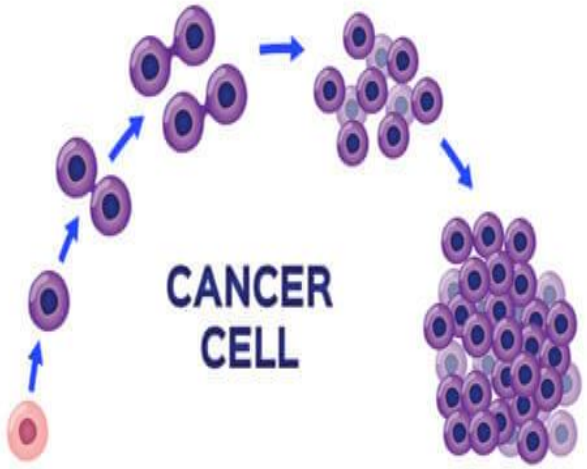
Cancers that are still in stage zero are usually treatable and are considered pre-cancerous by most healthcare providers. Different types of cancers effect the body in various ways, typically there are five main types of cancers these include Carcinoma, Sarcoma, Melanoma, Lymphoma and leukemia3-4. Carcinoma is a cancer that affects organs and glands such as the lungs, breasts, pancreas, and skin it is considered as the most common type of cancer. Sarcoma is a type of cancer that affects soft or connective tissues, such as muscle, fat, bone, cartilage, or blood vessels. Cancer can sometimes develop in the cells that pigment ourskin;Melanoma is the name given to these types of cancers. Lymphoma is a type of cancer that affects the lymphocytes or the white blood cells and the cancer that affects the blood refers to leukemia5-6



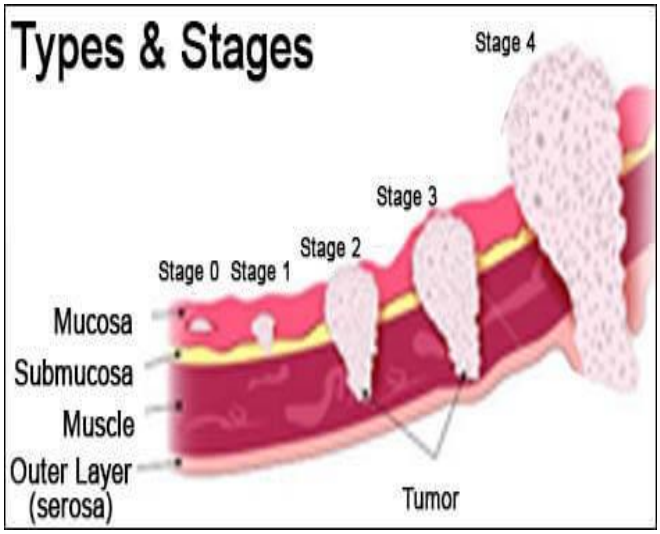


Fig: -Shows different stages of cancer, Stage-1: -the cancer is limited to small area and does not spread to lymph nodes or other tissues, stage-2 the cancer grows but does not spread where as in 3RD stage cancer spreads to lymph nodes &in the final stage i.e., stage-4 cancer spreads to other organs or areas of your body

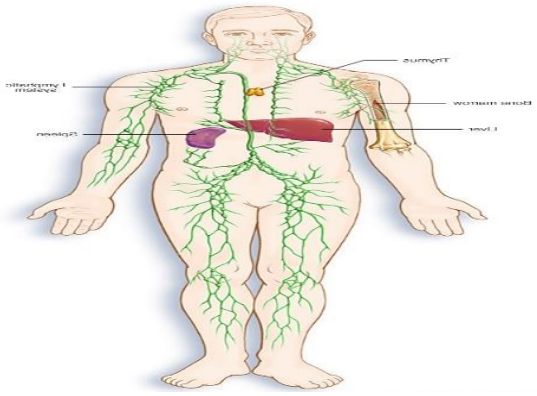


Fig:- The lymphatic system is a component of the immune system, which protects the body from infection and disease. The lymphatic system consists of the spleen, thymus, lymph nodes, lymph channels, tonsils, and adenoids.

Lymphoma: - Dissorder

Thomas Hodgkin published his description of seven patients suffering from massive enlargement of lymph nodes and spleen as a new disease entity as early as 1832. In his Systematic analyses of epidemiological data, it pointed towards an infectious agent as a potential cause for this disorder Hodgkin's lymphoma is an uncommon disorder with an annual incidence of 2–3 per 100000 in Europe and the USA7-8. Lymphoma is a cancer of the lymphatic systemwhich is part of the body's germ-fighting network. It affectsthe lymph glands, spleen, thymus and bone marrow as well as other organs throughout the body. Lymphomas are classified as either Hodgkin or non-Hodgkin lymphomas based on the type of cell they contain. Marginal zone lymphomas are low-grade, slow-growing non-Hodgkin lymphomas that develop from B cells. They are known as marginal zone lymphomas because they develop at the edge of normal lymphoid tissues (collections of lymphocytes) called the marginal zone. Follicular lymphoma (FL) & Marginal zone lymphoma (MZL) are two sub-types of indolent B-cell non-Hodgkin lymphoma (NLH) that accounts for approximately 20% & 12% of all NHLs, respectively, these are slow- growing cancers that start in WBC called lymphocytes, which are a part of body's immune system9-10. Hodgkin lymphoma is B-cell lymphoma that arise from Reed-Sternberg cell, this has different therapy options than non-Hodgkin's lymphoma. The etiology of this disorder was found after a decade from its emergence. Patients in their 20s and 30s are most commonly diagnosed with supra-diaphragmatic lymphadenopathy and systemic B symptoms. Even in its advanced stages, HL is highly curable with a combination of chemotherapy, radiation, or a combination of modality treatment. Despite the fact that the same ABVD chemotherapeutic regimen has been the mainstay of therapy for the last 30 years, risk-adapted approaches have helped to de-escalate therapy in low-risk patients while intensifying treatment in higher risk patients11-12. Even patients who do

not respond to initial therapy can often be saved with different

chemotherapy regimens, the novel antibody-drug conjugate Brentuximab, or high dose autologous or allogeneic hematopoietic stem cell transplant (allo-HCT). Nivolumab and Pembrolizumab, both PD-1 inhibitors, have shown high response rates and long-term remissions in relapse/refractory HL. Allo-HCT has become a viable option for more HL patients due to alternative donor sources and reduced intensity conditioning.

The primary treatments for HL are chemotherapy and radiation therapy. Depending on the circumstances, one or both of these treatments may be employed. Certain patients may be treated with immunotherapy or a stem cell transplant if other treatments have failed. Surgery, with the exception of biopsy and staging, is rarely used to treat 13-14.

Epidomology Of the Dissorder

The chemotherapy drugs used are the same as those used for follicular lymphoma, and may include single agents like chlorambucil or fludarabine, as well as combinations like CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CVP (cyclophosphamide, doxorubicin, vincristine, prednisone) (cyclophosphamide, vincristine, prednisone)15-16. Cancer care teams include a variety of other health care professionals, such as physician assistants, nurse practitioners, oncology nurses, social workers, pharmacists, counselors, dietitians, and others there are 4 major treatments for NLH, these include chemotherapy, radiation therapy, targeted therapy, immune therapy.

Chemotherapy is the use of drugs to destroy cancer cells, usually by keeping the cancer cells from growing, dividing, and making more cells. It is the main treatment for NHL. A chemotherapy regimen, or schedule, usually consists of a specific number of cycles given over a set period of time17-18. A patient may receive 1 drug at a time or a combination of different drugs given at the same time. The stage and type of NHL determines which chemotherapy is used. The most common chemotherapy combination for the first treatment of aggressive NHL is called CHOP and contains 4 medications:

Cyclophosphamide (available as a generic drug)

Doxorubicin (available as a generic drug)

Prednisone (multiple brand names)

Vincristine (Vincasar)

For patients with B-cell lymphoma, adding an anti-CD20 monoclonal antibody, such as rituximab (Rituxan) or Obinutuzumab (Gazyva), to CHOP works better than using CHOP alone (see “Targeted therapy,” below). There are other common combinations of chemotherapy regimens, including:bendamustine (Treanda) and rituximab,

Combinations using fludarabine (available as a generic drug) and R-CVP (cyclophosphamide, prednisone, rituximab, and vincristine). The side effects of chemotherapy depend on the individual drug and the dose used. They can include fatigue, temporary lowering of blood counts, risk of infection, nausea and vomiting, hair loss, loss of appetite, rash, and diarrhea. These side effects can be managed during treatment and usually go away after treatment is finished.19-20

Immunotherapy, also known as biologic therapy, is used to boost the body's natural defenses against cancer. Modified T cells and checkpoint inhibitors are among the lymphoma treatments in this category. It employs anti-lymphoma strategies to improve, target, or restore immune system function21-22. Further it has different therapy sessions through which the cancer treatment is carried out, these include: Chimeric antigen receptor (CAR) T-cell therapy, Axicabtageneciloleucel (Yescarta- CART t-cell therapy), Tisagenlecleucel (Kymriah)Brexucabtageneautoleucel (Tecartus) and Lisocabtagenemaraleucel (Breyanzi).

Targeted therapy is a type of cancer treatment that targets specific genes, proteins, or the tissue environment that contributes to cancer growth and survival. This type of treatment inhibits cancer cell growth and spread while protecting healthy cells. The targets of all tumors are not the same. Your doctor may order tests to identify the genes, proteins, and other factors in your tumor in order to find the most effective treatment. This enables doctors to provide the most effective treatment to each patient whenever possible23-24.Targeted therapies used for NHL include monoclonal antibodies, kinase inhibitors, immunomodulatory drugs, and nuclear export inhibitors. In general, monoclonal antibodies are the main form of targeted therapy used for many types of NHL.

Radiation therapy is the use of high-energy x-rays, electrons, or protons to destroy cancer cells. A radiation oncologist is a doctor who specializes in using radiation therapy to treat cancer. External-beam radiation therapy, which delivers radiation from a machine outside the body, is typically used to treat NHL. Radiation therapy is usually given after or in addition to chemotherapy, depending on the NHL subtype. It is usually given to people who have localized lymphoma, which involves only one or two adjacent areas, or to people who have a large lymph node, which is usually more than 7 to 10 centimeters across.It may also be given in very low doses to people with advanced disease who have localized symptoms that can be relieved by radiation therapy, such as a painful bony lesion (only two treatments). Radiation therapy can make you tired and nauseated. The majority of side effects are related to the radiation-exposed area of the body. Possible side effects include mild skin reactions, dry mouth, temporary hair loss,

and loose bowel movements.

Table 1: Describes thedrugs utilized for treatment of Non-Hodgkin lymphoma

S.no	(Epidemiology)	Drugs used for specific therapies
		Cyclophosphamide (available as a generic drug)
		Doxorubicin (available as a generic drug)
		Prednisone (multiple brand names)
		Vincristine (Vincasar)
		BR, which includes bendamustine (Treanda) and rituximab
		Combinations using fludarabine (available as a generic drug)
		R-CVP (cyclophosphamide, prednisone, rituximab, and vincristine)
1.	Chemotherapy	
		Chimeric antigen receptor (CAR) T-cell therapy
2.	Immuno-therapy	Axicabtageneciloleucel (Yescarta)
		Tisagenlecleucel (Kymriah)
		Brexucabtageneautoleucel (Tecartus)
		Lisocabtagenemaraleucel (Breyanzi)
		Immune checkpoint inhibitors
		Monoclonal antibodies
		Rituximab (Rituxan)
		Brentuximab vedotin (Adcetris)
		Loncastuximabtesirine-lpyl (Zynlonta)
		Obinutuzumab (Gazyva)
		Ofatumumab (Arzerra)
		Polatuzumabvedotin-piiq (Polivy)
		Radiolabeled antibodies
3.	Targeted therapy	Tafasitamab-cxix (Monjuvi)
		Kinase inhibitors
		Ibrutinib (Imbruvica)
		Acalabrutinib (Calquence)
		Zanubrutinib (Brukinsa)
		Copanlisib (Aliquopa)
		Immunomodulatory drugs
		Tazemetostat (Tazverik)
		BCL2 inhibitor
		Venetoclax (Venclexta)
		Nuclear export inhibitors
		Selinexor (Xpovio)
4.	Radiation therapy	Bone marrow/stem cell transplantation
		Allogeneic (ALLO)
		Autologous (AUTO)

Umbralisib

There were many drugs enlisted for clinical trial testing these include: Umbralisib, Epratuzumab, rituximab (1997), kyamirah.**Umbralisib** is a kinase inhibitor which is used to treat rare forms of refractory lymphoma.it is sold under the brand name Ukoniq&its molecular formula is C31H24F3N5O3.

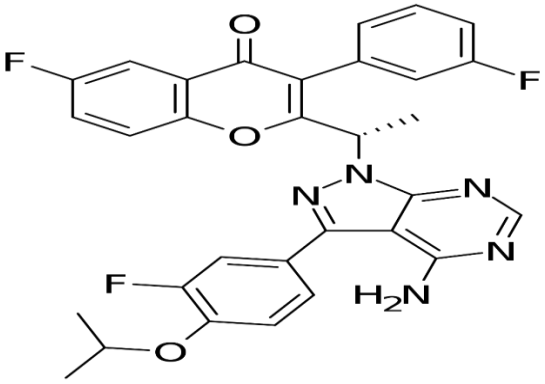


Fig: -Molecular structure of Umbralisib

Umbralisib works against marginal zone lymphoma by blocking the PI3K pathway, which is required for B-cell receptor signaling and the progression of lymphoma. Umbralisib also inhibits other pathways involved in certain types of lymphoma, such as the casein kinase pathway. During clinical trials, the overall response rate was 55%, and the 1-year progression-free survival rate from marginal zone lymphoma was 71%. During clinical trials, a link was discovered between higher umbralisib steady-state exposures and a higher incidence of adverse reactions, including diarrhea and elevated AST/ALT. This drug's effect on the QT interval has not been thoroughly studied. Umbralisib is rapidly absorbed in the GI tract & has a Tmax of about 4 hours. The AUC increased by 61% and the Cmax increased by 115% after consuming a high-fat, high-calorie meal while taking the drug. The average apparent central volume of distribution of umbralisib is 312 L.itis more than 99.7 % protein bound. in During in vitro studies, umbralisib was metabolized by CYP2C9, CYP3A4, and CYP1A2 enzymes& its effective half-lifewas about 91 hours, the drug is always taken with food as food increases the bio-availability & concentration of umbralisib.The average apparent clearance was found to be 15.5 L/h.Approximately 81% of the umbralisib dose was recovered in faeces (17% unchanged) during pharmacokinetic studies. Following a radiolabeled dose of 800 mg, approximately 3% was detected in the urine (0.02% unchanged).

MOA: -The PI3K pathway is dysregulated in cancer, resulting in the overexpression of p110 isoforms (p110α, p110β, p110δ, p110γ) that induce malignant transformation in cells. Umbralisib act by inhibiting several protein kinases, including PI3K and casein kinase CK1. PI3K is expressed in both healthy and malignant B-cells. CK1ε actually thought to be involved in the pathogenesis of malignant cells, including lymphomas. This slows the progression of relapsed or refractory lymphoma. In biochemical tests, it also inhibited a mutated form of ABL1. In vitro, umbralisib tends to inhibit malignant cell proliferation, CXCL12-mediated cell adhesion, and CCL19-mediated cell migration.

Approval Of Lymphoma Medicine and Withdrawal by Fda

All drugs that are currently in the market have undergone clinical trials, the results of which determine whether the drug meets its clinical specifications and is considered safe for the general public. Clinical trials are the primary way that the researchers find out if the new treatment (for e.g.-pacemaker) is safe and effective in people.The prime purpose of conducting clinical trial is to quantify clinical trial risk of new drug development in Non-Hodgkin's Lymphoma for which clinical trials were conducted on the drug Umbralisib.

Clinical Trials

A retrospective observational study of clinical trials was conducted, which undertook NHL in four subtypes in order to compare the success rate with the industry average (to trace out the risks and benefits). Risk estimates for this disease have not been reported before Further inclusion criteria required that the drug must have initiated its Phase 1 trial in one of the four NHL subtypes between 1998 and June 2008 in the US. In addition, clinical trials of new drug candidates that pertain to four subtypes of NHL were retrieved from clinicaltrial.gov. Drug candidates that did not meet these criteria were excluded from the study. The results showed that the overall success rate (8-11%) was significantly lower than the industry standard (17%). Overall survival (OS) as a secondary outcome appeared more predictive than primary endpoints that were surrogate of overall success. Further, targeted therapies appear more successful in these lymphoma sub-types than broad acting drugs and the Clinical trial risk in NHL, with an 89% failure rate reported here, may be reduced by basing decisions on OS secondary endpoints and the use of targeted therapies. The figure shows clinical trial success rates in NHL Drugs that entered Phase 1 clinical testing during or after 1998 were trackedup until June 2008.

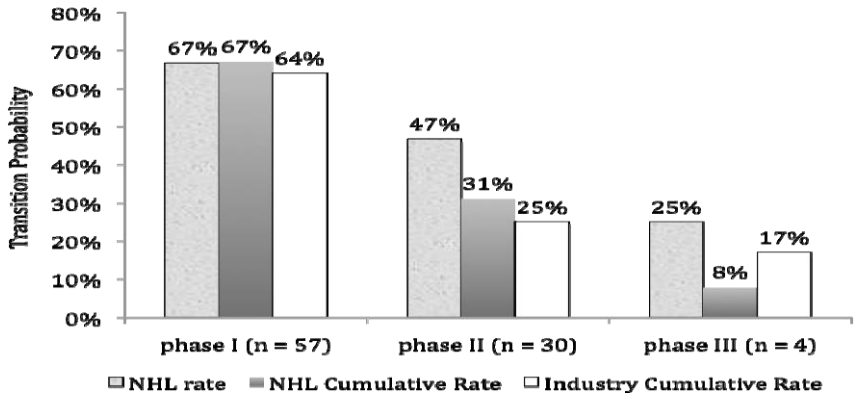


Fig: - graph shows CL success rates in NHL drugs that entered phase-1 clinical testing.'Pass rates' refer to the likelihood that drug would complete the current phase and advance to the nextphase of clinical testing (or approval if currently in Phase 3). 'Cumulative pass rates' represents the product of probabilitiesfor each prior phase, which for NHL is 11% for a product approval.

Reasons For Withdrawal

Umbralisib is a prescription medicine which was approved in February 2021 that works by blocking the action of an abnormal protein that signals cancer cells to multiply, which helps stop their spread. The medicine is available as a tablet administered by mouth. Marginal zone lymphoma is a rare, slowly progressing type of non-Hodgkin lymphoma that is initially treated with rituximab (an anti-CD20 drug), either alone or in combination with chemotherapy. Unfortunately, many patients relapse or develop resistance to these drugs. Treatment options are then limited, and alternative lymphoma treatments are required to control disease progression. umbralisib and other chemotherapeutic agents are used to treat follicular lymphoma, which has a similar progression

On February 5, 2021, the Food and Drug Administration granted accelerated approval to umbralisib, a kinase inhibitor for PI3K-delta and casein kinase CK1-epsilon, based on promising results from clinical trials. It was marketed as Ukoniq by TG Therapeutics and has been approved for the treatment of relapsing and refractory marginal cell lymphoma and follicular lymphoma in adults. Umbralisib inhibits casein kinase, a primary regulator of protein translation, kinase-1ε, distinguishing it from other lymphoma treatments. While it initially offered a promising therapy for patients experiencing relapsing or refractory disease, it was later withdrawn from the market due to safety concerns as the drug was associated with a possible increased risk of death outweighing the benefits.

The drug safety communication FDA on 6th January 2022, reported that the lymphoma medicine Ukoniq (Umbralisib) drug is withdrawn due to safety concerns.Prior to issuing the safety communication, the FDA convened an Oncologic Drug Advisory Committee meeting to evaluate the benefits and risks of umbralisib and requested overall survival (OS) data from the manufacturer, despite the fact that the first two sets of data did not yield statistically significant findings. The FDA issued a drug safety communication in February, addressing a possible safety concern with umbralisib treatment, which would be investigated further. However, another set of updated OS data revealed an increased risk of death, which the FDA determined outweighed the therapy's benefits, prompting an official withdrawal25-26.The updated data also prompted the manufacturer to voluntarily withdraw its biologics license application and supplemental new drug application for umbralisib.

FDA investigation Further updated that there's possible increased risk of death with this particular lymphoma medicine -Umbralisib. Earlier Ukoniq was approved to treat 2 specific types of lymphoma (cancer that effects the immune system): Marginal zone lymphoma (MZL) and Follicular Lymphoma (FL). The updated findings from the UNITY -cell clinical trial continued to show a possible increased risk of death in patients receiving Ukoniq as a result determined that "the risk of the treatment with Ukoniq

outweighs benefits". Based upon this determination, the drug's manufacturer, TG Therapeutics was voluntarily withdrawing Ukoniq from the market for the approved uses in MZL and FL.

FDA insisted Health care professional tostop prescribing ukoniq and switch patients to alternative treatments. Patients currently taking Ukoniq of the increased risk of death which is proven in the clinical trial are advise to stop taking the medicine. In limited circumstances in which a patient may be receiving benefit from Ukoniq, TG Therapeutics plans to make it available under expanded access.

Because of the seriousness of the safety concerns and similarities between 2 types of cancer for which the drug was approved and the type of cancer that was studied in the clinical trial, FDA alerts patients and health care professionals that they are reevaluating this risk against the benefits of Ukoniq for its approved uses." UNITY "clinical trial suspended enrollment of new patients in the on-going trials and review the Unity-findings.

Press Release

TG Therapeutics Announces Voluntary Withdrawal of the BLA/sNDA for U2 to Treat Patients with CLL and SLL

Apr 15, 2022

PDF Version

Company voluntarily withdraws UKONIQ® from sale for approved indications of relapsed/refractory MZL and FL Company to host conference call, Monday, April 18, 2022 at 8:30 AM ET

NEW YORK, April 15, 2022 (GLOBE NEWSWIRE) -- TG Therapeutics, Inc. (NASDAQ: TGTX), today announced that the Company has voluntarily withdrawn the pending Biologics License Application (BLA)/supplemental New Drug Application (sNDA) for the combination of ublituximab and UKONIQ® (umbralisib) (combination referred to as U2) for the treatment of adult patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). The decision to withdraw was based on recently updated overall survival (OS) data from the UNITY-CLL Phase 3 trial that showed an increasing imbalance in OS. Additional details are included below in the section entitled "ABOUT UNITY-CLL PHASE 3 TRIAL AND THE WITHDRAWAL OF THE BLA/sNDA SUBMISSION."

In addition, the Company announced that it has voluntarily withdrawn UKONIQ from sale for the approved indications of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen and for the treatment of adult patients with follicular lymphoma (FL) who have received at least three prior systemic therapies. UKONIQ was granted accelerated approval in these indications in February 2021. The Company's decision to withdraw UKONIQ from sale was primarily based on the withdrawal of the BLA and sNDA for U2 in CLL.

Michael S. Weiss, Chairman and Chief Executive Officer of TG Therapeutics stated, "We were very disappointed to see that the recently updated overall survival data showed an increasing survival imbalance in favor of the control arm. Accordingly, we and our advisors determined that we should withdraw the BLA/sNDA for U2 in CLL. Additionally, we made the difficult decision to withdraw UKONIQ from sale for the approved indications in MZL/FL. We want to thank the patients, families and practitioners who worked with us in our search for novel treatment options for patients with B-cell malignancies."

Mr. Weiss continued, "While we had hoped to bring U2 to patients with CLL, this will now permit us to focus our attention, passion and energy to building out our multiple sclerosis and autoimmune platform. With our ublituximab BLA pending for patients with relapsing forms of multiple sclerosis and a PDUFA goal date of September 28, 2022, we are excited about the possibility of bringing ublituximab to patients with RMS. If approved, we believe the differentiated profile of ublituximab with its one-hour infusion will be welcomed by the MS community."

About Unity-Cll Phase 3 Trial And The Withdrawal Of The Bla/Snda Submission

Unity-Cll, a global, Phase 3, randomized, controlled clinical trial, compared the U2 combination, to an active control arm of obinutuzumab plus chlorambucil in patients with both treatment-naïve and relapsed or refractory chronic lymphocytic leukemia (CLL). The trial met its primary endpoint, with U2 significantly prolonging independent review committee (IRC) assessed progression-free survival (PFS) vs. the control arm. The UNITY-CLL Phase 3 trial was conducted under a Special Protocol Assessment (SPA) agreement with the U.S. Food and Drug Administration (FDA). Based on the results of the UNITY-CLL trial, a BLA and sNDA were submitted to the FDA for U2 to treat patients with CLL/SLL.

In November 2021, the FDA notified the Company that it planned to host an Oncologic Drug Advisory Committee (ODAC) meeting in connection with its review of the pending BLA/sNDA and to discuss the benefit risk of UKONIQ in its approved indications. While the FDA identified a number of concerns, the FDA's desire to host an ODAC appeared to stem from an early ad hoc analysis of overall survival (OS) from the UNITY-CLL trial. OS was designated as a secondary efficacy endpoint in the UNITY-CLL protocol but was not part of the primary analysis in accordance with the study's statistical analysis plan agreed upon via a SPA, and therefore, was not analyzed or included in the BLA/sNDA. Additionally, the study was not powered for overall survival. As part of the ongoing review of the BLA/sNDA, the FDA requested an early analysis of OS from the UNITY-CLL trial. In a first analysis of OS using a cut-off date of September 2021, there was an imbalance in favor of the control arm (HR: 1.23). However, based on the ad hoc nature of the analysis, approximately 15% of patients had missing or outdated survival data. Further, when excluding deaths related to COVID-19, the two arms were approximately balanced (HR: 1.04). In February 2022, the Company submitted updated OS data with the same September 2021 cut-off date, but with reduced missing data and additional OS events, which showed an improvement from the previously reported OS data. Neither the original preliminary OS results nor the updated preliminary OS results were statistically significant.

Pursuant to a recent information request made by the FDA, updated OS data were collected that showed an increasing imbalance in favor of the control arm, differing from the improved results provided to the FDA in February 2022. Based on these new data, the Company decided to withdraw the pending BLA/sNDA for U2 to treat CLL/SLL and accordingly the April 22, 2022, ODAC meeting will be canceled.

In addition, based on the Company's decision to withdraw UKONIQ from sale, we anticipate that the FDA will withdraw the accelerated approval for the product.

The FDA also has scheduled an ODAC meeting for April 21, 2022, in which it plans to discuss the appropriate approach for phosphatidylinositol-3-kinase inhibitors under development for treatment of hematologic malignancies. UKONIQ is within this class of drugs and may be discussed during this meeting.

Important Safety Information

Infections: Serious, including fatal, infections occurred in patients treated with UKONIQ. Grade 3 or higher infections occurred in 10% of 335 patients, with fatal infections occurring in <1%. The most frequent Grade ≥3 infections included pneumonia, sepsis, and urinary tract infection. Provide prophylaxis for Pneumocystis jirovecii pneumonia (PJP) and consider prophylactic antivirals during treatment with UKONIQ to prevent CMV infection, including CMV reactivation. Monitor for any new or worsening signs and symptoms of infection, including suspected PJP or CMV, during treatment with UKONIQ. For Grade 3 or 4 infection, withhold UKONIQ until infection has resolved. Resume UKONIQ at the same or a reduced dose. Withhold UKONIQ in patients with suspected PJP of any grade and permanently discontinue in patients with confirmed PJP. For clinical CMV infection or viremia, withhold UKONIQ until infection or viremia resolves. If UKONIQ is resumed,

administer the same or reduced dose and monitor patients test at least monthly for CMV reactivation by PCR or antigen.

Neutropenia: Serious neutropenia occurred in patients treated with UKONIQ. Grade 3 neutropenia developed in 9% of 335 patients and Grade 4 neutropenia developed in 9%. Monitor neutrophil counts at least every 2 weeks for the first 2 months of UKONIQ and at least weekly in patients with neutrophil count <1 x 109/L (Grade 3-4) neutropenia during treatment with UKONIQ. Consider supportive care as appropriate. Withhold, reduce dose, or discontinue UKONIQ depending on the severity and persistence of neutropenia.

Diarrhea or Non-Infectious Colitis: Serious diarrhea or non-infectious colitis occurred in patients treated with UKONIQ. Any grade diarrhea or colitis occurred in 53% of 335 patients and Grade 3 occurred in 9%. For patients with severe diarrhea (Grade 3, i.e., > 6 stools per day over baseline) or abdominal pain, stool with mucus or blood, change in bowel habits, or peritoneal signs, withhold UKONIQ until resolved and provide supportive care with antidiarrheals or enteric acting steroids as appropriate. Upon resolution, resume UKONIQ at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue UKONIQ. Discontinue UKONIQ for life-threatening diarrhea or colitis.

Hepatotoxicity: Serious hepatotoxicity occurred in patients treated with UKONIQ. Grade 3 and 4 transaminase elevations (ALT and/or AST) occurred in 8% and <1%, respectively, in 335 patients. Monitor hepatic function at baseline and during treatment with UKONIQ. For ALT/AST greater than 5 to less than 20 times ULN, withhold UKONIQ until return to less than 3 times ULN, then resume at a reduced dose. For ALT/AST elevation greater than 20 times ULN, discontinue UKONIQ.

Severe Cutaneous Reactions: Severe cutaneous reactions, including a fatal case of exfoliative dermatitis, occurred in patients treated with UKONIQ. Grade 3 cutaneous reactions occurred in 2% of 335 patients and included exfoliative dermatitis, erythema, and rash (primarily maculo-papular). Monitor patients for new or worsening cutaneous reactions. Review all concomitant medications and discontinue any potentially contributing medications. Withhold UKONIQ for severe (Grade 3) cutaneous reactions until resolution. Monitor at least weekly until resolved. Upon resolution, resume UKONIQ at a reduced dose. Discontinue UKONIQ if severe cutaneous reaction does not improve, worsens, or recurs. Discontinue UKONIQ for life-threatening cutaneous reactions or SJS, TEN, or DRESS of any grade. Provide supportive care as appropriate.

Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5: UKONIQ contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons, frequently in patients who also have aspirin hypersensitivity.

Embryo-fetal Toxicity: Based on findings in animals and its mechanism of action, UKONIQ can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females and males with female partners of reproductive potential to use effective contraception during treatment and for at least one month after the last dose.

Serious adverse reactions occurred in 18% of 221 patients who received UKONIQ. Serious adverse reactions that occurred in ≥2% of patients were diarrhea-colitis (4%), pneumonia (3%), sepsis (2%), and urinary tract infection (2%). Permanent discontinuation of UKONIQ due to an adverse reaction occurred in 14% of patients. Dose reductions of UKONIQ due to an adverse reaction occurred

in 11% of patients. Dosage interruptions of UKONIQ due to an adverse reaction occurred in 43% of patients.

The most common adverse reactions (>15%), including laboratory abnormalities, in 221 patients who received UKONIQ were increased creatinine (79%), diarrhea-colitis (58%, 2%), fatigue (41%), nausea (38%), neutropenia (33%), ALT increase (33%), AST increase (32%), musculoskeletal pain (27%), anemia (27%), thrombocytopenia (26%), upper respiratory tract infection (21%), vomiting (21%), abdominal pain (19%), decreased appetite (19%), and rash (18%).

Lactation: Because of the potential for serious adverse reactions from umbralisib in the breastfed child, advise women not to breastfeed during treatment with UKONIQ and for at least one month after the last dose. Pleasevisit www.tgtherapeutics.com/prescribing-information/uspi-ukon for full Prescribing Information and Medication Guide.

Cautionary Statement

This press release contains forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995, including statements relating to overall survival information from the UNITY-CLL study, a potential path forward for U2 in the future, the withdrawal of sale of UKONIQ in its approved indications and the potential FDA approval of ublituximab in RMS. In addition to the risk factors identified from time to time in our reports filed with the U.S. Securities and Exchange Commission, factors that could cause our actual results to differ materially are the following: the risk that the FDA does not approve the pending BLA for ublituximab in RMS; the risk that we are unable to successfully launch, market and sell ublituximab in RMS, if approved by the FDA; the risk that we decide not to continue to treat and/or follow patients in the UNITY-CLL study or that the FDA issues a full clinical hold for the UNITY-CLL study preventing us from continuing to treat patients, the risk that we are unable or choose not to find a path forward for bringing to market UKONIQ and/or

ublituximab in CLL or any other hematologic indication; the risk that the Company no longer develops investigational products in oncology indications, including the development of any combinations of our proprietary investigational products or third-party products with UKONIQ and/or ublituximab for oncology indications; our ability to advance drug candidates into and successfully initiate, progress or complete clinical trials; the uncertainties inherent in research and development; and our ability to attract and maintain key management and other personnel necessary to continue development and commercialization activities.
Further discussion about these and other risks and uncertainties can be found in our Annual Report on Form 10-K for the fiscal year ended December 31, 2021, as updated by our subsequent Quarterly Reports on Form 10-Q, and in our other filings with the U.S. Securities and Exchange Commission. Any forward-looking statements set forth in

this press release speak only as of the date of this press release. We do not undertake to update any of these forward-looking statements to reflect events or circumstances that occur after the date hereof.

This press release and prior releases are available at www.tgtherapeutics.com. The information found on our website is not incorporated by reference into this press release and is included for reference purposes only.

Conclusion

As per the records there were nearly 18.1 million cancer cases around the world, it a disease that involves abnormal cell growth with the potential to invade or spread to other parts of the body. Treatment for cancer include therapies like chemotherapy, immune therapy, radiation therapy and targeted therapy. Different drugs that passed the clinical trials were approved for marketing, out of which umbralisib (ukoniq) drug is known to treat 2 types of cancer Molecular zone lymphoma (MZL) and Follicular lymphoma (FL). Treatment for Hodgkin lymphoma has improved significantly since the ABVD chemotherapeutic combination (It has been the most effective and least toxic chemotherapy regimen available for treating early-stage Hodgkin Lymphoma) was invented over 30 years ago. Despite using the same ABVD regimen in most patients treated first line, now a much better understanding of disease biology, late side effects of therapy and have moved towards a personalized risk adapted approach

Umbralisib was earlier approved by FDA on February 2021, for treatment of 2 types of cancer namely MZL & FL. Later on, on June 1, 2022 Umbralisib was withdrawn as it failed the clinical trials.based on the results of the phase III UNITY-CLL trials, these possibly showed increased risk of death in patients as a result the risks of the treatment with ukoniqoutweighedbenefits. TG Therapeutics voluntarily withdrew a biologics license application andsupplemental new drug application seeking approval for umbralisib plus ublituximab (TG-1101) in adults with chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) in April 2022. The company also plans to make umbralisib available in limited circumstances for patients who are benefiting from expanded access.According to the FDA, safety concerns may be a broader issue for the class of drugs umbralisib belongs to. “Clinical trials of other medicines in the same PI3 kinase inhibitor class as Ukoniq have shown similar safety concerns,” the FDA stated.

Conflict of Interest

The authors declared no conflict of interest.

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