Accelerated Approvals Reconsidered

None

Changes in Dosing/Administration

None

Changes in Labeled Indications

Xalkori® (*crizotinib*) – Pfizer received approval to market its kinase inhibitor for the treatment of adult and pediatric patients with ALK-positive unresectable, recurrent, or refractory inflammatory myofibroblastic tumor, a rare soft-tissue malignancy. The approval was based on responses being achieved in 12 of the 14 pediatric patients and in 5 of the 7 adults enrolled in two small single arm trials. Dosing of Xalkori® for the new indication is the same as that for its previously approved uses in treating ALK-positive systemic anaplastic large cell lymphoma and ALK- or ROS1-positive metastatic non-small cell lung cancer.

New Biosimilars and Generics

Full approvals were granted for:

- *Bortezomib* from Accord Healthcare, Dr. Reddy's, Hospira Inc., Intas Pharma USA, Jiangsu Hansoh Pharma, Kindos, Maia Pharm Inc., MSN, and Sandoz;
- *Paclitaxel* from HBT Labs Inc.; and
- *Pemetrexed* from Accord Healthcare Inc.

Tentative Approvals granted for:

- *Bendamustine hydrochloride* from Celerity Pharms;
- *Dasatinib* from Teva;
- *Neratinib maleate* from Sandoz;

- *Paclitaxel* from Teva;
- *Palbociclib* from Eugia Pharmaceutical; and
- *Plerixafor* from AuroMedics

New Data

Bavencio® (*avelumab*) – More mature survival data from the pivotal trial that served as the basis for initial approval for use of the PD-L1 inhibitor in urothelial carcinoma were added to its prescribing information. The updated results from the study—in which 700 patients with unresectable, locally advanced, or metastatic urothelial cancer were randomized to receive either Bavencio® plus best supportive care (BSC) or BSC alone—still support the conclusion that Bavencio® offers an advantage in both median survival time (23.8 versus 15.0 months for treatment and control groups, respectively) and in the probability of survival (Hazard ratio of 0.76 associated with being in treatment group).

Cabometyx® (*cabozantinib*) and **Opdivo®** (*nivolumab*) – Updated data on overall survival from CHECKMATE 9ER--a trial comparing Exelixis' kinase inhibitor in combination with BMS's immuno-oncology agent against *sunitinib* alone as first-line treatment for advanced renal cell carcinoma—were added to the prescribing information of both products. The initial advantage in overall survival (which served as the basis for initial approval) was maintained in the updated data, with patients in the *cabozantinib* + *nivolumab* arm having a median survival of 37.7 months compared to 34.3 months in the *sunitinib* arm. The overall risk reduction associated with the combination therapy was 30 percent. However, in a preliminary analysis, that reduction was shown to be strongest among patients with "poor" or "intermediate/poor" risk scores and did not achieve significance among patients with "favorable" or "intermediate" risk scores (using the International Metastatic Renal Cell Carcinoma Database Consortium or IMDC score).

Cotellic® (*cobimetinib*) – A paragraph on use in pediatric patients was added to the prescribing information for Genentech's kinase inhibitor. The new language states that "(t)he safety and effectiveness of *cobimetinib* were assessed, but not established, in a study in 55 pediatric patients aged 2 to 17 years with solid tumors" and that "(e)xposure in pediatric patients who received *cobimetinib* at the maximum tolerated dosage were lower than those previously observed in adults who received the approved recommended dosage."

New Molecular Entities*

None

Safety-Related Changes

Gazyva® (*obinutuzumab*) – Warnings regarding "*disseminated intravascular coagulation (DIC)*" were added (in newly created subsection 5.9) to the prescribing information for Genentech's CD20-directed cytolytic antibody. The label now warns that both fatal and severe cases of DIC have occurred in chronic lymphocytic leukemia or follicular lymphoma patients treated with Gazyva®,

that the majority of cases occurred with the first infusion, and that most of those cases had spontaneous resolution (usually by Day 8). A new statement in the Warnings and Precautions Highlights encourages clinicians to "(e)valuate cause and monitor for bleeding, thrombosis, and need for supportive care" whenever DIC is encountered or suspected.

Reblozyl® (*luspatercept-aamt*) – A new subsection (5.3) that focuses on the risks of *extramedullary hematopoietic (EMH) masses* was added to the prescribing information for Celgene's growth factor. The new content includes: the rates of occurrence of *EMH masses in beta thalassemia* patients treated with Reblozyl® (3.2 percent); possible risk factors for *EMH masses* (history of masses, splenectomy, splenomegaly, hepatomegaly, or low baseline hemoglobin); and recommendations to discontinue treatment in case of serious complications due to *EMH masses*, as well as to avoid use in patients who have previously required treatment to control the growth of *EMH masses*.

Sarclisa® (*isatuximab-irfc*) – A recommendation to "(i)nitiate antiviral prophylaxis for herpes zoster reactivation based on standard guidelines" was added to the prescribing information for Sanofi's *multiple myeloma* drug.

Turalio® (*pexidartinib*) – Now that a sufficient time since initial approval (August 2019) has elapsed, a section on adverse events observed during the post-marketing period was added to the prescribing information for Daiichi Sankyo's kinase inhibitor. The new section (6.2) includes the single adverse reaction of "Investigations: blood creatine phosphokinase increased."

Other Changes

Rozlytrek® (*entrectinib*) – Links to FDA-approved companion diagnostics have been incorporated into the prescribing information for Genentech's kinase inhibitor in both Section 1 (Indications and Usage) and Section 2 (Dosage and Administration).

**Only five approved to date, putting this year behind recent years (all of which had 13-20 approvals).*

CLINICAL TRIALS INFORMATION

Current Trials MUSC - Hollings Cancer Center
Contact: Shanta Salzer, CCRP - **salzers@musc.edu**

DLBCL/Aggressive NHL

A Phase Ib Trial of Zanubrutinib in Combination with R CHOP (ZaRCHOP) for Patients with Newly Diagnosed Diffuse Large B Cell Lymphoma

Patient Population/Notes: Open to all patients with newly diagnosed DLBCL - likely to open up in later in August or in September. Please consider sending patients with newly diagnosed DLBCL patients, especially if non-GCB subtype. Once Pola is approved with R-CHP there may be an amendment to this protocol and will keep you all posted!

A Phase 1b Open-Label Study to Evaluate the Safety and Anti-cancer Activity of Loncastuximab Tesirine in Combination with Polatuzumab Vedotin in Patients with Relapsed or Refractory B-Cell Non-Hodgkin

Patient Population/Notes: Loncastuximab is a CD19 antibody drug conjugate (like BV but targets CD19) that received FDA approval in 2021 for R/R DLBCL. This Trial is investigating the combination of ADCT-402 with polatuzumab vedotin and will enroll R/R patients with DLBCL, FL, MCL, MZL, and BL and is open for enrollment.

A Phase 3 Randomized Study of Loncastuximab Tesirine Combined with Rituximab versus Immunochemotherapy in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL) (LOTIS-5)

Patient Population/Notes: Loncastuximab is a CD19 antibody drug conjugate (like BV but targets CD19) that recently received FDA approval. This trial is open to DLBCL patients after only 1 line of therapy. This would be a good option for patients who have progressed on R-CHOP/R-EPOCH and either are not good candidates for CAR-T/Auto SCT or not interested in either.

A Randomized Double-Blind Phase III Study of Ibrutinib During and Following Autologous Stem Cell Transplantation versus Placebo in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma of the Activated B-cell Subtype

Patient Population/Notes: Cooperative group trial for DLBCL patients being referred for Auto SCT. Please consider sending patients early on after relapse so they can be considered for this trial as they will need to have tissue sent off for confirmation of ABC (MUSC team can take care of tissue request, etc.).

A Phase II/III Randomized Study of R-MiniCHOP with or Without CC-486 (Oral Azacitidine) in Patients Age 75 Years or Older with Newly Diagnosed Diffuse Large B Cell Lymphoma, Grade IIIB Follicular Lymphoma, Transformed Lymphoma, and High-Grade B-Cell Lymphomas with MYC and BCL2 and/or BCL6 Rearrangements

Patient Population/Notes: Cooperative group trial for newly diagnosed elderly DLBCL patients. These patients typically do not do well and are not candidates for clinical trials, so we are very happy to offer this trial here at Hollings!

Safety and Efficacy of GEN3009 (DuoHexaBody®-CD37) in Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma - A First-in-Human, Open-label, Phase 1/2a Dose Escalation Trial with Dose Expansion Cohorts

Patient Population/Notes: Phase 1 study utilizing bispecific monoclonal antibody targeting CD37 (antigen widely expressed on B-cells). This is a phase 1 so open to multiple R/R subtypes of NHL.

Hodgkin Lymphoma

Phase III Trial of Nivolumab Plus AVD vs. Brentuximab Vedotin Plus AVD in Patients with Newly Diagnosed Advanced Stage Classical Hodgkin Lymphoma

Patient Population/Notes: Cooperative group study for advanced stage HL patients - please consider emailing or texting right away if you think you may have a patient who is a candidate for this study. We are one of the highest enrolling centers in the country thus far - thanks for referring!

Mantle Cell Lymphoma

A Randomized 3-Arm Phase II Study Comparing 1.) Bendamustine, Rituximab and High Dose Cytarabine (BR/CR) 2.) Bendamustine, Rituximab, High Dose Cytarabine, and Acalabrutinib (BR/CR-A), and 3.) Bendamustine, Rituximab, and Acalabrutinib (BR-A) in Patients </= 70 Years Old with Untreated Mantle Cell Lymphoma
Patient Population/Notes: Cooperative group study for frontline therapy in newly diagnosed MCL patients < 70. Please contact Brian Greenwell if you have a patient.

A Randomized Phase III Trial of Consolidation with Autologous Hematopoietic Cell Transplantation Followed by Maintenance Rituximab vs. Maintenance Rituximab Alone for Patients with Mantle Cell Lymphoma in Minimal Residual Disease Negative First Complete Remission

Patient Population/Notes: Cooperative group study where patients will be randomized to auto SCT + maintenance rituximab vs. maintenance rituximab alone. If you have any patients currently receiving induction for MCL please consider sending them here during induction for initial visit and we can plan on screening them once induction is completed.

A Phase 1b Open-Label Study to Evaluate the Safety and Anti-cancer Activity of Loncastuximab Tesirine in Combination with Polatuzumab Vedotin in Patients with Relapsed or Refractory B-cell Non-Hodgkin

Patient Population/Notes: Loncastuximab is a CD19 antibody drug conjugate (like BV but targets CD19) that received FDA approval in 2021 for R/R DLBCL. This Trial is currently going thru a major amendment to only include the combination of ADCT-402 with polatuzumab vedotin and will enroll R/R patients with DLBCL, FL, MCL, MZL, and BL, and is open for enrollment.

Safety and Efficacy of GEN3009 (DuoHexaBody®-CD37) in Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma - A First-in-Human, Open-label, Phase 1/2a Dose Escalation Trial With Dose Expansion Cohort

Patient Population/Notes: Phase 1 study utilizing bispecific monoclonal antibody targeting CD37 (antigen widely expressed on B-cells). This is a phase 1 so open to multiple R/R subtypes of NHL.

A Phase 1/2, Open-Label, Dose- Escalation Trial of GEN3013 in Patients with Relapsed, Progressive, or Refractory B-Cell Lymphoma

Patient Population/Notes: GEN3013 is a Bi-specific T-cell engager (binds CD3 on T-cells and CD20 on lymphoma B-cells) - this class of drug showed very exciting results at ASH in 2020 and recent ASCO meeting. Open for enrollment in both mantle cell lymphoma and indolent NHL (follicular, marginal zone, SLL) as well as certain subsets of aggressive NHL (double hit, PMBCL, FL3B). Will be a great option for patients who progress after CD19 CAR-T or not a candidate for CD19 CAR-T.

Indolent NHL

Randomized Phase II Trial in Early Relapsing or Refractory Follicular Lymphoma - Enrollment on Hold

Patient Population/Notes: Cooperative group trial open to follicular lymphoma patients who have progressed within 2 years of completion of front-line therapy. There are three arms: obinutuzumab + revlimid, obinutuzumab + PI3K inhibitor, and chemo-immunotherapy. Please call us if you think you have a potential patient, and we will send right away!

Multicenter, Phase 2 Study of CLR 131 in Patients with Relapsed or Refractory (R/R) Select B-Cell Malignancies (CLOVER-1) and Expansion Cohort in Patients with Waldenstrom Macroglobulinemia (CLOVER-WaM)

Patient Population/Notes: This is an exciting trial specifically for R/R WM patients, which is great because they are often excluded from clinical trials. This trial utilizes a radioimmunoconjugate. We are happy to work with our nuclear medicine colleagues to offer this trial to WM patients throughout SC.

A Phase 1b Open-Label Study to Evaluate the Safety and Anti-cancer Activity of Loncastuximab Tesirine in Combination with Polatuzumab Vedotin in Patients with Relapsed or Refractory B-cell Non-Hodgkin

Patient Population/Notes: Loncastuximab is a CD19 antibody drug conjugate (like BV but targets CD19) that received FDA approval in 2021 for R/R DLBCL. This Trial is currently going thru a major amendment to only include the combination of ADCT-402 with polatuzumab vedotin and will enroll R/R patients with DLBCL, FL, MCL, MZL, and BL and is open for enrollment.

Safety and Efficacy of GEN3009 (Duo HexaBody®-CD37) in Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma - A First-in-Human, Open-label, Phase 1/2a Dose Escalation Trial with Dose Expansion Cohort

Patient Population/Notes: Phase 1 study utilizing bispecific monoclonal antibody targeting CD37 (antigen widely expressed on B-cells). This is a phase 1 so open to multiple R/R subtypes of NHL.

A Phase 1/2, Open-Label, Dose- Escalation Trial of GEN3013 in Patients with Relapsed, Progressive, or Refractory B-Cell Lymphoma

Patient Population/notes: GEN3013 is a Bi-specific T-cell engager (binds CD3 on T-cells and CD20 on lymphoma B-cells) - this class of drug showed very exciting results at ASH in 2020 and recent ASCO meeting. Open for enrollment in both Mantle cell lymphoma and indolent NHL (follicular, marginal zone, SLL). Will be a great option for patients who progress after CD19 CAR-T or not a candidate for CD19 CAR-T.

CLL/SLL

A Randomized Phase III Study of Early Intervention with Venetoclax and Obinutuzumab Versus Delayed Therapy with Venetoclax and Obinutuzumab in Newly Diagnosed Asymptomatic High-Risk Patients with Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma (CLL/SLL): EVOLVE CLL/SLL Study

Patient Population/Notes: This trial randomizes patients dx with CLL/SLL that do not currently have a treatment indication but have 'high risk' disease. High risk disease is defined as having a CLL-IPI score of ¡Ã 4 OR having complex cytogenetics (3+ chromosomal abnormalities). Patients can be enrolled up to 12 months from their initial diagnosis and would be assigned to Ven+obinutuzumab at randomization or to 'delayed therapy' once they develop a traditional treatment indication. Whether patients are treated 'early' or 'delayed' they would have treatment paid for by study - Please call if any questions about patients or trial!

Safety and Efficacy of GEN3009 (Duo HexaBody®-CD37) in Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma - A First-in-Human, Open-label, Phase 1/2a Dose Escalation Trial with Dose Expansion Cohort

Patient Population/Notes: Phase 1 study utilizing bispecific monoclonal antibody targeting CD37 (antigen widely expressed on B-cells). This is a phase 1 so open to multiple R/R subtypes of NHL.

A Phase 1/2, Open-Label, Dose- Escalation Trial of GEN3013 in Patients with Relapsed, Progressive, or Refractory B-Cell Lymphoma

Patient Population/Notes: GEN3013 is a Bi-specific T-cell engager (binds CD3 on T-cells and CD20 on lymphoma B-cells) - this class of drug showed very exciting results at ASH in 2020 and recent ASCO meeting. Open for enrollment in both Mantle cell lymphoma and indolent NHL (follicular, marginal zone, SLL). Will be a great option for patients who progress after CD19 CAR-T or not a candidate for CD19 CAR-T.

T-cell NHL

A Randomized Phase II Study of CHO(E)P vs CC-486-CHO(E)P vs Duvelisib-CHO(E)P in Previously Untreated CD30 Negative Peripheral T-Cell Lymphomas

Patient Population/Notes: Cooperative group study for frontline PTCL patients that are CD30 negative (standard for CD30+ patients frontline is CHP+BV). Duvelisib is a PI3K inhibitor and CC-486 is an oral hypomethylating agent. Patients would be eligible for auto SCT after trial. Please contact Brian Greenwell if you think you have a patient!

A Multi-Center Phase Ib Trial Evaluating the Safety and Efficacy of Lacutamab in Patients with Relapse Peripheral T-Cell Lymphoma that Express KIR3DL2

Patient Population/Notes: Lacutamab is a monoclonal antibody against KIR3DL2, which is expressed in ~50% of PTCL. Promising activity has already been seen in CTCL (MF/SS) and has been well tolerated. Enrolls patients with between 1 and 3 lines of therapy, but of note, they cannot have primary refractory disease. Brian G recommends referral of any T-cell lymphoma patients (even if currently in remission) who may be candidates in the future, as the company allows us to “pre-screen” patients for KIR3DL2 expression from their initial diagnostic sample.

An Open-Label, Phase 2 Trial of Nanatinostat in Combination with Valganciclovir in Subjects With Epstein-Barr Virus-Positive (EBV+) Relapsed/Refractory Lymphomas (NAVAL-1)

Patient Population/Notes: This trial will be open for multiple subtypes of EBV+ R/R NHL including PTCL, AITL, PTLD, or other EBV+ NHL. Great trial for many patients without clinical trial options otherwise. Just activated this week!

Do you have clinical trial information to share? Please contact **Christy Levine** at clevine@accc-cancer.org.