Accelerated Approvals Reconsidered

None

Changes in Dosing/Administration

None

Changes in Labeled Indications

Kyprolis® (*carfilzomib*) – FDA notified Amgen that its proteasome inhibitor—acquired as part of the company's 2013 purchase of Onyx Pharmaceuticals—was approved for use in combination with Sarclisa® (*isatuximab*) and *dexamethasone* for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) who have received one to three lines of therapy. Support for the new regimen comes from a trial that randomized 302 MM patients to receive either *carfilzomib + dexamethasone* or those two drugs in combination with Sarclisa®. While response rates were not significantly different between the treatment groups, patients in the Sarclisa® arm had almost half the risk of disease progression as did those in the *carfilzomib + dexamethasone* only arm (Hazard Ratio of 0.58 with a 95% CI of 0.366—0.822). The approval brings to 5 the number of MM-directed combination regimens approved for Kyprolis®, which also remains approved for use as a single agent.

Mekinist® (*trametinib*) and **Tafinlar®** (*dabrafenib*) – Novartis received its first tumor-agnostic approval for use of its MEK and BRAF targeting kinase inhibitors in combination for "*the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.*" Support for the approval comes from an open-label study that used the combination to treat 163 adult patients with BRAF V600E mutation positive cancers, the most prevalent of which were high-and low-grade gliomas (n=48 and 14, respectively) and biliary tract cancers (n-48). The approval for pediatric use relied on response rates seen in a study of 48 children, most of whom had either high- or low-grade gliomas. Responses observed in both studies were modest (36.8 percent in the adult study and 50 percent in the pediatric trial) but were deemed sufficient to warrant the granting of an accelerated approval. Final approval remains

contingent on the submission of evidence of clinical benefit from a confirmatory trial. The approval is the first in pediatrics for a BRAF-MEK inhibitor combination. In addition to the new indication, both drugs now include a new "Limitation of Use" statement that warns that neither is indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition.

Rubraca® (*rucaparib*) – Clovis Oncology announced its decision to voluntarily withdraw the indication for use of its PARP inhibitor as third-line monotherapy for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer. The drug retains its approvals as second-line maintenance treatment of recurrent disease, as well as an accelerated approval for third-line use treating BRCA mutation positive metastatic castration-resistant prostate cancer.

Riabni ™ (rituximab-arrx) – Amgen's *rituximab* biosimilar was granted approval for treating rheumatoid arthritis, thereby bringing it in line with the approved indications for its reference product. As with Rituxan, the approval was specifically for "treatment of Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to-severely-active RA who have inadequate respond to one or more TNF antagonist therapies."

New Biosimilars and Generics

Full approvals were granted for:

- ***Abiraterone acetate*** from Teva Pharm USA;
- ***Cabazitaxel*** from Breckenridge;
- ***Carmustine*** from Ingenus Pharmaceuticals;
- ***Erlotinib*** and ***leuprolide acetate*** from Eugia Pharma;
- ***Imatinib mesylate*** from Qilu Pharm Hainan;
- ***Leuprolide acetate*** from Eugia Pharma;
- ***Pemetrexed*** and ***pemetrexed ditromethamine*** from Hospira; and
- ***Sorafenib tosylate*** from Dr. Reddy's.

Tentative Approvals granted for:

- ***Cabazitaxel*** from Accord Healthcare;
- ***Dasatinib*** from Alembic Pharma Ltd.; and
- ***Nilotinib hydrochloride*** from Apotex Inc.

New Data

Lutathera® (*lutetium dotatate Lu-177*) – Initial approval of the radiolabeled hormone analog was supported by evidence from a randomized trial showing a significant improvement in progression-free survival (PFS) compared to treatment with octreotide—with a risk reduction of approximately 80 percent. An interim analysis of overall survival (OS) among patients in that study—conducted

after a median follow-up of 10.5 months--also pointed to an advantage for Lutathera®. However, in a final analysis of OS (conducted 66 months after the first analysis of PFS) the survival advantage has disappeared, and the updated Clinical Studies section (14.1) now states that there was no statistically significant difference in OS between the two treatment arms.

New Molecular Entities

None

Safety-Related Changes

Copiktra® (*duvelisib*) – Less than two months after it convened its Oncology Drug Advisory Committee (ODAC) to review concerns about PI3K inhibitors, FDA took the unusual step of issuing a warning for Copiktra®, one of the drugs discussed at the ODAC meeting. The FDA statement alerts physicians and patients that updated results from a randomized study comparing Copiktra® to *ofatumumab* show more deaths and serious adverse events occurring in the group treated with Copiktra® than in the patients receiving *ofatumumab*. The statement, which closely parallels a "Dear Healthcare Professional" letter issued by Secura Bio earlier in the month, urges physicians to consider the risks and benefits of continuing Copiktra® in the context of other available treatments and also directs them to advise their patients of the possible increased risk of death and higher risk of serious adverse events associated with use of the drug. Of note, the elevated risks in the Copiktra® group, while concerning, did not achieve statistical significance.

Lutathera® (*lutetium dotatate Lu-177*) – The Highlights section of the prescribing information for AAA USA's treatment for GEP-neuroendocrine tumors had a warning added that *hypersensitivity reactions, including angioedema*, occurred in patients treated with the radiolabeled somatostatin analog. More details on hypersensitivity are contained in a newly added subsection (5.6), which recommends that 1) physicians monitor patients closely for signs and symptoms of *hypersensitivity* during (for a minimum of 2 hours after) administration, 2) premedicate patients with any history of Grade 1 or 2 *hypersensitivity* before subsequent doses, and 3) "permanently discontinue" in patients with Grade 3 or 4 *hypersensitivity reactions*.

Other Changes

Keytruda® (*pembrolizumab*) **–** The phrase "as determined by an FDA-approved test" was added to the indications for use of Merck's PD-1 inhibitor in treating Microsatellite Instability-High or Mismatch Repair Deficient Cancer generally (subsection 1.7) and Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (subsection 1.8).

Lutathera® (*lutetium dotatate Lu-177*) – Updates were made in carton and container labeling, including the addition of a 2D matrix code for product traceability, an increase in vial/lead shielding label sizes, and minor editorial changes.

Trodelvy® (*sacituzumab govitecan-hziy*) – Quantitative values for the ULN and AST levels defining "moderate" and "severe" hepatic impairment were incorporated into the discussion (in section 8.6) on use of Gilead's antibody-drug conjugate in patients with *hepatic impairment*. In addition, editorial changes for purposes of clarification were made in the instructions for "reconstitution" and "dilution" (subsection 2.4) and the characterization of Trodelvy® was changed from a "cytotoxic" to a "hazardous" drug.

Venclexta® (*venetoclax*) – AbbVie is introducing a new packaging option for its leukemia/lymphoma drug, a bottle with 28 100 mg tablets. (The 100 mg tablet is the largest dose for the BCL-2 inhibitor and was previously available only as a single tablet, or in bottles of 120 or 180 tablets.) Perhaps coincidental to the new package, the patient counseling information (Section 17) now includes instructions for proper storage of the oral drug, as well as a recommendation that patients should tell their healthcare provider if they have trouble swallowing the 100 mg tablets—given that smaller tablets are available.

CLINICAL TRIALS INFORMATION

Current Trials MUSC - Hollings Cancer Center

Contact: Shanta Salzer, CCRP - **salzers@musc.edu**

DLBCL/Aggressive NHL

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, Placebo-Controlled, Phase 3 Study of Brentuximab Vedotin or Placebo in Combination with Lenalidomide in Subjects with Relapsed or Refractory DLBCL

Patient Population/Notes: Likely to be very effective in certain subsets of patients with DLBCL including those relapsing after CAR-T cell as well.

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 Ibrutinib plus Obinutuzumab versus Ibrutinib plus Venetoclax plus Obinutuzumab in Untreated Older Patients (>/=70 years of age) with CLL

Patient Population/Notes: Cooperative group trial for patients >/= 70. Patients are excluded if they have SLL, but can have 17p or TP53 mutation.

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 who do not currently have a treatment indication but have 'high risk' disease. High risk disease is defined as having a CLL-IPI score of ≥ 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. 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.

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