Accelerated Approvals Reconsidered

None

Changes in Dosing/Administration

None

Changes in Labeled Indications

Imfinzi® (*durvalumab*) – AstraZeneca's PD-L1 inhibitor was newly approved for use, in combination with gemcitabine and cisplatin, as treatment for adult patients with locally advanced or metastatic biliary tract cancer (BTC). The expansion beyond lung cancer—where the IO agent had already been approved for both unresectable non-small cell and extensive small cell disease—was supported by data from a large (n=685) trial that enrolled treatment-naïve BTC patients as well as patients who had a recurrence of their BTC more than 6 months after surgery and/or completion of adjuvant therapy. Patients were randomized to receive either Imfinzi® or placebo, each in combination with gemcitabine and cisplatin. Overall survival rates were 42 and 34 percent for the Imfinzi® and placebo groups, respectively; median survival was also slightly longer in the Imfinzi® group (12.8 versus 11.5 months), as was the overall response rate (27 versus 19 percent).

Zejula (*niraparib*) – Citing evidence from "two independent randomized clinical trials" that (non-GSK) PARP inhibitors have "potential detrimental effect on overall survival" when used in heavily pretreated BRCA mutant ovarian cancer", GSK notified healthcare professionals in a Sept 14 letter that it was voluntarily withdrawing use of Zejula as 4th line therapy for this population from the approved indications in its prescribing information. Initial approval had been granted in 2019 based on a 28 percent response rate and an 8-month median duration of response observed in a small (N=98) single arm study. Zejula retains its approvals for use as maintenance therapy for patients with either advanced or recurrent disease who are in complete or partial response to platinum-based chemotherapy.

New Biosimilars and Generics

Full approvals were granted for:

- *Lenalidomide* from Zydus (5, 10, 15, and 25 mg capsules); and
- *Lenalidomide* from CIPLA

Tentative Approvals granted for:

- *Gefitinib* from Apotex*;*
- *Lenalidomide* from Zydus (2.5 and 20 mg capsules); and
- *Mitomycin from Hong Kong*

New Biosimilars:

- *Stimufend® (pegfilgrastim)* from Fresenius Kabi; and
- *Vegzelma® (bevacizumab)* from Celltrion

New Data

Halaven® (*eribulin mesylate*) – In response to a late-2021 request from FDA, Eisai incorporated results from three open-label clinical studies on the safety and effectiveness of use in pediatric populations into the prescribing information for the microtubule inhibitor (in Section 8, Use in Specific Populations, Subsection 8.4, Pediatric Use). While no new safety signals were observed for the 77 patients with relapsed or refractory solid tumors and lymphomas who were enrolled in those studies, the evidence remains insufficient to reach any conclusions regarding the safety or effectiveness of Halaven® use in pediatric populations.

Inlyta® (*axitinib*) – Updated data on overall survival (OS) of patients enrolled in the pivotal trial supporting first-line use of Pfizer's kinase inhibitor in combination with an IO agent (either Keytruda or Bavencio) to treat advanced renal cell carcinoma were added to Table 11 in the prescribing information. The new data show that OS of patients randomized to receive the Inlyta® + IO agent regimen continued to be superior to that of patients treated with *sunitinib* (Hazard Ratio of 0.73 with 95 percent CI of 0.60, 0.88). However, as might be expected with the substantially longer follow-up period, the survival differences were somewhat dampened and the newly reported median survival times of 45.1 and 40.1 months for the Inlyta and *sunitinib* groups, respectively, did not achieve statistical significance.

New Molecular Entities

Lytgobi® (*futibatinib*) – FDA granted accelerated approval for use of Taiho Oncology's novel FGFR inhibitor as treatment for adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements. The approval was supported by an observed 42 percent response rate in a single arm trial (n=103). The median time to response in that study was 2.5

months and the median duration of response was 9.7 months (95 percent CI of 7.6 – 17.1 months). Approximately 10-15 percent of the estimated 8,000 cholangiocarcinomas detected annually in the US present with the actionable FGFR2 gene fusion.

Rolvedon (*eflapegrastim-xnst*) – Almost four years after it first applied for a license to market its novel anti-neutropenic agent, Spectrum Pharmaceuticals learned that Rolvedon had been approved for use to "decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with non- myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia." The approval, partially delayed by FDA's limited plant inspection capabilities during the COVID pandemic, was for a drug that has a portion of an immunoglobulin G (IgG) molecule affixed to a recombinant human granulocyte colony-stimulating factor (*pegfilgrastim*) analog. (Data from animal models suggest that the Ig G fragment—known as Fc fragment—might increase uptake by the bone marrow and reduce clearance.) Evidence in support of approval came from two randomized "non-inferiority" trials (total n=643) that enrolled early-stage breast cancer patients and randomized them to receive either Rolvedon or *pegfilgrastim* in combination with their chemotherapy. The trials were designed to determine whether Rolvedon was *at least as effective as pegfilgrastim* at limiting the duration of severe neutropenia (DSN) and showed that to be true. In one trial, 16 percent of patients in the Rolvedon arm and 24 percent treated with *pegfilgrastim* developed severe neutropenia and the mean DSN was 0.20 ± 0.5 days and 0.35 days± 0.7 days, respectively, for the two arms. No significant difference in outcomes was observed in the other trial as well where the median DSN for each arm was 0.31 ± 0.70 days (Rolvedon) and 0.39 ± 1.0 days (*pegfilgrastim*). No differences in the safety of the two agents were observed in either study.

Safety-Related Changes

Avastin® (*bevacizumab*) – *Anaphylactic/anaphylactoid-type reactions* were added to the possible infusion-related reactions listed in section 5.9 (Warnings and Precautions) and an explicit statement recommending "Use sterile needle and syringe to prepare Avastin" was added in section 2.10 (Dosage and Administration).

Tagrisso® (*osimertinib*) – A warning regarding the possibility of *aplastic anemia* associated with use was added to the prescribing information for AZ's targeted NSCLC therapy. The warning (added to sections 2.4 Dosage Modifications, 5.7 Warnings and Precautions, 6.2 Postmarketing Experience, and 17 Patient Counseling Information) recommends that clinicians withhold the kinase inhibitor if aplastic anemia is suspected and discontinue it if the condition is confirmed.

Vidaza® (*azacitidine*) – *Pericardial effusion and pericarditis* were added to the bulleted list of adverse events observed during the post-marketing period for Celgene's MDS therapy.

Vyxeos® (*daunorubicin and cytarabine*) – Recommendations for use of Jazz Pharmaceuticals' novel drug combination in patients with renal impairment (in section 8.6 of its prescribing information) were updated to now state that dosage modification is not necessary even for patients with severe impairment. In addition, *infusion-related reactions* were listed in a new section on adverse events observed during the post-marketing period.

Other Changes

Inlyta® (axitinib) – A number of formatting changes were made in the dose modification guidelines for Pfizer's renal cell carcinoma treatment: a) the recommendations for general dosage increases or decreases were placed in tabular format; b) new tables were created to show recommended dosage modifications for specific adverse reactions encountered with use of Inlyta® either as a single agent or in combination with either *avelumab* or *pembrolizumab*; c) *diarrhea* was added to the adverse events potentially requiring dose modification; and d) new subsections were created to clarify the modifications recommended to avoid drug-drug interactions and for treating patients with hepatic impairment (subsections 2.3 and 2.4, respectively).

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.