Accelerated Approvals Reconsidered

Enhertu® (*fam-trastuzumab*) – The accelerated approval for adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting was converted to full approval.

Changes in Dosing/Administration

Emend® (*fosaprepitant dimeglumine*) – The Dosage and Administration section of the prescribing information for Merck's antiemetic was revised to include the option of a 3-day course of Emend for injection for pediatric patients. Previous recommendations for children who required a 3-day course of the antiemetic to prevent or treat chemotherapy-associated nausea, was to rely on IV delivery on Day 1 only, and to follow with oral administration on Days 2 and 3. Evidence for the safety of 3 successive infusions in children comes from an open-label study involving 100 patients between 6 months and 17 years of age. The recommendation that infusions of Emend® for children be administered through a central venous catheter remains in place.

Leukine® (*sargramostim*) – The 500 mcg per mL multi-dose vial has been removed from the growth factor's prescribing information.

Opdivo® (*nivolumab*) and **Yervoy®** (*ipilimumab*) – The weight-based dosing for **Opdivo® --**when is used in combination with **Yervoy®** for treating metastatic NSCLC--has been replaced with a standard dose for all patients. In addition, the interval between treatment cycles of the PD-1 inhibitor was extended from 2 to 3 weeks. The new regimen now reads 360 mg *nivolumab* once every 3 weeks with *ipilimumab* 1 mg/kg every 6 weeks.

Changes in Labeled Indications

Enhertu® (*fam-trastuzumab deruxtecan-nxki*) – When AstraZeneca and Daiichi Sankyo's antibody-drug conjugate first came to market—in late 2019—it was with an accelerated approval as third-line therapy for adult patients with unresectable or metastatic HER2-positive breast cancer. The role of Enhertu® in breast cancer treatment was more firmly established this month--with FDA's

replacing the *accelerated* with a full approval—and also expanded to now include approved use after a single prior anti-HER2 therapy for both metastatic patients and patients who recur during or within six months of adjuvant or neoadjuvant treatment. Both labeling changes were supported by newly submitted evidence from a large (n=524) trial that randomized patients to either Enhertu® or *ado-trastuzumab emtansine* and in which the patients randomized to Enhertu® had both superior response rates (82.7 percent compared to 36.1 percent), fewer recurrences or deaths (33.3 versus 60.1 percent), and longer durations of response (median of 6.8 months in the comparator group and not yet reached among Enhertu® patients).

Kymriah® (*tisagenlecleucel*) – FDA approved Novartis' CAR-T cell therapy for treating adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. The approval was based on results from a study in which 86 percent of the 90 evaluable patients responded (and 68 percent had complete responses) and in which the median duration of response had not yet been reached (after a median follow-up of 9.1 months). Kymriah now joins Kite's Yescarta® as the second CAR-T therapy approved for FL.

Opdivo® (*nivolumab*) – Two years after it was first approved for use in treating esophageal cancer—as second-line therapy—BMS' checkpoint inhibitor had its therapeutic role expanded to include use in the first-line setting. The approval is for use of Opdivo® in combination with fluoropyrimidine- and platinum-containing chemotherapy or in combination with Yervoy® (another BMS immuno-oncology agent) as first-line therapy for patients with for unresectable advanced, recurrent, or metastatic squamous cell disease. Support for the expansion comes from a large (n=970) trial that randomized patients to one of three treatment arms: Opdivo® in combination with fluoropyrimidine- and platinum-containing chemotherapy, Opdivo® in combination with Yervoy® and, chemotherapy alone. In that trial, patients in each of the Opdivo® arms had a reduced risk of death compared to the chemo only patients (risk reductions of 22 and 26 percent for the Yervoy® and chemo groups, respectively). The survival advantage was particularly stark among patients with tumor cell PD-L1 expression of greater than 1 percent, among whom the Opdivo® patients enjoyed a 36 to 46 percent reduction in the risk of death (for the Yervoy® and chemo groups, respectively).

Tibsovo® (*ivosidenib*) – Serviers' drug targeting IDH1 mutations was approved for use in combination with azacitidine for newly diagnosed patients with AML (and a susceptible IDH1 mutation) who are 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy. Tibsovo® had already been approved for use as a single agent in this population based on a small (n=28) study in which 8 patients achieved a complete remission and 4 others had remission with partial hematologic recovery. The newly included regimen was approved based on a larger trial (n=146) in which patients were randomized to receive either Tibsovo + azacitidine or azacitidine + placebo, and in which the Tibsovo® arm demonstrated superiority in response rates (47 versus 15 percent), overall survival (61 versus 38 percent), and median number of months of survival (24.0 versus 7.9).

Vidaza® (*azacitidine*) – Celgene's MDS drug was granted a new indication and is now approved for the treatment of pediatric patients aged one month and older with newly diagnosed juvenile myelomonocytic leukemia (JMML). The approval was based on outcomes observed in 18 pediatric

patients with newly diagnosed JMML who were awaiting hematopoietic stem cell transplantation and were treated with the nucleoside metabolic inhibitor. Efficacy in the study was assessed by confirmed clinical remission—an outcome achieved by 9 of the 18 enrolled patients (3 of whom had complete, and 6 of whom had partial remissions).

New Biosimilars and Generics

May turned out to be a busy month for generics at the FDA. Full approvals were granted for:

- ***Bortezomib*** from Apotex, Baxter Healthcare, Eugia Pharma, Fresenius Kabi USA, Hospira, Pharmascience Inc., Qilu Pharm (Hainan), Teva, and Zydus Pharmaceuticals;
- ***Carmustine*** from Accord Healthcare;
- ***Exemestane*** from Eugia Pharmaceuticals;
- ***Pemetrexed*** from Accord Healthcare, Apotex, Biocon Pharmaceuticals, Dr. Reddy's, Eugia Pharmaceuticals, Fresenius Kabi USA, Hospira, Jiangsu Hansoh Pharmaceuticals, Nang Kuang Pharmaceuticals Co., Qilu Pharma (Hainan), Sandoz, Waverly Pharmaceuticals Inc., and Zydus Pharmaceuticals; and
- ***Pomalidomide*** from Teva Pharmaceuticals USA.

Tentative Approvals granted for:

- ***Bortezomib*** from Waverly Pharmaceuticals; and
- ***Pemetrexed*** *(lyophilized)* from Accord Healthcare.

New Biosimilars

- ***Fylnetra***™ (*pegfilgrastim-pbbk*) from Kashiv Biosciences.

New Data

Keytruda® (*pembrolizumab*) – FDA's decision to approve the PD-1 inhibitor for use—in combination with chemotherapy—for treating unresectable recurrent or metastatic triple negative breast cancer was supported by evidence showing a 35 percent reduction in the risk of recurrence (or death) for patients treated with Merck's immunotherapy and chemotherapy compared to patients who received a placebo with their chemo. Data on overall survival of the patients in that randomized study, which had not yet matured at the time the indication was first approved, have now been added (in section 14.18) to the prescribing information. Those data show that adding Keytruda to chemotherapy reduces risk of death by more than a quarter (27 percent) in this often-intractable disease.

Mekinist® (*trametinib*) and **Tafinlar®** (*dabrafenib*) – The combination of Novartis' MEK and BRAF inhibitors was first approved for treating metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation in 2017. The approval was primarily based on response rates observed in a non-randomized, open label, study that offered patients either Tafinlar® as a single agent (for

pretreated patients) or in combination with Mekinist® (for both pretreated and treatment naïve patients). Data on duration of response, which had not yet matured at the time of the initial approval, have now been incorporated into the prescribing information for both kinase inhibitors. As might be expected, the data show longer median duration of response (15.2 months) in patients who were treatment-naive when they received the combination therapy, than in patients who had already failed previous chemotherapy (for whom the MDoR was 9.8 months).

New Molecular Entities

None

Safety-Related Changes

Imbruvica® (*ibrutinib*) – Pharmacyclics' kinase inhibitor had the warnings related to potential cardiotoxicity associated with its use strengthened throughout the prescribing information. Specifically, "*sudden death*" was added to the list of cardiac-related adverse events observed during clinical trials, and Table 1, which describes dosage modifications in response to adverse reactions, now includes more detailed information on recommended modifications in the event of cardiac failure and/or arrythmias. Of note, the label explicitly states that many of the cardiac-related adverse events occurred in patients receiving Imbruvica® for unapproved indications or in unapproved combinations.

Piqray® (*alpelisib*) – Two updates were made in the Warnings and Precautions section of the prescribing information for Novartis's breast cancer drug. A statement that "(*a)ngioedema* has been reported in the post-marketing setting" was added to subsection 5.1 (Severe Hypersensitivity). In addition, subsection 5.5, which describes GI-related toxicities associated with the use of the kinase inhibitor, was expanded to include *colitis.* The revised subsection now recommends that clinicians actively monitor patients for "diarrhea and additional symptoms of colitis." It also concludes by observing that "(f)or patients with *colitis,* additional treatment, such as enteric-acting and/or systemic steroids, may be required."

Prolia® (*denosumab*) – The approved risk evaluation and mitigation strategy (REMS) for Prolia was updated to address a risk of hypercalcemia in pediatric patients with osteogenesis imperfecta and to clarify that Prolia® is not approved for use in pediatric patients.

Vidaza® (*azacitidine*) – A warning not to substitute Vidaza® for oral azacitidine has been added to the prescribing information for Celgene's MDS drug. The label warns that treatment of patients using Vidaza® at the recommended dosage of oral azacitidine may result in a fatal adverse reaction. Similarly, treatment of patients using oral azacitidine at the doses recommended for Vidaza® may not be effective.

Other Changes

Imfinzi® (*durvalumab*) – *Pancreatitis* and *encephalitis*, which had already been listed as adverse events sometimes observed in Imfinzi® patients, were added to the Patient Counseling Information. Physicians are encouraged to inform patients that immune-mediated adverse reactions might require corticosteroids or discontinuation of Imfinzi®.

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. Just activated this week!

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