Accelerated Approvals Reconsidered

Tabrecta® (*capmatinib hydrochloride*) – Novartis was notified that the accelerated approval it had received for use of its kinase inhibitor for treating adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping (as detected by an FDA-approved test) has been converted to a full approval. The full approval remains based on overall response rates observed in the same open-label trial that served as the basis for the accelerated approval, albeit with a larger number of patients now having been included in the study.

Changes in Dosing/Administration

Calquence® (*acalabrutinib)* – AstraZeneca received approval to introduce a tablet formulation of its kinase inhibitor. As with the capsule, the tablets will be 100 mg.

Imbruvica® (*ibrutinib*) – Pharmacyclics was given approval to market an oral suspension formulation of its kinase inhibitor. The oral suspension bottle is provided in a carton with two 3 mL reusable oral dosing syringes.

Changes in Labeled Indications

Enhertu® (*fam-trastuzumab deruxtecan*) – With two approvals this month, Daiichi Sankyo's HER2-directed antibody drug conjugate gained a wider role in treating breast cancer (BC) as well as a new indication for use in non-small cell lung cancer (NSCLC).

- The BC approval is for the treatment of adult patient with HER2-low unresectable or metastatic disease who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. It was based on a comparative survival for patients randomized to receive Enhertu (n=373) over that of patients randomized to physician's choice of chemotherapy (n=184). The advantage (a 36 percent reduction in the risk of death and an approximate 50 percent reduction in the risk of recurrence) held for patients irrespective of their hormone receptor status.

- The approval for use as second-line therapy for patients with unresectable or metastatic NSCLC whose tumors have activating HER2 mutations was "accelerated" and based on response rather than demonstrated clinical benefit. Supporting data came from a dose-optimization trial (n=52) in which 57.7 percent of patients responded therapy (95 percent CI of 43.2 – 71.3 percent) and had a median duration of response of 8.7 months. HER2 point mutations are estimated to occur in approximately 4 percent of NSCLCs.

Nubeqa® (*darolutamide*) – Bayer's androgen receptor inhibitor, which came to market in mid-2019 approved for non-metastatic hormone-resistant prostate cancer, is now also approved (in combination with *docetaxel*) for adult patients with metastatic hormone-sensitive disease. The expanded role in the second most common U.S. cancer was supported by evidence from a large (n=1,306) multicenter trial in which patients randomized to receive "Nubeqa® + *docetaxel*" demonstrated superior overall survival compared to patients randomized to treatment with "placebo + *docetaxel*." By study's end, 65 percent of the Nubeqa® patients remained alive and the median number of months of survival for them had not yet been reached. By comparison, only 54 percent of patients in the placebo arm remained alive and they had already reached their median survival time (which was 48.9 months). Overall, the risk of death among Nubeqa® treated patients was 68 percent (95 percent CI or 0.57 – 0.80) of that for patients in the placebo group.

Pemazyre® (*pemigatinib*) – Incyte's small molecule targeting fibroblast growth factor receptors (FGFR), which came to market in 2020 approved for treating cholangiocarcinoma with FGFR2 rearrangements, is now approved for treating patients with relapsed or refractory myeloid/lymphoid cancers with FGFR1 rearrangements. The approval, which includes use for patients in both chronic and blast phases, was based on response to therapy observed in a small single-arm study (n=28). Among the study patients who were in chronic phase, 78 percent achieved a complete response, their median time to response was 104 days, and the median duration of response had not yet been reached. A complete cytogenic response was achieved in 79 percent of all patients (95 percent CI of 59-92 percent).

Imbruvica® (*ibrutinib*) – The kinase inhibitor from Pharmacyclics, which was approved in 2017 for treating adults with chronic graft versus host disease (cGVHD), had its role expanded this month to also include use in pediatric patients ≥ 1 year of age. The expansion was supported by results from a dose finding Phase I/II study of 47 children with moderate to severe cGVHD (median age of 13) who required additional treatment after failure of one or more lines of systemic therapy. Efficacy was established based on an overall response rate of 60 percent (95 percent CI of 44-74 percent), and a 5.3-month median duration of response (95 percent CI of 2.8 – 8.8 months). The median time to response in the study was a little less than one month and the median time from first response to death (or the need for new systemic therapy) was 14.8 months.

Lynparza® (*olaparib*) – AstraZeneca announced its intention to voluntarily withdraw approval for use of its PARP inhibitor for treating patients with advanced ovarian cancers that have deleterious (or suspected deleterious) germline BRCA mutations. The decision was accompanied by a letter alerting healthcare professionals of a "potential detrimental effect on overall survival" of Lynparza compared to chemotherapy that was observed in a subgroup analysis of the results of a Phase III

study. Initial approval for the indication had been based on response rates and duration of response observed in a single-arm trial.

New Biosimilars and Generics

Full approvals were granted for:

- *Lenalidomide* from Apotex, Mylan, and Lotus Pharmaceuticals (5, 10, 15, and 25 mg);
- *Lenalidomide* from Dr. Reddy's (2.5 and 20 mg); and
- *Pemetrexed* from both Amneal and Baxter Healthcare

Tentative Approvals granted for:

- *Bendamustine hydrochloride* from Dr. Reddy's and Slayback but the latter is branded as Vivimusta;
- *Dasatinib* from Lupin;
- *Enzalutamide* from Sandoz;
- *Lenalidomide* from Apotex, Mylan and Lotus Pharmaceuticals (2.5 and 20 mg);
- *Midostaurin* from Lotus Pharmaceuticals; and
- *Trabectedin* from Natco Pharma

New Data

Alimta® (*pemetrexed disodium*) – An update—involving the addition of a single case of an event—was made to the overall survival data for the study examining the combination of Alimta®, pembrolizumab and platinum chemotherapy for the initial treatment of patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.

New Molecular Entities

None

Safety-Related Changes

Gleevec® (*imatinib*) – '*Panniculitis (including erythema nodosum)*' has been added (in subsection 6.1) to the list of skin and subcutaneous tissue disorders observed during clinical trials with Novartis' breakthrough kinase inhibitor.

Other Changes

Keytruda® (*pembrolizumab*) and **Lenvima®** (*lenvatinib mesylate*) – The prescribing information for both products, which are approved for use in combination to treat advanced endometrial carcinoma that is mismatch repair proficient (pMMR) or not microsatellite instability high, has been

revised to reflect the recent approval by FDA of the Ventena MMR RxDx Panel, a test for identifying patients with pMMR advanced endometrial carcinoma.

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.