From: Gene B. Saylors, MD <ossn@accc-cancer.org> Subject: Your Oncology Drug Newsletter: April 2022

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New SCOS Member Online Community Now Live!

The South Carolina Oncology Society (SCOS) is excited to officially announce the launch of its new online community—a state-specific forum within the ACCCeXchange platform—where you can engage in real-time conversations with local peers, get to know your fellow members, and share your insights on issues occurring at the state level.

Join the Conversation

Accelerated Approvals Reconsidered

None

Changes in Dosing/Administration

None

Changes in Labeled Indications

After an unusual two-month hiatus in approvals for new indications, the FDA returned to form this month with the approval of expanded labeling for three products.

- **Keytruda®** (*pembrolizumab*) – Merck's IO drug was approved for use, as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. The approval was supported by an overall response rate of 46 percent (95% C.I. of 35-56 percent). The median duration of response was still not reached after 16 months of follow up, but among those who responded to the PD-1 inhibitor, 68 percent had responses of at least 12 months in duration.
- **Lynparza®** (*olaparib*) – AZ secured a second indication for use of its PARP inhibitor in breast cancer with FDA's approval of Lynparza® for the "adjuvant treatment of adult patients with deleterious or suspected deleterious gBRCA mutated HER2-negative high-risk early breast cancer who have previously been treated with neoadjuvant or adjuvant chemotherapy." Support for the new indication comes a large (n=1,836) randomized trial in which patients with early, high-risk breast cancer treated with adjuvant Lynparza exhibited superior outcomes to patients randomized to placebo. Specifically, 88 percent of patients in the Lynparza arm remained free of invasive disease at the 3-year mark (compared to 77 percent of patients in the placebo arm) and treatment with Lynparza reduced the overall risk of death by 32 percent (95% CI of 0.50 to 0.91).
- **Opdivo®** (*nivolumab*) – BMS was granted yet another label expansion for its PD-1 inhibitor with the approval of its use, in combination with platinum-doublet chemotherapy, for the neoadjuvant treatment of adult patients with resectable (tumors ≥ 4cm or node positive) non-small cell lung cancer. Approval was based on findings from a randomized trial that showed that NSCLC patients who had the IO agent added to platelet doublet chemotherapy exhibited a better response (24 percent) and had superior event-free survival (median of 31,6 months) than did

patients treated with chemotherapy alone (only 2.2 percent of whom responded and whose median event free survival was 20.8 months).

New Biosimilars and Generics

Tentative approvals were issued for three products. Final marketing approval for each awaits expiration of patent exclusivity for the relevant branded reference product.

- *Bortezomib* from both Hospira and Sandoz;
- *Lenalidomide* from Eugia Pharma, and joins Lotus and Zydus but Arrow and Dr. Reddy's new capsule strength already approved; and
- *Vivimusta* (*bendamustine hydrochloride*) from Slayback Pharma.

New Data Added

Alunbrig® (*brigatinib*) – Takeda's kinase inhibitor was initially approved based on the clear response it achieved in a single-arm study of ALK+ non-small cell lung cancer patients who had progressed on (or were intolerant to) *crizotinib*. A subsequent head-to-head comparison to *crizotinib*, in which Alunbrig® achieved superior progression-free survival, supported its approval as first line therapy. However, at the time of that approval (in May 2020) the median duration of response had not yet been reached for the patients randomized to receive Alunbrig®. An update to Table 7, which shows the efficacy results, was approved this month. It shows a median duration of response of 33.1 months for the Alunbrig® patients (compared to a 13.8 month median duration for the *crizotinib* patients).

Darzalex® (*daratumumab*) – Support for first-line use of Janssen's cytolytic antibody (in combination with lenalidomide and low-dose dexamethasone) for multiple myeloma patients came from a study showing that the addition of Darzalex® reduced the risk of disease progression by about 44 percent. With a longer follow-up period, it is now clear that Darzalex® also confers a benefit in terms of overall survival (OS). The newly added OS data show that patients on the 3-drug regimen had a 32 percent reduction in risk of death (Hazard Ratio of 0.68) compared to patients treated only with lenalidomide and dexamethasone.

Empliciti® (*elotuzumab*) – Data on overall survival (OS), which had not yet matured when BMS' multiple myeloma drug was first approved for use in combination with pomalidomide and dexamethasone (in late 2018) have now been added to the product label. Those data show that 38.3 percent of the patients in the Empliciti® arm of the randomized study remained alive at study's end compared to only 25.5 percent of patients treated in the pomalidomide/dexamethasone arm. Additionally, the Empliciti® patients enjoyed longer overall survival (median of 29.8 months) than did their counterparts (median of 17.4 months).

New Molecular Entities

Opdualag™ (*nivolumab and relatlimab-rmbw*) – Working under the assumption that inhibiting two immune checkpoints was better than blocking just one, BMS combined its workhorse PD-1 inhibitor (*nivolumab*) with a novel inhibitor of another checkpoint that has been implicated in limiting the immune system's response to melanoma (lymphocyte-activation gene 3). The company's gamble paid off this month with FDA's approval of Opdualag™ for use in adult and pediatric (12 years or older) patients with unresectable or metastatic melanoma. Support for the approval comes from a randomized head-to-head comparison of the new IO-agent to *nivolumab* in which patients randomized to the new therapy had a 25 percent lower risk of progression or death than did patients treated with *nivolumab*. In addition, the median time to progression for the OpdualagTM group (10.1 months) was more than double that of *nivolumab* patients (4.6 months). Although the differences in overall survival (61 versus 55 percent) did not achieve statistical significance, the promise of the new approach seems important, as attested to by the wide range of phase II studies already underway testing Opdualag™ in many of the indications for which *nivolumab* is currently a standard therapy.

Pluvicto™ (*lutetium Lu 177 vipivotide tetraxetan*) – The tumoricidal potential of radiation therapy has always been limited by the dangers it poses to normal tissue. With the approval of a novel radioligand for use in treating progressive, PSMA-positive castration-resistant prostate cancer, Novartis took an important step to overcoming that limitation. The new therapy—a radioligand therapeutic agent--packages a radioactive

molecule (lutetium-177) along with a moiety (*tetraxetan*) that targets and specifically binds to a transmembrane protein (PSMA) that is over-expressed in prostate cancer. Upon binding to the PSMA expressing cells, the radioactive emissions from Pluvicto™ enter and kill them. Evidence of therapeutic effectiveness for the approach comes from a large trial (n=831) in which men with progressive PSMA-positive prostate cancer were randomized to either Pluvicto plus best standard of care (BSoC) or best standard of care (BSoC) alone. After a median follow-up of almost two years, the median imaging-based progression-free survival of patients treated with Pluvicto™ was 8.7 months (compared to 3.4 months in the BSoC group) and the median time to first symptomatic skeletal event was 11.5 months (compared to 6.8 months in the BSoC group). Importantly, the indication for use includes a recommendation that a scan for PSMA be used as part of selecting patients for care.

Safety-Related Changes

Alunbrig® (*brigatinib*) – A new section on hepatoxicity, which recommends that clinicians regularly monitor patients' ALT, AST, and total bilirubin levels during treatment, was added to the Warnings and Precautions section of the prescribing information for Takeda's ALK inhibitor. In addition, recommendations for dosage modifications in the event of hepatoxicity were newly included in Table 2 of the label. The new recommendations suggest permanent discontinuation of Alunbrig for patients experiencing a Grade 2 to 4 elevation of ALT or AST when it occurs with a total bilirubin elevation greater than 2 x ULN (in the absence of cholestasis or hemolysis).

Caprelsa® (*vandetanib*) – Warnings about use of vandetanib in patients with renal impairment (RI) have been strengthened. The prescribing information a) now explicitly states that "renal failure has occurred in patients treated with Caprelsa," b) suggests that clinicians can withhold or permanently discontinue based on severity of adverse reaction, and c) states that *vandetanib* is not recommended for use in patients with severe RI.

Cyramza® (*ramucirumab*) – Heart failure was added (in Section 6.3) to the list of adverse events observed during the post-marketing period of Lilly's VEGF receptor 2 antagonist.

Darzalex® (*daratumumab*) – A more definitive statement regarding the development of neutralizing antibodies has been added to the discussion of the potential immunogenicity of the MM drug. Whereas that discussion (in Section 6.3 of the prescribing information) had previously concluded that "the incidence of antibody development might not have been reliably determined' the label now states "(i)n clinical trials of patients with multiple myeloma treated with Darzalex as monotherapy or as combination therapies, 0.35% (6/1,713) of patients developed treatment-emergent anti-daratumumab antibodies. Of those, 4 patients tested positive for neutralizing antibodies."

Poteligeo® (*mogamulizumab*) – Kiowa Kirin's monoclonal antibody for mycosis fungoides and Sezary syndrome had two updates approved—*glomerulonephritis* was added (in section 5.4) as one of the autoimmune complications associated with treatment, and *cytomegalovirus* infection was added to the list of adverse events observed in more than 1 percent of patients enrolled in clinical trials.

Tykerb® (*lapatinib*) – "*Skin fissures*" was added (in section 6.2) to the list of skin-related adverse events observed during the post-marketing period of Novartis' kinase inhibitor.

Xpovio® (*selinexor*) – A statement that "no clinically significant differences in *selinexor* pharmacokinetics were observed when was co-administered with clarithromycin (a strong CYP3A4 inhibitor)" was added (in section 12.3) to the prescribing information for Karyopharm's multiple myeloma (MM) drug. Evidence for the new conclusion comes from a large ongoing study of drug-drug interactions in 11 different MM treatment regimens.

Other Changes

Calquence® (*acalabrutinib*) – Table 2 in the prescribing information was reformatted so as to provide clearer guidance on the recommendations for dose modifications in the event of adverse reactions.

Promacta and Promacta Kit (*eltrombopag*) – The term "East- /Southeast-Asian ancestry" replaced "Asian ancestry" in the prescribing information for both of Novartis's formulations of its thrombopoietin receptor agonist.

Yonsa® (*abiraterone acetate*) – Formatting changes were approved—mostly in the discussion on drug interactions—in order to bring the labeling for Sun Pharma's prostate cancer drug in line with that of its reference product, Zytiga®.

Zydelig® (*idelalisib)* – The REMS materials for the kinase inhibitor were updated to reflect Gilead's recent voluntary withdrawal of the indications for use of Zydelig® in treating follicular lymphoma and small lymphocytic lymphoma.

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 Other Anti-cancer Therapies Agents in Patients with Relapsed or Refractory B-cell Non-Hodgkin (enrollment on hold)

Patient Population/Notes: Loncastuximab is a CD19 antibody drug conjugate (like BV but targets CD19) that received FDA approval in 2021. This trial is currently going through a major amendment to only include the combination of ADCT-402 with Polatuzumab. We anticipate this trial opens in May.

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: Now activated! Cooperative group trial for newly diagnosed elderly DLBCL patients. These patients typically do not 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. Have enrolled a lot of patients on this trial - thanks for referring!

Multiple Part Clinical Trial of Brentuximab Vedotin in Classical Hodgkin Lymphoma Subjects

Patient Population/Notes: Very exciting trial that combines Brentuximab and Nivolumab with cytotoxic chemotherapy (Adriamycin and Dacarbazine) in the frontline setting. We are excited about this trial because there will be no vinblastine given with BV so hopefully less neuropathy and improvement in efficacy as BV+Nivo alone looks to have very promising efficacy in frontline/relapsed setting. Results of AD+BV in this setting already promising so this is likely to be a very effective treatment option! Great trial for early stage non-bulky patients which is a big % of newly dx cHL!

Mantle Cell Lymphoma

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 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.

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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.

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.

A Phase 2 Randomized Study of Loncastuximab Tesirine versus Idelalisib in Patients with Relapsed or Refractory Follicular Lymphoma (LOTIS 6) - Enrollment on Hold

Patient Population/Notes: Trial of ADCT-402 (loncastuximab tesirine), CD19 antibody drug conjugate, vs idelalisib after > 2 more lines of therapy in Follicular lymphoma. Most of these patients are currently evaluated for CAR-T after > 2 lines of therapy, but if patient not a candidate or not interested in CAR-T would consider for this trial or the BITE trial below.

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. Trial to be activated at the end of April.

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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

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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.

Do you have clinical trial information to share? Please contact **Christy Levine**.

ACCC's digital **Patient Assistance & Reimbursement Guide** provides up-to-date information on cancer drug assistance and reimbursement programs to help alleviate the financial burden of cancer treatment.

The digital Guide enables you to search for applicable oncology-related products and manufacturers, and you can use any applicable filters to streamline your results.

Download the Guide

This newsletter is provided by the South Carolina Oncology Society (SCOS) as a valuable **member benefit**. SCOS is committed to providing the most updated and accurate information on newly approved oncology drugs, indications, and changes in administration.

Content for the newsletter is drawn from publicly available FDA data sources and is assembled by the Cancer Policy Group, a Maryland-based consultancy specializing in oncology drug policy. Questions about newsletter content should be directed to **Christy Levine**.

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