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Importance of a Multidisciplinary Team Approach in BCC

Treating locally advanced or metastatic BCC (laBCC or mBCC, respectively) may involve a variety of treatment modalities, including surgery (standard excision, electrodessication and curettage [ED&C], Mohs micrographic surgery, and/or resection with complete circumferential peripheral and deep margin assessment [CCPDMA]), radiation therapy (RT), and / or systemic immunotherapies.[NCCN,2021;pBCC-4;pBCC-3][Migden,2018;figure1] Therefore, involving surgical oncologists, radiation oncologists, and medical oncologists who specialize in each of these areas is key to achieving optimal outcomes for patients.[Peris,2019;p24,col1,para1(entire)] A multidisciplinary approach to care of patients with laBCC or mBCC is recommended and endorsed in the NCCN guidelines.[NCCN,2021;pBCC-3]

Hedgehog Inhibitors (HHIs) in the First-Line

If systemic treatment is to be used for recurrent or advanced BCC disease, the NCC commend the use of a Hedgehog inhibitor (HHI) as a first-line option.[NCCN,2021;pBCC-4]

Mechanism of Action of HHIs

The Hedgehog (HH) signaling pathway is involved in proper mai regeneration of tissues.[Harris,2019;p2,para3,ln1-3][Migden,2018;p4,col2,para2(entire)] A gene kn ogue 1 (*PTCH1*)[Sekulic,2012;p2172,col1,para2,ln5-10] codes for the HH rece however, this gene is highly susceptible to ultraviolet (UV)-induced damage from th ,para3,ln5-6;p3,para1(entire);para3,ln4-5] Under normal circumstances, the PTCH1 protein c gene acts to inhibit the signaling activity of a transmembrane oncogenic protein l omologue (SMO).[Sekulic,2012;p2172,col1,para2,ln5-10][Peris,2019;p24 protein signals for DNA replication within basal cells.[Harris,2019;p3,para3,ln4-6][Sekulic,2012;p2 ted version of the PTCH1 protein does not properly inhibit the SMO protein, wh mains in a constant state of activation, ultimately leading to uncontrolled proliferati 19;p3,para3,ln4-6][Sekulic,2012;p2172,col1,para2,ln1-5]

Aberrant activation of the H through a mutated *PTCH1* gene or a mutated *SMO* gene, is responsible for nearly a CC, accounting for 85% and 10% of cases, respectively.[Migden,2015;p716,col1,para1 1,para2,ln9-12;para3,ln4-7]

Vismoedgib and S

There are currently 2 H approved for use in the advanced BCC setting. They are vismodegib and sonidegib. Vismodegib is approved for use in either laBCC or mBCC[Vismodegiv_PI;sect1(entire)]; sonidegib currently has an indication for laBCC only.[Sonidegib_PI;sect1(entire)] The ERIVANCE (NCT00833417)[Sekulic_NEnglJMed_2012] and BOLT (NCT01327053) trials[Migden_LancetOncol_2015] were the phase 2 trials that established the safety and efficacy of vismodegib and sonidegib in the advanced BCC setting, respectively.[Sekulic,2012;p2172,col1,para2,ln15-19][Migden,2015;p717,col1,para1(entire);para2(entire)][Migden,2018;p5,col2,para2,ln4-6;p7,col1,para4,ln1-4][Peris,2019;p24,col1,para4,ln1-2;col2,para2,ln2-4]

The HHI vismodegib is a small molecule inhibitor of SMO.[Sekulic,2012;p2172,col1,para2,ln10-11][Migden,2018;p5,col1,para1,ln1-5] In ERIVANCE, patients (33 with mBCC and 63 with laBCC) were given 150 mg vismodegib once daily.[Sekulic,2012;p2172,col1,para3,ln4-5;p2175,table2] The primary endpoint, as assessed by an independent review

committee (IRC), was objective response rate (ORR).[Sekulic,2012;p2172,col1,para4(entire)] After a median duration of drug exposure of 10 months in the mBCC group and 9.7 months in the laBCC group[Sekulic,2012;p2177,col1,para3,ln3-4;p2175,table2] ORR was experienced by 30% and 43%, respectively, which was significantly higher than the predicted 10% and 20% expected for the null hypothesis in both groups, respectively (P =.001 and P < .001, respecitively).[Sekulic,2012;p2175,table2;p2173,col2,para4,ln7-10;p2175,col1,para2(entire);p2175,col2,para3(entire);p2176,col1,para1(entire)]

The most common AE of any grade across both cohorts of patients included muscl 8%), alopecia (63%), dysgeusia (51%), weight loss (46%), fatigue (36%), nausea (29%), loss and diarrhea (22%).[Sekulic,2012;p2178,table3] Twelve percent (12%) experienced an AE leadin vismodegib, with the most common reason being muscle spasms.[Sekulic,2012;p2177,col1,par

Sonidegib is also an inhibitor of SMO.[Migden,2015;p716,col2,para1,ln1-2][M n the BOLT trial, patients with laBCC or mBCC were randomized 1:2 to receiv ice daily or 800 mg once daily.[Migden,2015;p717,col1,para3,ln1-4;col2,para2(entire);para3,ln2-5;p718,col2, para6,ln3-6] The median follow-up time among all patients included in the trial was 13 ,col1,para5,ln11]

The primary efficacy endpoint as assessed by IR uded 55 patients in the 200 mg cohort and 116 patients in 800 mg cohort.[Migden,2015;p719 ,ln1-4;p717,figure1] The ORR's were 36% and 34%, respectively.[Migden,2015;p723,col1,para6,ln y disease extent, the ORR's were 43% and 38% among those with laBCC (200 mg a , respectively) and 15% and 17% among those with mBCC (200 mg and 800 mg dos .[Migden,2015;p719,table2]

The safety analysis includ 0 mg dose cohort and 150 patients in the 800 mg dose cohort.[Migden,2015;p717,figu ation of drug exposure of 8.9 months in the 200 mg cohort and 6.5 in the 800 mg coho ,ln1-4] there were numerically lower proportions of patients who experienced AE e most common being muscle spasms (49% and 67%, respectively), alopecia (43% d (38% and 59%), nausea (33% and 45%), increased serum creatinine (29% and 36%), fatig %), weight loss (27% and 38%), and diarrhea (24% and 22%).[Migden,2015;p7 1-5;p725,table5] Loss of appetite and myalgias were also commonly experienced in the 800 mg cohort (31% 26%, respectively).[Migden,2015;p725,table5]

The rate of study drug discontinuation due to AEs was numerically lower in the 200 mg dose cohort compared to the 800 mg dose cohort (22% vs 36%, respectively), and the most common reason for study drug discontinuation in either cohort was muscle spasm.[Migden,2015;p724,col2,para4,ln1-5;ln13-16] A numerically higher proportion of patients in the 200 mg dose group were able to remain on therapy for 4 months or longer (91% vs 70%, respectively).[Migden,2015;p724,col2,para3,ln5-8]

The study investigators concluded that since antitumor activity was observed in both dose cohorts but that the lower dose was associated with a more favorable AE profile, the 200 mg dose of sonidegib should be suggested for patients with advanced BCC.[Migden,2015;p726,col2,para3,ln1-4;p727,col1,para3,ln1-3;p727,col2,para3,ln1-3]

Unmet Needs and Challenges

Many patients who initially experience a complete clinical response on an HHI eventually experience tumor regrowth or become intolerant to HHI therapy.[Regeneron_PressRelease,2021;p1,para4,ln3-5] In the final analysis of the ERIVANCE trial, which included 39 months of follow-up data, only 8 of 104 patients (7.7%) were continuing to receive treatment with vismodegib per protocol, while the vast majority (n = 96; 92.3%) had discontinued treatment. The most common reasons for discontinuation were AE (21.2%) or disease progression (27.9%).[Sekulic,2017;p2,col1,para2,ln14-18;p3,col1,para4(entire);p3,table1]

HHIs are associated with an adverse effect (AE) profile that results in treatment discontinuation in up to 30% of patients.[Peris,2019;p24,col2,para6(entire)] Muscle spasms, dysgeusia (taste alterations), alopecia (hair loss), asthenia (fatigue), and weight loss are common among the HHIs as a class and are experienced by the majority of patients.[Peris,2019;p24,col2,para6,ln1-6][Lacouture,2016;p1219,col2,para2,ln2-3;ln6-8;p1226,col1,para2,ln1] In addition, vismodegib and sonidegib have a moderate to high emetogenic potential.[Lacouture,2016;p1226,col2,para2,ln2-3] ...egies utilized to attenuate toxicities and improve drug tolerability and quality of life include inte... ...ing schedules (treatment interruptions [drug holidays] or every-other-day dosing), dose red... ...pportive care with pharmacological agents.[Migden,2018;p9,col1,para1,ln1-8][Peris,2019;p24,col2,para7-8(entire);p25,col1,para1(entire);para2(entire)][Lacouture,2016;p1220,col1,para1,ln4-5;p1225,table3]

Calcium channel blockers (amlodipine, diltiazem, or verapami... ...abapentin, pregabalin), muscle relaxers (cyclobenzaprine), lidocaine, levetiracetam... ...lex have demonstrated effectiveness in treating HHI-induced muscle spasms o... ...p1221,col2,para1,ln6-11;14-15;p1222,col1,para1,ln1-2] For muscle spasms of grade 3 a... ...nterruption for at least 2 cycles or changing to a 1 week on / 1 week off dosing reg... ...to be helpful.[Lacouture,2016,col1,para2,ln1-7]

A variety of dietary modifications (e.g., ..., lemon, and sweetened drinks) can be recommended for those who experien... ...couture,2016;p1223,col1,para1,ln1-11] A dose interruption of at least 4 weeks is usually required... ...normalize, considering the half-life of HHIs and the life span of taste cells (10-24 d... ...,para1,ln11-16]

Use of minoxidil, dihyd... ...rs (spironolactone, finasteride) can be recommended for HHI-induced alopecia.[Lac... ...;col2,para1,ln1;p1226,table3] However, it is important for patients to understand that t... ...cia is different in nature than chemotherapy-induced alopecia in that it develops gra... ...d, and occur after HHI therapy is stopped.[Lacouture,2016;p1225,col1,para1,ln9-14]

Use of levoca... ...a-9-tetrahydrocannabinol (medical marijuana) may also be useful for treating muscle spasms ... ...disturbances, respectively, associated with HHI therapy.[Lacouture,2016;p1222,col1,para2,ln9-12;p1223,col1,para2,ln1-...

Even with supportive care strategies to help lessen the AE burden of HHI, patients who progress on HHI therapy or still cannot tolerate the side effects need a second-line option.

Immune Checkpoint Inhibitors in the Second-Line

Cancerous cells can evade T-cell mediated immune responses directed against them by ensuring that T-cell inhibition is continuously turned on. One mechanism by which this can be done is through continually activating a receptor on T-cells known as programmed cell death 1 (PD-1). Upregulation of the ligands that bind to and stimulate PD-1 (PD-L1 and PD-L2) has been implicated in several cancers, including BCC.[Regeneron_PressRelease,2021;p2,para5(entire)][Walter,2010;p3562,col2,para2,ln7-10][Chang,2019;p564,col1,para1,ln1-8][Cemiplimab_PI;sect11,para1,ln1-3;sect12.1,para1(entire);para2(entire)][Pembrolizumab_PI;sect12.1(entire)][Nivolumab_PI;sect12.1,para1(entire)]

The PD-1 pathway is an immune checkpoint pathway. When cancer cells exploit this pathway for their own survival, it prevents a person's T-cells from proliferating and producing cytokines against the tumor. Immune checkpoint inhibitors (ICIs) seek to reverse this nefarious inhibition and re-stimulate the immune system to promote T-cell activity and surveillance of cancer.[Walter,2010;p3562,col2,para2,ln7-10][Regeneron_PressRelease,2021;p2,para5(entire)][Patel,2019;p478,col2,para1(entire)][Cemiplimab_PI;sect11,para1,ln1-3;sect12.1,para1(entire);para2(entire)][Pembrolizumab_PI;sect12.1(entire)] [Nivolumab_PI;sect12.1,para1(entire)]

Cemiplimab-rwlc

Cemiplimab is an ICI that specifically targets PD-1 on the surface of T-cells.[Regeneron_PressRelease,2021;p2,para5(entire)] On February 9, 2021, the FDA approved cemiplimab-rwlc for use in laBCC and, at the same time, placed it under accelerated approval for use in mBCC.[Regeneron_PressRelease,2021;p1,para1(entire);para3(entire)] Cemiplimab is the first (and currently only) ICI therapy to be approved for use in patients with laBCC who have been previously treated with an HHI or for whom an HHI is not appropriate.[Regeneron_PressRelease,2021;p1,para3(entire)][Cemiplimab_PI,2021;sect1.2(entire)]
Prior to this approval, patients with laBCC had no approved therapeutic option beyond first-line treatment with an HHI.[Regeneron_PressRelease,2021;p1,para3,ln2-4]

Cemiplimab gained its first U.S. approval in the year 2018 for use in locally advanc r metastatic cutaneous squamous cell carcinoma (laCSCC or mCSCC, respectively).[Regeneron_PressRelease,202 ln3-5] The expanded indication to BCC thus marks its second approval in the U.S.[Regeneron_PressReleas Of note, cemiplimab is also being investigated for use in other difficult-to-treat ca g advanced non-small cell lung, cervical, and blood cancers.[Regeneron_PressRelease,2021;p1,para2 4]

Clinical Trial Data for Cemiplimab

Study 1620 (NCT03132636) was a an open-label, multi d, single-arm, phase 2 study investigating the efficacy and safety of cemiplimab 3 weeks in patients with laBCC or mBCC who had previously been treated with an HHI.[Regeneron_PressRelease,2021;p2,para1(entire);para3,ln1][C ;sect6.1,para9,ln2] Patients who had progressed on, failed (did not achieve an objective re , or were intolerant to HHI therapy were included in the trial.[Regeneron_PressRelease,20 PI;sect14.2,para1,ln1-5] In addition, patients had to be ineligible for curative surgery or c Gov_Cemiplimab;p5,bullet9] The primary efficacy endpoint was ORR, as assessed by IRC.[R para2(entire)]

Results of the NCT0313 the **Table**.[Regeneron_PressRelease,2021;p2,table] Among the efficacy population (N = 121) and 21% for the laBCC and mBCC cohorts, respectively.[Regene Cemiplimab_PI;sect14.2,ln1;table9] After a median duration of cemiplimab exposure of 4 opulation (N = 132), [Cemiplimab_PI;sect6.1,para9,ln1;ln4-5] the most common AEs of any grade sculoskeletal pain (33%), diarrhea (25%), rash (22%), pruritus (20%) and upper respi on (15%).[Regeneron_PressRelease,2021;p2,para4,ln1-3][Cemiplimab_PI;sect6.1,table4] Discontinuation of cemiplimab d l due to AEs occurred in 13% of patients, with the most common reason being colitis and overall phy ealth deterioration.[Regeneron_PressRelease,2021;p2,para4,ln5-7][Cemiplimab_PI;sect6.1,para12(entire)]

Table. Efficacy results for NCT03132636 (Phase 2 trial of cemiplimab in advanced BCC)

Efficacy Endpoint	laBCC (n = 84) n (%)	mBCC (n = 28) n (%)
Primary Efficacy Endpoint		
ORR	24 (29%)	6 (21%)
Secondary Efficacy Endpoints		
CR	5 (6%)	0 (0%)
PR	19 (23%)	6 (21%)
DOR (median, months)	Not Reached	Not Reached
Patients with observed DOR > 6 months	19 (79%)	6 (21%)

CR, complete response; DOR, duration of response; ORR, objective response rate; PR, partial response

Mechanism of Action of Cemiplimab-rwlc

Cemiplimab-rwlc is a human IgG4 monoclonal antibody that binds to and blocks the PD-1 receptor on T-cells, thus blocking the inhibitory effects PD-L1 and PD-L2.[Regeneron_PressRelease,2021;p2,para5(entire)][Cemiplimab_PI;sect11,para1,ln1-

3;sect12.1,para1(entire);para2(entire)] In mouse models, blocking PD-1 activity resulted in decreased tumor growth.[Cemiplimab_PI;sect12.1,para2,ln4-5] By binding to PD-1, cemiplimab blocks cancer cells from suppressing T-cell activation. [Regeneron_PressRelease,2021;p2,para5(entire)]

Conclusions and Future Directions

Cemipilimab provides patients, providers, and payers a second-line treatment option for those with advanced BCC. [Regeneron_PressRelease,2021;p1,para4,ln3-6] Prior to its approval, there were no approved second-line agents for those who had progressed on first-line therapy with an HHI or who could not tolerate an HHI.[Regeneron_PressRelease,2021;p1,para4,ln3-6]

Although cemipilimab is currently only approved for use in laBCC, it has been granted accelerated approval by the FDA for patients with mBCC who have been previously treated with an HHI and for patients with mBCC for whom an HHI is not appropriate.[Regeneron_PressRelease,2021;p1,para1(entire);para3(entire)]

Additional ICIs being investigated for use in BCC which have been approved for use in other cancers but not yet BCC include pembrolizumab[Pembrolizumab_PI;sect1(entire)][Patel,2019;p479,table1;p480,table2] and nivolumab +/- ipilimumab[Nivolumab_PI;sect1(entire)][Ipilimumab_PI;sect1(entire)][Patel,2019;p479,table1;p480,table2] Like cemiplimab, pembrolizumab and nivolumab are both monoclonal antibodies that block the PD-1 receptor on T-cells.[Pembrolizumab_PI;sect11,para1,ln1-2;sect12.1(entire)][Nivolumab_PI;sect11,para1,ln1-2;sect12.1,para1(entire)] Ipilimumab is a monoclonal antibody that binds to an inhibitor of T-cell activity known as cytotoxic T-lymphocyte antigen 4 (CTLA-4).[Ipilumamb_PI;sect11,para1,ln1-2] Blockade of CTLA-4 allows effector T-cells to activate, and infiltrate tumors instead of remaining in a quiescent state.[Ipilimumab_PI;sect12.1(entire)]

In a proof-of-principle, non-randomized, open-label study (N = 16) vismodegib given to patients with advanced BCC, the ORR was 38% at 18 weeks (44 mab monotherapy group and 29% for the dual therapy group).[Chang,2019;p564,col1,para1,ln8-15 6 patients that demonstrated a response, the median DOR was 67.3 weeks.[Chang,2019;col1 -free survival (PFS) and OS at 1 year were 70% and 94%, respectively.[Chang,2019;p564,col1 98 AEs observed (any grade), none were life-threatening and only 3 were considered s 9;p564,col2,para2,ln1-5] Of the 3 severe AEs observed, only 1 (hyponatremia) could be dire olizumab.[Chang,2019;p564,col2,para2,ln1-5] No deaths occurred during the study. [Chang,2019;p

Nivolumab +/- ipilimumab is being C and mBCC in an ongoing phase 2 open-label trial (NCT03521830).[ClinicalTrialsDotGov_ ab monotherapy is being given to patients who are PD-1 inhibitor naïve and have unre ously treated ≤ 2 prior systemic therapies (cohort A). [ClinicalTrialsDotGov_Nivolumab,202 umab dual therapy is being given to patients with disease progression after bein rapy (cohort B). [ClinicalTrialsDotGov_Nivolumab,2021] The primary outcome measure is ORR, a ome measures include PFS, DOR, and OS. [ClinicalTrialsDotGov_Nivolumab,2021]

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