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**American Society of Clinical Oncology Annual Meeting**

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## Promising Phase 1 Interim Data of Cemiplimab Treatment For Non–Small Cell Lung Cancer

THE INTRODUCTION OF AGENTS that target mechanisms of tumor cell immune evasion have led to additional treatment options for patients with non–small cell lung cancer (NSCLC). NSCLC tumor cells can exploit the programmed death-1 (PD-1) pathway to evade immune surveillance and destruction through upregulation of suppressive cell surface immune checkpoint regulators, making inhibitors of this pathway an attractive target in NSCLC cancer therapy.

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## Cutaneous Squamous Cell Carcinoma: Toward a Multigene Expression Risk Signature

CUTANEOUS SQUAMOUS CELL CARCINOMA (cSCC) is diagnosed more frequently in the United States than any other cancer except basal cell carcinoma, with an estimated 700,000 new cases diagnosed each year.[1,2] The widespread incidence and relatively low mortality rate of cSCC has led to its exclusion from national cancer registries such as SEER.

Because the precise incidence of cSCC is not known, data regarding associated metastases and deaths remain tentative. The standard of care in cSCC is surgical removal of the primary lesion, which is curative in most cases involving early-stage disease. The outlook, however, is not

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## *Promising Phase 1 Interim Data of Cemiplimab Treatment For Non–Small Cell Lung Cancer*

*(continued from cover)*

The PD-1 is an inhibitory receptor expressed on the surface of activated B and T lymphocytes and is involved in the antitumor immune response. Its high-affinity ligand, primary PD-1 ligand (PD-L1), is expressed on the surface of tumor cells and antigen-presenting cell, such as dendritic cells and macrophages. When PD-L1 on tumor cells complexes with highly expressed PD-1 on attacking tumor-infiltrating T cells, the receptor complex activation induces immune effector dysfunction and reduction of lymphocyte infiltration. Therefore, tumor cells can escape destruction through immune evasion by exploiting this pathway.[1]

As PD-1 and its ligand, PD-L1, regulate the physiological immune response to tumor antigens, this inhibitory immune checkpoint is an attractive target for therapeutic intervention and antibodies against PD-1 may be a viable treatment option in multiple malignancies. The blockade of PD-1 and PD-L1 with anti–PD-1 antibodies has resulted in durable objective responses (ORs) in patients with advanced melanoma, lung cancer, and renal cancer in clinical trials.[1]

### Cemiplimab

Cemiplimab is a high-affinity human monoclonal antibody directed against PD-1. In preclinical studies, cemiplimab treatment demonstrated antitumor activity through disruption of the PD-1/PD-L1 receptor complex in murine models, and was well-tolerated at weekly doses of 2, 10, or 50 mg/kg administered intravenously with no observations of unexpected deaths or drug-related adverse events (AEs) in primates. Promising results from preclinical studies have led to the investigation of cemiplimab for the treatment of several advanced malignancies, including NSCLC.[1]

### Interim Results from Phase 1 Trial on Cemiplimab Efficacy and Safety in NSCLC

Cemiplimab is currently being investigated in a phase 1 dose escalation trial as a monotherapy and in combination with other anticancer therapies in patients with advanced malignancies (N = 398).[2] Interim results from the phase 1 dose escalation phase and expansion cohorts of 21 patients with advanced NSCLC were presented in an abstract published in conjunction with the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting. The safety and antitumor activity of cemiplimab in NSCLC was demonstrated.[3]

Patients enrolled had at least 1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria and an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1. As part of the exclusion criteria, patients were not enrolled if they were treated with systemic immunosuppressants for a recent or ongoing autoimmune disease, or had received prior treatment with anti–PD-1 agents, immune modulating agents or immunosuppressive corticosteroids (doses of more than 10 mg of prednisone daily or an equivalent) within 4 weeks of treatment with cemiplimab. Patients with untreated active brain metastases

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**TABLE 1.** Patient Baseline Characteristics From the Phase 1 Dose-Escalation and NSCLC Expansion Cohort[3]

| Characteristic | Enrolled Patients (n = 21) n (%) |
|---|---|
| Median age, years (range) | 65 (50-82) |
| Sex | |
| • Male | • 14 (66.7) |
| • Female | • 7 (38.3) |
| ECOG performance status, n (%) | |
| • 0 | • 4 (19.0) |
| • 1 | • 17 (81.0) |
| History of adenocarcinoma, n (%) | |
| • Yes | • 13 (61.9) |
| • No | • 8 (38.1) |

ECOG indicates Eastern Cooperative Oncology Group; NSCLC, non–small cell lung cancer.

were also excluded from the trial.[2]

The interim data as of September 1, 2017, included 1 patient in the dose escalation phase, receiving cemiplimab 1 mg/kg, and 20 patients in the expansion cohort. The median age was 65 years, and the majority of patients had an ECOG performance status of 1 (81%). Additional patient baseline characteristics from the NSCLC cohort are shown in **Table 1**.[3]

In the dose escalation phase, patients with a confirmed diagnosis of an advanced malignancy with progression of a solid tumor and no alternative standard-of-care treatment options were enrolled. The dose escalation cohort received 1, 3, or 10 mg/kg of cemiplimab intravenously every 2 weeks for up to 48 weeks. Patients whose disease had worsened after initial improvement or not responded (relapsed/refractory) after at least 1 course of chemotherapy as first-line therapy were enrolled in the NSCLC expansion cohort. In the expansion phase, patients received a 200 mg fixed dose of cemiplimab every 2 weeks for up to 48 weeks.[3]

Primary end points included in the interim data were the incidence of treatment-emergent adverse events (TEAEs) and the number of patients with dose-limiting toxicities. Cemiplimab treatment was well tolerated. The most common TEAEs were asthenia, pneumonitis, and rash, each with an occurrence of 14.3% (n = 3). Reported grade 3 or higher TEAEs were pneumonitis, diabetic ketoacidosis, and nephritis, each with an occurrence of 5.8% (n = 1).[3]

All patients underwent tumor imaging by computed tomography or magnetic resonance imaging every 8 weeks. Secondary end points reported in the interim data included response to cemiplimab therapy, evaluated according to RECIST 1.1 criteria and measured through tumor biopsies from baseline to day 29 and disease progression, if possible. Tumor measurements were performed every 8 weeks from baseline to week 48.[2,3]

As shown in **Table 2**, the overall response rate (ORR) of all patients receiving cemiplimab was 28.6%; 6 patients achieved partial responses (PR) and none of the patients achieved complete responses (CR). Of the patients who had a PR (n = 6), 83.3% had a duration of response for longer than 8 months. Six patients had stable disease (SD) or non-CR/progressive disease (PD), and 9 patients had PD. The disease control rate was 57.1%, including ORR and SD (n = 12). After the planned discontinuation of treatment with cemiplimab at week 48 of the study, 19.0% of patients maintained disease control (n = 4).[3]

Of the 17 patients with tissue for PD-L1 testing, the majority of patients had a tumor proportion score (TPS) <1% (64.7%); only 14.3% of patients had a TPS >50%. Typically, PD-L1 expression is a predictive biomarker for the efficacy of agents that target PD-1; cemiplimab demonstrated potent antitumor activity regardless of the level of PD-L1 expression, represented by the majority of patients with a TPS <1%.[3]

Interim results from this phase 1 advanced NSCLC interim data supports the tolerability and the efficacy of cemiplimab in patients with NSCLC who have relapsed after or were refractory to at least first-line treatment.

## Cemiplimab Clinical Trials in Development

With the positive interim phase 1 data, several phase 2 and phase 3 clinical trials are in development which will

**TABLE 2.** Interim Clinical Outcomes in Patients With NSCLC[3]

| Response Outcomes | Cemiplimab treated patients (n=21) n (%) |
|---|---|
| • ORR (CR + PR) | 6 (28.6%) |
| • CR | 0 (0) |
| • PR | 6 (28.6%) |
| • SD or non-CR/PD | 6 (28.6%) |
| • PD | 9 (42.9%) |
| • Disease control rate (ORR + SD) | 12 (57.1%) |
| **TEAEs** | |
| • Asethenia | 3 (14.3%) |
| • Pneumonitis | 3 (14.3%) |
| • Rash | 3 (14.3%) |
| **AEs (Grade ≥ 3)** | |
| • Diabetic ketoacidosis | 1 (5.8%) |
| • Pneumonitis | 1 (5.8%) |
| • Nephritis | 1 (5.8%) |

AE indicates adverse event; CR, complete response; NSCLC, non–small cell lung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; TRAE, treatment-emergent adverse event.

investigate the efficacy and safety of cemiplimab in NSCLC with different PD-L1 expression levels and as a monotherapy or part of doublet or triplet combinations in the first- and second-line treatment settings. Three phase 3 clinical trials will evaluate cemiplimab as a first-line treatment as monotherapy, in combination with a platinum-based doublet chemotherapy, as triple therapy with a platinum-based doublet chemotherapy and ipilimumab, an antibody that targets cytotoxic T-lymphocyte antigen 4, or therapy in combination with ipilimumab alone in patients with advanced or metastatic NSCLC.[4,5,6]A phase 2 trial will investigate the combination of cemiplimab with ipilimumab as a second-line treatment for patients with metastatic NSCLC.[7]

**"Interim results from this phase 1 advanced NSCLC interim data supports the tolerability and the efficacy of cemiplimab in patients with NSCLC who have relapsed after or were refractory to at least first-line treatment."**

Following the results of successful phase 2 data and data from phase 1 expansion cohorts of patients with advanced cutaneous squamous cell carcinoma (CSCC), the FDA has granted priority review status to the Biologics License Application for cemiplimab as a potential treatment for metastatic CSCC or locally advanced CSCC who are not candidates for surgery. A decision is expected by October 28, 2018. The primary analysis of cemiplimab treatment from a phase 2 expansion cohort of 59 patients with metastatic CSCC was presented at ASCO. Treatment with 3 mg/kg of cemiplimab administered intravenously every 2 weeks showed substantial antitumor activity and durable responses in patients with metastatic CSCC and had an acceptable safety profile.[8,9]

In addition to trials in CSCC and NSCLC, cemiplimab is also being investigated in trials as a monotherapy for basal cell carcinoma and cervical cancer.[10,11] Several exploratory trials are underway to investigate cemiplimab in relapsed/refractory multiple myeloma, prostate cancer, Hodgkin lymphoma and non-Hodgkin lymphoma, and other advanced malignancies.[12-16] ◆

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## *Cutaneous Squamous Cell Carcinoma: Toward a Multigene Expression Risk Signature*

*(continued from cover)*

always positive for patients with cSCC: approximately 3% of patients are at risk for nodal metastasis, and as many as 8700 individuals in the United States (or approximately 1% of those affected) die each year as a result of cSCC.[1,3,4]

### A Novel Gene Expression Signature

Researchers are currently attempting to refine existing staging systems to better to distinguish between patients with low-risk disease and those with high-risk disease.[3-7] Current staging systems rely on clinical features, not genetic signatures.

Chrysalyne Schmults MD, MSCE, director of the Mohs and Dermatologic Surgery Center at Brigham & Women's Hospital, Boston, and an associate professor at Harvard Medical School, notes that current staging systems do not adequately identify cSCC recurrences and metastases, due of low sensitivity levels. "[These screening systems] also are prone to misidentify patients as high-risk who will not go on to experience secondary events, meaning these systems have a low positive predictive value," she said. "There is an unmet clinical need for an objective predictor of cSCC recurrence and metastasis to inform treatment decisions."

Schmults presented a poster at the 2018 American Society of Clinical Oncology (ASCO) annual meeting detailing the development of a gene expression signature associated with cSCC.[7] "Identifying the subset of patients at risk of recurrence is critical for development of clinical trials in cSCC, which has no FDA-approved treatments and very few phase 2 trials," she told *The American Journal of Managed Care®* in an interview. "Therefore, we set out to develop a gene expression-based biomarker associated with disease recurrence and metastasis in cSCC."

Schmults emphasized that the relatively low morbidity and mortality statistics of cSCC belie a distressing clinical trend. "Only about 15% of deaths in this disease occur in patients who have internal metastases. That means that 85% of cSCC deaths occur in people with uncontrolled local disease, or local and nodal disease," she observed. "That makes these deaths underrecognized and underappreciated… [M]any of these patients don't make their way to a cancer center to see a medical oncologist because so many of them never got to that stage where internal metastases would make it clear that they needed systemic therapy."

According to Schmults, patients often undergo multiple rounds of surgery and radiation. "But after patients fail surgery and radiation several times, it is common for them to become ill with this large tumor burden. And then they often die from the disease without ever having gotten internal organ met[astase]s."[8]

Schmults and colleagues identified 73 candidate genes for analysis. They developed a multicenter protocol, ultimately collecting primary cSCC tumors and their accompanying clinical data from 14 US medical centers. They analyzed the tumors for messenger RNA expression of the genes potentially associated with cSCC metastasis. Patients included in the study were diagnosed later than 2006 and received at least 3 years of follow-up care if their cSCC had not recurred.[7]

Investigators accrued 541 samples. Of these, 305 cases included gene expression data. The investigators further refined the development set to 221 cases. Within the development set, there were 25 recurrences including 18 local and 13 metastases.[7] To achieve predictive modeling, the study team used significantly varied genes and multiple machine-learning methods. Researchers also performed k-fold cross validation and bootstrapping and evaluated performance metrics.[7] They recorded various demographic factors among the development cohort. Of the 221 patients, the median age was 74 among all patients, including those who did not experience a recurrence. Among the 25 patients who did experience recurrence, the median age was 69; however, according to the Pearson correlation test, this *P* value was not statistically significant. Males composed 74% of the cohort; of those who experienced recurrence, 84% were men, although the threshold for statistical significance was not met.[7]

A total of 6 patient attributes did have statistically significant *P* values. These include being immunocompromised and having a larger tumor diameter; median 2.9 cm among recurrent cases versus median 1.4 cm in the total cohort ($P < .0001$, for both). Three attributes had *P* values of <.001: Values for poorly differentiated or undifferentiated status, Clark Level IV/V, and the presence of perineural invasion were significant ($P < .0001$). Invasion into subcutaneous fat occurred in 10% of the total cohort and 12% of patients with recurrence ($P = .015$).[7]

The investigators also assessed probe performance. They considered gene expression to be detectable for a sample if the cycling time value was less than 40. Probe performance analysis showed that 69 of the target genes were expressed in 75% to 100% of the samples in recurrent and/or nonrecurrent cases.[7]

Six genes demonstrated consistent expression across all tested samples. The researchers used these genes as controls to normalize expression values of the remaining genes. Eighteen genes expressed differently between recurrent and nonrecurrent cases. Evaluation of the genes with multiple predictive modeling methods compared to existing staging methods included American Joint Committee on Cancer (AJCC) Version 7, AJCC Version 8, and Brigham and Women's Hospital staging methods.[7]

Schmults's team identified an optimal model for local recurrence activity that was 75% sensitive, 92% specific, had a 50% positive predictive value (PPV), and a 96% negative predictive value (NPV) for recurrence. The PPV of 50% compared favorably with AJCC staging at approximately 24% and BWH staging at approximately 18%, while maintaining a high NPV.[7]

## Conclusions

The investigators concluded that high-risk cSCC patients can be identified when machine learning is applied to gene expression data. Characterizing their prognostic test as "robust," they further concluded that applying the test in clinical settings can guide postsurgical treatment planning for high-risk cSCC patients, such as nodal staging or adjuvant radiation. The test may also help identify patients who would benefit from enrollment in clinical trials that examine systemic therapies for cSCC. The data suggest that a test for predicting recurrence and metastases outcomes in cSCC patients is possible, Schmults said, noting that further sample collection and model development are underway.[7,8] ◆


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# Phase 2 Results Support Entinostat + Pembrolizumab Combination in Non–Small Cell Lung Cancer

IN THE SEARCH FOR treatment options for patients with cancer who progress while taking anti-programmed death-1 (PD-1) or anti-programmed death ligand-1 (PD-L1) therapy, much attention has focused on histone deacetylase (HDAC) inhibitors. This class of drugs may be able to affect myeloid-derived suppressor cells (MDSCs) and how they function. They may also be active in PD-L1 inhibition.[1]

Entinostat is an oral HDAC inhibitor that targets Class 1 HDACs.[1] Clinical trials are underway to determine the efficacy of entinostat, in tandem with immunotherapeutic agents like pembrolizumab, in modulating immunosuppressive activity.[2-5]

## The ENCORE-601 Trial

ENCORE-601 is an open-label, dose escalation study of entinostat in combination with pembrolizumab in patients with non–small cell lung cancer (NSCLC). Lead author Leena Gandhi, MD, PhD, former director of thoracic medical oncology at NYU Perlmutter Cancer Center in New York and recently appointed head of immuno-oncology medical development for Eli Lilly, presented preliminary results of this phase 2 trial at the American Society of Clinical Oncologists (ASCO) held June 1-5, 2018.[4]

The investigators concluded that the combination regimen showed antitumor activity and a reasonable safety profile among patients with NSCLC whose disease had previously progressed on anti–PD-1 or anti–PD-L1 therapy. During the ENCORE-601 trial, 6 patients out of 57 had a confirmed partial response (PR) using immune-related RECIST criteria, for an overall response rate (ORR) of 11% (95% CI: 4-21%). ORR was the trial's primary end point.[4]

All patients in this trial had recurrent and/or metastatic NSCLC and had previously failed anti-PD-1/PD-L1 therapy. Their diagnosis was confirmed via either histology or pathology and disease progression assessed objectively. Previous treatment could have been with either a PD-1 or a PD-L1 antibody.[4]

Patients were not excluded based on either their histology or their baseline PD-L1 expression status, but they must

have been previously treated with at least 1 course of chemotherapy for recurrent or metastatic disease. Patients with *EGFR* mutation-positive disease must have received an EGFR inhibitor. Likewise, patients who had *ALK* translocation-positive disease must have received an ALK inhibitor to be eligible.[4]

To participate, patients also needed an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and measurable disease as defined by RECIST 1.1 criteria. They also had to be willing to provide fresh tumor samples during the screening process and at other times by investigator request.[4]

In the phase 2 expansion, the trial assessed drug activity using a Simon 2-stage design. During phase 1, 3 out of 31 patients showed responses; this met the criteria to expand to stage 2 and enroll up to 56 patients. The investigators then decided to allow accrual of up to 70 patients to increase the study's statistical power.[4]

Recently, Krieg et al showed an association in melanoma patients between higher levels of classical circulating monocytes and better response to anti–PD-1 blockade.[5] No one has yet reported similar observations in anti–PD-1 relapsed/refractory NSCLC, so the ENCORE-601 investigators measured circulating classical monocytes in baseline blood samples.[4] In the phase 1 trial, investigators wished to determine whether the entinostat + pembrolizumab combination would show an association between clinical benefit and monocyte levels. They also evaluated gene expression in pretreatment biopsies to determine if the levels of circulating monocytes accurately represented the tumor microenvironment's immune status.[4]

Dosing consisted of 5 mg of oral entinostat weekly, plus 200 mg of intravenous pembrolizumab every 3 weeks. These 21-day cycles continued until discontinuation or disease progression. Investigators assessed disease status every 6 weeks. Classical monocyte data, which were available from 51 patients, were described in terms of CD14-positive, CD16-negative, and human leukocyte antigen D related high.[4]

Patient enrollment began in December 2015 and continued through September 2017. Of the first 57 patients enrolled, 24 (42.1%) were female and 33 (57.9%) were male. The median age was 66, with a range of 48 to 85 years. Forty-nine patients (86%) were white, 3 (5.3%) were black or African American, and 5 (8.8%) belonged to other races. Only about one quarter of patients had an ECOG performance score of 0 (n = 14; 24.6%). The rest had an ECOG performance score of 1 (n = 42; 73.7%), while 1 patient had an unknown performance score.[4]

Two patients (3.5%) were current smokers, while 50 patients (87.7%) were former smokers. The remaining 5 patients (8.8%) were never-smokers. Most patients had stage IV disease (n = 48, 84.2%), although 5 patients (8.8%) had stage IIIA disease and 2 patients (3.5%) had stage IIIB disease. The disease stage of 2 patients (3.5%) was unknown.[4]

Approximately one-third of patients had tumors with PD-L1 expression of <1% (n = 21, 36.8%) and another third of patients had PD-L1 expression of 1-49% (n = 20, 35.1%). Eight patients each had PD-L1 expression of >50% or were not evaluable (14.0%). Most patients had visceral involvement (n = 45, 78.9%). Eighteen patients (31.6%) had abnormally high LDH levels.[4]

**"The investigators concluded that the combination regimen [etinostat + pembrolizumab] showed antitumor activity and a reasonable safety profile among NSCLC patients whose disease had previously progressed on anti-PD-1 or anti-PD-L1 therapy."**

The median number of lines of prior therapy was 3. Two-thirds of patients had received a PD-1 antagonist as their most recent prior therapy (n = 38, 66.7%). The median duration of prior PD-1 or PD-L1 therapy was 162 days (range, 19 to 693). In evaluating patients' best response to prior PD-1 or PD-L1 therapy, nearly half (n = 27, 47.4%) had stable disease and 22 patients (38.6%) experienced disease progression. Three patients (5.3%) experienced a PR and 1 patient (1.8%) had a complete response. The median time span between the most recent dose of prior PD-1/PD-L1 therapy and joining the trial was 65 days (range, 21 to 1614).[4]

Of the 6 patients with partial responses, 4 of them showed baseline PD-L1 expression of <1%. The longest ongoing response has been more than 14 months, but the median response duration is 4.5 months. As of data cutoff, 7 patients remained on treatment, including 4 partial responders. The median progression-free survival was 82 days (95% CI: 43, 124). Investigators observed stable disease in 25 patients (44%).[4]

Among patients with PR, one patient had baseline PD-1/PD-L1 expression of 1% to 49%. This patient was negative

for both *EGFR* and *ALK* and had previously been treated with pembrolizumab for 12.8 months with resulting stable disease. The patient had been off pembrolizumab for 1.1 months before starting the combined regime. This patient responded for 12.9 months and was still on treatment at data cutoff.[4]

Another partial responder had also had a prior partial response of 9.7 months to nivolumab. This patient's baseline PD-1/PD-L1 expression was <1% and *EGFR*/*ALK* testing was negative. Nearly 11 months had elapsed since treatment with nivolumab. As of data cutoff, this PR had lasted 7.6 months and treatment was ongoing.[4]

Another patient had achieved stable disease with a duration of 5.2 months with nivolumab 1.4 months prior to starting the entinostat + pembrolizumab regimen. This patient's baseline PD-1/PD-L1 expression was <1%. As of data cutoff, the partial response with the combined regimen had lasted 4.8 months and treatment was ongoing.[4]

A patient whose baseline PD-1/PD-L1 expression was >50% had previously achieved a PR with 22.8 months of treatment with nivolumab. That treatment had concluded 0.7 months prior to beginning the combined regimen. At data cutoff the patient, whose *EGFR*/*ALK* testing was negative, had a treatment duration of 1.9 months and was continuing treatment.[4]

Two patients achieved a PR with the combined regimen but discontinued treatment due to disease progression. Both patients had baseline PD-1/PD-L1 expression of <1%. One patient had been treated with nivolumab for 7.3 months but had unknown results. The time elapsed from the nivolumab treatment was 1.7 months and the PR with the combined regimen lasted 3.9 months. The other patient had received prior treatment with pembrolizumab alone for 19.7 months and achieved stable disease. This patient received the experimental regimen for 4.2 months before disease progression.[4]

Study investigators found that patients who benefited from the trial regimen had higher baseline classical monocytes (CD14-positive, CD16-negative, and HLA-DR high) than those without response or healthy donors. Additionally, trial patients with elevated classical monocytes had an improved progression-free survival (PFS) of 5.4 months and an ORR of 29% compared with participants with lower classical monocytes.[4]

## Evaluating Gene Expression

Investigators obtained tumor biopsy samples at screening and used the NanoString PanCancer IO 360 panel to assess their gene expression. They also used flow cytometry to assess relative blood monocyte levels. They found via signature analysis that samples from patients with elevated monocyte levels showed upregulation in several pathways associated with tumor inflammation. These include lymphoid, IFN gamma, inflam chemokines, B cells, CD8 T cells, and TIS.

"Our data indicate that higher levels of classical monocytes may correlate with an inflamed tumor microenvironment that is poised to respond to anti-PD1 blockade with the addition of entinostat to relieve immunosuppression and restore a robust anti-\tumor T-cell response," said Gandhi, in an interview with *The American Journal of Managed Care®*.

The safety profile of the combined entinostat + pembrolizumab regimen was largely as expected. About three-quarters of the patients (n = 44, 77.2%) experienced at least 1 treatment-emergent adverse events (TEAEs) related to the trial regimen. Additionally, 24 patients (42.1%) had TEAEs of grade 3 or higher.[4]

Five patients (8.8%) experienced immune-related TEAEs of grade 3 or 4, including 2 incidents of pneumonitis and colitis and 1 of hyperthyroidism. One-third of patients (n=19, 33.3%) experienced other grade 3 or 4 treatment-related AEs. Only fatigue, anemia, hypophosphatemia, and hyponatremia occurred in more than 2 patients.[4]

Twelve patients (22.2%) discontinued treatment due to TEAEs. These AEs included fatigue (3 patients) and pneumonitis (2 patients). Encephalitis, acute respiratory failure, hyponatremia, ventricular arrhythmia, asthenia, colitis, and vomiting/diarrhea led to study discontinuation for 1 patient each. Other less-common TEAEs that affected 1 patient each included acute respiratory failure, atrial fibrillation, *Clostridium difficile* colitis, encephalitis, and mental status changes, although, as Gandhi noted, they were infrequent and not unexpected.[4]

Future plans include a randomized phase 2 trial with stratified, preselected patients to focus on tumor gene-expression signature, said Gandhi. ◆

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# Cemiplimab Shows Durable Response in Cutaneous Squamous Cell Carcinoma

IN RECENT DECADES, the number of Americans treated for nonmelanoma skin cancers has risen dramatically, from an estimated 900,000 to 1.2 million treated cases in 1994, to more than 2.1 million in 2012.[1] Cutaneous squamous cell carcinoma (cSCC) is second only to basal cell carcinoma as the most common cancer in the United States, and approximately 8700 cSCC-related deaths are reported per year.[1,2]

The standard of care in cSCC is surgery for tumor excision, which cures approximately 95% of patients. In cases that are not surgically curative, metastatic disease and locally advanced recurrent cSCC are especially difficult to treat, as there are currently no approved systemic therapies.[2,3] However, new data suggest potential for investigational therapies.

## A Promising Systemic Therapy

New techniques in genomic engineering have overcome immune deficiencies seen in previous iterations, and the resulting antibodies show great promise in a number of immunotherapeutic areas.[4-6] Cemiplimab (REGN2810), one of the first such agents, is an investigational IgG4 that has been awarded breakthrough status by the FDA.[7] Cemiplimab targets the checkpoint inhibitor programmed death-1 (PD-1) receptor, blocks the interactions of PD-1 with PD-ligand 1 (PD-L1) and PD-ligand 2 (PD-L2), and enhances T cell function.[6] Trials are currently underway to evaluate cemiplimab in metastatic cutaneous SCC (mCSCC).[7,8] In April 2017, the FDA granted a priority review to a biologics license application (BLA) for cemiplimab for the treatment of patients with mCSCC or patients with locally advanced cSCC who are not eligible for surgery. The agencyis scheduled to make its decision on the BLA by October 28, 2018.[7,8]

According to Danny Rischin, MD, MBBS, FRACP, director of the Division of Cancer Medicine and head of the Department of Medical Oncology at the Peter MacCallum Cancer Centre, Melbourne, Australia, 2 features of advanced cSCC led investigators to predict the disease might be susceptible to immunotherapy. "One of those was the fact that this tumor type has the highest mutation burden of any tumor," he said in an interview with *The American Journal of Managed Care®*. "We know now that tumor mutation burden [TMB] seems to correlate with a response to immune checkpoint inhibitors. This disease is also associated with patients who have immunosuppression, which also made us think that immune therapy may be active."

Cemiplimab's BLA was based on the phase 2 EMPOWER-CSCC 1 study (NCT02760498).[10] Rischin presented the primary analysis of the mCSCC cohort from the trial at the 2018 American Society of Clinical Oncology (ASCO) annual meeting.[11] Among the study results: cemiplimab achieved a 47.5% response rate (95% CI, 34.3-60.9) and a durable disease control rate (DCR) of 61.0 (95% CI, 47.4-73.5). Results also indicated cemiplimab's safety profile as comparable to that of other immune checkpoint inhibitors.[11]

EMPOWER-CSCC 1's primary objective was to evaluate cemiplimab's overall response rate (ORR) and partial response (PR). The investigators also pursued several secondary objectives, including an estimation of response duration, durable DCR, progression-free survival (PFS), and overall survival (OS). Additionally, investigators set out to study cemiplimab's safety and tolerability.[11]

In the phase 2 study design, Group 1 consisted of adult patients with nodal and/or distant mCSCC. The key inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ function, and at least 1 lesion measureable by RECIST version 1.1 criteria. Group 1 patients received cemiplimab infusions of 3 mg/kg every 2 weeks for up to 96 weeks (retreatment was available for patients who showed progressive disease during follow up). Treatment efficacy was assessed by tumor imaging every 8 weeks. Once tumor response was documented via scan, at least 4 weeks passed before the response was confirmed with additional scans.[11]

Exclusion criteria were autoimmune disease that required systemic immunosuppression within the previous 5 years and prior treatment with anti–PD-1 or anti–PD-L1 therapy. Additionally, participants were excluded for a history of solid organ transplant, hematologic malignancies or concurrent life-threatening malignancies. Indolent or noninvasive cancers such as basal cell carcinoma were permitted under study rules, and the severity of treatment-related adverse events (TRAEs) was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).[11]

Investigators enrolled 59 patients. Of these, 35 patients (59%) remained on treatment at the data cutoff date of October 27, 2017, and 24 patients (41%) had discontinued treatment due to disease progression (n = 14; 24%). Four patients (7%) discontinued treatment due to AEs.[11] Of the 59 enrolled patients, 54 (92%) were men. Patients were aged 38 to 93 years, with a median age of 71. Of these, 43 patients (73%) were aged 65 years or above. ECOG performance status was divided, with 23 patients (39%) at 0 and 36 patients (61%) at 1.[11]

The head and neck were the primary cSCC sites in nearly two-thirds of patients (n = 38; 64%), while 12 patients (20%) had a primary lesion on the extremities. The primary lesion was on the trunk in only 9 patients (15%). About half of patients had received prior systemic therapy for cSCC (n = 33; 56%) and a clear majority had received prior radiotherapy for cSCC (n = 50; 85%).[11] The median exposure duration to cemiplimab was 32.7 weeks, with a range of 2 to 69 weeks. The median number of doses given was 17, with a range of 1 to 35 doses. The median duration of follow up at data cutoff was 7.9 months, with a range of 1.1 month to 15.6 months.[11]

Rifschin described the target lesion reductions in most patients as "rapid, deep, and durable" among those who had at least one tumor assessment during the treatment period.[11,12] ORR was 47.5% (95% CI, 34.3-60.9). DCR was 61.0% (95% CI: 47.4 to 73.5) and the median observed time to response was 1.9 months (range: 1.7 to 6.0 months). Independent central review found that 4 patients (7%) experienced a complete response (CR), while 24 patients (41%) had a PR. Nine patients (15%) had stable disease and 4 patients (7%) had an incomplete response or nonprogressive disease. Eleven patients (19%) had progressive disease and 7 patients (12%) were nonevaluable. Importantly, the median response duration had not been reached at data cutoff, nor had median PFS and median OS. The investigators estimated progression-free probability at 12 months as 52.5% (95% CI, 37.0-65.8) and survival probability at 12 months as 80.6% (95% CI, 67.7-88.8).[11]

Rischin noted that responses to cemiplimab were observed regardless of prior systemic therapy. The ORR in patients without prior systemic therapy was 57.7 (15 of 26 patients; 95% CI, 36.9-76.6). Among patients who had received prior systemic therapy, ORR was 39.4% (13 of 33 patients; 95% CI, 22.9-57.9).[11]

Of the 59 enrolled patients, 25 (42.4%) experienced any TEAEs. Twenty-one patients (35.6%) experienced a serious AE of any grade and 17 patients (28.8%) experienced a serious AE of grade 3 or higher. These AEs led to death in 3 patients (5.1%) and study discontinuation in 7 patients (3 or 6.8%; any grade; 3 or 5.1%, grade 3 or higher). The patient deaths were determined to be unrelated to the study drug. One patient died in his sleep, 1 died of complications of pneumonia, and 1 patient who experienced disease progression died of hypercalcemia and deep vein thrombosis.[11]

Diarrhea was the most common AE, with 16 patients (27.1%) experiencing any grade; of these, 1 patient had grade 3 or higher. Other common TEAEs of all grades included fatigue (14 patients, 23.7%), nausea (10 patients, 16.9%), constipation (9 patients, 15.3%), and rash (9 patients, 15.3%). Of these, only 1 patient each experienced serious diarrhea, fatigue, and constipation. Serious AEs that occurred in more than 1 patient were cellulitis, pneumonitis, hypercalcemia, pleural effusion, and death. Investigator-assessed TEAEs of any grade occurred in 44 patients (74.6%). Of these, 7 patients (11.9%) had treatment-related AEs of grade 3 or higher.[11] Investigator-assessed serious immune-related AEs occurred in 6 patients (10.2%) and included 2 patients with pneumonitis. Single patients experienced serious arthritis, aseptic meningitis, colitis with diarrhea, confusion, hypophisitis, neck pain, and polyarthritis.[11]

## Expansion Cohorts

In addition to considering the phase 2 study when granting cemiplimab a priority review, the FDA also considered the expansion cohorts of the phase 1 study of cemiplimab for patients with locally advanced or metastatic cSCC. Taofeek Kunle Owonikoko, MD, PhD, MS, presented final efficacy and safety data from the phase 1 study expansion cohorts at ASCO 2018 (NCT20383212).[13] Additionally, the combined phase 1 and phase 2 results have been published in the *New England Journal of Medicine* as a single article.[12]

In the phase 1 trial, investigators accrued two expansion cohorts. Expansion cohort 7 contained 10 patients with distantly metastatic cSCC, while expansion cohort 8 consisted of 16 patients with locally and/or regionally advanced cSCC. Dosing was identical to that in the phase 2 trial: 3 mg/kg of cemiplimab were infused every 2 weeks. Treatment could continue for up to 48 weeks. RECIST 1.1 criteria were used to evaluate tumor size every 8 weeks and to determine ORR. An independent central review committee assessed tumor response. Data cutoff occurred on October 2, 2017. The investigators observed that half of the expansion patients achieved a response (13 patients, 50%; 95% CI, 30-70). Durable DCR was 65.4% (95% CI, 44.3-82.8). The investigators also concluded that cemiplimab was generally well tolerated and that the AEs were as expected among similar drugs.[12]

Exclusion criteria in phase 1 included autoimmune disease requiring systemic immunosuppression, either at the time of the trial or during the previous 5 years, active brain metastases, or invasive malignancies within the past 5 years. Patients were also excluded if they received 10 mg or more of prednisone or its equivalent daily or had primary tumors on their eyelids or lips. Similarly, a solid organ transplant or systemic anticancer treatment within 4 weeks of the first dose of cemiplimab were exclusionary factors.[12]

Of the 26 patients, 21 were male. The overall median age was 72.5 (range, 55-88). Sixteen patients had an ECOG status of 0 and 10 patients were ECOG status 1. The most common primary tumor location was the head and/or neck, with 5 patients in the metastatic group (50%) and 13 patients in the locally advanced group (81%), for a total of 69% of the patients. Five patients (19%) had primary tumors on their extremities (3 in the metastatic group and 2 in the locally advanced group). One patient in each group had primary

lesions on their trunk, and the primary tumor of 1 patient with metastatic disease was located on his penis.[12]

Overall, just over half the patients had received prior systemic therapy for cSCC (15 patients, 58%). In the metastatic cohort, all but 1 patient (n = 9, 90%) had received systemic therapy, while only 6 patients in the locally advanced cohort had (38%). About three quarters of both cohorts had received prior radiotherapy for cSCC (20 patients, 77%). At data cutoff, 1 patient was still on treatment. Of the 25 patients who were off treatment, 11 patients had completed their planned treatment and 14 discontinued treatment. Seven of these patients experienced disease progression while on treatment.

The median number of cemiplimab doses was 16 (range, 2-36); exposure lasted a median of 36 weeks. The low end of duration was 4 weeks and 1 patient received cemiplimab for 71 weeks, well beyond the planned maximum treatment duration of 48 weeks. At data cutoff, the median duration of follow-up was 11.0 months (range, 1.1-17.0 months).[12]

According to investigator assessment, TEAEs of any grade occurred in 15 patients (58%). Five patients (16%) experienced grade 3 or higher TEAEs. These included adrenal insufficiency, asthenia, increased alanine aminotransferase, increased aspartate aminotransferase, maculo-papular rash, and myalgia. Fatigue was the most common AE of any grade, experienced by 7 patients (27%). The other most prevalent AEs of any grade were arthralgia, diarrhea, hypothyroidism, muscle weakness, and maculo-papular rash, with 4 patients (15%) each.[12]

An 80-year-old man with baseline congestive heart failure and renal insufficiency was the sole death in the study. Post study, this participant had a treatment-related urinary tract infection and became anuric; investigators considered the fatal renal failure to be unrelated to treatment with cemiplimab.

Two patients discontinued treatment due to TEAEs. After 3 doses of cemiplimab, an 85-year-old woman developed a grade 3 rash and halted treatment. She did complete follow-up care, however. After 4 doses of cemiplimab, a 58-year-old man developed grade 2 muscle weakness and discontinued treatment after receiving 5 additional doses.[12]

In determining the clinical efficacy of cemiplimab in this trial, independent reviewers assessed patient response. There were no CRs among the 26 patients. Half the patients (n = 13, 50%) achieved a PR: 6 patients from the metastatic cohort (60%) and 7 patients from the cohort with locally advanced disease (44%). A total of 6 patients (23%) had stable disease, including 2 patients from the metastatic group (20%) and 4 patients with locally advanced disease (25%).[12]

No patients in the metastatic cohort experienced disease progression; 3 patients with locally advanced disease experienced progression (12% of the total study population). Additionally, 3 total patients were not evaluable (12%). Importantly, the median response duration had not been reached by data cutoff.[12] ◆

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# Novel Checkpoint/Targeted Therapy Combinations: Understanding the Paradigm

NEARLY 1000 AGENTS ARE currently in clinical development in immune-oncology (IO), with nearly 300 targets. More than half of these efforts focus on 40 targets, including 164 agents targeting programmed death-1 (PD-1) or programmed death ligand-1 (PD-L1).[1] According to Jennifer Wargo, MD, MMedSC, associate professor at The University of Texas MD Anderson Cancer Center in Houston, the fact that multiple key strategies are being tested, with various levels of success, indicates a critical need for coordinated efforts and better trial design.[1,2]

Leading an educational session at the 2018 American Society of Clinical Oncology (ASCO) annual meeting on combination treatment regiments, Wargo noted that investigators must better understand the body's responses to therapies and then optimize their treatment regimens accordingly to achieve truly novel trial designs and strategies. She stressed the importance of improved understanding of the tumor genome, epigenome, systemic immunity, tumor microenvironment, and environmental influences, such as the gut microbiome, and the interaction of these elements create both favorable and unfavorable responses to immune checkpoint blockade.[3] As this understanding evolves, investigators can develop more effective treatment strategies, she said.

## Reverse Translation

Wargo explained the "reverse translation" paradigm used in her lab, in which findings are taken from "bench to bedside," and then back to the bench, to better understand various responses to checkpoint blockade. She and colleagues perform longitudinal tumor biopsies and blood draws using a variety of different strategies. The researchers gain mechanistic insight from the test data, then optimize them within mouse models. "We then bring these insights gained back to our patients via clinical trials," she said.

To demonstrate how reverse translation works, Wargo summarized more than a decade of her research in melanoma. Drawing on the knowledge that oncogenic mutations in *BRAF* are found in more than half of melanoma patients, and that this mutation can be targeted therapeutically, she and colleagues used reverse translation in their patients to identify potential targets of therapeutic resistance. Those targets were then brought forward to clinical trials.

The investigators biopsied tumors before starting patients on BRAF-targeted therapy and learned that these tumors were poorly infiltrated and had low antigen expression. But within two weeks of initiating treatment with the BRAF inhibitor, the tumors had a dense T-cell infiltrate and an increase in melanoma antigen expression, suggesting an immune mechanism of response. Once the T cells were introduced, the investigators observed upregulation of PD-L1 in the tumor microenvironment, suggesting a mechanism of immune resistance, thus providing the rationale for combining targeted therapy with immune checkpoint blockade.

Another effective example of reverse translation was also shown at ASCO 2018, Wargo said, referring to poster research presented by her MD Anderson colleague Hussein Tawbi, MD, PhD, that outlined safety and preliminary activity data from TRIDENT, a phase 2 study of a triplet combination of nivolumab with dabrafenib and trametinib in patients with *BRAF*-mutated metastatic melanoma.[4] Tawbi et al reported that their preclinical murine data showed combined BRAF inhibition and PD-1 blockade in *BRAF*-mutated tumors is associated with enhanced responses. These findings lead the investigators to hypothesize that their triplet regimen is safe and will be clinically active in advanced melanoma patients with *BRAF* mutations.[4]

To date, the Tawbi et al trial has accrued 14 patients. Of the 11 patients whose response has been evaluated, 10 have achieved a partial response, for an objective response rate (ORR) of 91%, the study's primary outcome. Significantly, 6 of the 10 patients with a partial response had received prior immunotherapies, as had the single patient who experienced progressive disease.[4]

Wargo also cited the work of colleague Zachary Cooper, MD, who applied this principle to a murine model, treating mice first with targeted therapy only, then adding checkpoint blockade.[5] "But when [Dr Cooper] combined targeted therapy with anti–PD-1, what he found was a dramatic increase in the CD8 T-cell infiltrate, which was associated with improved survival and a decrease in tumor growth," she explained, noting that multiple clinical trials combining targeted therapy and immune checkpoint blockade are currently underway.[5] These trials have moved beyond melanoma, Wargo continued, to examine various solid and liquid tumors, and other oncogenic mutations beyond *BRAF*.

Returning to the question of how researchers can identify better biomarkers of response to immune checkpoint blockade, Wargo noted that, although a variety of such biomarkers have been identified through the work of several colleagues, these biomarkers are not always completely predictive and are not as consistently effective as single biomarkers. For example, Snyder et al posited that

mutational load and neoantigens may help explain why some patients respond to therapy but others don't, while Tumeh et al found that CD8 T-cells' baseline density and distribution can help predict tumor response.[6,7] Similarly, Taube et al reported that baseline PD-L1 staining showed PD-L1 tumors are more likely to respond to checkpoint blockade, while Spranger et al found that T-cell–inflamed tumors are more likely to respond to immune checkpoint blockade than those which are not inflamed.[8,9]

Wargo noted that she and colleagues of the Moon Shot Cancer Team at MD Anderson and elsewhere wanted to build on this work. The combined team studied a cohort of patients with metastatic melanoma who had been treated with sequential immune checkpoint blockade, first with CTLA-4 blockade, and then with PD-1 blockade.[10] In keeping with their translational approach, the investigators assembled tissue biopsies throughout the course of treatment, including prior to treatment with CTLA-4, during early treatment, and at the time of disease progression on CTLA-4. They then assembled tumor biopsies from patients during treatment with anti–PD-1 and then again when patients experienced disease progression. Throughout, the team's focus was on performing both molecular profiling and immune profiling to examine potential mechanisms of therapeutic resistance that could then be targeted, said Wargo. Molecular profiling included whole exome sequencing, a custom nanostring panel, and reverse phase protein arrays. Immune profiling included immunohistochemistry, flow cytometry, and T-cell receptor sequencing.

Chen et al found that immune signatures in pretreatment biopsies in these patients largely failed to predict therapeutic response.[10] "When you look at the CD8 T-cell density, and responders versus nonresponders, the difference is fairly modest, and it's highly overlapping," Wargo said. "This suggests that you cannot pick a set point at which you know that a given patient is going to respond or not respond to anti-PD-1–based therapy."

The data were quite different when Chen et al examined the early on-treatment biopsies. They found the differences between responders and nonresponders were highly statistically significant and nonoverlapping.[10] "If we look for an adaptive response on-treatment, we may get a better answer," said Wargo. "Our findings suggest that early, on-treatment biomarkers may have more utility, at least in the short term, until we can identify better pretreatment biomarkers."

Wargo also addressed the related issue of the role of the gut microbiome in response to immune checkpoint blockade, noting that she and her colleagues were inspired by the work of Vétizou et al and Sivan et al.[11,12] In both investigators' preclinical models, the composition of the gut microbiome in mice dictated whether or not the animal subjects responded to checkpoint blockade. Furthermore, the investigators could change the microbiome to enhance therapeutic responses.[11,12]

To gain an understanding of the role of the gut microbiome in response to checkpoint blockade in patients with metastatic melanoma, Wargo and her colleagues, including lead investigator Vikya Gopalakrishnan, PhD, studied oral and fecal microbiome samples in a large cohort of patients with metastatic melanoma who were starting systemic therapy (n = 233).[13] Following the reverse translation paradigm, researchers obtained an initial oral and gut microbiome sample, performed a tumor biopsy when feasible, started anti–PD-1 therapy, restaged patients, and then obtained repeat samples.

Gopalakrishnan et al found in both mice and humans that responders to anti–PD-1 therapy had a much higher diversity of bacteria within the gut microbiome. When the researchers stratified patients into either high, intermediate, or low diversity of the gut microbiome, patients with a more diverse microbiome saw improved PFS. They also found compositional differences in microbiomes, suggesting that both composition and biodiversity may play a role in immune response.[13]

The researchers also found that favorable signatures within the gut microbiome were associated with enhanced immune responses within the tumor microenvironment. After determining that patients who responded to therapy had a higher density of CD8 T cells at baseline, they compared the bacteria's appearance in the gut to the cytolytic T-cell markers expressed in the tumor microenvironment. The researchers found that patients who had a favorable gut microbiome, with a higher abundance of *Clostridiales*, *Ruminococcus*, and *Faecali* bacteria, had a higher expression of these cytolytic T-cell markers within the tumor microenvironment. In contrast, patients who had an unfavorable microbiome, with a higher abundance of *Bacteroidetes*, had a low expression of these markers, suggesting the 2 might be linked.[13]

To understand the relevant mechanism, Wargo and her colleagues took fecal samples from both responders and nonresponders to anti–PD-1 therapy and performed fecal microbiota transplant into germ-free mice. They subsequently implanted melanoma tumors into the mice and found that the tumors in mice that had received a fecal transplant from a responding patient either grew slowly or were rejected outright. The opposite was also true: in mice that had received a fecal transplant from a nonresponding patient, the tumors grew quickly and failed to respond to checkpoint blockade.[13]

## "Window" Trials

The final issue Wargo addressed in her talk was the possibility that researchers can successfully study responses to known and novel agents in neoadjuvant "window" trials. In her opinion, a strong case exists to also use targeted therapy

and immunotherapy in the neoadjuvant metastatic melanoma setting, and not in the adjuvant setting only.

The current standard of care is upfront surgery for patients with bulky nodal metastasis from melanoma in the groin or axilla. However, up to 70% of those patients will relapse and many of those patients will die of disease, Wargo said. Further, preclinical models suggest that neoadjuvant use of immune checkpoint blockade is superior to adjuvant use due to the ability to stimulate antigen-specific T cell responses.

**"Combination therapy holds tremendous promise, but there are many complexities with regard to the ideal combinations, dosing schedules, as well as optimal biomarkers of response."**

Accordingly, Wargo collaborated with Roda Amaria, MD, and others to design a phase 2 trial of neoadjuvant therapy for patients with locoregional metastatic melanoma.[14] The investigative team hypothesized that patients who received neoadjuvant and adjuvant BRAF and MEK inhibitors would experience improved, relapse-free survival (RFS) over standard-of-care surgery.

Investigators randomized patients with bulky stage III melanoma to either upfront surgery or neoadjuvant and adjuvant treatment with BRAF and MEK inhibitors (1:2 randomization). Investigators restaged these patients after 8 weeks of therapy, continuing with adjuvant therapy. Once again, the reverse translation paradigm ensured that regular tumor biopsies and blood draws illuminated mechanisms of therapeutic resistance. Patients in the BRAF/MEK inhibitors group showed a RECIST response rate of 85%. The pathological complete response (CR) rate in this group was 58%. "The monitoring board stopped this trial early because many of the patients in the upfront surgery arm relapsed and several patients in that arm died," Wargo said.[14]

Regarding RFS, the primary endpoint, the investigators found that patients who had received the neoadjuvant and adjuvant *BRAF* and MEK inhibitors had significantly improved survival. Among the 58% of patients who achieved a pathologic CR, all had distant-metastasis–free survival, compared with those who had failed to achieve a pathologic CR. Translational exploration via pretreatment biopsy revealed that patients who failed to achieve a pathologic CR had a higher frequency of known resistance-conferring mutations, which activated their MAP kinase pathways. The researchers also performed immune profiling on these tumors and found that in patients without a CR, T cells were functionally exhausted, despite having adequate infiltration at baseline.[14] "Additionally, the longitudinal biopsies showed that patients who had a pathologic CR went from essentially a kind of a cold tumor microenvironment to a hot tumor microenvironment, while the patients who failed to achieve a pathologic CR didn't have any change from baseline to on-treatment," Wargo said.[14]

## New Trials and Future Directions

Building on their earlier preclinical work showing that neoadjuvant immune checkpoint blockade may be more effective than adjuvant therapy, Wargo and Amaria designed a phase 2 randomized trial to determine the safety and activity of frontline nivolumab, with and without ipilimumab, in patients with high-risk but metastatic melanoma in whom surgery was possible.[15]

Patients were randomized to receive either neoadjuvant nivolumab at 3 mg/kg every 2 weeks for up to 4 doses (arm A), or frontline ipilimumab at 3 mg/kg + nivolumab 1 mg/kg every 3 weeks for up to 3 doses (arm B). Following surgery, both trial arms received nivolumab 3 mg/kg every 2 weeks for 13 doses. The investigators planned to accrue 40 patients at a 1:1 randomization with stratification by stage and PD-L1 status. They chose the pathologic complete response (pCR) rate as the primary end point.[15]

Enrollment was closed at 23 patients (arm A = 12, arm B = 11). Patients in arm A achieved 25% pCR and 25% radiographic response (RR) rates. However, 17% were unable to undergo surgery due to rapid disease progression on nivolumab monotherapy. All patients who received combination therapy were able to undergo surgery, and the pCR and RR rates were 45% and 73%, respectively. Nearly three-quarters of arm B patients (73%) experienced grade 3 treatment-related adverse events, as did 8% of patients in arm A.[15] The investigators concluded that the combination therapy given in the neoadjuvant setting can produce pCR in high-risk metastatic melanoma, but with significant toxicity.[15]

Wargo closed by stressing the importance of both geographic and cross-disease collaboration, exemplified by the emergence of the International Neoadjuvant Melanoma

Consortium and her own work on neoadjuvant blockade with fellow MD Anderson investigators in other disciplines, including Christy Roland, MD, on sarcoma, and Boris Sepesi, MD, on non–small cell lung cancer. "Combination therapy holds tremendous promise, but there are many complexities with regard to the ideal combinations, dosing schedules, as well as optimal biomarkers of response," she said. "As we move forward, I think we need to embrace novel biomarkers and targets, like the microbiome. And we also need to engage in a concerted and organized effort with novel clinical trial designs." ◆

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# Maintenance Therapy Found Beneficial in Patients With High-Risk Rhabdomyosarcoma

RESULTS FROM THE 10-YEAR randomized RMS 2005 trial from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) suggest that patients with high-risk rhabdomyosarcoma given 6 months of maintenance therapy after completing standard treatment fared better than comparable patients who discontinued therapy.[1,2]

Specifically, median disease-free survival (DFS), the primary outcome, was 8 months longer in the experimental group (hazard ratio [HR] 0.68; 95% CI, 0.45-1.02; *P*, .0613). Overall survival (OS) at 5 years was 87% for the maintenance therapy group , compared with 74% for the standard treatment group.[3]

Presenting the findings on behalf of EpSS at the American Society for Clinical Oncology (ASCO) 2018 annual meeting, Gianni Bisogno, MD, PhD, of the University Hospital of Padova, Padua, Italy, called for maintenance therapy to be adopted as the new standard of care in high-risk rhabdomyosarcoma.[2] ASCO selected the RMS 2005 results for presentation as part of the plenary session of the annual event, declaring the results one of the 4 most important clinical findings among the 5800 available abstracts at the conference.[1]

## About the RMS 2005 Trial

EpSSG, founded in 2001, includes 108 centers in 14 European and South American countries. According to Bisogno, in developing the RMS 2005 protocol to explore maintenance chemotherapy in high-risk rhabdomyosarcoma, the EpSSG considered the more than 90% of children who achieve a complete remission following chemotherapy, radiotherapy, and surgery, as well as the 30% to 40% who will relapse, most often within a year of completing treatment. The prognosis is poor among relapsed patients, said Bisogno, and most will die from their disease.[2]

Beginning in 2005, RMS 2005 investigators enrolled all patients aged >6 months to 21 years with nonmetastatic rhabdomyosarcoma whose diagnoses were confirmed pathologically. They included patients who were treatment-naïve and able to give written informed consent.[3]

EpSSG used known prognostic factors to classify patients into 4 different risk groups ranging from low to very high. The high-risk group, which includes 60% to 65% of all rhabdomyosarcoma patients, is characterized by an unfavorable primary tumor location, like the head, neck, or pelvis. High-risk tumors also feature unfavorable alveolar histology, and/or the involvement of a lymph node.[3]

As they developed their protocol, the investigators considered the HD CWS-96 trial, in which patients who had completed standard therapy prospectively received either high-dose chemotherapy plus stem cell rescue, or an oral maintenance regimen.[4] The high-dose regimen included thiotepa plus cyclophosphamide and melphalan plus etoposide. Oral maintenance therapy consisted of trofosfamide plus etoposide and trofosfamide plus idarubicin.[4]

HD CWS-96 included 51 patients in the maintenance therapy cohort, while 45 patients were assigned to the high-dose treatment arm. Klingebiel et al found after a median follow-up of 57.4 months that 57.8% (26 of 51) of patients in the oral maintenance arm survived, while 24.4% (11 of 45) of patients in the high-dose arm survived (0.52 vs 0.27, $P = .03$). Because this trial was not randomized, each patient's clinician could choose high-dose or oral maintenance therapy.[4]

In RMS 2005, patients completed standard therapy for high-risk disease, which in Europe consists of 9 cycles of ifosfamide, vincristine, and actinomycin plus or minus doxorubicin, as well as surgery and radiotherapy. All children who had no evidence of tumor at the end of this standard treatment were randomized to either stop treatment (control arm) or to receive 6 more months of maintenance therapy (experimental arm). After conducting a pilot study to determine RMS 2005's dosing schedule, the EpSSG investigators agreed upon a maintenance therapy regimen of vinorelbine (25 mg/m$^2$ given intravenously on days 1, 8, and 15 of a 28-day cycle) and cyclophosphamide (25 mg/m$^2$ given orally each day).[3] Patients in RMS 2005 completed this 1-month regimen 6 times over 24 weeks.[3]

The trial's 1:1 randomization was stratified by country and by risk group. The primary endpoint was disease-free survival (DFS), as measured from the randomization date to the patient's relapse or death. Overall survival (OS) was the trial's secondary end point, based on the time elapsed between patient randomization and death. The study design had 87% power and a 2-sided alpha of 5%.[3]

The investigators assessed 670 patients for eligibility, then excluded 299. Of these, 145 patients did not meet the eligibility criteria and 120 patients met the criteria but declined to participate; 34 patients were excluded for other reasons. With 371 patients available for randomization, which occurred between April 2006 and December 2016, the control arm consisted of 186 patients and the experimental cohort, 185 patients. Nineteen of these patients either did not start or discontinued maintenance therapy due to parent refusal (n = 10), tumor relapse (n = 6), or toxicity (n = 3). All 371 randomized patients were included in the intention-to-treat analysis. Of the 185 patients in the maintenance therapy group, 3 patients did not commence therapy after randomization and data were

missing for 2 patients. Just over 90% of patients completed maintenance therapy (n = 164, 91%). A clear majority of experimental patients required the modification of at least 1 therapy cycle (n = 143, 79%). In nearly half of these cases, investigators reduced doses according to the protocol guidelines to avoid myelotoxicity (n = 69).[3]

The investigators characterized the toxicity of the maintenance regimen as "acceptable." There was less myelotoxicity, especially anemia and thrombocytopenia, compared to what is often seen with standard intensive therapy, and no organ dysfunction. Only 29% of the experimental group patients developed an infection, compared with 56% of the control group. Two maintenance patients developed neurotoxicity from the vinorelbine but they recovered after the drug was stopped.[3]

In the 185-patient experimental group, 40 survival events occurred, yielding a 5-year median DFS of 77.6 months (range, 70.6 to 83.2). Among the 186 control patients, 54 survival events occurred; median 5-year DFS was 69.8 months (range, 62.2-76.2). The HR was 0.68 (95% CI, 0.45-1.02; $P = .0613$).[3]

The differences in OS between the 2 groups were even larger. Twenty-four survival events occurred in the maintenance arm for a 5-year OS of 86.5 (range, 80.2-90.9). In the control group, 42 patients experienced a survival event; the 5-year OS was 73.7 (range, 65.8-80.1). The HR was 0.52 (95% CI, 0.32-0.86; $P = .0111$).[3]

A post hoc analysis was performed to determine if any prognostic factors, subgroups, or previous treatment could have had an impact on RMS 2005's results. Post-hoc analysis showed neither DFS nor OS were affected.[5]

Bisogno reiterated RMS 2005's conclusions: maintenance therapy should be the new standard of care in high-risk rhabdomyosarcoma.[2,3] The investigators believe it represents a novel, effective, and well-tolerated strategy for these patients. Further, they believe the RMS 2005 findings may be applied to other pediatric solid tumors.[2,3]

## The Value of Maintenance Therapy

Douglas S. Hawkins, MD, presented a discussion of the RMS 2005 trial, placing it in context. Hawkins, chief of the Hematology/Oncology Division at Seattle Children's Hospital, Seattle, Washington, also set out to discuss why maintenance therapy improved outcomes and to address the issue of who should receive maintenance therapy in the future.[6]

Hawkins noted that RMS 2005 is only the third positive randomized study in pediatric rhabdomyosarcoma to be reported in the literature. In 1974, Heyn et al demonstrated an improvement in outcomes for children who received adjuvant chemotherapy following surgery and radiotherapy.[7]

Then, in 2014, Mascarenhas et al published a randomized phase II trial that evaluated bevacizumab and temsirolimus in combination with vinorelbine and cyclophosphamide for the first relapse/disease progression of rhabdomyosarcoma.[8] The authors, representing the Children's Oncology Group, found that patients randomized to the temsirolimus arm had superior event-free survival (EFS) compared to the bevacizumab cohort. The median 6-month EFS for the temsirolimus regimen was 65% (95% CI, 44%-79%) but only 50% for the bevacizumab arm (95% CI 32%-66%). The 2-sided $P$ value of.0031 favored the regimen with temsirolimus.[8]

According to Hawkins, researchers have fielded 20 randomized trials involving rhabdomyosarcoma since 1972, most conducted in North America by the Intergroup Rhabdomyosarcoma Study Group (IRSG). He noted that several studies have concluded that outcomes improved over time, but an investigational arm never outperformed its control arm in any trials. It is possible that improvements in supportive care, better delivery of radiation therapy, improved surgical techniques, and an intensification of the control-arm chemotherapies account for the improved outcomes, he said.[6]

In considering the question of why OS increased in the RMS 2005 patients who received the low-dose maintenance chemotherapy following intensive chemotherapy, Hawkins offered four possible explanations. First, the low-dose oral cyclophosphamide may have proven exceptionally effective. Two early IRSG studies addressed this issue, in which patients with completely resected rhabdomyosarcoma received oral cyclophosphamide for 2 years in addition to standard chemotherapy.[9,10] But neither of those randomized studies showed an improvement with the addition of oral cyclophosphamide, leading Hawkins to think it unlikely that the addition of oral cyclophosphamide led to the improved OS in RMS 2005.

Second, Hawkins considered the possibility that the OS improvements came from the addition of vinorelbine. Two published phase 2 evaluations of vinorelbine as a single agent have reported objective response rates (ORRs) of 50% and 36%, respectively.[11,12] "Despite this high level of activity, vinorelbine has never previously been incorporated into front-line therapy for rhabdomyosarcoma," Hawkins said. "Patients on the EpSSG maintenance arm received 18 doses of vinorelbine, so perhaps the explanation for the improved outcome was the incorporation of a new active agent."[6]

Third, the combined effects of cyclophosphamide and vinorelbine may have been the reason OS increased, Hawkins observed. The RMS 2005 researchers had completed their pilot study that showed the combination was feasible and pharmacologically active.[5] "But there were no pre-clinical data that would have suggested greater than additive activity of the combination of vinorelbine and cyclophosphamide," he said. "It was a hypothesis that it would work in a different metronomic manner."

However, a phase 2 study used the same schedule of cyclophosphamide and vinorelbine in 2012.[6,13] In 50 patients with recurrent/refractory rhabdomyosarcoma, the ORR was 36%.

"That objective response rate is strikingly similar to that seen with vinorelbine as a single agent, again suggesting that perhaps the benefit was the vinorelbine rather than the combination of cyclophosphamide and vinorelbine," Hawkins explained.[6]

The final possible explanation for improved OS in RMS 2005 may have been the duration of therapy. Hawkins noted that the EpSSG rhabdomyosarcoma standard length of therapy is 27 weeks. Study patients in the experimental arm received an additional 24 weeks' therapy for a total duration of 51 weeks.[3] "Contrast that with the standard therapy used in the Children's Oncology Group for most patients with rhabdomyosarcoma, which is 42 weeks," he said. "We could compare the results from these two different strategies to try to tease out whether it's really just duration of therapy, rather than maintenance itself, that led to the improved overall survival on the EpSSG study."[6]

Hawkins then discussed which patients should receive maintenance chemotherapy in the future. In RMS 2005, patients with low- or standard-risk disease were not eligible for the randomization.[3] Because these patients have a relatively favorable outcome, the trial does not address whether the addition of maintenance therapy would improve their outcome further.

Furthermore, not all high-risk patients were eligible for the maintenance randomization. In order to be eligible for randomization, a patient had to have achieved a radiographic CR at the end of the 27-week standard therapy.[3] Those who had less than a complete response were excluded from the randomization. "The treatment and outcome of those patients is not reported here, but it would be of some interest to look at a total outcome for the patient population," Hawkins said.

At the far end of the disease spectrum, the highest-risk patients were also excluded from the randomization. The very-high-risk group includes patients with alveolar histology and regional lymph node involvement, as well as patients with distant metastatic disease.[3] "The EpSSG has decided to nonrandomly assign maintenance therapy to both groups of patients," said Hawkins. "They have either recently published or have in press single-arm experiences with the addition of maintenance, either 24 weeks for the alveolar regional node-positive patients, or 24 weeks for those who have distant metastatic disease. But this has not been studied in a randomized setting."

## Conclusions

Although agreeing with RMS 2005's overall conclusions, Hawkins says that the role of maintenance in other populations, including other groups of children with rhabdomyosarcoma and those with other pediatric solid tumors, will require further investigation. "It would be interesting and instructive to compare similar patients from the Children's Oncology Group and EpSSG who were included in the higher-risk groups, such as the metastatic patients or those with alveolar histology and regional lymph node involvement," he said. "These comparisons will require careful adjustments, but I think they may give us some insight into the benefit of maintenance chemotherapy."[6] ◆

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# CARMENA Phase 3 Results in Advanced RCC Suggest a Shift Toward Multidisciplinary Care

THE STANDARD OF CARE in metastatic renal cell carcinoma (mRCC) has long been cytoreductive nephrectomy followed by systemic treatment for patients who are acceptable surgical candidates. Two key randomized controlled trials supporting this regimen were published in 2001.[1,2] At that time, available systemic treatments were limited to cytokine-based therapies such as interferon-alpha, with about 6% to 20% of patients responding.[3] Half of patients with mRCC did not live as much as a year, even with surgery and chemotherapy.[3] Within a few years, new drugs targeting angiogenesis were brought to market. Sunitinib, a targeted tyrosine kinase inhibitor, was proven superior to interferon-alpha, and, after receiving FDA approval in 2006, soon became the standard of care following cytoreductive nephrectomy.[3,4]

In 2013, the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) published retrospective data that continued to support cytoreductive nephrectomy as the standard of care. Heng et al looked at the survival outcomes of patients with metastatic RCC who did or did not have the primary tumor removed. They found that most patients benefited from tumor removal, except for those with 4 or more IMDC risk factors.[5] Among many clinicians, however, concerns remained about perioperative complications and the risk of progressing disease during the recovery period, especially for poor-risk patients.

However, findings from a long-term study initiated in 2009 showed that cytoreductive nephrectomy was potentially promising. In the CARMENA (Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques) trial, investigators set out to answer the question of whether cytoreductive nephrectomy should still be the standard of care in metastatic RCC in the era of targeted therapy.

At the recent American Society of Clinical Oncology (ASCO) annual meeting, CARMENA principal investigator Arnaud Méjean, MD, PhD, revealed that the study's primary endpoint of overall survival (OS) had been met, indicating treatment with sunitib alone produced similar or better results to cytroreductive nephrectomy and sunitib.[6]

The study was published the *New England Journal of Medicine*.[7]

## CARMENA: Design and Results

Between September 2009 and September 2017, investigators enrolled 450 patients at 79 medical centers in France, the United Kingdom, and Sweden. At the September 9, 2017, data cutoff for the second interim analysis, 326 survival events had occurred with a median follow-up of 50.9 months. The CARMENA steering committee determined that the results from this interim analysis were sufficient to meet the overall study objectives and declared the study complete.[6]

CARMENA's design had 80% power and a 1-sided significance level of 5% to assess the study hypothesis that cytroreductive nephrectomy is not necessary. The investigators determined that treatment with sunitinib alone would be considered clinically acceptable if the upper band of the 95% CI met the upper threshold for OS. With a hazard ratio of 0.89 at the 95% CI and a range of 0.71 to 1.1, the OS threshold did not exceed the trial's noninferiority margin of 1.20.[6]

The investigators included 576 patients with synchronous mRCC to demonstrate noninferiority and determined the need to observe 456 survival events. They planned 2 interim analyses, one after 152 survival events occurred and the second after 302 events.[7]

Eligibility for the trial included a diagnosis of clear cell RCC confirmed by biopsy, as well as documented metastatic disease and a willingness to undergo nephrectomy if assigned. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and eligibility for treatment with sunitinib were also required. Exclusionary conditions included growing metastases; any metastases must have been successfully controlled with surgery or radiotherapy. Additionally, patients could not have received prior systemic therapy for RCC.[7]

Patients with intermediate or poor risk were randomized between two arms. In arm A, patients received the standard of care: nephrectomy followed after 3 to 6 weeks by sunitinib. Patients in arm B received sunitinib alone. Sunitinib was given at the usual dose of 50 mg daily for 4 weeks, followed by 2 weeks off.[7] Arm A contained 226 patients, while 224 were assigned to arm B. In arm A, 40 patients did not receive sunitinib due to rapid deterioration, and 16 did not receive surgery. In arm B, 11 patients did not receive sunitinib and 38 patients did undergo secondary nephrectomy.[7]

The safety population of arm A, used for the second interim and final analyses, consisted of 186 patients. Of these, 3 withdrew consent, and 2 were lost to follow up. There were 165 deaths in this cohort. The safety population in arm B included 213 patients, 3 of whom did not receive sunitinib. Two patients were lost to follow-up and there were 161 deaths. Thus, arm A contained 205 patients who had nephrectomy and 176 who received the assigned protocol of surgery plus sunitinib. In arm B, 206 of 224 assigned patients received sunitinib.[7]

The patient characteristics in both arms were comparable. The median age was 63 and 62, respectively. Three-quarters of each arm were male (A = 169, B = 167). Slightly more than half the patients in each arm had an intermediate Memorial Sloan Kettering Cancer Center (MSKCC) score (A = 125, 56%; B = 131, 59%). In arm A, 100 patients (44%) were stratified as poor using MSKCC criteria, as were 93 patients (41%) in arm B. ECOG performance status was also comparable: 130 patients (57%) in arm A were 0 and 96 patients (42%) were 1. In arm B, 122 patients (54%) were 0 and 102 patients (45%) were 1.[7]

**"Sunitinib alone was not inferior to nephrectomy followed by sunitinib in patients with metastatic renal-cell carcinoma who were classified as having intermediate-risk or poor-risk disease."**

The median primary tumor sizes in the intent-to-treat (ITT) population were likewise similar: 88 mm in arm A and 86 mm in arm B. Patients in each arm had a median of 2 metastatic sites. In arm A, the median tumor burden was 140 mm by RECIST 1.1 criteria (range, 23-399); in arm B, it was 144 mm (range, 39 to 313). The most common sites of metastases (lung, bone, lymph nodes, and other) were also comparable.[7]

The median OS in the ITT population in arm A was 13.9 months (range, 11.8-18.3) and 18.4 months in arm B (range, 14.7 to 23.0) with a HR of 0.89 (95% CI, 0.71-1.1). Among MSKCC intermediate-risk patients, median OS was 19.0 months (Arm A range, 12.0 to 28.0) and 23.4 months (Arm B range, 17.0-32.0), with an HR of 0.92 (95% CI, 0.6-1.24). Among MSKCC poor-risk patients, median OS was 10.2 months (Arm A range, 9.0-14.0) and 13.3 months (Arm B range, 9.0-17.0), with an HR of 0.86 (95% CI, 0.62-1.17).[7]

OS data were stratified by patient population. In arm A, the median OS for the entire 226-patient ITT cohort was 13.9 months (95% CI, 11.8-18.3). For arm A's per-protocol 1 (PP1) group of 205 patients who had nephrectomy, the median OS was 14.5 months (95% CI, 11.9-20.2). Arm A's 176 patients who had both surgery and sunitinib as planned (PP2) had a median OS of 18.3 months (95% CI, 13.7-23.2).[7]

In arm B, the median OS for the entire 224-patient ITT cohort was 18.4 months (95% CI: 14.7-23.0). Arm B's 206 combined PP1/PP2 patients, who received sunitinib alone, had a median OS of 20.5 months (95% CI, 15.6-25.2). For the secondary outcome of PFS in the ITT population, the median PFS in arm A was 7.2 months (95% CI, 6.5-8.5). In arm B, the median PFS was 8.3 months (95% CI, 6.2-9.9). The HR was 0.82 (95% CI, 0.67-1.00).[7]

PFS data by patient population were comparable. In arm A, the median PFS in the PP1 population was 7.6 months (95% CI, 6.8-9.4) and 8.7 months in arm B (95% CI, 7.2-10.2). The combined PP1/PP2 population of arm B had a median PFS of 8.5 months (95% CI, 7.5-10.2); the PFS of the ITT population HR of 0.82 (95% CI, 0.67-1.00) was identical to that of the PP1 (95% CI, 0.66-1.01).[7]

Among the 186 patients in arm A who had both nephrectomy and sunitinib, 1 patient had a complete response (CR); no patient in arm B had a CR. Fifty patients in arm A (28%) had a partial response, as did 62 patients (30%) in arm B. About a quarter of patients (n = 49, 27%) in arm A and 97 patients (47%) in arm B had stable disease. Progressive disease was seen in 49 patients (27%) and 40 patients (19%) in arms A and B, respectively.[7]

ORR was 27.4% (95% CI, 21-34) and 29.1% (95% CI, 23-36) in arms A and B, respectively, while disease control rates (DCRs) in arms A and B, respectively, were 61.8% (95% CI, 54-69) and 74.6% (95% CI, 68-80). Patients in arm A derived clinical benefit (defined as disease control beyond 12 weeks) at a rate of 36.6%, while clinical benefit in arm B (sunitinib alone) was 47.9% ($P$ =.022).[7]

In the arm A group receiving both surgery and sunitinib (n = 210), 4 patients (2%) died within 1 month of surgery. Nearly 40% of arm A patients experienced postoperative morbidity (n = 82, 39%), with most of these categorized as Clavien-Dindo grade 1 (n = 45, 55%).[7]

The CARMENA study assessed the safety of sunitinib as a secondary outcome. Of the 186 arm-A patients who took sunitinib as part of their treatment, the median treatment duration was 6.7 months (range, 1.4-67.2) and about one-third of these patients required dose reductions (n = 57, 31%). Similarly, one-third of this cohort experienced adverse events (AEs) of grade 3 or 4 (n = 61, 33%). The most common serious AE was asthenia, seen in 16 patients (9%).[7]

The median treatment duration was slightly longer in the sunitinib-alone arm B (8.5 months; range 0.9 to 63.7); 65 patients (30%) required dose reduction and more patients experienced grade 3 or 4 AEs (43%, n = 91) Of these, 10% had asthenia (n = 21). Other AEs affecting more than 3 patients included hand-foot syndrome, anemia, neutropenia, and kidney or urinary tract disorder.[7]

Additionally, 38 patients in the sunitinib-only arm required secondary nephrectomy (17%). Of these, 7 patients (18.9%) required the surgery on an emergent basis to treat their primary tumor. The median interval between randomization and surgery was 11.1 months (range, 0.7-85.4). Nearly one-third of patients were able to restart sunitinib following surgery (31.3%).[7]

The CARMENA investigators concluded, "Sunitinib alone was not inferior to nephrectomy followed by sunitinib in patients with metastatic renal-cell carcinoma who were classified as having intermediate-risk or poor-risk disease."[7] They found that patients in the sunitinib-only arm received significantly greater clinical benefit than the sunitinib plus surgery arm.[7]

## Future Implications

To address the question of whether the CARMENA results should change standard practices, ASCO selected as discussant Daniel J. George, MD, director of the Genitourinary Oncology Institute at Duke University.[8] George began by reviewing the reasons cytoreductive nephrectomy became the standard of care in metastatic RCC. He reminded colleagues that sunitinib received FDA approval in 2006, followed by the publication in 2009 of the pivotal 1034 trial, which demonstrated a PFS benefit for sunitinib over interferon alpha in patients with metastatic RCC.[3] Since then, sunitinib has become the first-line standard of care in mRCC.[8]

George noted that the study took 8 years to accrue, perhaps because of the widespread belief that cytoreductive nephrectomy's benefits have been too great to ignore. He also found it significant that, while the study population contained only patients with an ECOG performance status of 0 or 1 and were thus appropriate surgical candidates, more than 40% met the criteria for MSKCC poor risk (A: n = 100, 44%; B: n = 93, 41%).[8]

Additionally, the study population had a significant tumor burden. Although the primary tumor's median size was about 8 to 9 centimeters in the 2 arms, the study population's median total tumor burden of approximately 14 cm indicated that about 40% of patients' tumor burden was metastatic and therefore not relieved by surgery. "It's perhaps this lack of equipoise that may have influenced the results of this study because clearly inclusion of these patients in the study could favor the cytoreductive nephrectomy arm versus the patients that have much bulkier metastatic disease," George said, adding that the HR of 0.89 for OS showed an upper-index CI of 1.10, well below the 1.20 threshold that was set.[8]

In considering the planned PP2 analysis, George noted that the upper limit of that confidence interval exceeds the 1.20 threshold (HR 0.98, 95% CI, 0.77-1.25), which makes this particular analysis inconclusive rather than supportive of the primary analysis. "The clinical trialist in me would like to see that PP2 analysis under the 1.20 threshold and a larger number of patients accrued, but the clinician in me treats by intention-to-treat [data] as a practical end point that's most appropriate for my decision making," he said.[8]

George says that one of CARMENA's most important contributions is that it furthers the cause of multidisciplinary care in renal cell carcinoma for patients presenting with metastatic disease. "Traditionally, patients would come into an emergency room [department] with metastatic renal cell carcinoma and undergo a urology consult before being whisked away to surgery within a day or two," he said. "Now I think we have the justification to say we need a multidisciplinary discussion and a thoughtful approach to the sequence of treatments for these patients."[8]

After noting that the standard of care remains unchanged for patients with stage I, II, or III disease, George closed by reiterating his support for an updated standard of care in advanced RCC: "The results in general support the use of sunitinib alone and in lieu of surgery, particularly in poor-risk and high-metastatic burden patients. Patient selection and reduced accrual somewhat limit the broad application of these results," he said. "In the absence of other data, some of these results need to be extrapolated to other systemic therapies. But ultimately, we should be evaluating more immediate nephrectomy versus systemic therapy with possible delayed nephrectomy in low-volume metastatic disease burden patients. This is our next opportunity in the field."[8] ◆

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