2019 ASCO Annual Meeting Highlights for the Advanced Practitioner: Other Solid Cancers

Trials studying additional solid cancers, such as pancreatic cancer, head and neck cancer, glioblastoma, and glioma are reviewed in this section and accompanied by advanced practitioner commentaries. In addition, a study exploring the benefits of proton therapy over photon therapy is discussed.

Abstract LBA4

POLO Trial Shows Maintenance Olaparib Improves Progression-Free Survival in Metastatic Pancreatic Cancer

By Caroline Helwick

Visit https://meetinglibrary.asco.org/record/174488/abstract to read the full abstract and view disclosures.

In patients with metastatic pancreatic cancer and germline mutations in *BRCA1* or *BRCA2*, maintenance therapy with olaparib doubled the time to disease progression and the proportion of patients who were progression-free at 2 years, in the phase III POLO trial (Kindler et al., 2019).

"Maintenance olaparib provided a statistically significant and clinically meaningful 47% improvement in progression-free survival," said Hedy Lee Kindler, MD, Professor of Medicine at the University of Chicago, who presented the POLO trial findings at the 2019 ASCO Annual Meeting's Plenary Session. Patients receiving maintenance therapy after stable or responding disease to initial platinum-based chemotherapy had a median progression-free survival of 7.4 months, compared with 3.8 months for those on placebo (hazard ratio [HR] = 0.53; P = .0038).

The findings were concurrently published in *The New England Journal of Medicine* (Golan et al., 2019). The inhibitor of poly (ADP-ribose) polymerase (PARP) is approved by the U.S. Food and Drug Administration in the treatment of patients with ovarian and breast cancers who have *BRCA* mutations.

Oncologists applauded these study findings. At a press briefing, ASCO spokesperson Suzanne Cole, MD, Director of the University Hospital Simmons Cancer Clinic at the UT Southwestern Medical Center at Richardson/Plano, commented, "These results are practice-changing for our patients. I can't wait to go back to the clinic and look for *BRCA* mutations in my patients."

Dr. Cole continued: "Now that we have a targeted medicine that can benefit patients with *BRCA* mutations, it is our duty to search for this mutation to identify those who will benefit from a treatment that could extend their life."

Rationale Behind Novel Therapy

As Dr. Kindler noted, metastatic pancreatic cancer is a "dismal disease," with a median progression-free survival of about 6 months and a median overall survival of 8 to 12 months with

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the current standard-of-care chemotherapy. Fewer than half of patients are able to proceed to second-line therapy, and, until now, there has been no effective targeted therapy. Maintenance treatments aim to delay disease progression following chemotherapy without compromising quality of life.

Some 4% to 7% of patients with metastatic pancreatic cancer harbor a germline *BRCA* mutation. In other tumor types, these *BRCA*-deficient tumors have derived a benefit from platinum-based chemotherapy and from PARP inhibitors. Olaparib works by trapping PARP at sites of DNA single-strand breaks, causing an accumulation of DNA damage and tumor-cell death.

"Our results are the first from a phase III trial to validate a targeted treatment in a biomarker-selected population of patients with pancreatic cancer," Dr. Kindler noted.

POLO Details

The phase III POLO trial was conducted at 119 sites in 12 countries. Of 3,315 patients with pancreatic cancer screened, 247, or 7.5%, had germline *BRCA* mutations, and 154 were enrolled after not experiencing disease progression during 16 weeks or more of platinum-based chemotherapy. The investigators randomly assigned 92 patients to treatment with olaparib at 300 mg twice daily and 62 patients to the placebo arm. Maintenance was initiated 4 to 8 weeks after the last dose of chemotherapy and continued until radiologic disease progression by investigator assessment.

Improvements in All Key Outcomes

The primary endpoint was progression-free survival by blinded independent central review. The progression-free survival was 7.4 months with maintenance olaparib, compared with 3.8 months with placebo (hazard ratio [HR] = 0.53; P = .0038). From 6 months onward, more than twice the proportion of olaparib-treated patients were progression-free (Table 1 online). Time to second disease progression was improved by 24% as well, "which may indicate the durability of treatment benefit beyond disease progression," she suggested.

"What was truly remarkable was that the median duration of response in patients with metastatic pancreatic cancer was more than 2 years," Dr. Kindler emphasized. She predicted that this could signal a change in the disease trajectory of a pancreatic cancer subset.

The objective response by blinded independent central review was 23.1% with olaparib and 11.5% with placebo. Two olaparib-treated patients had complete responses, and both were ongoing at the time of data cutoff. The planned interim analysis of overall survival (at 46% maturity) demonstrated no difference in survival, with median survival times of approximately 18 months.

Adverse events grade ≥ 3 were observed in 39.6% of the olaparib arm and 23.3% of the placebo arm, mainly anemia and fatigue, with a toxicity profile similar to that seen in other tumor types. Patient-reported global health-related quality of life was preserved, over time, with no clinically meaningful differences from baseline in either arm or between the arms.

"We conclude that a strategic approach of first-line platinum-based chemotherapy followed by maintenance olaparib treatment should become a new standard of care for patients with metastatic pancreatic cancer who have a germline *BRCA* mutation," said Dr. Kindler.

References

Golan, T., Hammel, P., Reni, M., Van Cutsem, E., Macarulla, T., Hall, M. J.,...Kindler, H. L. (2019). Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *New England Journal of Medicine, 381*(4), 317–327. https://doi.org/10.1056/NEJMoa1903387

Kindler, H. L., Hammel, P., Reni, M., Van Cutsem, E., Mercade, T. M., Hall, M. J.,...Golan, T. (2019). Olaparib as maintenance treatment following first-line platinum-based chemotherapy in patients with a germline BRCA mutation and metastatic pancreatic cancer: Phase III POLO trial [Abstract LBA4]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 37*(18_suppl). https://doi.org/10.1200/JCO.2019.37.18_suppl.LBA4

Continued on the following page

The Advanced Practitioner Perspective

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The recent POLO trial is very exciting and could be beneficial to certain populations of pancreas cancer patients. However, many patients do not always understand trial details and the fact that benefits may only be applicable to a certain group, like this study was in patients with *BRCA* mutations (which only occurs in about 4% to 7% of patients).

Patient Education

As an advanced practitioner (AP), it is critical to understand the trial process and educate patients efficiently since pancreas cancer is very time sensitive. I have found that many patients will read the title of a trial or the highlight of the results and immediately want to pursue it. As APs, we have to understand data sets and enrollment processes to help educate and guide patients better in their decisions. I know many patients bring me studies, spend exorbitant amounts of time researching, get all excited with headline results, and then are not candidates and become extremely disappointed.

You will never know every trial, but you can be familiar with the larger ongoing studies as well as preliminary testing that may be required for qualification. Advanced practitioners can take time to educate patients about enrollment criteria and time frames for testing for things like *BRCA*. Also, APs can help patients understand that if they do not fit the inclusion criteria, it could be a treatment that may not be beneficial to them. It may help relieve some anxiety if they did not qualify.

Disclosure: Ms. Hacker-Prietz has no conflicts of interest to disclose.

Abstract 4000

APACT Trial: Nab-paclitaxel/Gemcitabine vs Gemcitabine Alone in Adjuvant Treatment of Pancreatic Cancer

By Caroline Helwick

Visit https://meetinglibrary.asco.org/record/173181/abstract to read the full abstract and view disclosures.

The largest adjuvant trial in pancreatic adenocarcinoma, the global phase III APACT trial, evaluated the combination of adjuvant nab-paclitaxel/gemcitabine vs gemcitabine monotherapy in patients with resected pancreatic cancer. Results of the study were reported by Margaret A. Tempero, MD, of the University of California, San Francisco, at the 2019 ASCO Annual Meeting (Tempero et al., 2019).

The primary endpoint of independently assessed disease-free survival did not show a difference with the combination. Disease-free survival by prespecified sensitivity analysis of investigator assessment, however, showed a prolonged disease-free survival, Dr. Tempero reported. Dr. Tempero noted that overall survival data are still immature.

"The primary endpoint of independently assessed disease-free survival was not met, but investigator-assessed disease-free survival appeared to align more closely with the overall survival results," Dr. Tempero said. Hazard ratios (HR) for disease-free survival were 0.88 (P = .1824) by independent assessment and 0.82 (P =.0168) by investigator assessment. She noted that these results send a message about clinical trial design.

Unusual Trial Design

This trial represents the first time that an independent-assessed disease-free survival endpoint was used in an adjuvant trial for pancreatic adenocarcinoma. And, according to Dr. Tempero, study investigators are now questioning this approach. When asked by an attendee what her recommendations as a trialist would be, based on APACT outcomes, she responded, "It's simple. Don't use independent assessment."

With independent assessment, she now realizes, assessors are not privy to information used by local investigators to determine disease progression, such as postoperative changes, patient-reported pain, and rise in CA 19-9 levels. Perhaps because they lacked such information, the independent reviewers in APACT experienced some discordance that needed to be adjudicated, she said.

"We all recognize that clinically, it's often difficult to distinguish recurrence in the pancreatic bed from postoperative changes. Independent assessment had never been used before, and we thought we were introducing more rigor into the trial. Clearly, this is a lesson learned for the field going forward: avoid this endpoint," Dr. Tempero suggested.

APACT Details

The hypothesis was that the combination of nab-paclitaxel/gemcitabine would improve outcomes over gemcitabine alone, the standard of care at the time of the trial in patients who underwent resection. In the landmark MPACT trial in metastatic patients, nab-paclitaxel/gemcitabine yielded an absolute 2.1 months of survival time ($P < .001$; Von Hoff et al., 2013). After the launch of the APACT trial, gemcitabine plus capecitabine and modified FOLFIRINOX demonstrated survival benefits in the adjuvant ESPAC-4 (Neoptolemos et al., 2017) and PRODIGE 24 trials (Conroy et al., 2018) and so became preferred treatments.

The global APACT study enrolled 866 treatment-naive patients (median age, 64 years) who had undergone macroscopic complete resection. Most had lymph-node positive disease (72%) and R0 resections (76%), and all patients showed no evidence of persistent disease.

Patients were randomly assigned to receive, within 12 weeks of surgery, nab-paclitaxel at 125 mg/m^2 plus gemcitabine at 1,000 mg/m^2 or gemcitabine alone at 1,000 mg/m^2 for 6 cycles. The primary endpoint was radiologic disease–free survival, independently assessed without reviewers' knowledge of clinical circumstances.

Outcomes in Disease-Free Survival

After a median follow-up of 38.5 months, median disease-free survival by independent review was 19.4 months with nab-paclitaxel/gemcitabine vs 18.8 months with gemcitabine (HR = 0.88; $P = .1824$). The benefit was greatest in patients with moderately differentiated tumors, lymph node–positive disease, R1 resection, and normal CA 19-9 level.

For the prespecified sensitivity analysis of investigator-assessed disease-free survival, a benefit was shown for the combination, with a median disease-free survival of 16.6 months vs 13.7 months for the single agent (HR = 0.82; $P = .0168$). Overall survival was a secondary endpoint, for which the data are immature. At data cutoff, interim median survival was 40.5 months vs 36.2 months, respectively (HR = 0.82; $P = .045$).

Grade ≥ 3 treatment-emergent adverse events were reported in 86% of the experimental arm and 68% of the single-agent arm. The most common grade ≥ 3 hematologic and nonhematologic toxicities were for nab-paclitaxel/gemcitabine vs gemcitabine, neutropenia (49% vs 43%) and fatigue (10% vs 3%). Patients in the combination arm also had more peripheral neuropathy, diarrhea, and asthenia.

"Overall survival is encouraging, and longer follow-up will clarify the role for this combination as adjuvant therapy for pancreatic adenocarcinoma," Dr. Tempero said. "The interim analysis suggests that continued investigation of this regimen in patients with lymph node–positive disease, R1 resection, or an inability to tolerate modified FOLFIRINOX is warranted."

References

Conroy, T., Hammel, P., Hebbar, M., Bed Abdelghani, M., Wei, A. C., Raoul, J.-L.,...Bachet, J.-B. (2018). Unicancer GI PRODIGE 24/CCTG PA.6 trial: A multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine in patients with resected pancreatic ductal adenocarcinomas [Abstract LBA4001]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 36*(18_suppl). https://doi.org/10.1200/JCO.2018.36.18_suppl.LBA4001

Neoptolemos, J. P., Palmer, D. H., Ghaneh, P., Psarelli, E. E., Valle, J. W., Halloran, C. M.,...Büchler, M. W. (2017). Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): A multicenter, open-label, randomised phase 3 trial. *Lancet, 389*(10073), 1011–1024. https://doi.org/10.1016/S0140-6736(16)32409-6

Tempero, M. A., Reni, M., Riess, H., Pelzer, U., O'Reilly, E. M., Winter, J. M.,...Biankin, A. (2019). APACT: Phase III, multicenter, international, open-label, randomized trial of adjuvant nab-paclitaxel plus gemcitabine vs gemcitabine for surgically resected pancreatic adenocarcinoma [Abstract 4000]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 37*(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.

Von Hoff, D. D., Ervin, T., Arena, F. P., Chiorean, E. G., Infante, J., Moore, M.,...Renschler, M. (2013). Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *New England Journal of Medicine, 369*, 1691–1703. https://doi.org/10.1056/NEJMoa1304369

Continued on the following page

The Advanced Practitioner Perspective

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Advanced practitioners will see many pancreas cancer patients in the adjuvant setting. These patients may have been treated with neoadjuvant therapy, just had surgery, and are now coming in for follow-up with you and want to know what to do next.

Patient Communication

The APACT study of gemcitabine/nab-paclitaxel vs gemcitabine alone in the adjuvant setting emphasizes why you really need to ask questions and listen to your patients. Although radiographic imaging may come up negative for recurrence on review by an independent assessment, it is important to investigate symptoms such as pain, appetite, weight, fatigue, and bowel habits. Some of these symptom changes in a pancreas cancer patient could indicate an early recurrence prior to seeing clear radiographic evidence. Investigator assessments of laying eyes on the patient and following symptoms and lab changes (cancer antigen [CA] 19-9 or carcinoembryonic antigen [CEA] level) may be more effective for earlier detection of a recurrence.

Symptom Management

Symptom assessment and management of these patients is critical. To qualify for studies or even standard-of-care treatment, a patient's performance status often needs to be ECOG 0 or 1. If their symptoms are not managed appropriately, it could really limit which treatments they can handle as well as impact their life quality of life. Ask questions, and if you make changes to address symptoms, then follow up on those changes for effectiveness. It is difficult to rationalize quantity of life without quality of life; they must go hand-in-hand, and APs are in a good position to help patients maintain that quality of life.

Disclosure: Ms. Hacker-Prietz has no conflicts of interest to disclose.

Abstract 6000

Improved Survival Shown With First-Line Pembrolizumab in Advanced Head and Neck Cancer

By Caroline Helwick

Visit https://meetinglibrary.asco.org/record/171051/abstract to read the full abstract and view disclosures.

In the final analysis of KEYNOTE-048, first-line pembrolizumab monotherapy led to a significant improvement in overall survival, vs standard chemotherapy with targeted therapy (EXTREME regimen), in patients with recurrent or metastatic head and neck squamous cell carcinoma expressing programmed cell death ligand 1 (PD-L1; Rischin et al., 2019). In the total population as well, the combination of pembrolizumab plus chemotherapy improved overall survival, and single-agent pembrolizumab was noninferior to chemotherapy.

"The data from KEYNOTE-048 support pembrolizumab plus platinum-based chemotherapy and pembrolizumab monotherapy as new first-line standard-of-care therapies for recurrent head and neck squamous cell carcinoma," said Danny Rischin, MD, of Peter MacCallum Cancer Centre in Melbourne, speaking at the 2019 ASCO Annual Meeting.

In the first-line setting for recurrent or metastatic disease, the EXTREME regimen was the standard of treatment for more than 10 years, but median overall survival with this regimen is only about 10 months, and the incidence of grade 3 to 4 toxicity is high. Immunotherapy could improve upon outcomes in terms of both efficacy and toxicity, KEYNOTE-048 investigators suggested.

The previous interim analysis of KEYNOTE-048, presented by principal investigator Barbara Burtness, MD, of Yale School of Medicine, New Haven, Connecticut, at the European Society for Medical Oncology (ESMO) 2018 Congress found a survival benefit for pembrolizumab with or without chemotherapy (Burtness et al., 2018). That benefit was seen in the total population with pembrolizumab and chemotherapy in patients with a PD-L1 combined positive score (CPS) ≥ 1 and ≥ 20 with pembrolizumab monotherapy.

The study provided the first evidence of prolonged survival with immunotherapy in the first-line recurrent or metastatic setting for advanced head and neck cancer, and the data were submitted to the U.S. Food and Drug Administration (FDA). After the ASCO meeting, pembrolizumab was approved by the FDA for the first-line treatment of patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma—as monotherapy in patients whose tumors express PD-L1 (with a CPS ≥ 1) or in combination with a platinum and fluorouracil for this population irrespective of PD-L1 expression.

KEYNOTE-048 Details

The phase III trial included 882 patients with recurrent or metastatic head and neck squamous cell carcinoma who were tested for PD-L1 expression. Patients were randomly assigned 1:1:1 to the following three regimens:

- 200 mg of pembrolizumab every 3 weeks for 24 months (n = 301)
- Pembrolizumab for 24 months plus six cycles of chemotherapy consisting of cisplatin at 100 mg/m^2 or carboplatin at AUC 5 every 3 weeks plus fluorouracil at 1,000 mg/m^2/d for 4 days every 3 weeks (n = 281)
- EXTREME regimen: cetuximab at a 400 mg/m^2 loading dose followed by 250 mg/m^2 once a week plus six cycles of chemotherapy (n = 300).

The study followed a hierarchic design, testing a number of initial hypotheses, with the remaining hypotheses tested for statistical significance only if the initial one was positive. Hypotheses tested in the final analysis included the superiority of pembrolizumab alone in the total population, superiority of pembrolizumab plus chemotherapy in the CPS ≥ 20 population, and superiority of pembrolizumab plus chemotherapy in the CPS ≥ 1 population (only if superiority in the CPS ≥ 20 population was demonstrated).

Overall Survival Improved

Overall survival was improved by both pembrolizumab monotherapy and pembrolizumab plus chemotherapy, with some nuances. In the total population, median overall survival was 11.5 months with pembrolizumab vs 10.7 with the EXTREME regimen (hazard ratio = 0.83; P = .0199). Median overall survival was 13.0 months with pembrolizumab plus chemotherapy, for a hazard ratio of 0.72 compared with the EXTREME regimen.

Dr. Burtness noted that although the trial was not designed to compare the two investigational arms, the median overall survival and hazard ratios suggest there is no added survival benefit of chemotherapy for the CPS ≥ 20 population. The hazard ratio for progression-free survival was 1.29 (95% confidence interval [CI] = 1.09–1.53) for single-agent pembrolizumab. For pembrolizumab/chemotherapy, it was 0.76 (95% CI = 0.58–1.01) for CPS ≥ 20 and 0.84 (95% CI = 0.69–1.02) for CPS ≥ 1. The response rate was higher with chemotherapy, indicating that in the most symptomatic patients, there could be an advantage for including chemotherapy even with a CPS > 20.

Response rates for pembrolizumab plus chemotherapy were 42.9% vs 38.2% in the CPS ≥ 20 population and 36.4% vs 35.7% in the CPS ≥ 1 population. The median duration of response with the combination was around 7 months—almost double that for EXTREME. Interestingly, with the single agent, response rates were approximately half those achieved with chemotherapy (16.9% vs 36.0% in the total population), but the duration of response was much longer (median 22.6 vs 4.5 months).

All-cause grade 3 to 5 adverse event rates were 54.7% for pembrolizumab alone, 85.1% for pembrolizumab/chemotherapy, and 83.3% for cetuximab/chemotherapy.

References

Burtness, B., Harrington, K. J., Greil, R., Soulières, D., Tahara, M., De Castro, G., Jr.,...Rischin, D. (2018). KEYNOTE-048: Phase 3 study of first-line pembrolizumab for recurrent/metastatic head and neck squamous cell carcinoma [Abstract LBA8_PR]. Presented at ESMO 2018 Congress.

Rischin, D., Harrington, K., Greil, R., Soulieres, D., Tahara, M., de Castro, G.,...Burtness, B. (2019). Protocol-specified final results of the KEYNOTE-048 trial of pembrolizumab as first-line therapy for recurrent/metastatic head and neck squamous cell carcinoma [Abstract 6000]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 37*(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.6000

Continued on the following page

The Advanced Practitioner Perspective

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The phase III clinical trial KEYNOTE-048 provides evidence for the role of pembrolizumab with or without chemotherapy as first-line treatment for metastatic or inoperable recurrent head and neck cancer. This is practice-changing in the management of head and neck cancer, in which the EXTREME regimen (cetuximab plus chemotherapy) has been the standard of care for first-line treatment for years.

KEYNOTE-048

This study found improved overall survival in patients in the pembrolizumab plus chemotherapy arm, regardless of PD-L1 expression, although survival rates were higher in groups with enhanced PD-L1 expression (CPS ≥ 1) and high PD-L1 expression (CPS > 20). It also found single-agent pembrolizumab was noninferior to cetuximab plus chemotherapy in the total population. This is an interesting finding, as noninferiority trials are typically employed when there is an expectation that the control (EXTREME) and experimental (pembrolizumab) treatments are similar.

Considerations for Advanced Practitioners

As advanced practitioners, this provides nuanced considerations for treatment. For patients who have symptomatic cancer burden, when clinicians would want to take advantage of rapid cytoreduction, pembrolizumab plus chemotherapy demonstrated a higher response rate than the EXTREME regimen, with similar rates of severe toxicities.

However, in minimally symptomatic patients, those whose tumor expresses PD-L1, who are platinum-refractory, or are poor chemotherapy candidates, pembrolizumab monotherapy may be the first-line treatment of choice as it has lower rates of severe toxicities than either chemotherapy arm. This is a significant consideration, as fewer toxicities lead to enhanced quality of life and better tolerance of cancer treatment overall.

Disclosure: Dr. Fuoto has no conflicts of interest to disclose.

Abstract 2016

Combination Therapy With SurVaxM in Newly Diagnosed Glioblastoma

By The ASCO Post

Visit https://meetinglibrary.asco.org/record/174784/abstract to read the full abstract and view disclosures.

Ahluwalia et al shared research results on SurVaxM at the 2019 ASCO Annual Meeting, reporting that combination therapy with the immunotherapy vaccine was more effective than standard therapy for nearly all patients with newly diagnosed glioblastoma in a phase II trial (Abstract 2016).

SurVaxM (SVN53-67/M57-KLH) was developed at Roswell Park Comprehensive Cancer Center by Robert Fenstermaker, MD, and Michael Ciesielski, PhD. The vaccine is a new and unique cancer immunotherapy designed to stimulate a multifaceted immune response targeting survivin, a tumor-survival antigen not generally present in nonmalignant cells.

Results were reported from a five-center, single-arm phase II clinical trial, in which 63 patients with newly diagnosed glioblastoma with a median age of 60 years were followed for safety, 6-month progression-free survival, 12-month overall survival, and immunologic response. All patients underwent standard treatment involving craniotomy, radiation, and treatment with temozolomide both before and after surgery. Immune response was assessed by detection of a survivin-specific antibody and CD8-positive T-cell levels.

Study Results

The team reported that, compared to a historical analysis of patients receiving standard therapy alone, combination therapy with SurVaxM generated encouraging efficacy and immunogenicity in patients with newly diagnosed glioblastoma, with minimal toxicity or side effects. The majority of patients (96.8%) did not experience disease progression within 6 months of treatment, and 93.5% were alive 1 year after diagnosis, compared to an expected 65% survival rate based on historical comparisons.

"We saw significant increase[s] in both PFS and OS, which [are] noteworthy in patients with such a notoriously aggressive and treatment-resistant disease," said Dr. Fenstermaker.

"We were pleased to see that even patients with poor prognostic factors like high levels of survivin responded well to this combination of standard therapy plus SurVaxM," added Dr. Ciesielski.

SurVaxM was awarded Orphan Drug designation by the FDA in 2017.

Reference

Ahluwalia, M. S., Reardon, D. A., Abad, A. P., Curry, W. T., Wong, E. T., Belal, A.,...Fenstermaker, R. (2019). SurVaxM with standard therapy in newly diagnosed glioblastoma: Phase II trial update [Abstract 2016]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 37*(15_suppl).

The Advanced Practitioner Perspective

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While this study shows promising results, it must be validated in a larger randomized study using SurVaxM, concurrent radiation, temodar, adjuvant temodar vs. standard therapy in order to significantly impact clinical practice and treatment options.

Study Design

There are other elements of this study that must be considered. First, eligibility criteria for this study included an MRI documenting a 1 cm^3 or less tumor volume post-resection, which is a narrow criterion impacting interpretation of efficacy results of this study, as well as eligibility of future patients. Further studies could consider including patients with more than 1 cm^3 residual tumor volume, as this would be of greater clinical significance and would broaden treatment choices.

Second, antibody titers of patients receiving SurVaxM produced an increase in SurVaxM. Results showed that this correlated with increased survival rate. Stratification by survivin expression level as a biomarker should be considered. This finding should also be replicated in patients with subtotal resections.

Third, in the era of pseudo-progression, it is not clear if the study took into consideration any MRI changes that may be reactive changes in the setting of immunotherapy vs. true tumor progression. Clearly understanding and detailing the criteria that were used to differentiate tumor response/stabilization vs. tumor progression is critical before considering use in clinical practice.

SurVaxM represents a promising immunotherapy strategy for glioblastoma that targets survivin. Additional clinical studies will be required to validate these results.

Disclosure: Ms. Fong has no conflicts of interest to disclose.

Abstract 2002

Subgroups of Patients With Low-Grade Glioma May Benefit From PCV Chemotherapy Plus Radiotherapy

By The ASCO Post

Visit https://meetinglibrary.asco.org/record/173360/abstract to read the full abstract and view disclosures.

A recent, updated predictive analysis of the three World Health Organization (WHO)-defined molecular subgroups based on *IDH* mutation status and 1p/19q codeletion status represented in the high-risk treatment arms of a phase III trial found that both *IDH*-mutant subgroups may derive benefit from the addition of PCV (procarbazine, lomustine, and vincristine) chemotherapy to radiotherapy. These data were presented by Bell et al at the 2019 ASCO Annual Meeting (Abstract 2002).

NRG-RTOG 9802

NRG-RTOG 9802 was a phase III trial that assessed patients with high-risk low-grade gliomas (defined as patients at least 40 years old or who have had incomplete tumor removal) that were treated with radiotherapy with or without PCV chemotherapy after the patients received a biopsy or surgical resection. This analysis studied a subset of the specimens from which tissue was available for molecular profiling.

"This is the first phase III trial to evaluate the predictive value of WHO subgroups in low-grade gliomas using long-term overall survival data with

the current standard of care. The results support the notions that there are benefits of PCV therapy to RT for both *IDH*-mutated, 1p/19q noncodeleted and *IDH*-mutated, 1p/19q codeleted subgroups; whereas, high-risk low-grade glioma patients with *IDH* wild-type tumors did not demonstrate any benefit from this treatment," stated first author Erica H. Bell, PhD, Associate Professor of the Department of Radiation Oncology at The Ohio State University.

Findings

One hundred and six specimens of the 251 eligible patients from the trial could be analyzed as they had sufficient tissue and quality DNA for profiling. Of these specimens, 41% were categorized as *IDH*-mutated, 1p/19q noncodeleted, 35% were *IDH*-mutated, 1p/19q codeleted, and 24% were *IDH* wild-type. No statistically significant differences between progression-free survival (PFS) and overall survival (OS) were observed with the addition of PCV chemotherapy in the *IDH* wild-type subgroup; however, both *IDH*-mutant subgroups were significantly correlated with longer PFS (*IDH*-mutated, 1p/19q noncodeleted, P = .003; *IDH*-mutated, 1p/19q codeleted, P < .001) and OS (*IDH*-mutated, 1p/19q noncodeleted, P = .013; *IDH*-mutated, 1p/19q codeleted, P = .029) in the radiotherapy plus PCV chemotherapy arm.

"This study demonstrates the importance of incorporating the new WHO subgroups into the clinical routine, as it enhances the prognostic and now predictive clarification of patients with low-grade glioma, provides further insight into resistance to radiation and PCV [chemotherapy], and guides clinical decision-making," stated senior author Arnab Chakravarti, MD, Chair of Radiation Oncology at The Ohio State University Comprehensive Cancer Center–Arthur G. James Cancer Hospital.

Reference

Bell, E. H., Won, M., Fleming, J. L., Becker, A. P., McElroy, J. P., Shaw, E. G., Mehta, M. P.,...Chakravarti, A. (2019). Updated predictive analysis of the WHO-defined molecular subgroups of low-grade gliomas within the high-risk treatment arms of NRG Oncology/RTOG 9802 [Abstract 2002]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 37*(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.2002

The Advanced Practitioner Perspective

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Since the completion of the NRG-RTOG 9802 trial, clinical practice at the UCLA Neuro-Oncology Program has changed in the treatment of low-grade *IDH* mutated, 1p/19q codeleted and 1p/19q noncodeleted patients. There are no standard treatment guidelines of low-grade gliomas. Previously, treatment recommendations would depend on extent of resection, Ki-67, age, and functional status. Historically, treatment recommendations that would be considered included temozolomide alone in order to delay radiation in some patients, radiation therapy followed by adjuvant temozolomide, or radiation therapy alone.

Practice Changes

With molecular testing now being performed to determine *IDH1* status, changes to the UCLA Neuro-Oncology treatment recommendations followed. When recommending treatment, based on the data presented in NRG-RTOG 9802, the current first-line treatment recommendation includes radiation therapy followed by PCV chemotherapy. With PCV, issues with myelosuppression can occur requiring dose reduction and increased symptom management of nausea/vomiting, peripheral neuropathy, and drug reaction rash.

Given the increase in risk of potential side effects with PCV, other treatments to discuss with patients include the use of temozolomide. While temozolomide may be a more tolerable chemotherapy, there is no head-to-head clinical trial comparing radiation followed by PCV vs. radiation with temozolamide. Lastly, a randomized study comparing radiation/temozolomide vs. radiation/PCV would be beneficial for this patient population.

Disclosure: Ms. Fong has no conflicts of interest to disclose.

Abstract 6521

Study Finds Proton Therapy Reduces Adverse Events, Results in Similar Survival vs Photon Therapy

By The ASCO Post

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In a trial presented by Baumann et al at the 2019 ASCO Annual Meeting (Abstract 6521), patients with locally advanced cancer treated with proton chemoradiotherapy instead of traditional photon chemoradiotherapy were at a lower risk of experiencing side effects. However, cure rates were almost identical between the two groups.

"We looked at grade 3 side effects, including pain or difficulty swallowing, difficulty breathing, nausea, or diarrhea, among others, [which were] often severe enough for patients to be hospitalized," said the study's lead author Brian Baumann, MD, Adjunct Assistant Professor of Radiation Oncology in the Perelman School of Medicine at the University of Pennsylvania and Assistant Professor of Radiation Oncology at Washington University School of Medicine in St. Louis. "Our clinical experience is that [patients treated with] concurrent chemoradiation therapy [and] treated with protons rather than photons tend to have fewer side effects. While there is some literature supporting that finding for several disease sites, we did not expect the magnitude of the benefit to be this large."

Study Methods

For this study, researchers evaluated data on 1,483 patients, 391 of whom received proton therapy and 1,092 who underwent photon treatment. All patients had nonmetastatic cancer and were undergoing chemotherapy and radiation intended to be curative. Patients with brain cancer, head and neck cancer, lung cancer, gastrointestinal cancer, and gynecologic cancer treated with concurrent chemoradiation were included. The primary endpoint was 90-day adverse events associated with unplanned hospitalizations (Common Terminology Criteria for Adverse Events, version 4.0, grade ≥ 3).

Findings

Data showed 11.5% (45) of patients treated with proton therapy experienced a grade 3 or higher side effect. In the photon therapy group, 27.6% of patients (301) experienced a grade 3 or higher side effect. A weighted analysis of both patient groups, which controlled for other factors that may have led to differences between the patient groups, found that the relative risk of a severe toxicity was two-thirds lower for patients treated with proton therapy vs patients treated with photon therapy. Overall survival and disease-free survival were similar between the two groups.

"There are several trials underway, but they are all dealing with a variety of barriers, so it will be years before we have that data. That's why the information we do have is so critical, and our findings here point to a real benefit for our patients," said senior study author James Metz, MD, Chair of Radiation Oncology, leader of the Roberts Proton Therapy Center at the University of Pennsylvania, and a member of the Abramson Cancer Center.

Reference

Baumann, B. C., Mitra, N., Harton, J., Xiao, Y., Wojcieszynski, A., Gabriel, P. E.,...Metz, J. M. (2019). Comparative effectiveness of proton therapy versus photon therapy as part of concurrent chemoradiotherapy for locally advanced cancer [Abstract 6521]. *Journal of Clinical Oncology 37*(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.6521

Continued on the following page

The Advanced Practitioner Perspective

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This is a rare prospective comparative effectiveness study of 1,483 patients who underwent concurrent chemoradiation with proton therapy or photon therapy between 2011 to 2016 to definitively treat nonmetastatic brain, head and neck, lung, gastrointestinal, and gynecologic cancers.

The primary endpoint was 90-day adverse events leading to unplanned hospitalization; in other words, grade 3 or greater side effects based on CTCAE, version 4.0. This endpoint was chosen to assess treatment tolerability to justify increased costs associated with proton therapy. Patients who received chemoradiation with proton therapy had significantly fewer grade 3 or greater side effects despite being significantly older and less healthy. No differences were observed in overall survival (OS) and disease-free survival (DFS) between the two groups.

Study Limitation

While this study was prospective, presumably multicentered, well powered, and reported promising morbidity and mortality results in an older and less healthy population, it was limited as participants were nonrandomized and unblinded, and the follow-up time frame for OS and DFS was brief.

Real-World Implications

Apart from the study design, the high cost of proton therapy compared with photon therapy and the relatively low number of proton therapy centers across the country and world make this potentially safer form of chemoradiation inaccessible to many cancer patients. However, with an improved safety profile, new chemoradiation clinical trials are needed to evaluate if increased doses of either chemotherapy or proton therapy increase OS and/or DFS while maintaining acceptable safety profiles.

Disclosure: Mr. Allred has no conflicts of interest to disclose.