閉経前進行乳がんにおける生存率の改善（Abstract LBA1008）

MONALEESA-7：ホルモン療法にribociclibを併用することで閉経前進行乳がんにおける生存率が改善する

MONALEESA-7: Adding ribociclib to endocrine therapy improves survival in premenopausal advanced breast cancer

HR陽性／HER2陰性進行乳がんを有する閉経前女性に対し、ribociclib を標準治療であるホルモン療法に併用することで、ホルモン単独療法に比べ全生存率の顕著な改善がみられた、と2019 ASCO Annual Meeting で発表された。国際共同ランダム化第III相試験 MONALEESA-7 は、42か月後の生存率が併用療法を受けた女性で70% であり、ホルモン単独療法を受けた女性では46% であったことを明らかにした。これは、相対死亡リスクが29% 低下したことを示している。Ribociclib 投与群女性における増悪なしの期間中央値は23.8か月であり、プラセボ群においては13か月であった。

Full Text

The international, randomized phase III MONALEESA-7 trial found that adding ribociclib to standard-of-care endocrine therapy significantly improved overall survival for premenopausal women with advanced HR-positive/HER2-negative breast cancer compared with endocrine therapy alone. After 42 months of follow-up, the survival rate was 70% for women who took the combination therapy compared with 46% for women who received endocrine therapy only. Advanced breast cancer is the leading cause of cancer death in women 20 to 59 years of age.

The study was featured in a late breaking trial presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting.

"This is the first study to show improved survival for any targeted therapy when used with endocrine therapy as a first-line treatment for advanced breast cancer," said lead study author Sara A. Hurvitz, MD, Director of the Breast Cancer Clinical Research Program at UCLA Jonsson Comprehensive Cancer Center in Los Angeles, CA. "The use of ribociclib as a front-line therapy significantly prolonged overall survival, which is good news for women with this terrible disease."

Advanced breast cancer is less common in premenopausal women than in older women, and incidence is increasing. MONALEESA-7 is the first trial to focus exclusively on women under age 59 who were premenopausal and had advanced breast cancer for which they had not received prior endocrine therapy.

Ribociclib is a therapy that inhibits the activity of cancer-cell promoting enzymes known as cyclin-dependent 4/6 kinases (CDK 4/6).

Investigators randomly assigned women to ribociclib (a tablet), or to a placebo tablet. All women also received goserelin, an injectable endocrine therapy that suppresses estrogen, and one of three other therapies: the nonsteroidal aromatase inhibitors letrozole or anastrozole, which lower estrogen production, or tamoxifen, which has been used to treat breast cancer for over 40 years and blocks the effects of estrogen in breast tissue.

Six hundred and seventy-two women were enrolled in the study. After a median follow-up of 34.6 months, 173 (26%) were still receiving the therapies, with 116 (35%) of the women still receiving ribociclib and 57 (17%) still receiving the placebo.

The women who received ribociclib lived a median of 23.8 months without the disease progressing compared with 13 months for women who received the placebo. The researchers observed that after 42 months of follow-up, for patients receiving ribociclib, the survival rate was 70% when given with endocrine therapy compared with 46% when given with placebo. Overall this represented a 29% relative reduction in the risk of death.

In addition, the survival rate of 71% and 70% for women who took ribociclib in combination with tamoxifen or a nonsteroidal aromatase inhibitor, respectively, compared with a survival rate of 55% and 43%, respectively, for women who received placebo in combination with tamoxifen or aromatase inhibitors only.

"Advanced breast cancer in pre-menopausal women can be very aggressive. It is important and encouraging to see a targeted therapy that significantly increases survival for younger women with this disease," said ASCO Expert Harold J. Burstein, MD, PhD.

The researchers are doing analyses of patient-reported outcomes as well as sub-analyses of the clinical findings, including looking at biomarkers and circulating tumor DNA that may help them determine which women might benefit most from ribociclib.

The investigators are studying the use of ribociclib in women and men with early-stage HR+, HER2-negative breast cancer in combination with endocrine therapy and other cancer indications.

This study received funding from Novartis.

ASCO2019 特集

新たに診断された進行胃がんに対する有望な代替手段(Abstract LBA4007)

KEYNOTE-062：ペンブロリズマブは進行胃がんおよび胃食道接合部腺がんに対する化学療法に匹敵する

KEYNOTE-062: Pembrolizumab comparable to chemotherapy for advanced gastroesophageal junction and gastric cancers

PD-L1 陽性、HER2 陰性の進行胃がんおよび胃食道接合部（G/GEJ）がんを有する患者に対し、ペンブロリズマブによる一次治療は標準化学療法に匹敵する生存率をもたらした、と2019 ASCO Annual Meeting で発表された。ランダム化第III相試験 KEYNOTE-062 はまた、PD-L1 高発現腫瘍を有する患者に対し、ペンブロリズマブの全生存率における臨床的に意味のある改善も示した。2年後、ペンブロリズマブを単剤投与された患者の39%（すべてPDL-1 高発現患者）は生存しており、標準化学療法を受けた患者では22% であった。重篤な副作用の発現率は、ペンブロリズマブを単剤投与された患者群で最も低かった。

Full Text

The KEYNOTE-062 phase III randomized clinical trial achieved its primary endpoint, showing that for patients with PD-L1-positive, HER2-negative, advanced gastric or gastroesophageal junction (G/GEJ) cancer, initial therapy with pembrolizumab resulted in comparable (non-inferior) overall survival as standard chemotherapy. Additionally, pembrolizumab showed clinically meaningful improvement in overall survival among patients with tumors that had high levels of PD-L1 expression. At two years, 39% of patients (all of whom had high PD-L1 levels) that received pembrolizumab alone were alive, compared with 22% of people who received standard chemotherapy. The trial also evaluated combined treatment with pembrolizumab and standard chemotherapy but found this regimen did not improve survival relative to chemotherapy alone.

"This trial shows that front-line pembrolizumab is effective and could provide a new opportunity for people newly diagnosed with advanced gastric or gastroesophageal junction cancers," said lead study author Josep Tabernero, MD, PhD, Head of the Medical Oncology Department at the Vall d'Hebron Barcelona Hospital University Hospital and Institute of Oncology, Barcelona, Spain. "There remains a significant unmet need for treatments for these cancers and our results reinforce the importance of continued research in this field."

The study was featured in a late breaking trial presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting.

Gastric cancers are the fifth most frequently diagnosed cancer worldwide. GEJ, a less common cancer, has seen increasing incidence rates during this decade, particularly in Western nations but the reasons for this increase are not entirely clear.

Pembrolizumab was given accelerated approval by the U.S. Food and Drug Administration in September 2017 for patients with recurrent, locally advanced or metastatic, gastric or GEJ cancer with tumors that express PD-L1 with a combined positive score (CPS) of one or more. The CPS is calculated based on the number of PD-L1 positive cells derived from biopsied tissue and the number of viable tumor cells.

The trial enrolled 763 patients with a median age of 62 and 26% had previous gastric surgery to remove a tumor. In total, 69% had gastric cancer and 30% had GEJ cancer, which are typically very similar types of tumors despite their adjacent locations according to Dr. Tabernero. Investigators focused only on HER2-negative cancers, which studies have shown have a higher chance of recurrence after treatment, to limit factors that could affect outcomes.

PD-L1 expression was assessed via CPS. Previous studies of gastric or GEJ cancers have demonstrated that patients with a PD-L1 CPS of one or more may benefit from pembrolizumab, while a PD-L1 CPS of 10 or more indicates a higher likelihood of benefit. In the current trial, all patients had a PD-L1 CPS of one or greater, and 281 (37% of the enrollees) had a score of 10 or more.

The investigators randomly assigned patients, in equal numbers, to receive one of three treatment options as initial therapy: intravenous pembrolizumab, pembrolizumab and chemotherapy, or chemotherapy plus placebo. The patients were followed for a median of 11.3 months.

Treatment with Pembrolizumab Alone: The trial reached its primary endpoint, demonstrating that overall survival for pembrolizumab was non-inferior to standard chemotherapy. A favorable survival outcome was seen among enrolled patients with PD-L1 CPS of 10 or more. Specific findings include:

- Patients with PD-L1 CPS of one or more: Survival was non-inferior to chemotherapy [hazard ratio = 0.91] – median overall survival was 10.6 months for those receiving pembrolizumab compared with 11.1 months for those who received chemotherapy
- Patients with PD-L1 CPS 10 or more: Survival with pembrolizumab was superior to chemotherapy [hazard ratio = 0.69] – median overall survival was 17.4 months for those receiving pembrolizumab compared with 10.8 months for those receiving chemotherapy. After 2 years, 39% of people taking pembrolizumab were alive compared with 22% of those taking chemotherapy.

Overall survival and progression-free survival, regardless of CPS score, for the combination treatment of pembrolizumab and chemotherapy was comparable to that of chemotherapy alone.

The rates of serious side effects were lowest among patients treated with pembrolizumab alone. Grade 3 or higher toxic treatment-related adverse events were found in 17% of people receiving pembrolizumab, 73% of people receiving pembrolizumab and chemotherapy, and 69% receiving only chemotherapy. The most common adverse events were nausea and fatigue. The safety profile of pembrolizumab was consistent with prior experiences of patients who have been treated with it.

"Chemotherapy has been our only option for many years. These results introduce a potential alternative in pembrolizumab that comes with fewer side effects, and importantly, for some it can greatly extend survival. This opens the door to helping patients live longer and better lives," said Richard L. Schilsky, MD, FACP, FSCT, FASCO, Senior Vice President and Chief Medical Officer (CMO) of ASCO.

The investigators are currently analyzing subsets of the data to determine who benefitted the most. Dr. Tabernero noted that better biomarkers than PD-L1 are needed to truly determine who the best responders might be to pembrolizumab alone, as well as in combination with chemotherapy.

The trial enrolled 58% of patients from North America, Europe, and Australia; 25% from Asia; and 17% from other regions of the world. Prior population-based studies have shown that people from Asia usually have better survival rates for gastric and GEJ cancers, have lower amounts of tumor, and slower disease progression. The researchers are currently analyzing the effectiveness of the medicines based on pre-specified geographical regions.

This study received funding from Merck & Co., Inc.

ASCO2019 特集

レナリドミドは多発性骨髄腫の発症を遅延させる (Abstract 8001)

レナリドミドは、前がん状態の骨髄腫が明らかな多発性骨髄腫に進展する高リスク患者におけるリスクを軽減する

Lenalidomide reduces risk that precancer myeloma will progress to overt multiple myeloma in high risk individuals

2019 ASCO Annual Meeting で発表されたランダム化第II/III相試験 E3A06 で、レナリドミドは中等度または高リスク患者におけるくすぶり型多発性骨髄腫（SMM）－前がん病態－が、がんに進展するのを有意に減少させることを明らかにした。一般的に、多発性骨髄腫においては臓器障害がみられ、これがSMMと鑑別する方法である。3年後、レナリドミドを投与されたSMM患者の87%（第II相）および91%（第III相）で病態が多発性骨髄腫に進展しなかったのに対し、この治療を受けず病態進展の可能性を経過観察のみで行った患者におけるこの割合は66% であった（第III相）。経過観察がこの疾患における現在の標準治療である。

Full Text

The phase II/III E3A06 randomized clinical trial found that lenalidomide significantly reduces the risk of smoldering multiple myeloma (SMM) – a precancerous condition – from progressing to cancer in patients at moderate or high-risk. Organ damage is typically seen in multiple myeloma, which is a way to differentiate it from SMM. At three years, in 87% (phase II) and 91% (phase III) of people with SMM receiving lenalidomide, the condition did not progress to multiple myeloma compared with 66% of people who did not receive the therapy and were just observed for potential progression (phase III). Observation is the current standard of care. The study is being presented at the 2019 ASCO Annual Meeting in Chicago.

"We typically see two types of patients – those who are anxious and want to do something to prevent cancer from developing, and those who are more cautious and are willing to watch and wait," said lead study author Sagar Lonial, MD, Chief Medical Officer at Winship Cancer Institute of Emory University, Atlanta, GA. "It's gratifying to know that especially for the first group of patients there may now be a viable treatment option."

Lenalidomide is an analog of thalidomide, a therapy developed decades ago as a sedative. Lenalidomide prevents the formation of blood vessels that can feed tumors, such as those found in multiple myeloma, and it also carries the risk of serious side effects.

A recent study looking at over 86,000 people with multiple myeloma found that 13.7% were first diagnosed as having SMM, with a median age of 67 at diagnosis. When extrapolated to multiple myeloma diagnosis data for the entire United States, this amounts to roughly 4,400 people in the United States being diagnosed with SMM each year. In only half of people diagnosed with SMM, however, the condition progresses to multiple myeloma in the first five years. Once diagnosed with multiple myeloma, the 5-year survival rate is over 50%. Survival rates have steadily increased over the last decade thanks to the availability of several new therapies.

Earlier this year, ASCO included "Identifying Strategies to Detect and Treat Premalignant Lesions" in its list of Research Priorities to Accelerate Progress Against Cancer. The findings of this trial support this critical need and help provide a new preventive therapy for patients with this precancerous condition.

The E3A06 trial enrolled people with intermediate or high-risk SMM in two phases. In phase II, 44 people received lenalidomide to assess potential efficacy. In phase III, investigators randomly assigned 182 people to a 25 mg pill of lenalidomide daily for 21 of the first 28 days of a therapy cycle, or observation, and stratified them based on whether they were diagnosed with high-risk SMM within that past year or more than a year after enrollment.

In this trial, researchers used MRIs of the spine and pelvis to detect disease at enrollment, which is more sensitive than routine x-rays, which were used in previous studies exploring interventions for SMM. A 2015 trial in Spain demonstrated that the combination of lenalidomide and dexamethasone lengthened the time before people with SMM developed multiple myeloma and extended survival.

In both the phase II and phase III trials, lenalidomide led to improved outcomes for patents with moderate and high-risk SMM.

- Progression-free survival: In phase II, after 3 years on the trial, 87% of the enrollees were alive without SMM progressing to multiple myeloma (progression-free survival). In phase III, after 1, 2, and 3 years on the trial, respective progression-free survival rates were 98%, 93%, and 91% for those who received lenalidomide and 89%, 76%, and 66%, respectively, for those who did not receive the treatment and were just observed.
- Toxicity: The proportion of people who could not tolerate lenalidomide was concerning, with 80% of people in phase II and 51% of people in phase III discontinuing the medicine due to toxicity. The most common side effects, seen in 28% of patients, included fatigue and non-blood or bone related side-effects. High-grade neutropenia was seen in about 5% of people. There was no patient-reported difference in quality of life between those who took lenalidomide and those who did not.

According to the researchers, the combined positive results of this trial and the 2015 Spanish trial may support a change in clinical practice.

"Living with the uncertainty of whether cancer will develop is very difficult, so it's exciting to be able to tell patients at high risk of multiple myeloma that they can take a pill to prevent or delay cancer. This approach is not for everyone, however, because it comes with potentially heavy side effects and costs, so watching and waiting still has clear advantages that every patient should discuss with their doctor," said ASCO President Monica M. Bertagnolli, MD, FACS, FASCO.

The investigators are currently performing an analysis of people who stopped taking lenalidomide due to toxicity to see if even limited doses of the medicine may have delayed progression to multiple myeloma. Dr. Lonial noted that a major hallmark of this trial is that it shows that intervening early can prevent patients from developing organ damage, the current criteria by which patients are defined as having myeloma.

This study received funding from the National Institutes of Health.

ASCO2019 特集

小児プレシジョン・メディシンの試験は予測を超える (Abstract 10011)

Pediatric MATCH：試験の結果、小児がんにおいて標的とされる遺伝子変異が予測を上回る高頻度で認められた

Pediatric MATCH: Trial finds more frequent targetable genetic alterations in pediatric cancers than predicted

2017年のPediatric Molecular Analysis for Therapy Choice (NCI-COG Pediatric MATCH) 試験の開始時点で、難治性がんを有する小児、青少年、および若年成人における腫瘍シーケンシングにより、試験対象の標的薬に適合する遺伝子変異が発見されるのは、スタディ参加者の10% であろうと推定された。スクリーニングされた患者400人超の中間解析の結果、適合率はそれよりもかなり高いようで、24% の患者が今回の試験対象となった薬剤の少なくとも1つを用いた治療に適合した。このスタディの最新情報が、2019 ASCO Annual Meeting で発表される。

Full Text

At the launch of the National Cancer Institute-Children's Oncology Group Pediatric Molecular Analysis for Therapy Choice (NCI-COG Pediatric MATCH) trial in 2017, it was estimated that tumor sequencing in children, adolescents, and young adults with treatment-refractory cancers would identify genetic alterations that matched an investigational targeted therapy in 10% of study participants. An interim analysis of more than 400 patients screened has revealed the match rate appears to be significantly higher, with 24% of participants eligible to receive treatment with at least one drug being tested in the trial. The first update on the study is being presented at the 2019 ASCO Annual Meeting in Chicago.

The expectation of a 10% match rate prior to the trial launch was based on experience from pediatric disease-specific research studies, the majority of which had focused on newly diagnosed pediatric cancers as opposed to treatment-refractory tumors, as well as similar adult trials, such as the NCI-MATCH study.

"Our study shows that we can successfully create a nationwide molecular screening trial for children, adolescents, and young adults with cancers that have been resistant to treatment," said COG study chair Will Parsons, MD, PhD, Associate Professor of Pediatrics-Oncology at Baylor College of Medicine in Houston, TX. "One of our key goals has been to expand access to targeted therapies for pediatric cancer patients across the country, and these early results suggest that goal is within reach."

"We're encouraged by these early results that underscore the value of public-private collaboration in understanding and treating cancers occurring in children, adolescents, and young adults," said NCI study chair Nita Seibel, MD, Head of Pediatric Solid Tumor Therapeutics in the Clinical Investigations Branch of NCI's Cancer Therapy Evaluation Program. "Pediatric MATCH depends on active partnership between NCI, COG, the U.S. Food and Drug Administration, pharmaceutical companies, and other and key pediatric cancer research stakeholders."

Precision medicine treatment approaches have not been routinely incorporated into the care of childhood cancer patients but are now being tested through trials such as Pediatric MATCH. To date, only a small number of targeted therapies have been approved for the treatment of pediatric cancer. By comparison, there are more than 150 U.S. approvals for targeted therapies in adult cancers. For these reasons, earlier this year ASCO identified "Increase Precision Medicine Research and Treatment Approaches in Pediatric Cancers" as a critical research priority.

NCI-COG Pediatric MATCH is the first nationwide pediatric precision oncology trial for patients with cancers that have not responded to standard treatments. The study seeks to identify the specific genetic alterations occurring in each patient's cancer, match patients to drugs targeted at those alterations (regardless of the cancer type), then evaluate the impact of the treatments. Study patients are first enrolled on a screening protocol in which their tumors are sequenced and any matching alterations are identified based on previous evidence linking the alterations to targeted therapies. If a match is found for a study patient, they are then offered enrollment on the corresponding Pediatric MATCH phase II treatment trial. Ten different targeted therapies are currently being studied as part of Pediatric MATCH.

As of the end of 2018, trial investigators had enrolled 422 children, adolescents, and young adults from one to 21 years of age (median age of 13 years) on the study, including patients from nearly 100 participating Children's Oncology Group sites across the U.S. This included 101 patients (24%) with brain tumors, 300 (71%) with other solid tumors, and 21 (5%) with lymphomas or histiocytic disorders, which are rare disorders affecting the immune system. Tumor samples from 390 patients were submitted for DNA and RNA sequencing of more than 160 genes in order to identify alterations that would match patients to one of the 10 targeted therapies being tested in the study. The treatments, many of which are being tested in children for the first time, included:

- Larotrectinib – targeting NTRK
- Erdafitinib – targeting FGFR
- Tazemetostat – targeting EZH2 and other SWI/SNF complex genes
- LY3023414 – targeting the PI3K/MTOR pathway
- Selumetinib – targeting the MAPK pathway
- Ensartinib – targeting ALK or ROS1
- Vemurafenib – targeting BRAF
- Olaparib – targeting defects in DNA damage repair
- Palbociclib – targeting cell cycle genes
- Ulixertinib – targeting the MAPK pathway

Tumor testing was completed for 357 patients (92%). Targetable genetic alterations – mutations, fusions or gene copy number changes targeted by one of the 10 medicines included in the trial – were identified in 112 (29%) patients, with 95 of those patients (24%) eligible to be assigned to one of 10 treatments available in the trial. As of the end of 2018, 39 patients (10%) had enrolled on a Pediatric MATCH treatment trial, with additional matched patients still eligible for treatment at a later date.

Targetable alterations were detected in more than 40% of patients with brain tumors and more than 25% of patients with the other cancer types tested (other solid tumors, lymphomas, and histiocytic disorders) demonstrating the utility of tumor screening for children with both common and rare cancers. No significant difference in detection rate was seen between younger patients (under 12 years of age) and older children, adolescents and young adults on the study.

The targetable alterations detected in Pediatric MATCH patients involved diverse cancer genes: most commonly RAS gene mutations, found in 16 patients; BRAF mutations or fusions, found in 14 patients; SMARCB1 mutations or deletions, found in 14 patients; NF1 mutations, found in 11 patients; and numerous alterations occurring in fewer than 10 patients each.

"Today we cure a large number of children with cancer, but there are still many patients needing better treatments. These results bring us one step closer to bringing the precision medicine era to pediatric cancer care. Now that we know that targetable genetic alterations are fairly common in pediatric cancers, we have an exciting opportunity to boost success rates," said ASCO President Monica M. Bertagnolli, MD, FACS, FASCO.

In addition to tumor samples, blood samples are also being sequenced as part of the study, in order to see if any of the mutations identified in each tumor are hereditary and require additional genetics evaluation for the patient and family. These results could assist doctors in informing families about cancer risk, the need for additional genetic testing, and screening strategies for cancer prevention.

Pediatric MATCH is anticipated to enroll at least 1,000 patients. Study investigators plan to continue to add new targeted therapies to the trial in an attempt to further increase the number of patients who could be matched to drug treatments on the study – protocols for four additional drugs are currently under development. Strategies for future adaptations of the trial may include testing combinations of drugs as well as immunotherapies, and optimized plans for molecular testing and assignment of patients to study treatment arms.

This study is sponsored by and received funding from the National Cancer Institute, part of the National Institutes of Health.

ASCO2019 特集

転移性前立腺がんの新たな治療選択 (Abstract LBA2)

ENZAMET：標準治療にエンザルタミドを併用することにより転移性ホルモン感受性前立腺がん男性の生存率が改善する

ENZAMET: Adding enzalutamide to standard treatment improves survival for men with metastatic hormone-sensitive prostate cancer

標準治療にアンドロゲン受容体阻害薬であるエンザルタミドを併用した場合、従来の非ステロイド性抗アンドロゲン薬（NSAA）併用に比べ、転移性ホルモン感受性前立腺がん男性に対する有効性は高い、と2019 ASCO Annual Meeting で発表され、同時に *New England Journal of Medicine* に掲載された。第III相 ENZAMET 試験の中間解析の結果、エンザルタミドを投与された患者においてはその他のNSAAを投与された患者に比べ、死亡リスクが33% 低下したことが示された。重篤な有害事象の発現は、エンザルタミド群の42% に対し、NSAA群では34% であった。

Full Text

An interim analysis of the international randomized, phase III ENZAMET trial found that 80% of men with metastatic hormone-sensitive prostate cancer (mHSPC) who received the non-steroidal anti-androgen (NSAA) medicine enzalutamide along with the standard of care treatment were alive after 3 years compared with 72% of men who received other NSAAs along with standard treatment (p=0.0016). The study was led by the Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group.

The findings from this late breaking clinical trial were presented in the Plenary Session at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting and simultaneously published in the *New England Journal of Medicine*.

"Physicians and patients with prostate cancer now have a new treatment option with enzalutamide, and this is especially relevant for men who cannot tolerate chemotherapy and have a lower burden of disease seen on scans," said study co-chair Christopher Sweeney, MBBS, a medical oncologist at the Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA.

"In men with metastatic prostate cancer starting testosterone suppression, enzalutamide and docetaxel are both active and are reasonable alternatives but have different side effects, costs, risks, and benefits," said study co-chair Ian D. Davis, PhD, Monash University Eastern Health Clinical School in Melbourne, Australia.

Metastatic HSPC is initially treated with surgical removal of the testes or injection with a hormone analogue to reduce the blood levels of androgens. Depending on the situation, other treatments can be added as well, including abiraterone, another hormone treatment that decreases non-testicular male hormones, or docetaxel chemotherapy. If the cancer continues to progress, additional hormone treatments and chemotherapy are used, and these can also improve longevity.

The study found that enzalutamide is a more effective inhibitor of the androgen receptor than bicalutamide, nilutamide, or flutamide, the comparison standard NSAAs used in the trial, but it can lead to different side effects.

Men with mHSPC were randomly assigned between March 2014 and March 2017 to receive an injection of a testosterone-suppressing medicine (such as goserelin, leuprolide, or degarelix) with either a 160-milligram enzalutamide pill daily or one of three standard NSAAs: bicalutamide, nilutamide, or flutamide. Of the 1,125 men enrolled in the trial, 503 men received early doses of docetaxel and 602 did not. Men were followed for a median of 34 months.

After 3 years, 80% of men with metastatic hormone-sensitive prostate cancer who received enzalutamide along with testosterone suppression, with or without early docetaxel, were alive compared with 72% of men who received one of the other three NSAAs in the trial. Overall, there was a 33% decrease in the risk of death in men receiving enzalutamide compared to those who took an NSAA.

Researchers further analyzed the data to identify the impact of enzalutamide in key groups at the 3-year mark:

- Of 596 men with a higher amount of disease on imaging scans, 71% taking enzalutamide were alive compared with 64% taking another NSAA.
- Of 529 men with a low amount of disease on imaging scans, 90% taking enzalutamide were alive compared with 82% taking another NSAA.
- The increase in survival with enzalutamide was most obvious in men who did not receive docetaxel: among patients who received enzalutamide without docetaxel, 83% were alive compared with 70% taking another NSAA.
- 64% of men were still taking enzalutamide compared with 36% of men taking another NSAA at the time of the first analysis of the data.
- Serious adverse events occurred in 42% of men taking enzalutamide compared with 34% of the men taking one of the other NSAAs.

Dr. Sweeney noted that a survival benefit is not seen with docetaxel in men with a low volume of disease, but that enzalutamide does improve survival in these men. Enzalutamide is a new option for men with metastatic hormone-sensitive prostate cancer and is superior to current standard therapy.

"We see here that giving enzalutamide early can offer worthwhile benefits, especially for certain groups of men. In addition to helping men live longer overall, this approach means they can also likely go longer without having to take steroids or receive chemotherapy," said ASCO Expert Neeraj Agarwal, MD.

The results from this trial are being compiled with results from other similar trials so that researchers have a dataset that includes over 10,000 men. With that large dataset at hand, researchers hope to be able to make extensive comparisons between medicines and determine which might benefit specific groups of men the most, according to Dr. Sweeney.

ENZAMET is a global collaborative investigator-initiated trial led by ANZUP Cancer Trials Group and sponsored by the University of Sydney, in collaboration with Canadian Cancer Trials Group, Dana-Farber Cancer Institute, and Cancer Trials Ireland (enrolling patients from Ireland and the United Kingdom).

Astellas Pharma provided drug and financial support but was not involved in study conduct or data analysis. ANZUP receives infrastructure funding from the Australian Government through Cancer Australia.

ASCO2019 特集

肝転移において低侵襲がん手術は有効である (Abstract LBA3516)

OSLO-COMET：肝転移を有する大腸がん患者の生存期間は腹腔鏡手術と開腹術とで同等である

OSLO-COMET: Colorectal cancer patients with liver metastases live just as long after laparoscopic surgery as open surgery

ランダム化OSLO-COMET 試験の結果、大腸がん患者の肝転移巣切除にあたり、腹腔鏡手術は開腹術に比べ生存期間は同等であることが示された、と2019 ASCO Annual Meeting で発表された。全体として、腹腔鏡手術または開腹術にかかわらず、術後患者は6.5年超生存した（p=0.91）。腹腔鏡手術群における無再発生存期間中央値は19か月であり、開腹術群では16か月であった。患者は腹腔鏡手術後に健康関連のQOL が改善したと報告し、また術後合併症も少なかった（腹腔鏡手術19% 対開腹術31%）。

Full Text

The randomized OSLO-COMET trial found that laparoscopic surgery did not change chances of survival, when compared to open surgery, to remove metastases that had spread to the liver in patients with colorectal cancer. Overall, patients lived more than 6.5 years after surgery, regardless of whether it was laparoscopic or open (P=0.91).

The study was presented as a late breaking clinical trial at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting.

"Laparoscopic liver surgery not only had a lower rate of post-operative complications, an improved quality of life, and was cost-effective, compared to open liver surgery, it also had life expectancies that are similar to open surgery," said lead study author Åsmund Avdem Fretland, MD, Surgeon in the Intervention Centre and the Department of HPB Surgery at Oslo University Hospital, Norway. "After many years of improvements in laparoscopic surgery, we now have results showing that survival is as good with this procedure as with open surgery, and morbidity is lower, so we expect that this will cause a shift to even more operations on the liver being done laparoscopically," noted Bjørn Edwin, MD, PhD, Intervention Centre and the Department of HPB Surgery at Oslo University Hospital, Norway, who is leading the research effort.

The first report of laparoscopic liver surgery was in 1991, with several other reports worldwide occurring shortly thereafter. The use of laparoscopic surgery has become more common, but until this study, no one had looked at long-term outcomes in cancer that has metastasized to the liver in a randomized trial, according to the researchers.

The surgeons in this study had extensive training in laparoscopic liver surgery. Open surgery is considered a good option if a surgeon does not have sufficient training for laparoscopy.

From February 2012 to January 2016 the investigators randomly assigned 280 colorectal cancer patients with liver metastases to either laparoscopic surgery or open surgery. The operations were performed with a liver sparing technique, which means that the surgeons removed only the tumors and a minimal amount of surrounding liver tissue. One-hundred and thirty-three people received laparoscopic surgery, while 147 people had open surgery. About half of the patients received chemotherapy before or after their surgery, following standard Norwegian guidelines, which included the use of chemotherapy medicines 5-fluorouracil plus leucovorin and oxaliplatin.

Based on ongoing outcomes (patients who were enrolled in 2015-2016 have not yet been observed for 5 years), the researchers found the following comparable, non-statistically significant results:

- People who had the laparoscopic procedure lived a median of 80 months after surgery compared to 81 months for those who had open surgery.
- For people who had a laparoscopic procedure, median recurrence-free survival was 19 months compared to 16 months for those who had open surgery.
- After a minimum of 3 years of follow-up (the last patients were enrolled in early 2016), the researchers were able to estimate that 56% of people who had open surgery would be alive 5 years after their procedure compared to 57% of those who had a laparoscopic procedure.
- An estimated 31% of people who had open surgery would have no recurrence of disease 5 years later compared to 30% of those who had laparoscopy.

When looking solely at the surgical process, there was no difference between the groups in terms of the rate of complete tumor removal, or the amount of tissue removed beyond the observable tumor.

Patients reported improved health-related quality of life after laparoscopy, which also had less post-operative complications (19% with laparoscopy vs. 31% with open surgery). The researchers found that the monetary costs for either type of surgery were comparable, however, differences in costs may vary in other countries.

"Minimally invasive laparoscopic surgery is becoming more common for many types of solid tumors in the abdomen as patients have a less complicated, faster recovery. However, for technically challenging operations such as liver surgery, concerns regarding long-term survival from cancer remain. This study is the first to show that laparoscopic surgery is just as effective long-term as open surgery for patients undergoing removal of colorectal cancer that has spread to the liver, which should give patients confidence when choosing between these options. The experience of your surgeon with these techniques is key," said ASCO Expert Nancy N. Baxter, MD.

Dr. Fretland and colleagues are now using artificial intelligence, genetic, and digital-image analyses to parse results from the study so that they can improve the diagnosis and treatment of future patients. They plan to explore new aspects of minimally invasive liver surgery, including enrolling patients in multicenter randomized trials to examine other types of liver operations. The researchers are also exploring ablation of liver tumors using heat to kill cancer cells.

This study received funding from South-East Norway Regional Health Authority.

ASCO2019 特集

ペムブロリズマブは非小細胞肺がん患者の生存率を上昇させる(Abstract LBA9015)

KEYNOTE-001:進行非小細胞肺がんに対するペムブロリズマブの効果を調査したスタディにおいて、PD-L1の高発現は生存期間が最長であることの予測因子であった

KEYNOTE-001: Higher levels of PD-L1 expression predict longest survival in study of pembrolizumab for advanced non-small cell lung cancer

第Ib相KEYNOTE-001試験の5年間データから、ペムブロリズマブは安全かつ有効であり、進行非小細胞肺がん（aNSCLC）の全生存率を大幅に上昇させることが示された。特に、化学療法の前治療歴のない患者の23.2% および化学療法の前治療歴のある患者の15.5% が5年後に生存しており、最も有益性が認められたのはPD-L1の高発現患者であった。これは、aNSCLC の5年生存率が平均5.5% であった免疫療法以前の時代から、著明に改善したことを示している。このスタディ結果は2019 ASCO Annual Meeting で発表され、*Journal of Clinical Oncology* に掲載される。

Full Text

Five-year data from the phase Ib KEYNOTE-001 clinical trial show that pembrolizumab was safe and effective and substantially increased overall survival for advanced non-small cell lung cancer (aNSCLC). Specifically, 23.2% of people who had not previously been treated with chemotherapy and 15.5% of previously-treated patients were alive after five years, with the greatest benefit observed in patients with higher PD-L1 expression. This represents a marked improvement over 5-year survival rates from the pre-immunotherapy era, which averaged 5.5% for aNSCLC. This is the longest follow-up study to date of people with aNSCLC treated with pembrolizumab, according to the researchers.

The study was featured at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting and is in press with the *Journal of Clinical Oncology*.

"The uniformly negative outlook that has been associated with a diagnosis of advanced non-small cell lung cancer is certainly no longer appropriate," said lead study author Edward B. Garon, MD, MS, Associate Professor of Medicine at UCLA, Los Angeles, CA. "The fact that we have patients on this trial that are still alive after 7 years is quite remarkable. We also have evidence that most patients who are doing well after 2 years on pembrolizumab live for 5 years or more."

Pembrolizumab binds to a protein on the surface of T cells called PD-1. PD-1 binds to ligands including PD-L1, inhibiting an immune response. By blocking PD-1, pembrolizumab activates T cells to attack tumor cells.

In 2011, when KEYNOTE-001 began enrollment, immunotherapy treatments were not widely available, so most participants had previously been treated with systemic medicines, or targeted therapies. There were 550 people with aNSCLC in the trial, including 101 patients who had not previously received any treatment and 449 patients who had received prior treatment. All patients received 2 mg/kg of their body weight of pembrolizumab every 3 weeks or 10 mg/kg every two or three weeks. In recent years, however, the protocol was changed to a single dose of 200 mg regardless of body weight every 3 weeks, the typical regimen in clinical practice.

Patients were followed for a median of 60.6 months, or about 5 years. At that point, 18% of enrollees (100 participants) were still alive. Of those who had not received prior treatment, 23% were still alive after 5 years compared with 15.5% of those previously treated.

Researchers observed that higher levels of PD-L1 expression predicted longest survival. Specifically:

- In previously untreated people, 29.6% with PD-L1 expression of 50% or more were alive after 5 years compared with 15.7% with expression levels below 50%.
- In people who had been previously treated, 25% who had PD-L1 expression levels of 50% or more were alive after 5 years compared with 12.6% with expression levels between 1 to 49%. Only 3.5% of people with expression levels below 1% were alive after 5 years.

Among people receiving pembrolizumab after undergoing previous treatment, 42% had responses that lasted for a median of 16.8 months. For those who received pembrolizumab as initial therapy, 23% had responses that lasted a median of 38.9 months.

Immune-related toxic side effects occurred in 17% of enrollees. The most common side effect was hypothyroidism, where the immune system attacks the body's thyroid glands. The most serious side effect seen was pneumonitis, an inflation of lung tissue, but that was not very common.

"These data are similar to what we have seen in other cancers treated with immunotherapy in that there are a population of patients who can live for five years or more. It's truly remarkable that for more patients than ever before, we no longer have to count survival in months. However, we still have a long way to go to improve outcomes for all advanced NSCLC patients. We look forward to more research helping us determine how to identify these patients," said ASCO Expert David L. Graham, MD, FACP, FASCO.

Dr. Garon noted that the researchers will try refining their understanding of which patients received the most benefit from pembrolizumab as well as identifying impediments that prevent the immune system from destroying tumors so that these mechanisms could also be combatted. The investigators hope to explore possible combination therapies of pembrolizumab with conventional or other immunotherapies.

This study received funding from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

"While poor fitness is already known to predict future cardiovascular disease, this is the first study to explore fitness as a marker of future cancer risk prognosis," said lead study author Susan Lakoski, M.D., assistant professor of medicine at the University of Vermont. "This finding makes it clear that patients should be advised that they need to achieve a certain fitness level, and not just be told that they need to exercise. And unlike exercise behavior, which relies on patient self-reporting, fitness can be objectively and accurately measured in a clinical setting."

The study included 17,049 men who had a single cardiovascular fitness assessment as part of a specialized preventive health check-up visit at a mean age of 50 years offered at the Cooper Institute. The fitness test, which is similar to a stress test for heart disease risk, entailed walking on treadmill under a regimen of changing speed and elevation. The men's performance was recorded in established units of fitness called metabolic equivalents or METs. Study participants were divided into five quintiles according to their fitness performance.

Researchers subsequently analyzed Medicare claims data to identify the participants of this study who had developed lung, colorectal, or prostate cancer – the three most common types of cancer among U.S. men. Over a median follow-up period of 20-25 years, 2,332 men were diagnosed with prostate cancer, 276 were diagnosed with colorectal cancer, and 277 were diagnosed with lung cancer. There were 347 deaths due to cancer and 159 men died of cardiovascular disease.

Researchers found that the risk of being diagnosed with lung or colorectal cancer was reduced by 68 and 38 percent, respectively, in men who were the most fit, relative to those who were the least fit. Fitness did not significantly impact prostate cancer risk. In the analysis, data were adjusted for smoking and other factors, such as body mass index and age.

Among the men who developed cancer, those who were more fit at middle age had a lower risk of dying from all the three cancers studied, as well as cardiovascular disease. Even a small improvement in fitness (by 1MET) made a significant difference in survival – reducing the risks of dying from cancer and cardiovascular disease by 14 and 23 percent, respectively.

Another interesting finding was that men who had low fitness had an increased risk of cancer and cardiovascular disease even if they were not obese. This suggests that patients should focus on improving their fitness, regardless of their body weight. Adequate fitness level depends on gender and age. In this study, men who fell in the lowest quintile for fitness achieved less than 13.5 minutes during the treadmill exercise test if they were 40-49 years old, less than 11 minutes if they were 50-59, and less than 7.5 minutes if they were 60 or older.

ASCO Perspective: "This important study establishes cardiorespiratory fitness as an independent and strong predictor of cancer risk and prognosis in men. While more research is needed to determine if similar trends are valid in relation to other cancers and among women, these results indicate that people can reduce their risk of cancer with relatively small lifestyle changes," said ASCO President Sandra M. Swain, M.D., FACP.

This research was supported by the National Cancer Institute

ASCO2019 特集

オラパリブはBRCA変異を有する膵臓がんの増悪を遅延させる(Abstract LBA4)

POLO：PARP阻害薬オラパリブを用いた維持療法はBRCA変異を有する膵臓がんの増悪を遅延させる

POLO: Maintenance therapy with PARP inhibitor olaparib delays progression of BRCA-related pancreatic cancer

2019 ASCO Annual Meeting で発表された第III相POLO試験の結果、PARP阻害薬オラパリブを用いた維持療法により、プラセボに比べ、BRCA 遺伝子変異を有する転移性膵臓がん患者の増悪が著明に遅延することが明らかにされた。一次治療であるプラチナ製剤ベースの化学療法終了後、疾患が増悪しなかった患者に対しオラパリブが投与された。オラパリブはプラセボに比べ、疾患増悪リスクを47% 減少させた（ハザード比=0.53）。無増悪生存期間中央値はオラパリブ群で7.4か月、不使用群で3.8か月であった。2年後、オラパリブ投与患者の22.1% において疾患の増悪を認めず、一方、プラセボ投与患者におけるその割合は9.6% であった。

Full Text

The randomized, phase III POLO trial found that maintenance therapy with the PARP inhibitor olaparib significantly delayed the progression of metastatic pancreatic cancer in patients with BRCA gene mutations compared with placebo (median progression-free survival: 7.4 months vs. 3.8 months, respectively). In the trial, olaparib was administered to patients with cancer that had not progressed after completion of initial platinum-based chemotherapy, and after two years, 22.1% of people receiving olaparib had no disease progression vs. 9.6% for those treated with placebo. While overall survival data are not yet mature, this is a significant advance given that the median survival of metastatic pancreatic cancer is currently less than one year.

The findings from this late breaking clinical trial were presented in the Plenary Session at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting.

"POLO is the first phase III randomized study to establish a biomarker-driven approach in the treatment of metastatic pancreatic cancer, and it opens the door to a new era of personalized care for this difficult-to-treat cancer," said lead study author Hedy L. Kindler, MD, FASCO, Professor of Medicine, University of Chicago Medicine. "Roughly one in five patients responded to olaparib for a median of two years, which is truly remarkable for metastatic pancreatic cancer. For patients with BRCA-driven metastatic pancreatic cancer, we may be seeing a change in patients' disease trajectory."

Olaparib is a targeted therapy that inhibits PARP enzymes, which are important in DNA transcription and repair. Germline BRCA mutations are inherited and are known to increase the chances of developing several other cancers, including ovarian, breast, and prostate cancer. Previous phase III studies have to date shown the benefit of olaparib in other BRCA-driven cancers (ovarian, breast). About 5% to 6% of pancreatic cancers are caused by mutations in one or both BRCA genes.

In January 2019, ASCO issued a Provisional Clinical Opinion (PCO) recommending that people with pancreatic cancer undergo risk assessment for hereditary syndromes that increase pancreatic cancer risk. The PCO also states that germline genetic testing for cancer susceptibility – including testing for BRCA mutations – may be discussed with individuals diagnosed with pancreatic cancer, even if family history does not clearly suggest an inheritable cancer-related syndrome.

The current trial builds on phase II data from a 2015 trial finding 22% response rates in pancreatic cancers with BRCA1/2 gene mutations treated with olaparib, following chemotherapy with gemcitabine. The POLO trial examined if olaparib could delay disease progression after 16 weeks or more of initial platinum-based chemotherapy. Toxicities to platinum-based chemotherapy often increase the longer they are taken, so some people stop the medicines after 16 weeks. The use of an oral, non-chemotherapeutic medicine with lower toxicities, such as olaparib, would provide an important option, according to the authors.

After screening 3,315 people with pancreatic cancer, the investigators identified 247 with germline BRCA mutations. The researchers randomly assigned 154 patients on a 3:2 basis, with 92 people assigned to olaparib and 62 assigned to placebo. Treatment started 4 to 8 weeks after a patient's last dose of platinum-based chemotherapy. The median duration of treatment was 6 months for those taking olaparib and 3.7 months for people who received a placebo.

Enrollees were a median age of 57; 58% of the people who received olaparib were men and equal numbers of men and women received placebo. Two-thirds of those enrolled had BRCA2mutations, and the remainder had BRCA1 mutations.

Patients were initially evaluated for disease progression every 8 weeks, then subsequently for 40 weeks, and every 12 weeks thereafter. At 6, 12, 18, and 24 months after the investigators randomly assigned people to a treatment, those who received olaparib were at least twice as likely to have no disease progression compared with those who received placebo.

Olaparib reduced the risk of disease progression by 47% (Hazard ratio = 0.53) compared with those getting a placebo. The median progression-free survival for patients receiving olaparib was 7.4 months, compared with 3.8 months for patients who received a placebo. After one year, 33.7% of patients receiving olaparib showed no signs of disease progression compared with 14.5% of those who received a placebo. After two years, 22.1% of people receiving olaparib had no cancer progression compared with 9.6% of those receiving a placebo.

Serious side effects (grade 3, 4, or 5) occurred in 40% of people taking olaparib compared with 23% of those taking a placebo. In addition, 5.5% of those taking olaparib and 1.7% of those on placebo discontinued treatment due to toxicity. Olaparib was well tolerated and there was no difference in quality of life between those taking olaparib and placebo.

"We are eagerly awaiting longer-term data to understand the full impact of the results from this trial. It's encouraging to see that olaparib is consistently delaying the progression of metastatic pancreatic cancer in patients with a BRCA mutation. We're potentially on the cusp of a new age of treatment for pancreatic cancer, where for the first time we can tailor therapy based on a biomarker and where having a BRCA mutation opens up more treatment options," said Suzanne Cole, MD.

Dr. Kindler notes that the results of this trial are likely practice-changing. The long-term goal is to demonstrate the utility of olaparib in pancreatic cancer beyond the patients who benefitted from the medicine in the POLO trial.

This study received funding from AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

ASCO2019 特集

新たな治療法は進行尿路上皮がんに対し有効である(Abstract LBA4505)

新たな分子標的抗体治療は進行尿路上皮がん患者の約半数に有効性を発揮した

Novel targeted-antibody treatment produced responses in nearly half of patient with advanced urothelial cancer

単一群第II相臨床試験の結果、尿路上皮がんの97% に認められるネクチン-4を標的とした新たな薬剤enfortumab vedotin（EV）が、局所進行または転移性尿路上皮がん患者の44% において奏効し、うち12% は完全奏効であったことが示された。患者はプラチナ製剤による化学療法およびPD-1 またはPD-L1 免疫チェックポイント阻害薬の治療歴を有していた。免疫チェックポイント阻害薬が奏効しなかった患者の41% 、および肝転移を来した患者の38% においてEV が奏効した。このスタディ結果は2019 ASCO Annual Meeting で発表された。

Full Text

A single arm, phase II clinical trial of 125 patients showed treatment with enfortumab vedotin (EV) – a new agent targeting Nectin-4, a protein found in 97% of urothelial cancers – produced responses in 44% of patients with locally advanced or metastatic forms of urothelial cancer. Patients had previously been treated with platinum chemotherapy and a PD-1 or PD-L1 immune checkpoint inhibitor, but the cancer had progressed despite these treatments.

The study was featured at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting.

"These phase II results replicate the phase I results very closely, which is not often the case in clinical trials," said lead study author Daniel P. Petrylak, MD, a Professor of Medicine (Medical Oncology) and Urology at Yale Cancer Center, New Haven, CT. "The fact that we have a therapy that can help people who don't benefit from checkpoint inhibitors is very gratifying."

Urothelial cancer includes cancer of the bladder (90% of cases), the urethra, ureters, renal pelvis, and a few other adjacent organs. After a locally advanced or metastatic urothelial cancer diagnosis, patients are usually treated first with platinum-based chemotherapy. If their disease progresses, second-line therapy is a checkpoint inhibitor, an immunotherapy that works to modulate immune responses, thereby allowing T cells to attack cancer cells.

There are five checkpoint inhibitors approved for use in urothelial cancer: pembrolizumab, atezolizumab, durvalumab, nivolumab, and avelumab. However, cancer progresses in 75-80% of people with advanced urothelial cancer who receive an immune checkpoint inhibitor. There is no remaining approved standard of care treatment option for this cancer if it progresses after immunotherapy has been used.

Phase I trial results of EV provided sufficient evidence that it was safe to administer.

For phase II, investigators enrolled urothelial patients who had been treated with platinum-based chemotherapy and/or checkpoint inhibitors to two groups: group one had been previously treated with both medicines, and group two consisted of people who had not received platinum chemotherapy. Only results from the first group are currently being reported.

In group one, 70% of enrollees were male and the median age was 69; 35% of people had cancers in their upper urinary tract, a relatively uncommon site; and enrollees had a median of three prior systemic treatments in the locally advanced or metastatic setting but had not received treatment for at least two weeks prior to enrolling in this trial.

Forty-four percent of people responded to EV resulting in either no growth or shrinkage in their tumors, and 12% had a complete response with no detectable sign of cancer. The median overall survival time was 11.7 months.

Among those patients with cancer that had not responded to a checkpoint inhibitor, 41% responded to EV, and 38% of people with cancer that had metastasized to the liver responded to EV.

EV was well-tolerated among patients enrolled in the trial. The most common side effects included fatigue (50%), alopecia (49%), and decreased appetite (44%).

"If advanced urothelial cancer progresses following treatment with platinum-based chemotherapy and immunotherapy with checkpoint inhibitors there are no FDA approved treatment options. Although this is a small, phase II trial, the anti-tumor activity demonstrated in patients whose disease progressed on chemotherapy and immunotherapy is promising, we await larger studies to confirm these early findings." said ASCO Expert Robert Dreicer, MD, MS, MACP, FASCO.

A phase III study to confirm these findings is now underway. Group two is still enrolling people in the trial, and there is also a trial in progress to look at the benefits of providing EV for people newly diagnosed with advanced urothelial cancer. The trial is studying EV in combination with pembrolizumab, and EV in combination with a platinum-based chemotherapy.

This study received funding from Seattle Genetics and Astellas Pharma.

ASCO2019 特集

新しいクラスの薬剤は進行前立腺がん患者において有効である(Abstract 5006)

TITAN：転移性前立腺がん患者において新薬が強力な結果をもたらした

TITAN: New drug for men with metastatic prostate cancer yields strong result

転移性去勢感受性前立腺がん患者に対しapalutamide を用いた治療は、標準治療に比べ、全生存率を有意に改善し死亡リスクを33% 減少させた（p=0.0053）。Apalutamide はX線画像上の疾患増悪を有意に遅延させ、化学療法開始までの期間は有意に改善した。第III相TITAN 試験は、ドセタキセル投与歴を有する、腫瘍量の多いおよび少ない患者を対象とした。その結果、解析された全ての群において有益性が認められた。これらの早期結果に基づき、独立データモニタリング委員会は、全ての患者がapalutamide と標準治療の併用を受けられるよう、非盲検とするように勧告した。このスタディ結果は2019 ASCO Annual Meeting で発表され、*New England Journal of Medicine* に掲載された。

Full Text

First results of a phase III international clinical study called TITAN, which evaluated the effectiveness and safety of a new drug, apalutamide, to treat metastatic castration-sensitive prostate cancer were presented at the 2019 American Society of Clinical Oncology Annual Meeting. Researchers found that treatment with apalutamide significantly improved overall survival, with a 33% reduction in risk of death compared to standard-of-care therapy (P=0.0053). Additionally, this study showed apalutamide significantly delayed radiographic disease progression (P<0.0001) and time to initiation of chemotherapy was improved (P<0.0001).

The study was published in the *New England Journal of Medicine* at the time of presentation.

The study was led by Kim Chi, MD, medical oncologist with the British Columbia Cancer Agency and associate director of clinical research at the Vancouver Prostate Centre in Canada. Neeraj Agarwal, MD, a prostate cancer physician-scientist at Huntsman Cancer Institute (HCI) and professor of medicine at the University of Utah (U of U), was member of the international steering committee for the trial and the second author on the publication. The trial included participation of 230 institutions worldwide and enrollment of more than 1,000 patients on the trial.

According to Chi, "This is a major study that showed, for the first time, significantly improved overall survival and delay of disease progression with this novel class of drugs known as 'potent and direct androgen receptor inhibitor' in men with advanced prostate cancer." Chi and Agarwal believe the results of this study may change the way a vast majority of men with advanced prostate cancers are treated.

This study was built upon prior evaluations of apalutamide. The aim was to conduct a large-scale assessment of apalutamide when used in combination with the standard-of-care treatment for men with prostate tumors that have metastasized. Apalutamide belongs to a class of drugs that inhibit the normal function of androgens like testosterone. These drugs act by blocking androgen receptors.

Prostate cancer is the second leading cause of cancer death in men. While survival is nearly 100% for men with early stage prostate cancers, the five-year survival rate for men with prostate tumors that have metastasized is only 30%, according to the American Cancer Society. Men with advanced forms of prostate cancer are typically treated with drugs that work to significantly lower testosterone levels, which slows disease progression. This study evaluated the combination of apalutamide plus the testosterone-reducing drugs.

Agarwal worked with colleagues from five continents to coordinate the sophisticated scientific review necessary to evaluate study results. Patients who received apalutamide plus standard-of-care therapy had significantly improved outcomes versus patients who only received the testosterone-reducing drug. After reviewing the early results, an independent data monitoring committee recommended that all participants in the study receive apalutamide plus the standard treatment.

Before apalutamide, other strategies to improve the survival rates for prostate cancer patients included chemotherapy and abiraterone, a drug that blocks testosterone production by prostate cancer cells, alongside long-term treatment including steroids. "With the potential approval and availability of apalutamide, we may have an option that will allow us to avoid the side effects of chemotherapy and long-term steroid use in our patients with advanced prostate cancer," said Agarwal.

This research was supported by the National Cancer Institute and by Huntsman Cancer Foundation. The study was sponsored by Aragon Pharmaceuticals and Janssen Research & Development, LLC.

ASCO2019 特集

新たなデータは若年乳がん患者における術後補助療法のガイドとなる(Abstract 503)

TAILORx：閉経前女性の乳がん再発予防目的の術後補助療法に関する新たな情報

TAILORx: New information about adjuvant therapy to prevent recurrence of breast cancer in premenopausal women

若年女性の乳がん再発リスクを、典型的な臨床像（腫瘍サイズおよび組織学的グレード分類）に基づき評価することにより、21-遺伝子アッセイによる再発スコア（RS）に補完的な予後情報が追加される、と2019 ASCO Annual Meeting で発表され、*New England Journal of Medicine* に掲載された。TAILORx試験の研究者らは、RSの結果が16～20で50歳以下の女性は臨床的にリスクが低く化学療法の必要性がない、と述べている。このことはまた、より効果的な抗エストロゲン療法でベネフィットを得られる若年女性を同定するのにも役立つ可能性がある。

Full Text

New information about adjuvant therapy to prevent recurrence of breast cancer in women 50 years of age or younger, or premenopausal, emerged from the landmark Trial Assigning IndividuaLized Options for Treatment (Rx), or TAILORx. An analysis of a pre-specified secondary endpoint in this largest-ever breast cancer treatment trial found that an assessment of a woman's recurrence risk based on classic clinical features (tumor size and histologic grade) adds prognostic information that is complementary to the 21-gene Recurrence Score (RS) test. Integration of the RS with clinical risk may help identify more young women who may be spared chemotherapy than originally reported. It may also help identify young women who stand to benefit from more effective anti-estrogen therapy. The analysis was published in the *New England Journal of Medicine* and presented at the 2019 meeting of the American Society of Clinical Oncology.

The new findings complement the original, definitive TAILORx conclusion reported last year, that 70 percent of women with the most common type of breast cancer; that is, hormone receptor (HR)-positive, HER2-negative, axillary lymph node-negative breast cancer, can forego chemotherapy when guided by the RS. The trial was supported by the National Cancer Institute, part of the National Institutes of Health, and designed and led by the ECOG-ACRIN Cancer Research Group.

"Last year's TAILORx results gave clinicians high-quality data to inform personalized treatment recommendations for women," said lead author Joseph A. Sparano, M.D., associate director for clinical research at the Albert Einstein Cancer Center and Montefiore Health System in New York City and vice chair of the ECOG-ACRIN Cancer Research Group. "With this new analysis, it is clear that women ages 50 or younger with a Recurrence Score result between 16 and 20 and at low risk clinically, do not need chemotherapy. Furthermore, the integration of the Recurrence Score with clinical risk information could identify premenopausal women with higher clinical risk who may benefit from ovarian function suppression and more aggressive anti-estrogen therapy."

The objective of the pre-specified secondary analysis was to evaluate whether clinical risk provides additional prognostic or predictive information to the RS results. Of 9,427 women in TAILORx with a RS and clinical risk information, 70 percent were determined to be low clinical risk (LCR: tumor ≤3 cm and low grade, <2 cm and intermediate grade, or ≤1 cm and high grade) and 30 percent were identified as high clinical risk (HCR: not meeting low clinical risk criteria). While clinical risk provided additional prognostic information across all RS groups, disease free survival and distant recurrence free interval rates were similar with and without chemotherapy in the entire RS 11-25 group irrespective of clinical risk.
For the overall population, clinical risk alone was not predictive of chemotherapy benefit. This was also true for the two-thirds of women who were over the age of 50. For the remaining women aged 50 or younger, there was trend favoring chemotherapy irrespective of clinical risk, though not significant. This finding is consistent with the treatment interaction originally reported, between age/menopausal status, RS, and chemotherapy benefit.

Researchers studied the association between age at diagnosis and chemotherapy benefit in the group of younger women (age 50 or less) in TAILORx with a RS of 16-25. This group was of particular interest because they were part (14 percent) of the 30 percent of women in the original TAILORx findings for whom it was suggested that chemotherapy may be considered. Researchers sought to determine whether integration of RS and clinical information would help define this group. They found there was no benefit from chemotherapy for younger women (age 50 or less) with a RS of 16-20 and at low risk, clinically.

Researchers then explored the association between age at diagnosis and chemotherapy benefit in this group, to determine if integration of RS and clinical risk could help identify premenopausal women who might stand to benefit from more effective anti-estrogen therapy. In the original TAILORx report, researchers noted that it was unclear if the modest chemotherapy benefit seen in this group was due to a cytotoxic effect in eradicating micrometastatic disease, a castration effect in inducing early menopause, or both. Integration of RS and clinical risk found a benefit for women aged 46-50 years who were premenopausal but not postmenopausal, and a trend toward chemotherapy in women aged 41-45 years, but no benefit in women aged 40 years or under who are less likely to develop premature menopause from chemotherapy. In addition, there was no consistent effect favoring chemotherapy in older women. Taken together, these findings suggest that the chemotherapy benefit observed for the RS 16-25 group may be due to a castration effect associated with cytotoxic therapy.

Based on evidence from several prior studies, the 21-gene expression assay (Oncotype DX Breast Recurrence Score®) is widely used to provide prognostic information about the risk of breast cancer recurrence within 10 years, and to predict which patients are most likely to derive a large benefit from chemotherapy. The test is performed on a tumor biopsy sample. Women with a low score (0-10) typically receive only hormone therapy and those with a high score (26-100) receive hormone therapy and chemotherapy.

ASCO2019 特集

ビタミンDはがん関連死を減少させる (Abstract 1534)

ビタミンDを3年以上摂取することは、がん患者に延命効果をもたらす可能性がある

Vitamin D taken three years or more could help cancer patients live longer

ビタミンDは単に骨の健康に寄与するだけでなく、重要なベネフィットをもたらすようである、と2019 ASCO Annual Meeting で発表された。少なくとも3年間摂取することで、ビタミンDはがん患者の生存期間を延長するのに役立つことが、試験の結果示された。研究者らは、79,000人超（平均年齢68.07歳、女性78.02%）の疾患予防に関するデータを調査した。ビタミンDはプラセボに比べ、がん関連死を有意に減少させた（p=0.05）。ビタミンDはプラセボに比べ、がん罹患率の有意な減少とは関連がなかった（p=0.46）。

Full Text

Michigan State University physicians have found that vitamin D, if taken for at least three years, could help cancer patients live longer. The findings suggest that the vitamin carries significant benefits other than just contributing to healthy bones and were presented at the American Society of Clinical Oncology annual meeting on June 3, 2019.

"Vitamin D had a significant effect on lowering the risk of death among those with cancer, but unfortunately it didn't show any proof that it could protect against getting cancer," said Tarek Haykal, a lead author on the study and an internal medicine resident physician at Michigan State University and Hurley Medical Center in Flint, Michigan.

The researchers looked at data related to disease prevention from more than 79,000 patients in multiple studies that randomly compared the use of vitamin D to a placebo over at least a three-year period. Patients had a mean age of 68.07 years and a 78.02% were female. Haykal and his team zeroed in on any information that involved cancer incidence and mortality.

Vitamin D was associated with significant reduction of cancer-related mortality compared with placebo (P = 0.05) Compared with placebo, Vitamin D was not associated with significant reduction of cancer incidence (P = 0.46).
"The difference in the mortality rate between the vitamin D and placebo groups was statistically significant enough that it showed just how important it might be among the cancer population," Haykal said.

While these findings show promise, Haykal cautioned that the exact amount of the vitamin to take and what levels are needed in the blood are still unknown. He also said that it's unclear how much longer vitamin D extends lifespan and why it has this result.

"There are still many questions and more research is needed," Haykal said. "All we can say is that at least three years of taking the supplement is required to see any effect."

Results show enough promise, however, that Haykal would like to see more doctors, especially oncologists, prescribe vitamin D to patients in general.
"We know it carries benefits with minimal side effects, he said. "There's plenty of potential here."

Other authors on the study included MSU and Hurley resident physicians Varun Samji, Yazan Zayed, Inderdeep Gakhal, Vijaysai Veerapaneni, Michele Obeid, Babikir Kheiri and Sunil Badami. Ghassan Bachuwa, internal medicine residency program director at Hurley, and Rizwan Danish, oncologist at Genesee Cancer and Blood Disease Treatment Center, also contributed to this research.

ASCO2019 特集

リンパ腫の特定の亜型を有する患者は化学療法を回避することができる可能性がある (Abstract 7508)

Smart Start：リンパ腫の試験により、化学療法前の分子標的薬併用療法は有効であることが示された

Smart Start: Lymphoma trial finds combination targeted therapy effective prior to chemotherapy

化学療法を用いないリツキシマブ、イブルチニブ、およびレナリドミドの併用療法は、新たに診断されたnon-germinal (non-GCB) 型びまん性大細胞型リンパ腫（DLBCL）患者において非常に効果的である、と2019 ASCO Annual Meeting で発表された。第II相Smart Start 試験の結果、新たに診断されたnon-GCB DLBCL患者に対し、全ての化学療法の前にこの分子標的薬併用療法を施行した場合、全奏効率は84.6% であり、完全完解は38.5% であることが示された。本試験対象患者の90% 超は、1年後も寛解を保ったままであった。副作用は軽度であり、多くが化学療法によるものであった。

Full Text

Results of a Phase II clinical trial conducted at The University of Texas MD Anderson Cancer Center revealed that combination targeted therapy, consisting of rituximab, lenalidomide and ibrutinib (RLI), had an 84.6 percent overall response rate (ORR) and 38.5 percent complete response rate (CRR) when given prior to any chemotherapy for newly diagnosed patients with a specific type of diffuse large b-cell lymphoma (DLBCL).

The first-of-its-kind study examined a treatment regimen without chemotherapy for patients with non-germinal center (non-GCB) DLBCL, and, while confirmatory trials are needed, the findings suggest that patients who respond to targeted therapy initially may not need chemotherapy, currently the standard of care.

The results of the trial were presented in an oral presentation at the 2019 American Society of Clinical Oncology Annual Meeting by principal investigator Jason Westin, M.D., assistant professor of Lymphoma & Myeloma.

"The responses we've seen have been remarkable. More than 80 percent of our patients have responded and around 40 percent have had a complete response, showing no evidence of cancer, prior to receiving any chemotherapy," said Westin. "All patients have gone on to receive standard chemotherapy in combination with these targeted treatments per the protocol, and, so far, we've had a 100 percent response rate."

Standard treatment for large-cell lymphomas is chemotherapy, but this subtype doesn't respond as well, reaching an estimated cure rate of just 50-60 percent, explained Westin.

The clinical trial enrolled 60 patients at MD Anderson with non-GCB DLBCL and treated those patients with two cycles of RLI, followed by six cycles of RLI with chemotherapy. Westin's team designed the trial to bring new treatment options to these patients based on promising findings in the lab.

"We called the trial 'Smart Start' because we thought this was a smarter way to start therapy for these patients," said Westin. "Standard treatment for large-cell lymphoma has been largely stagnant for the better part of 40 years, despite many advances in our understanding of the disease and a host of new medications. It's exciting to see an idea that worked in the lab now beginning to yield results and show this is a potentially new way forward to fight this disease."

More than 90 percent of patients on this trial remain in remission after one year, said Westin. Additionally, side effects on the trial have been mild, with most driven by the chemotherapy treatment.

Going forward, Westin and colleagues plan to launch clinical trials to investigate whether patients who respond well to RLI treatment upfront can receive little or no chemotherapy and still attain long-term remission.

This study was supported by the Conquer Cancer Foundation, Celgene and Janssen Pharmaceuticals.

ASCO2019 特集

乳房部分照射によりQOLが向上する (Abstract 508)

化学療法なしで乳房部分照射を施行された患者は、倦怠感は弱く、整容性はわずかに劣る

Patients who received partial breast irradiation without chemotherapy experienced less fatigue, slightly poorer cosmesis

患者報告アウトカムから、術後補助化学療法を受けない乳がん患者に対する乳房部分照射（PBI）は、全乳房照射（WBI）に比べ利便性が高いことが示された。PBI 群の参加者はまた、治療後36か月の時点で、倦怠感は弱く整容性はわずかに劣っていたが、整容性に関しては化学療法とPBI またはWBI を受けた患者で同等であった。両群において、PBI 患者の方が治療終了時点での痛みが少なく、治療関連症状はWBIの方が不良であった。これらの結果は2019 ASCO Annual Meeting で発表された。

Full Text

Patient-reported outcome (PRO) data indicates that partial breast irradiation (PBI) is more convenient than whole breast irradiation (WBI) for women with breast cancer who do not receive adjuvant chemotherapy. These participants on the NRG Oncology clinical trial NSABP B-39/RTOG 0413 also experienced less post-treatment fatigue and slightly poorer cosmesis at 36 months following treatment, whereas cosmesis was equivalent at 36 months in women who received chemotherapy and PBI or WBI. These outcomes were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting and the abstract was designated as a "Best of ASCO" abstract.

In December 2018, NRG Oncology presented the results of NSABP B-39/RTOG 0413 comparing PBI and WBI after lumpectomy in women with breast cancer at the San Antonio Breast Cancer Symposium (SABCS). Although these 10-year results did not show equivalence of PBI to WBI in controlling ipsilateral breast tumor recurrence in this patient population due to clinically small differences, data suggested that PBI could still be considered an acceptable alternative to WBI for certain women. This trial included a prospective substudy for PROs that evaluated breast cancer treatment outcomes including cosmesis, function, and pain, as well as fatigue, and is the subject of the current ASCO presentation.

"While PBI recurrence outcomes were statistically inferior to WBI on the NRG Oncology NSABP B-39/RTOG 0413 trial, it is still crucial that we measure how PBI compares to WBI in terms of quality of life (QOL) for women. As there were only slight clinical outcome differences between these two treatments, some women could still derive benefit from PBI treatment in terms of outcomes such as cosmesis or fatigue," stated Patricia Ganz, MD, Director of Cancer Prevention and Control Research at the University of California, Los Angeles Jonsson Comprehensive Cancer Center and lead author of the NRG Oncology NSABP B-39/RTOG 0413 abstract.

950 patients enrolled in the QOL substudy for NRG Oncology NSABP B-39/RTOG 0413 had follow up data and, of these patients, 446 received chemotherapy, while 504 did not receive chemotherapy. In non-chemotherapy patients, PBI did not meet the criteria for cosmesis equivalence, but caused less fatigue and was rated more convenient than WBI. In patients who received chemotherapy, PBI participants reported equivalent cosmesis to WBI. In both treatment groups, PBI patients reported less pain at the end of treatment, and treatment related symptoms were worse with WBI.

This study was supported by the National Cancer Institute.

ASCO2019 特集

チェックポイント阻害薬は肺がん再発を減少させるのに有望である(Abstract 8504)

NEOSTAR：早期肺がんに対する術前のチェックポイント阻害薬の併用は有効である

NEOSTAR: Combination checkpoint blockade effective in pre-surgical setting for early-stage lung cancer

免疫チェックポイント阻害薬を用いた術前補助療法による病理学的奏効率（MPR）は、治療された早期切除可能非小細胞肺がん患者において33% であった、と2019 ASCO Annual Meeting で発表された。第II相NEOSTAR 試験において、術前にニボルマブ（抗PD-1抗体）およびイピリムマブ（抗CTLA-4抗体）の併用療法を施行された患者21人中7人がMPR を達成したのに対し、ニボルマブ単独療法でMPR を達成したのは23人中4人であった。これら2群を比較するには検出力は不足しているが、併用療法は手術時点でviable な腫瘍を減少させるのにより有効と思われた。

Full Text

Neoadjuvant treatment with nivolumab plus ipilimumab resulted in an overall major pathologic response (MPR) rate of 33 percent of treated patients with early-stage, resectable non-small cell lung cancers, meaning these patients had less than or equal to 10 percent viable tumor remaining at surgery. With these results, the combination immunotherapy met the pre-specified trial efficacy endpoint of the phase II NEOSTAR trial conducted by researchers at The University of Texas MD Anderson Cancer Center.

The trial arm testing nivolumab alone in the treated population of patients achieved a 17 percent MPR rate, for an overall MPR rate across both trial arms of 25 percent. The results of the trial were presented in an oral presentation at the 2019 American Society of Clinical Oncology Annual Meeting by principal investigator Tina Cascone, M.D., Ph.D., assistant professor of Thoracic/Head & Neck Medical Oncology.

"The NEOSTAR trial results definitely tell us this combination is clinically promising and warrants further investigation, possibly in combination with other therapies" said Cascone. "By learning from these results and from our preclinical and translational findings, we can identify the best combination and make a major step forward in the field to limit tumor recurrence for our early-stage lung cancer patients."

Patients with early-stage or locally advanced lung cancer have the potential to be cured of their disease, but more than half of those patients will have a recurrence if treated with surgery alone, explained Cascone. Therefore, there is an urgent need to identify the most effective neoadjuvant therapy options to reduce the risk of relapse.

Preclinical studies in mice revealed that increased expression of PD-L1, an immune checkpoint protein, in lung adenocarcinoma tumors is critical for the development and survival of metastases, providing the rationale for testing immunotherapy in the neoadjuvant setting.

"Prior to this study, we knew that single agent neoadjuvant immunotherapy has achieved an MPR rate of 22 to 45 percent, but the combination of anti-PD-1 and anti-CTLA-4 immune checkpoint blockade before surgery in resectable NSCLC patients had not yet been tested," said Cascone. "In mouse models of resectable and spontaneously metastatic non-small cell lung cancer, the combination of immunotherapy prior to surgery was superior to adjuvant combined therapy in prolonging survival and reducing the frequency of lung metastases, supporting further investigation of neoadjuvant combined immune checkpoint blockade in the clinical setting."

The researchers designed the trial to test the effectiveness of combination immune checkpoint inhibitors priory to surgery. The trial enrolled 44 patients who were randomized to receive either neoadjuvant nivolumab (anti-PD-1) alone or nivolumab plus ipilimumab (anti-CTLA-4).

The trial's primary endpoint was MPR, hypothesized to be higher for single and/or combination immune checkpoint inhibitors compared to the rate induced by historical neoadjuvant chemotherapy controls. The pre-specified trial efficacy endpoint for a specific treatment to be considered promising was greater than or equal to six MPRs in the intent to treat population.

MPR has been adopted as a surrogate endpoint in neoadjuvant trials for patients with resectable non-small cell lung cancer patients, as it has been shown to positively correlate with improved overall and recurrence-free survival outcomes, explained Cascone.

Seven out of 21 patients treated pre-operatively with the combination therapy achieved an MPR, and four of 23 patients treated with nivolumab alone achieved an MPR.

Although the trial was not powered to make a comparison between the two arms, the combination therapy appeared more effective at reducing viable tumor at surgery. Six patients (38 percent) that received the combination therapy and underwent surgery on trial achieved a complete pathological response compared to just two patients (10 percent) receiving nivolumab alone. Also, the majority of patients with more than 50 percent viable tumor remaining at surgical resection received single-agent nivolumab therapy.

The treatments were generally well-tolerated, said Cascone, with no unacceptable toxicity or increased perioperative morbidity and/or mortality noted, however, careful perioperative monitoring is advised with these agents.

The trial also collected a variety of biospecimens from patients before, during and after treatment, which enabled researchers to investigate why results vary from patient to patient and understand the dynamic changes induced by therapy in potential biomarkers. They discovered that elevated tumor expression of the immune checkpoint protein PD-L1 prior to therapy was positively correlated with radiographic responses and with pathologic tumor regression at surgery.

Preliminary immunologic characterization of resected tumors from patients treated with immunotherapy indicated that the combination therapy is associated with an increased number of tumor-infiltrating lymphocytes as compared to monotherapy, and that some of these T cells might have tumor reactive activity. Additional results presented in a poster session show that combination therapy appeared to be associated with greater diversity and reactivity of T lymphocytes in resected tumors as compared to pretreatment tumor specimens.

"This is important because we don't see patients with early-stage lung cancer as often as patients with metastatic disease in the clinic, and we want to take advantage of this opportunity for our patients. There are limitations to this trial, as it was overall a small cohort, but the positive results suggest we should continue to evaluate neoadjuvant combination immunotherapy as an option for our patients. Our ongoing exploratory analyses will help us to better understand this response and to identify potential biomarkers that could inform future trials," said Cascone.
The researchers already have added and are nearing complete enrollment in a third arm of the NEOSTAR trial to evaluate neoadjuvant nivolumab plus platinum-based chemotherapy. Because of successful accrual, additional arms are being considered to evaluate further combination approaches.

This study was supported by Bristol-Myers Squibb-MD Anderson Lung Strategic Alliance, the Conquer Cancer Foundation ASCO Career Development Award, the MD Anderson Physician-Scientist Training Program, the NIH/NCI P30 CA016672 CCSG New Faculty Award, the Khalifa Scholar Award supported by the Khalifa Bin Zayed Al Nahyan Foundation, and the Bob Mayberry Foundation. The trial also was supported by the Lung Cancer Moon Shot™, part of MD Anderson's Moon Shots Program™, a collaborative effort designed to accelerate the development of scientific discoveries into clinical advances that save patients' lives.

ASCO2019 特集

HIV患者に対する免疫療法薬は安全であることが示された(Abstract 2500)

抗PD-1抗体治療は良好にコントロールされているHIV患者のがん治療に適切である

Anti-PD-1 therapy is appropriate for cancer patients with well-controlled HIV

HIVに感染し様々な致命的がんの1つを有する患者は、免疫療法薬ペムブロリズマブを用いて安全に治療することができる、と2019 ASCO Annual Meeting で発表され、同時に *JAMA Oncology* に掲載された。患者30人を対象としたこの試験では、抗PD-1抗体治療薬ペムブロリズマブのみを調査した。治療されたがんは肺がん、カポジ肉腫、非ホジキンリンパ腫、肝臓がん、肛門がんおよび進行扁平上皮がんであった。有害事象プロファイルは、HIV患者を除いた過去のスタディと実質的な差はなかった。この結果はT細胞表面のPD-1またはPD-L1 受容体をブロックする5つの類似薬にも適用できると思われる。

Full Text

The results of a study led by physicians at Fred Hutchinson Cancer Research Center in Seattle, Washington showed that patients living with HIV and one of a variety of potentially deadly cancers could be safely treated with the immunotherapy drug pembrolizumab.

During an ASCO presentation concurrent with release of a study in *JAMA Oncology*, Fred Hutch researcher and lead author Dr. Tom Uldrick said that in nearly all cases it was safe to use the drug in patients with cancer and HIV. The adverse events profile was not substantially different from prior studies that excluded such patients. The results, study authors said, are likely applicable to five similar drugs that block receptors known as PD-1 or PD-L1 on the surface T cells.

"Our conclusion is that anti-PD-1 therapy is appropriate for cancer patients with well-controlled HIV, and that patients with HIV and cancer can be treated with the drug and should be included in future immunotherapy studies," Uldrick said.
The 30-patient trial studied only pembrolizumab, the anti-PD-1 therapy manufactured by Merck. HIV-positive patients with different cancers that might respond to the drug were included in the trial. Among the cancers treated were lung cancer; Kaposi sarcoma, or KS; non-Hodgkin lymphoma; liver cancer; anal cancer and advanced squamous cell skin cancer.

Fred Hutch immunotherapy researcher Dr. Mac Cheever is director of the NCI-funded Cancer Immunotherapy Trials Network, which carried out the trial, and he is senior author of the JAMA Oncology paper. The study was conducted at seven different cancer centers across the United States, including the HIV and AIDS Malignancy Branch of the National Cancer Institute, in Bethesda, Maryland.

Overall, the safety profile of pembrolizumab in people with HIV and cancer was similar to that noted in clinical trials in the general population. Although the primary purpose of the study was to evaluate safety, it also provided a snapshot of the anti-cancer activity of the drug on these patients. One patient with lung cancer had a complete response to treatment, and activity was also noted in important HIV-associated cancers, including non-Hodgkin lymphoma, Kaposi sarcoma and liver cancer.

An unexpected death on study from a rare KSHV-associated B-cell lymphoproliferation was noted in one patient and while the association with therapy is still unclear, it has led to recommendations to use substantial caution if anti-PD-1 therapy is considered in the setting of KSHV-associated multicentric Castleman disease. The researchers concluded that anti-PD-1 therapy may be considered in patients with HIV who are on antiretroviral therapy and have a CD4 count above a certain threshold (100 cells per microliter of blood). However, more research is needed as to its effectiveness in the setting of HIV infection.

The U.S. Food and Drug Administration (FDA), Friends of Cancer Research, and the American Society of Clinical Oncology have all recommended that HIV patients should be included in more clinical trials. The National Cancer Institute (NCI) has generally allowed patients with HIV to enroll on the immuno-oncology studies that it sponsors with PD-1 and PD-L1 inhibitors. However, this trial was one of only two trials sponsored by the NCI to focus exclusively on patients living with HIV, and it has been the first prospective trial to report its results.

"Exclusion of people with HIV in clinical trials is a longstanding problem that grew out of the poor outcomes of AIDS patients with cancer, before there were effective antiviral therapies for HIV," Uldrick said. In prior research, Uldrick surveyed 46 recent clinical trials that led to approval of cancer drugs and found 30 contained explicit exclusions for patients with HIV, and nine others where an exclusion was implied.

This study was sponsored by the National Cancer Institute Cancer Therapy Evaluation Program (CTEP). Study drug was provided to the NCI by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., via a collaborative research and development agreement. It was supported by U.S. federal funds from the National Cancer Institute (NCI), National Institutes of Health (NIH), NIH Intramural Research Program Support to Dr. Uldrick and Dr. Robert Yarchoan, and to Dr. Cheever for the Cancer Immunotherapy Trials Network.

ASCO2019 特集