# ネララビンはT細胞性悪性腫瘍の生存率を改善する (Abstract 10500)

## 新たな治療法は小児および若年成人T細胞性悪性腫瘍の生存率を改善する

New regimens improve survival for children and young adults with T-cell cancers

T細胞性急性リンパ芽球性白血病(T-ALL)またはT細胞性リンパ芽球性リンパ腫(T-LL)を有する小児および若年成人の90%が標準的な化学療法にネララビンを上乗せすることで4年間生存し84%が再発しなかった、との第III相臨床試験の結果が2018 ASCO Annual Meetingで発表された。この結果は、これらのT細胞性悪性腫瘍に対してこれまで報告された生存率の中で最も高いものである。標準的な化学療法にネララビンを上乗せすることで、T-ALLの中等度または高リスク患者群に対してさらなるベネフィットが得られた; 4年後、ネララビン投与群の89%に再発がなかったのに対し、非投与群におけるその割合は83%であった。

## Full Text

In a randomized phase III clinical trial performed by the Children's Oncology Group (COG), 90% of children and young adults with T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LL) were alive four years after starting treatment regimens on this trial, and 84% were cancer free. These are the highest survival rates for these T-cell malignancies reported to date, according to the authors.

The addition of nelarabine to standard chemotherapy provided further benefit for the group of patients with moderate or high risk of T-ALL recurrence – at four years 89% of those who received nelarabine were leukemia-free vs. 83% of those who did not. The study is presented at the 2018 ASCO Annual Meeting in Chicago.

"T-cell ALL is a disease that requires the use of a very intense and complex chemotherapy regimen. Historically, about 80% of people live at least four years after being treated for their disease, but we felt we could and must do better," said lead study author Kimberly Dunsmore, MD, professor, Virginia Tech Carilion School of Medicine in Roanoke, Virginia, USA. "Our trial shows that we could further increase survival rates by about 10%, which is very encouraging."

The trial, begun in 2007, enrolled patients 1-30 years of age with either T-ALL (94% of trial participants) or T-LL (6% of participants). With 1,895 patients, this is the largest randomized clinical trial ever performed in these diseases.

The trial had four arms, with all patients receiving the standard, complex, multi-drug chemotherapy regimen known as COG augmented Berlin-Frankfurt-Munster (aBFM) chemotherapy. In addition to receiving aBFM, patients were randomly assigned to also receive either high-dose methotrexate in a hospital or escalating dose methotrexate in an outpatient setting.

The group of patients with moderate or high risk of cancer recurrence were also randomly assigned to receive or not receive nelarabine, in addition to chemotherapy, and cranial radiation.

Key findings:

- Overall, 90.2% of patients treated in this trial lived at least four years, and 84.3% had no sign of cancer at four years.
- In the group of patients with T-ALL who had increased risk of recurrence, 88.9% of those who received nelarabine were leukemia-free at four years compared to 83.3% of those not treated with nelarabine.
- While patients with T-LL did not benefit from the addition of nelarabine, more than 85% lived for four years without signs of disease.
- Contrary to results from previous, smaller trials, patients with T-ALL who received escalating doses of methotrexate did better than those who received high-dose methotrexate (four-year disease-free survival with escalating dose was 89.8% vs. 78% with high-dose).
- Among T-ALL patients randomly assigned to receive both nelarabine and escalating doses of methotrexate, 92.2% were leukemia-free at four years.
- Patients who did not have cancer remission following the induction phase of chemotherapy were assigned to receive high-dose methotrexate and nelarabine; 54.8% of survived four years without signs of the disease. This is a significant improvement, as historically only about 20% of people with T-ALL who did not experience cancer remission lived another three years, according to the authors.

Most doctors are moving to decreasing the use of cranial radiation for T-cell leukemia as late side effects can occur after cranial radiation. Late side effects include changes in cognitive abilities, learning disabilities, neuroendocrine changes, and development of secondary malignancy. The next step will be for clinicians to examine the implications and benefits that may accrue when using nelarabine in chemotherapy protocols without cranial radiation.

This study received funding from the Cancer Therapy Evaluation Program within the National Cancer Institute/National Institutes of Health and received support from the St. Baldrick's Foundation.

## ASCO2018特集

# 頭頸部がんの症状を緩和する高度技術 (Abstract 6063)

## モバイルセンサーソフトウェアを用いて頭頸部がん症状の重症度を低下させる

## Use of mobile and sensor technology lowers symptom severity for people with head and neck cancer

頭頸部がんに対し放射線療法を受けている患者で、モバイルセンサーソフトウェアを用いて症状の遠隔モニタリングを実施されている者は、がんとその治療による症状のいずれもがそれほどひどくないと報告した、と2018 ASCO Annual Meetingで発表された。参加者は、CYCOREと呼ばれるモバイルセンサーソフトウェア（169人）または通常のケアを受ける群（188人）にランダムに割り付けられた。CYCORE群はBluetooth対応の血圧計カフおよび体重計を使用した。放射線治療完遂後、CYCORE群は通常ケア群に比べ、平均全身症状および頭頸部がん特異的症状に関するスコア（それぞれ2.9対3.4および4.2対4.8）が低かった（すなわち良好）であった。

## Full Text

A randomized clinical trial of 357 people receiving radiation for head and neck cancer, using mobile and sensor technology to remotely monitor patient symptoms, resulted in less severe symptoms related to both the cancer and its treatment (both general and cancer-related).

Patients who used the technology – which included a Bluetooth-enabled weight scale, Bluetooth-enabled blood pressure cuff, and mobile tablet with a symptom-tracking app that sent information directly to their physician each weekday – had lower symptom severity than participants who had standard weekly visits with their doctors.

In addition, daily remote tracking of patient wellbeing, according to the researchers, enabled physicians to detect concerning symptoms early and respond more rapidly, compared to usual care. These findings will be presented at the upcoming 2018 ASCO Annual Meeting in Chicago.

"Our study generated evidence on how newer technologies can be integrated into cancer care relatively easily and improve patient outcomes without interfering too much in a person's daily life," said lead study author Susan K. Peterson, PhD, professor, Department of Behavioral Science, The University of Texas MD Anderson Cancer Center, Houston. "This study was done during a rather intense period in the patients' care for head and neck cancer. The system helped their physicians to provide valuable support that ultimately resulted in lower symptom severity."

This trial used a technology system called CYCORE (CYber infrastructure for COmparative Effectiveness REsearch), developed collaboratively by four institutions through a grant from the National Cancer Institute.

Participants were randomly assigned to CYCORE (169 people) or usual care (188 people), which consisted of weekly doctor visits. People in the CYCORE group received sensors (blood pressure cuffs and weight scales) that were Bluetooth-enabled. They also got mobile tablets with proprietary Wi-Fi. An in-home wide area network (WAN) hub/router transmitted their sensor readouts, and a mobile app transmitted their symptom data through a back-end cyber-infrastructure to secure firewall-protected computers at MD Anderson to ensure patient information confidentiality.

For the CYCORE group, physicians reviewed data from the app and sensor transmissions remotely each weekday and could intervene in a person's care if necessary. Both CYCORE and usual care participants had weekly in-person doctor visits.

At the start of radiation therapy, study participants completed a 28-item MD Anderson Symptom Inventory survey about their health and common activities of daily living. The survey covered general symptoms that are common in people with cancer, such as pain, fatigue, and nausea, as well as symptoms that are particularly relevant to people with head and neck cancer, such as difficulty swallowing or chewing, skin pain/burning/rash, and problems with tasting food. The participants completed a similar survey at the end of their radiation therapy, usually 6 to 7 weeks later. A final survey was completed 6 to 8 weeks after their radiation therapy ended.

There was no difference in self-reported health severity scores between the CYCORE participants and those who received usual care at the start of the trial. Symptoms severity was scored on a scale of 0 to 10, with zero being no symptom or pain and 10 being the highest level of symptom severity. After completion of radiation therapy, the CYCORE participants had lower (i.e. better) mean scores for general symptoms vs. usual care participants (2.9 vs. 3.4), as well as lower mean scores for symptoms specific to head and neck cancer (4.2 vs. 4.8).

Six to 8 weeks after completion of therapy, CYCORE participants had a mean score of 1.6 vs. 1.9 for usual care participants based on overall health. Both groups had slightly higher severity scores for specific head and neck symptoms (1.7 vs. 2.1).

Most patients (80% or more) adhered to daily monitoring, which was an excellent outcome given the intensity of their treatments, noted Dr. Peterson. Scores reflecting how various symptoms interfered in activities of daily living were about the same in both groups across the entire time of survey reporting.

"This study demonstrates the power of leveraging smart technology to improve the care of people with cancer. These tools helped simplify care for both patients and their care providers by enabling emerging side effects to be identified and addressed quickly and efficiently to ease the burden of treatment. I hope that these or similar technologies will be broadly available to patients soon," said ASCO President Bruce E. Johnson, MD, FASCO.

While the authors were able to recruit people from a wide range of ages, the study population was mostly white, which closely reflected the overall head and neck patient population at the cancer center. The next step for researchers may be to determine how long the benefit of a CYCORE intervention could persist. They also hope to implement the CYCORE intervention in non-academic cancer treatment settings where the majority of cancer patients receive their treatment.

This study received funding from the National Institutes of Health.

## ASCO2018特集

# 乳がんの治療期間を短縮することで心臓における副作用リスクは低下する(Abstract 506)

## HER2陽性乳がんに対するより短期間のトラスツズマブによる治療は、標準治療に比べ心臓における副作用は少なく有効性は同等である

## Shorter trastuzumab treatment for HER2+ breast cancer as effective as standard treatment with fewer cardiac side effects

2018 ASCO Annual Meetingで、HER2陽性早期乳がん女性4,088人を対象とした第III相試験の結果、6か月間のトラスツズマブ投与は現在の標準的な12か月間の治療に比べ非劣性であることが明らかにされた。4年無病生存率は、6か月治療群で89.4%であり12か月治療群で89.8%であった。さらに、心臓疾患によりトラスツズマブを早期中止した女性は、6か月治療群ではわずか4%であったのに対し、12か月治療群では8%であった。この試験は、HER2陽性乳がん患者の多くにおいて、トラスツズマブによる治療期間を6か月に短縮する方向への最初のステップを示している、と筆者らは述べている。

## Full Text

A phase III randomized clinical trial of 4,088 women with HER2-positive, early-stage breast cancer found that taking trastuzumab for 6 months was non-inferior to the current standard of 12 months. The disease-free survival rate at four years was 89.4% with 6 months of therapy and 89.8% with 12 months of therapy. In addition, only 4% of women in the 6-month arm stopped trastuzumab early because of cardiac problems, compared with 8% in the 12-month arm.

"The Persephone trial's researchers worked closely with patient advocates. Everyone involved in this study is very excited by these results," said lead study author Helena Earl, MD, Professor of Clinical Cancer Medicine at the University of Cambridge in the United Kingdom. "We are confident that this will mark the first steps towards a reduction of the duration of trastuzumab treatment to 6 months in many women with HER2-positive breast cancer."

This is the largest trial to date examining the impact of shortening the duration of trastuzumab treatment, according to the authors. The results of the trial, Persephone, is being presented at the 2018 ASCO Annual Meeting in Chicago.

Trastuzumab was granted FDA approval in the United States based on the results of three major trials reported in 2005. In these trials, the length of trastuzumab treatment was 12 months, and this treatment length quickly became the standard of care. Shortly thereafter, a small trial in Finland (FinHer) reported similar benefit from as little as 9 weeks of trastuzumab, prompting research interest in shortening treatment length to reduce side effects and costs.

In Persephone, half of the women took trastuzumab for 6 months and the other half for 12 months. Women also received chemotherapy (anthracycline-based, taxane-based, or a combination of both) while enrolled in the trial. The non-inferiority design allowed the trial to help determine whether reduced duration of treatment can be as good as the standard treatment within pre-specified limits, which are set before the trial starts.

The women in the trial were followed for a median of over five years. Researchers found that 89.4% of women in the 6-month arm and 89.8% in the12-month arm were alive and free of breast cancer at four years. The trial demonstrated that 6 months of trastuzumab treatment was non-inferior to 12 months.

Only 4% of women who received trastuzumab for 6 months stopped treatment early due to heart problems, compared to 8% of those who took trastuzumab for 12 months.

"The use of trastuzumab has been a major advance for women with HER2-positive breast cancer by increasing the cure rate, but no treatment is free of side effects, and heart damage has always been a concern with this treatment. This new trial shows that a shorter length of treatment can benefit patients just as much as a longer treatment, with less risk of cardiac side effects. This is a win-win for patients with breast cancer who are receiving this common treatment," said ASCO President Bruce E. Johnson, MD, FASCO.

The researchers are currently analyzing their results to determine the impact of treatment length on quality of life, with qualitative feedback from trial participants. A detailed cost-effectiveness analysis is also underway.

Professor Earl stated that more research needs to be done to define the particular patients for whom treatment duration can be safely reduced. The researchers plan to analyze blood and tissue samples collected within the trial to look for biomarkers to identify different risk groups.

This study was funded by the National Institute for Health Research (NIHR) in the UK.

## ASCO2018特集

# がんサバイバーにおける不眠症管理の選択肢 (Abstract 10001)

## がんサバイバーにおける不眠症治療のための認知行動療法および鍼治療の利用

## Use of cognitive behavioral therapy and acupuncture to treat insomnia in cancer survivors

がんサバイバーを対象としたランダム化臨床試験の結果、不眠症に対する8週間の鍼治療または認知行動療法（CBT-I）は、がんサバイバーの不眠症の重症度を低下させ、改善効果は認知行動療法を受けた患者において最大であったことが示された。8週間後、不眠症重症度スコアはCBT-I群で18.5から7.5へと10.9ポイント低下、鍼治療群では17.55から9.23へと8.3ポイント低下した。試験開始時に不眠症が軽度であった者の間では、鍼治療に比べCBT-Iで改善した者の方がはるかに多かった（85% vs. 18%）。このスタディ結果は、2018 ASCO Annual Meetingで発表されている。

## Full Text

A Patient-Centered Outcomes Research Institute (PCORI)-supported randomized clinical trial of cancer survivors showed that eight weeks of either acupuncture or cognitive behavioral therapy for insomnia (CBT-I) decreased the severity of insomnia among cancer survivors, though improvements were greatest among patients receiving cognitive behavioral therapy. The study is being presented at the 2018 ASCO Annual Meeting in Chicago.

"Up to 60% of cancer survivors have some form of insomnia, but it is often under diagnosed and undertreated," said lead study author Jun J. Mao, MD, Chief, Integrative Medicine Service, Memorial Sloan Kettering Cancer Center, New York. "Our trial showed that both CBT-I and acupuncture were effective in treating moderate to severe insomnia, although CBT-I was more effective for those with mild symptoms of insomnia. Now patients have more choices to manage their insomnia."

CBT-I is a newer form of psychotherapy that attempts to modify emotions, behaviors, and thoughts related to sleep. CBT-I has been the gold standard for treatment of insomnia, said Dr. Mao.

To find a therapy to compare with CBT-I, the researchers consulted a group of patient advisors who had cancer and who were knowledgeable about how insomnia could impact their health. Additionally, a survey of cancer survivors found that survivors preferred a natural, non-medicinal approach to treating insomnia. Based on this feedback, and results from other sleep studies that showed it could beneficial, acupuncture was deemed a reasonable comparison to be used in this trial.

The survivors in the trial had completed cancer treatment, and the mean time since cancer diagnosis was about six years. The survivors had received treatment for breast, prostate, head and neck, hematologic, and colorectal cancer. In addition, 6% had received treatment for more than one type of cancer.

All trial participants had been clinically diagnosed with insomnia by research staff through structured clinical interviews and were randomly assigned to receive either CBT-I or acupuncture for eight weeks.

The participants who received CBT-I worked with a therapist to re-establish a restorative sleep schedule by:

- Reducing the amount of time in spent in bed
- Limiting activities performed in bed to only sleep and sexual activity
- Modifying unhelpful beliefs about sleep
- Promoting good sleep hygiene (avoiding activities that included light from tablets and cellphones, eating too late, and performing vigorous activities; they also set a regular sleep schedule)

Reduction in insomnia severity, measured by the Insomnia Severity Index (ISI), from study entry to week 8 (end of treatment), was the primary study outcome. Survivors were also reassessed 20 weeks after having started the trial. The ISI is a questionnaire that asks people to rate the severity of insomnia problems, such as difficulty falling asleep and staying asleep, and the impact of insomnia on their daily functioning and quality of life. The ISI score ranges from 0-28, with scores 0-7 considered as no clinically significant insomnia, 8-14 mild insomnia, 15-21 moderate insomnia, and 22-28 severe insomnia. At the beginning of the trial, 33 survivors had mild insomnia, 94 had moderate insomnia, and 33 severe insomnia.

CBT-I was the more effective treatment overall: After eight weeks, insomnia severity scores fell 10.9 points, from 18.5 to 7.5 for those who received CBT-I vs. 8.3 points for those who received acupuncture treatments, from 17.55 to 9.23. Among people with mild insomnia at the start of the trial, far more had an improvement with CBT-I than with acupuncture (85% vs. 18%). Participants who started the trial with moderate to severe insomnia had somewhat similar response rates to CBT-I vs. acupuncture (75% vs. 66%). All survivors maintained improvement in insomnia up to 20 weeks after the start of the trial.

"We know that sleep is critical to the health of patients with cancer, from active cancer care through survivorship. This research reinforces the understanding that there are a variety of effective, non-medical tools, including psychological counseling and acupuncture, that can improve sleep and insomnia beyond traditional medicines, which can cause side effects that may diminish quality of life in other ways," said ASCO President Bruce E. Johnson, MD, FASCO.

This trial was a comparison between two interventions and determined which approach provided a greater relief of insomnia. Future research will focus on how best to deliver effective treatments to more diverse groups of cancer survivors to improve sleep management.

This study received funding from the Patient-Centered Outcomes Research Institute (PCORI).

## ASCO2018特集

# 新たな分子標的治療は進行乳がんの増殖を遅らせる(Abstract LBA1006)

## SANDPIPER：PI3K阻害剤は、転移性乳がんを有する閉経後女性において、がんの増殖を遅らせるのに成功した

## SANDPIPER: PI3K inhibitor successfully slows cancer growth in postmenopausal women with metastatic breast cancer

2018 ASCO Annual Meetingにおいて取り上げられた第III相臨床試験において、新たな分子標的薬taselisibを標準的なホルモン療法薬フルベストラントに上乗せすることにより、ホルモン療法単独に比べ進行乳がんの増殖が2か月遅延し、がん増悪の確率が30% 低下した。SANDPIPER試験における奏効率は、taselisibを上乗せすることにより2倍以上になった（28 vs. 11.9%）。全生存率のデータはまだ得られていない。Taselisibは一般的なPIK3CA遺伝子変異を標的とし、比較的新たなクラスのPI3K阻害薬において初めてのそして最も有望な治療である。

Full Text

In a phase III clinical trial, a new targeted medicine, taselisib, combined with standard hormone therapy fulvestrant, halted the growth of advanced breast cancer growth by 2 months longer than hormone therapy alone, and decreased the chance of cancer worsening by 30%. Taselisib targets a common genetic abnormality in breast cancer – PIK3CA gene mutation – and is the first and most potent treatment in a relatively new class of PI3K inhibitors, according to the authors.

The study is featured in a presentation at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.

"About 40% of all patients with advanced breast cancer estrogen receptor positive have PIK3CA mutations, which means they could benefit from taselisib," said lead study author José Baselga, MD, PhD, FASCO, the Physician-in-Chief at Memorial Sloan Kettering Cancer Center in New York. "Our findings are proof that that targeting this pathway in breast cancer is effective. However, the benefit to patients was more modest than we had hoped for, and there is a risk of considerable side effects with the addition of taselisib."

Taselisib is the first medicine that specifically blocks the type of PI3K protein (PI3Kalpha) that is mutated in estrogen receptor-positive breast cancers. Taselisib has also shown promising clinical benefit in early trials of patients with head and neck and certain gynecologic cancers.

The SANDPIPER trial is the first and largest phase III clinical trial of taselisib, according to the authors. The trial enrolled 516 postmenopausal women with locally advanced or metastatic ER-positive, HER2-negative metastatic breast cancer that worsened or recurred despite initial hormone treatment with aromatase inhibitors. Women were randomly assigned to receive fulvestrant and placebo (176 women) or fulvestrant and taselisib (340 women).

Women who received taselisib and fulvestrant had a 30% lower chance of cancer worsening than those who received fulvestrant and a placebo, and taselisib extended the time until the cancer worsened by a median of two months (7.4 months with taselisib and fulvestrant vs. 5.4 months with fulvestrant and placebo). The response rate to treatment was more than doubled when taselisib was added (28% vs. 11.9%). Overall survival data are not yet available.

The most common severe side effects for patients who received taselisib were diarrhea, high blood sugar, and colitis. Due to side effects, 17% of women who received taselisib stopped treatment early, compared to only 2% of those who did not receive the targeted therapy.

"We now know that it's possible to target this common breast cancer mutation, and it's heartening to see that a new therapy can provide some benefits to women with advanced breast cancer. However, because the treatment has side effects, doctors will have to weigh its benefits and risks with their patients," said ASCO Expert Harold Burstein, MD, PhD, FASCO.

When they looked at outcomes by geographic area, the researchers noted that taselisib provided more benefit to study participants who received treatment in North America and Europe, where cancer worsening was delayed by a median of 3.5 months (7.9 with taselisib plus fulvestrant vs. 4.5 months with only fulvestrant). In other countries including Eastern Europe and Latin America, taselisib appeared to provide very little or no added benefit. More research is needed understand the reasons for this discrepancy.

This study received funding from F. Hoffmann-La Roche Ltd.

## ASCO2018特集

# 21個の腫瘍遺伝子は乳がんの個別化治療の決定に役立つ(Abstract LBA1)

## TAILORx：早期乳がん患者の多くがある診断検査に従うと化学療法を見合わせることができる

## TAILORx: Most women with early stage breast cancer can forgo chemotherapy when guided by a diagnostic test

第III相臨床試験の結果、ホルモン受容体陽性、HER-2陰性、腋窩リンパ節転移陰性の早期乳がんで、21個の腫瘍遺伝子発現アッセイにおいて中程度のスコアである女性の多くは、術後の化学療法を必要としないことが示された、と2018 ASCO Annual Meetingで発表された。この結果は、50歳超でホルモン受容体陽性、HER-2陰性、リンパ節転移陰性で乳がん再発スコアが0～25の全女性（この年代の乳がん女性の約85%）において、化学療法は差し控えるべきであると示唆している。乳がん再発スコア16～25の50歳以下の女性においては、化学療法によりある程度ベネフィットが得られた。

## Full Text

A federally funded phase III clinical trial shows that most women with hormone receptor-positive, HER2-negative, axillary node-negative early-stage breast cancer and a mid-range score on a 21-tumor gene expression assay (Oncotype DX® Breast Recurrence Score) do not need chemotherapy after surgery. The study found no improvement in disease-free survival when chemotherapy was added to hormone therapy in this group, which accounts for about two-thirds of women who participated in the trial. The findings will have an immediate impact on clinical practice, sparing thousands of women the side effects of chemotherapy.

The study is being presented in ASCO's Plenary Session, which features four studies deemed to have the greatest potential to impact patient care, out of the more than 5,800 abstracts featured as part of the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting. This is the largest breast cancer treatment trial ever conducted, and the first precision medicine trial ever done, according to the authors.

"Half of all breast cancers are hormone receptor-positive, HER2-negative, and axillary node-negative. Our study shows that chemotherapy may be avoided in about 70 percent of these women when its use is guided by the test, thus limiting chemotherapy to the 30 percent who we can predict will benefit from it," said lead study author Joseph A. Sparano, MD, Associate Director for Clinical Research at the Albert Einstein Cancer Center and Montefiore Health System in New York, and Vice-Chair of the ECOG-ACRIN Cancer Research Group.

"Before TAILORx, there was uncertainty about the best treatment for women with a mid-range score of 11-25 on the Oncotype DX Breast Recurrence Score test. The trial was designed to address this question, and provides a very definitive answer," said Dr. Sparano. "Any woman with early-stage breast cancer 75 years or younger should have the test and discuss the results of TAILORx with her doctor to guide her decision regarding chemotherapy after surgery to prevent recurrence," said Dr. Sparano.

Based on evidence from several prior studies, the 21-gene expression assay 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.

The Trial Assigning IndividuaLized Options for TReatment (TAILORx) enrolled 10,273 women with hormone receptor-positive, HER2-negative, axillary node-negative breast cancer - the most common type of breast cancer. Of those, 6,711 had a mid-range recurrence score of 11-25 and were randomly assigned to receive hormone therapy alone or hormone therapy and chemotherapy.

The primary endpoint was disease-free survival, defined as recurrence of cancer in the breast, regional lymph nodes and/or distant organs, a second primary cancer in the opposite breast or another organ, or death from any cause.

At a median follow-up of 7.5 years, the study met its primary pre-specified endpoint indicating that hormone therapy alone was not less effective than chemotherapy plus hormone therapy in women with a Breast Recurrence Score of 11- 25. Nine-year rates were similar in the two treatment arms for disease-free survival (83.3% vs. 84.3%), distant recurrence (94.5% vs. 95.0%), and overall survival (93.9% vs. 93.8%), indicating no benefit from adding chemotherapy to hormone therapy. Another important finding was identification of the group that did have some chemotherapy benefit - women 50 years or younger who had a Breast Recurrence Score of 16-25.

The researchers also found that women with a recurrence score of 10 or less had very low recurrence rates with hormone therapy alone, irrespective of age or other clinical factors. In addition, those with a recurrence score of 26 or higher had a distant recurrence rate of 13% despite chemotherapy and hormone therapy, indicating the need to develop more effective therapies for this group.

According to the authors, the findings suggest that chemotherapy may be spared in:

- All women older than 50 years with hormone-receptor positive, HER2-negative, node-negative breast cancer and a Recurrence Score of 0 to 25 (about 85% of women with breast cancer in this age group)
- All women 50 years or younger with hormone-receptor positive, HER2-negative, node-negative breast cancer and a Recurrence Score of 0 to 15 (about 40% of women with breast cancer in this age group)

"This study, which never would have happened without federal funding for cancer research, will transform care immediately, and for the better. These data provide critical reassurance to doctors and patients that they can use genomic information to make better treatment decisions in women with early-stage breast cancer. Practically speaking, this means that thousands of women will be able to avoid chemotherapy, with all of its side effects, while still achieving excellent long-term outcomes," said ASCO Expert Harold Burstein, MD, PhD, FASCO.

This study received funding primarily from the National Cancer Institute, part of the National Institutes of Health. Additional support was provided by the Breast Cancer Research Foundation, Komen Foundation, and the U.S. Postal Service Breast Cancer Stamp. The ECOG-ACRIN Cancer Research Group designed and conducted the study.

## ASCO2018特集

# ペンブロリズマブは初回肺がん治療に有効 (Abstract LBA4)

## KEYNOTE-042：ペンブロリズマブは進行肺がんの治療として化学療法よりもよりベネフィットが得られる

KEYNOTE-042: Pembrolizumab provides more benefit than chemotherapy alone as initial treatment for advanced lung cancers

大規模ランダム化第III相KEYNOTE-042試験の結果、最も一般的なタイプの肺がん患者の大多数に対し、ペンブロリズマブによる免疫療法は化学療法（現在の標準治療）に比べより有効な初回治療であることが示された、と2018 ASCO Annual Meetingで取り上げられた。PD-L1が1% 以上発現している進行非小細胞肺がん患者で、ペンブロリズマブによる免疫療法で初回治療を施行された者は、化学療法を施行された者に比べ、生存期間中央値が4～8か月長かった。さらに、重篤な副作用の発現は、化学療法群に比べペンブロリズマブ群で少なかった（18% vs. 41%）。

## Full Text

A large, randomized phase III trial shows that the immunotherapy pembrolizumab is a more effective initial treatment than chemotherapy (the current standard of care) for the majority of patients with the most common type of lung cancer. People with advanced non-small-cell lung cancer (NSCLC) with a PD-L1 expression of 1% or more who were first treated with immunotherapy pembrolizumab lived a median of 4-8 months longer than those who received chemotherapy. In addition, severe side effects occurred in fewer patients receiving pembrolizumab than chemotherapy (18% vs. 41%).

According to the authors, this study (KEYNOTE-042) is the largest clinical trial of pembrolizumab as a standalone therapy. The findings are presented in ASCO's Plenary Session, which features four studies deemed to have the greatest potential impact on patient care, out of the more than 5,800 abstracts featured as part of the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.

"A large number of patients with lung cancer now have a new treatment option with ?better efficacy and fewer side effects than standard chemotherapy," said lead study ?author Gilberto Lopes, MD, MBA, a medical oncologist at the Sylvester Comprehensive Cancer Center, University of Miami Health System in Florida. "Our study shows that pembrolizumab provides more benefit than chemotherapy for two-thirds of all people with the most common type of lung cancer."

PD-L1 is a biomarker commonly used to predict response to immune checkpoint inhibitors, including pembrolizumab. Generally, tumors with more PD-L1 (high expression) respond better to these treatments, but in some studies, these immunotherapies were effective even against tumors with little or no detectable PD-L1. In prior trials of second-line therapy for NSCLC, pembrolizumab was effective in treating tumors with PD-L1 expression of at least 1%.

Researchers randomly assigned 1,274 people with locally advanced or metastatic NSCLC to receive chemotherapy (paclitaxel plus carboplatin or pemetrexed plus carboplatin) or pembrolizumab. Both squamous and non-squamous cancers were included, but not cancers with genetic changes that can be treated with targeted therapies (EGFR and ALK inhibitors).

For the analysis, researchers explored treatment benefits in three patient groups according to tumor PD-L1 expression score: at least 50% (599 patients), at least 20% (818 patients), and at least 1% (1,274 patients). Equal numbers of patients in each PD-L1 expression group received pembrolizumab and chemotherapy.

The median follow-up time was 12.8 months. Compared to those receiving standard chemotherapy, patients who received pembrolizumab had a longer median overall survival, regardless of PD-L1 expression in the tumor. The benefit of pembrolizumab was greater when the level of PD-L1 expression was higher:

- PD-L1 50% or more: 20 months with pembrolizumab vs. 12.2 months with chemotherapy
- PD-L1 20% or more: 17.7 months with pembrolizumab vs. 13 months with chemotherapy
- PD-L1 1% or more: 16.7 months with pembrolizumab vs. 12.1 months with chemotherapy

"Immunotherapy with pembrolizumab alone benefits a much larger number of patients than we had previously thought. This is yet another promising result with immunotherapy in lung cancer that brings new momentum to the treatment of this notoriously difficult disease," said ASCO Expert John Heymach, MD, PhD.

More research is needed to define patient groups who benefit from pembrolizumab. The three broad groupings by PD- L1 expression in the current analysis do not allow researchers to predict the benefit from pembrolizumab for patients with a specific PD-L1 expression level. Additionally, it is not yet clear whether pembrolizumab combined with chemotherapy is better than pembrolizumab alone in patients who express PD-L1, as there have not been head-to-head comparison trials of the two approaches.

Ongoing research is also exploring use of adjuvant pembrolizumab and combinations of immunotherapy with bevacizumab-containing combination regimens as part of initial therapy for NSCLC.

This study received funding from Merck.

## ASCO2018特集

# スタディによりいくつかの新たながんとLynch症候群が関連付けられた(Abstract LBA1509)

## ゲノム研究の結果、Lynch症候群は高MSI腫瘍を有する人々に多いことが示された

## Genomic study finds Lynch syndrome is common among people with MSI-high tumors

2018 ASCO Annual Meetingで発表された15,000を超える腫瘍検体のゲノム研究の結果、マイクロサテライト不安定性が高い（MSI-H）腫瘍を有する人々はLynch 症候群を有する確率が高いことが示された。MSI-H腫瘍を有する人々のうち、16%はその後Lynch症候群を有することが明らかになった。予想通り、1,025のMSI-H/MSI-I腫瘍の約25%は、大腸がんまたは子宮内膜がんであった。しかし、Lynch症候群を有することが同定されたMSI-H/MSI-Iを有する患者の50% 近くが、これまでこの症候群と関連がないとされていたかまたはまれであったタイプのがん（中皮腫、肉腫、副腎皮質がん、悪性黒色腫、前立腺および卵巣胚細胞がんなど）を有していた。

## Full Text

A genomic study of more than 15,000 tumor samples shows that people with tumors that have high microsatellite instability (MSI-H) - a genomic marker associated with a large number of genetic mutations in the tumor - are more likely to have Lynch syndrome, a hereditary condition that increases a person's risk of developing many different types of cancer. Among people with MSI-H tumors, 16% were subsequently found to have Lynch syndrome. Researchers also found that Lynch syndrome is linked to more types of cancer than previously thought.

The study was presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.

"Our findings suggest that all patients with MSI-H tumors should be tested for Lynch syndrome, regardless of cancer type or family or personal history of cancer," said senior study author Zsofia Kinga Stadler, MD, Clinic Director of the Clinical Genetics Service and a medical oncologist at Memorial Sloan Kettering Cancer Center in New York. "Diagnosing Lynch syndrome gives us the unique opportunity of helping not only our cancer patients, but also at-risk family members, as their cancer risk can be lowered through increased cancer surveillance and, in some cases, preventive surgery."

It is estimated that about 1 in 300 (0.3%) people in the general population has Lynch syndrome, which increases a person's risk of developing several cancers. The most common cancers associated with Lynch syndrome are colorectal and endometrial, but people with Lynch syndrome also have a higher risk of developing other gastrointestinal (beyond colorectal), ovarian, brain, and skin cancers. The hallmark of Lynch syndrome-associated tumors is MSI-H.

MSI is a genomic marker that indicates a defect in a cell's ability to repair damaged DNA, resulting in the accumulation of mutations. Traditionally, MSI testing has been performed on colorectal and endometrial cancers as an initial screening test to identify those patients who may be at risk for having Lynch syndrome.

Researchers analyzed more than 15,000 tumor samples collected from patients with more than 50 different types of advanced cancer using a comprehensive genomic test called MSK-IMPACT. All study participants were part of a prospective study of MSK-IMPACT and received cancer treatment at the Memorial Sloan Kettering Cancer Center in New York.

Researchers also tested blood samples from study participants for inherited mutations in genes involved in DNA repair: MLH1, MSH2, MSH6, PMS2, and EPCAM. Mutations in these genes cause Lynch syndrome. Tumors caused by Lynch syndrome have mismatch repair deficiency (MMR-D) and are MSI-H.

Based on the results of the genomic analysis, the tumor samples were classified into three groups: MSI-stable (MSS, no MSI instability found), MSI-indeterminate (MSI-I, moderate level of MSI), and MSI-H. The vast majority (93.2%) of tumors were found to be MSS; 4.6% were MSI-I; and 2.2% were MSI-H.

Inherited mutations in Lynch syndrome-associated genes were found in 16% of people with MSI-H tumors, compared to 1.9% of those with MSI-I tumors and only 0.3% of those with MSS tumors.

As expected, about 25% of the 1,025 MSI-H/MSI-I tumors were colorectal or endometrial cancers. These are the most common cancers linked to Lynch syndrome, and MSI testing is routinely performed on such tumors. However, nearly 50% of patients with MSI-H/MSI-I tumors who were identified as having Lynch syndrome had cancer types not previously, or rarely, linked to the syndrome, including: mesothelioma, sarcoma, adrenocortical cancer, melanoma, prostate, and ovarian germ cell cancer. Of these patients, 45% did not meet Lynch syndrome genetic testing criteria based on family or personal cancer history. According to the authors, this suggests that Lynch syndrome is linked to a broader spectrum of cancers than previously thought and that MSI-H/MMR-D is predictive of Lynch syndrome, regardless of cancer type.

In the final step of the study, 57 MSI-I/MSI-H tumor samples were also tested for abnormal DNA repair proteins - and MMR-D was found in nearly all (98.3%) of those tumors. These findings suggest that if either MSI-H or MMR-D is found in the tumor, hereditary genetic testing for Lynch syndrome should be performed.

"This study enhances our ability to catch Lynch syndrome where it may have been previously overlooked, thanks in large part to advances in precision medicine. This gives us a valuable opening to preempt future cancers in our patients through better, earlier, and more accurate diagnosis of Lynch syndrome," said ASCO Expert Shannon Westin, MD.

The chance of developing certain cancers linked to Lynch syndrome can be lowered through frequent screening (e.g., yearly colonoscopy and endoscopy for gastrointestinal cancers) and preventive surgery (e.g., removal of the uterus and ovaries for gynecologic cancers). More research is needed to develop screening and preventive strategies for other cancers linked to Lynch syndrome.

This study received funding from the Romeo Milio Lynch Syndrome Foundation, the Marie-Josée and Henry R. Kravis Center for Molecular Oncology, the Robert and Kate Niehaus Center for Inherited Cancer Genomics, the Fieldstone Family Fund, a Stand Up to Cancer Colorectal Cancer Dream Team Translational Research Grant, and the NIH/NCI Cancer Center Support Grant.

## ASCO2018特集

# 血液検査が早期肺がんを検出できる可能性が示された(Abstract LBA8501)

## CCGA：血液検体から得たゲノムシークエンシングは、早期および進行期肺がんのいずれも検出するのに成功した

## CCGA: Genome sequencing from blood samples successfully identifies both early- and late-stage lung cancer

現在進行中の大規模試験Circulating Cell-Free Genome Atlas (CCGA) により、血液検査が早期肺がんを検出できる可能性があるとの予備的なエビデンスが得られる。このサブ解析で研究者らは、I～IV期肺がんを有する患者127人において、3つの異なるアッセイのがん検出能を調査した。肺がんの生物学的シグナルは、試験したアッセイ全てにおいて同等であった。このシグナルは、がんのステージとともに増加し、偽陽性率が低かった。580のコントロール検体のうち、5例（<1%）は3つ全てのアッセイにおいてがん様シグナルを有していた。これらのうち、2例はその後がんと診断されており、これらの検査が早期がんを検出する可能性を強調している。

## Full Text

An initial report from the large, ongoing Circulating Cell-Free Genome Atlas (CCGA) study provides preliminary evidence that a blood test may be able to detect early-stage lung cancer. This is one of the first studies to explore blood tests analyzing free-floating or cell-free DNA as a tool for early detection of cancer.

The findings are featured at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.

"We're excited that initial results from the CCGA study show it is possible to detect early-stage lung cancer from blood samples using genome sequencing," said lead study author Geoffrey R. Oxnard, MD, Associate Professor of Medicine at Dana-Farber Cancer Institute and Harvard Medical School in Boston, MA. "There is an unmet need globally for early detection tests for lung cancer that can be easily implemented by health care systems."

Survival rates are significantly higher when lung cancer is diagnosed early. Globally, low-dose computed tomography (LDCT) is not widely adopted due to cost and lack of health infrastructure. Having a blood test that can be done through a simple blood draw at the doctor's office may improve lung cancer screening rates, but before such a test could be widely used, additional validation in larger data sets and in studies with people who have not been diagnosed with cancer would be needed.

Analysis of cell-free DNA from blood is already used to help choose targeted therapies (e.g., the cobas EGFR mutation test), but such "liquid biopsies" are used only for people with advanced lung cancer. Until recently there has been limited evidence to show cell-free DNA analysis may be feasible for early detection of lung cancer.

The CCGA study has enrolled more than 12,000 of the planned 15,000 participants (70% with cancer, 30% without cancer), across 141 sites in the United States and Canada. This report is from the first pre-planned sub-study from the CCGA, in which three prototype sequencing assays were performed on blood samples from approximately 1,700 participants. Twenty different cancer types across all stages were included in the sub-study (additional early results from the sub-study, including breast, gastrointestinal, gynecologic, blood and other cancers will be presented separately at the 2018 ASCO Annual Meeting, see abstracts #536 and #12021, and #12003).

In this initial sub-analysis, researchers explored the ability of three different assays to detect cancer in 127 people with stage I-IV lung cancer. The three assays that were designed to detect mutations and other genomic changes that could be used in the development of an early cancer detection test are:

- Targeted sequencing to detect somatic mutations, such as single nucleotide variants and small insertions and/or deletions
- Whole-genome sequencing (WGS) to detect somatic gene copy number changes
- Whole-genome bisulfite sequencing (WGBS) of cfDNA to detect abnormal cfDNA methylation patterns (epigenetic changes)

Among the 127 participants with lung cancer, the biologic signal for lung cancer was comparable across the assays, and the signal increased with cancer stage. At 98% specificity, the WGBS assay detected 41% of early stage (stage I-IIIA) lung cancers and 89% of late-stage (stage IIIB-IV) cancers. The WGS assay was similarly effective, detecting 38% of early-stage cancers and 87% of late-stage cancers, whereas the targeted assay detected 51% of early-stage cancers and 89% of late- stage cancers.

Initial results showed that all three prototype assays could detect lung cancer with a low rate of false positive findings. Of the 580 control samples in the sub-study, five (<1%) had a cancer-like signal across all three assays. Of those five participants, two were subsequently diagnosed with cancer (one with stage III ovarian cancer, and one with stage II endometrial cancer), highlighting the potential for such a test to identify early stage cancers.

The study also found that in the participants with lung cancer, more than 54% of somatic mutations detected in the blood samples were derived from white blood cells and not from tumors. These mutations are likely due to natural aging processes (so-called clonal hematopoiesis of indeterminate potential, or CHIP) and will be important to consider when developing blood tests for early detection of cancer, noted Dr. Oxnard.

"We're one step closer to being able to detect early lung cancer from a simple blood test. While there's still a way to go before cell-free DNA from blood can be used for cancer detection on a broad scale, this research serves as a building block for the development of future tests," said ASCO Expert David Graham, MD, FASCO.

The researchers are verifying these results in an independent group of approximately 1,000 participants from CCGA as part of the same sub-study.

"These are promising early results, and next steps are to further optimize the assays and validate results in a larger group of people," said Dr. Oxnard. With increased sample sizes, machine learning approaches are expected to improve assay performance, he noted.

This study was funded by GRAIL, Inc.

## ASCO2018特集

# 進行腎臓がんに対する腎摘出術回避 (Abstract LBA3)

## CARMENA：転移性腎細胞がん患者の多くが手術を必要としない
## CARMENA: Many people with metastatic renal cell carcinoma do not need surgery

2018 ASCO Annual Meetingで発表されたランダム化第III相臨床試験の結果、同時発症転移性腎細胞がんの患者の多くが生存期間を短縮することなく手術を回避できることが示された。このCARMENA試験対象患者の全生存期間は、スニチニブによる標的療法のみの群で18.4か月であったのに対し、現在の標準治療である手術後にスニチニブ投与群では13.9か月であった。治療奏効率はこれら2つの群で同等であり、がん増悪までの期間中央値はスニチニブのみを投与された患者でやや長かった（8.3か月対7.2か月）。

## Full Text

A randomized phase III clinical trial showed that many people with advanced kidney cancer can avoid a nephrectomy, without compromising survival. The median overall survival for people who received only the targeted therapy sunitinib was 18.4 months, compared to 13.9 months for those who received surgery followed by sunitinib, the current standard of care.

These findings will be presented in ASCO's Plenary Session, which features four studies deemed to have the greatest potential impact on patient care, out of the more than 5,800 abstracts featured as part of the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.

"Until now, nephrectomy has been considered the standard of care for patients with kidney cancer who have metastatic disease when the cancer is first diagnosed. These cases account for about 20% of all kidney cancers worldwide," said lead study author Arnaud Mejean, MD, a urologist at the Department of Urology, Hôpital Européen Georges-Pompidou - Paris Descartes University in Paris, France. "Our study is the first to question the need for surgery in the era of targeted therapies and clearly shows that surgery for certain people with kidney cancer should no longer be the standard of care."

In addition to putting patients at risk for complications, including blood loss, infection, pulmonary embolism, and heart problems, nephrectomy delays medical treatment for people with advanced kidney cancer for weeks. In some cases, the cancer worsens so rapidly during this delay that there is no time to start systemic treatment.

The CARMENA trial enrolled 450 patients with synchronous metastatic renal cell carcinoma (mRCC). An estimated 40,000 to 50,000 people each year are diagnosed with this type of cancer.

The patients were randomly assigned to receive surgery followed by sunitinib or sunitinib alone. In the surgery group, patients started sunitinib 4-6 weeks after surgery to allow time for recovery from surgery.

Patients were followed for a median time of 50.9 months. Survival was not worse with sunitinib alone than with surgery and sunitinib. This was true for the study population as a whole (median survival was 18.4 months without surgery vs. 13.9 months with surgery), as well as for subgroups with an intermediate (median survival was 23.4 months vs. 19 months) and poor prognosis (median survival was 13.3 months vs. 10.2 months) groups.

The difference in median survival seems to suggest a greater benefit with sunitinib alone. However, this cannot be concluded, as this trial was not designed to prove that one treatment is superior to the other, noted Dr. Mejean.

The rate of tumor response to therapy was the same in the two treatment groups (27.4% and 29.1%) and the median time until the cancer worsened was slightly longer for patients who received sunitinib alone compared with those who also had surgery (8.3 months vs. 7.2 months). Clinical benefit was experienced by 47.9% of patients treated with sunitinib only, compared with 36.6% of patients treated by surgery and sunitinib.

The authors remarked that kidney surgery is still the gold standard for people who do not need systemic therapy, such as those with only one metastasis. Those patients were not included in this clinical trial.

"Thanks to this research, many patients with advanced kidney cancer can be spared unnecessary surgery and a host of severe side effects that often accompany it. These findings will likely lead to a dramatic change in treatment for people who are diagnosed with metastatic kidney cancer," said ASCO Expert Sumanta K. Pal, MD.

Some patients in the study had a very good response to sunitinib alone and received surgery after completing systemic treatment. The researchers plan to continue following outcomes in these patients, as well as in other subgroups of study participants. Genomic research on tumor tissue collected on the study is underway.

This study received funding from PHRC (French governmental grants for clinical research).

## ASCO2018特集

# 膵がんにおいて術前化学放射線療法は有益である (Abstract LBA4002)

## PREOPANC：術前の放射線療法を併用した化学療法は膵がん患者の生存率を改善する可能性がある

## PREOPANC: Pre-operative chemotherapy with radiation may improve survival for people with pancreatic cancer

2018 ASCO Annual Meetingで取り上げられた第III相試験の結果、膵がんの術前に化学放射線療法を施行された患者は、治療を手術から開始する現在の標準治療を施行された患者に比べ無病生存期間が優れていたことが明らかにされた。このPREOPANC試験における全生存期間中央値は、術前化学放射線療法群で17.1か月であったのに対し、すぐに手術を施行された患者群では13.7か月であった（P=0.074）。膵がん再発までの期間もまた、術前治療群の方が長かった（9.9か月対7.9か月、P=0.023）。2年生存率についてもまた、術前化学放射線療法施行群において高かった（42% vs. 30%）。

## Full Text

A randomized, phase III trial found that people who received chemoradiotherapy before pancreatic cancer surgery had better disease-free survival than those who started their treatment with surgery, which is the current standard of care. In addition, the two-year survival rate was higher for those who received chemoradiotherapy before surgery (42% vs. 30%). The preliminary findings of this trial show that chemoradiotherapy before surgery may be beneficial for patients with pancreatic cancer.

The study was presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.

"This is the first randomized clinical trial to show that pre-operative treatment improves outcomes for people with early stages of pancreatic cancer who can have surgery," said principal investigator Geertjan Van Tienhoven, MD, PhD, radiation oncologist at the Department of Radiation Oncology, Academic Medical Center in Amsterdam, the Netherlands. "We believe that this may be a practice-changing trial."

The PREOPANC-1 trial enrolled 246 patients with pancreatic cancer that can be surgically removed. The patients were randomly assigned to receive immediate surgery or chemoradiotherapy for 10 weeks, followed by surgery. Both treatment groups also received chemotherapy after surgery, and the total amount of chemotherapy given was equal in both groups. (The chemoradiotherapy group received part of the chemotherapy before surgery and the rest after.)

The median overall survival was 17.1 months with preoperative chemoradiotherapy compared to 13.7 months (p=0.074) with immediate surgery. The time until pancreatic cancer recurrence was longer with preoperative therapy, as well (9.9 months vs. 7.9 months, p=0.023). The chance of surviving longer than two years was also higher with pre-operative treatment than with immediate surgery (42% vs. 30%). In the subset of patients in which the tumor was surgically removed successfully, the difference in median survival was even greater: 42.1 months with preoperative treatment vs. 16.8 months with immediate surgery.

Resection was performed in 72% of patients in the immediate surgery group and 62% in the chemoradiotherapy group. Among the patients who had a resection, the tumor was microscopically completely removed in a greater proportion of patients who received preoperative treatment (63% vs. 31%).

"This study is an example of how treatments can be refined in an attempt to work better for patients. It's also a step in the right direction for people with pancreatic cancer, a disease that has proved extremely difficult to cure," said ASCO Expert Andrew Epstein, MD.

According to the authors, after the final analysis and publication of this trial, the next step is to attempt to find even more effective preoperative treatments. FOLFIRINOX chemotherapy or FOLFIRINOX combined with stereotactic body radiation therapy appear promising from other studies and should be tested against pre- operative gemcitabine and radiation in a randomized clinical trial.

This study received funding from the Dutch Cancer Society KWF.

## ASCO2018特集

# 新たな化学療法レジメンは膵がんの生存率を改善する(Abstract LBA4001)

## 新たな化学療法レジメンは膵がん患者の生存期間を20か月近く延長させる

Chemotherapy regimen extends life by nearly 20-months for people with pancreatic cancer

第III相ランダム化試験において、膵がんを外科的に切除されmFOLFIRINOX（オキサリプラチン、ロイコボリン、イリノテカン、および5-フルオウラシルを含む化学療法）を施行された患者は、現在の標準治療であるゲムシタビンを投与された患者に比べ無病生存期間が有意に長かった。追跡期間中央値33.6か月の時点で、mFOLFIRINOX群における無病生存期間中央値は21.6か月であったのに対し、ゲムシタビン群では12.8か月であった。全生存期間中央値はmFOLFIRINOX群で54.4か月であったのに対し、ゲムシタビン群では35.0か月であった。mFOLFIRINOXの有益性は全てのサブグループにおいて認められた。この試験結果は、2018 ASCO Annual Meetingで取り上げられた。

## Full Text

In a randomized phase III trial people with surgically removed pancreatic cancer who received mFOLFIRINOX, a chemotherapy regimen containing four different medicines, lived a median of 20 months longer and were cancer-free nine months longer than those who received the current standard of care, gemcitabine.

The study was featured at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.

"For the first time, our trial shows a large benefit from adjuvant FOLFIRINOX chemotherapy over standard chemotherapy with gemcitabine, showing we can help patients with pancreatic cancer live much longer," said lead study author Thierry Conroy, MD, a medical oncologist and director of the Institut de Cancerologie de Lorraine in Nancy, one of the UNICANCER comprehensive cancer centers in France. "In addition, we were encouraged to see that the results were better than expected when we planned this trial."

After pancreatic cancer surgery, adjuvant chemotherapy with gemcitabine can substantially prolong survival compared to surgery alone, as well as increase the number of patients who are cured at 5 years (about 21% with gemcitabine vs. 10% with surgery alone). Gemcitabine has been the standard adjuvant therapy for the past 10 years.

The PRODIGE 24/CCTG PA.6 trial enrolled patients with non-metastatic pancreatic ductal adenocarcinoma (PDAC) who had surgery that removed all or nearly all of the tumor (no cancer cells were visible to the surgeon after surgery, but microscopic tumoral cells may have remained). PDAC is the most common type of pancreatic cancer and accounts for 90% of all cases. Surgery is possible in only 10-20% of patients with pancreatic cancer overall.

Three to 12 weeks after surgery, 493 patients were randomly assigned in France and in Canada to receive either gemcitabine or mFOLFIRINOX for six months. The mFOLFIRINOX regimen combines four chemotherapy medicines: oxaliplatin, leucovorin, irinotecan, and 5-fluorouracil. A very similar regimen is already used as an initial treatment for metastatic pancreatic cancer, and this study shows FOLFIRINOX can also benefit patients with earlier-stage disease.

At a median follow-up of 33.6 months, the median disease-free survival was much longer in the mFOLFIRINOX group than in the gemcitabine group (21.6 months vs. 12.8 months), as was the median overall survival (54.4 months with mFOLFIRINOX vs. 35.0 months with gemcitabine). The benefit of the mFOLFIRINOX is observed in all subgroups of patients. mFOLFIRINOX also markedly extended the time until metastases appeared (median 30.4 months vs. 17.0 months with gemcitabine).

Overall, more patients experienced severe side effects (mainly hematologic) in the mFOLFIRINOX group than in the gemcitabine group (76% vs. 53%), but the side effects were manageable, according to the authors. One treatment- related death occurred in the gemcitabine group, and none in the mFOLFIRINOX group.

The types of side effects also differed between the two groups. The most common side effects of gemcitabine were headache, fever, flu-like symptoms, swelling, and low white blood cell counts. Patients who received mFOLFIRINOX had more diarrhea, nausea, vomiting, and fatigue. There was no difference in the risk of febrile neutropenia between the two groups.

Past medical history of ischemic heart disease represents a risk with either regimen, but particularly mFOLFIRINOX.

"Pancreatic cancer is notoriously aggressive and typically has a poor prognosis, so it is a major win to find that a new treatment regimen significantly improves survival for patients with this disease," said ASCO Expert Andrew Epstein, MD.

The next step will be to explore the timing of chemotherapy. Patients may benefit from neoadjuvant chemotherapy to shrink the tumor, to destroy undetectable micrometastases and increase the chance that the tumor can be completely removed through surgery. Dr. Conroy noted that mFOLFIRINOX appears to be a good candidate for neoadjuvant chemotherapy. Another option is to give half the cycles of chemotherapy before, and the other half after surgery. Ongoing clinical trials are already testing both of these approaches.

This study, sponsored by UNICANCER, Paris, France, received funding from the Institut National du Cancer in France, French National Ligue Against Cancer, Canadian Cancer Society and "7 days in May," a charity cycling event in Canada.

## ASCO2018特集

# 進行大腸がんに対しては治療が少ない方がよい可能性がある(Abstract LBA3503)

## 癌性腹膜炎患者において腹腔内温熱化学療法は有益でない

## Heated abdominal chemotherapy not beneficial in patients with peritoneal carcinomatosis

2018 ASCO Annual Meetingで取り上げられた第III相ランダム化試験の結果、進行大腸がん患者には腹腔内温熱化学療法(HIPEC)は不要である可能性があることが示された。追跡期間中央値64か月の時点で、全生存期間中央値は2群間で差はなかった(非HIPEC群41.2か月対HIPEC群41.7か月、p=0.995)。無再発生存期間もまた、2群間で同様であった(非HIPEC群11.1か月対HIPEC群13.1か月、p=0.486)。長期の副作用は化学療法の方が多かった。

## Full Text

A randomized phase III clinical trial shows that people with advanced colorectal cancer may not need a frequently considered component of treatment – heated chemotherapy delivered to the abdomen during surgery. There was no difference in survival between patients with metastases in the abdomen who received heated chemotherapy during surgery and those who received surgery alone. Long- term side effects were more common with chemotherapy.

The study was featured at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.

Peritoneal carcinomatosis occurs in about 20% of people with metastatic colorectal cancer. When tumors can be completely removed, a treatment that has been used is surgery with hyperthermic intra-peritoneal chemotherapy (HIPEC). Surgery with HIPEC may prolong survival compared to systemic therapy alone, and surgery may cure up to 16% of patients with peritoneal carcinomatosis.

"When this approach was introduced more than 15 years ago, it was the first effective treatment for metastatic tumors on a patient's abdomen, but we didn't know whether delivering heated chemotherapy during surgery was an important component of the treatment or not," said lead study author Francois Quenet, MD, head of the hepato-biliary and peritoneal surface malignancy unit at the Regional Cancer Institute in Montpellier, France. "This is the first randomized study assessing the role of this special type of chemotherapy in advanced colorectal cancer, and it shows that it does not provide added benefit over surgery."

The PRODIGE 7 trial enrolled 265 patients in France who had stage IV colorectal cancer with peritoneal carcinomatosis, and no metastases elsewhere in the body. The patients were randomly assigned to receive surgery plus HIPEC (chemotherapy oxaliplatin heated to 43°C in an attempt to increase chemotherapy efficacy) or surgery alone. Most (96%) of the patients also received systemic chemotherapy, before surgery, after surgery or both. The type of systemic therapy was per physician choice.

At a median follow-up of 64 months, the median overall survival was 41.2 months in the non-HIPEC group vs. 41.7 months in the HIPEC group (p=0.995). The recurrence-free survival was also similar between the two groups: median 11.1 months in the non- HIPEC group vs. median 13.1 months in the HIPEC group (p=0.486).

The overall mortality rate at 30 days after surgery was 1.5% in both groups, and there was no difference in the rate of side effects during the first 30 days. At 60 days, however, the rate of complications in the HIPEC group was almost double that in the non-HIPEC group (24.1% vs. 13.6%).

"This study is an example where less is more. It suggests we can spare many people with colorectal cancer from unnecessary chemotherapy that often comes with harsh side effects," said ASCO Expert Andrew Epstein, MD.

More research is needed to determine if there are patients who would still benefit from receiving HIPEC with surgery. A subgroup analysis from this study suggests that HIPEC might be beneficial for patients with a mid-range peritoneal cancer index, but the numbers were too small to be conclusive. People with a low peritoneal cancer index can likely forgo HIPEC, whereas those with a high index may not benefit from either surgery or HIPEC. Meanwhile, other types of chemotherapy may be more effective than oxaliplatin, the type of chemotherapy used in HIPEC for this study.

This study received funding from R&D UNICANCER.

## ASCO2018特集

# ここ30年における横紋筋肉腫治療の一番の進歩 (Abstract LBA2)

## 維持化学療法は小児横紋筋肉腫の生存期間を延長する

Maintenance chemotherapy extends life for children with rhabdomyosarcoma

新たな化学療法戦略は、再発リスクの高い小児横紋筋肉腫の治癒率を改善する、と2018 ASCO Annual Meeting Plenary Sessionで取り上げられた。標準的な初期治療完遂後、371人が治療中止（以前の標準治療）群または低用量ビノレルビン静注およびシクロホスファミド経口投与6か月施行群に、ランダムに割り付けられた。診断後5年時点における無病生存率は、標準治療群の68.8%に対し維持療法群では77.6%であり、全生存率はそれぞれ73.7% 対 86.5% であった。

## Full Text

A new chemotherapy strategy improves cure rates for children with rhabdomyosarcoma who are at high risk for cancer recurrence. In a randomized phase III clinical trial, adding six months of low-dose maintenance chemotherapy after initial treatment increased the 5-year overall survival rate from 73.7% to 86.5%. Children with rhabdomyosarcoma who are alive at five years are considered cured, as tumor recurrence is very rare.

These findings were presented in ASCO's Plenary Session, which features four studies deemed to have the greatest potential to impact patient care, out of the more than 5,800 abstracts featured as part of the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.

"We have been treating rhabdomyosarcoma the same way for more than 30 years, and although different approaches have been tried, this is the first randomized trial in rhabdomyosarcoma to show improved outcomes. By using existing medicines in new ways, we are establishing a new standard of care and, most importantly, we're helping children and young adults with this rare cancer live longer, with less risk of their cancer returning," said lead study author Gianni Bisogno, MD, PhD, a professor at the University Hospital of Padova in Italy and Chair of the European Paediatric Soft Tissue Sarcoma Study Group.

Rhabdomyosarcoma originates in the muscle tissue and can occur in any part of the body, but it is most often found in the head, neck, pelvis, and abdomen. Rhabdomyosarcoma is rare, accounting for 4% of all childhood cancers.

The prognosis for rhabdomyosarcoma is generally good – 80% of children can be cured with modern treatment, which includes high-dose chemotherapy, radiation, and surgery. However, among children who have metastasis at diagnosis or a recurrence after initial treatment, only 20-30% can be cured.

This trial enrolled patients 6 months to 21 years of age who were considered at high risk for recurrence due to having large tumors located in a part of the body that is difficult to treat (e.g., the head).

After completing the standard initial treatment, 371 patients (79% of whom were 10 years old or younger) were randomly assigned to either stop treatment (the former standard of care) or receive six months of maintenance therapy with low doses of two chemotherapy medicines (intravenous vinorelbine and oral cyclophosphamide).

At five years from diagnosis, the disease-free survival (defined as five years without tumor recurrence or death from any cause) was 68.8% in the standard treatment group vs. 77.6% in the maintenance group, and overall survival rates were 73.7% vs. 86.5%, respectively.

The most common side effect in the maintenance group was low blood cell count, though it was usually mild. Febrile neutropenia occurred in 25% of patients. Infection rates were much lower with maintenance treatment than after initial standard chemotherapy, and neurologic side effects resolved after treatment ended. However, as with most kinds of chemotherapy, long-term side effects are still possible and patients will continue to be monitored.

"By keeping the pressure on this cancer longer with maintenance therapy, we are giving patients two wins – we are boosting cure rates by preventing relapses and doing so with few serious side effects. After three decades of research, this finding goes to show that we will continue innovating treatment, no matter how long it takes," said ASCO Expert Warren Chow, MD.

The findings of this trial have already changed the standard of care in Europe, where investigators shared the results with soft tissue sarcoma study group institutions in 14 countries.

This study received funding from Fondazione Città della Speranza, Italy.

## ASCO2018特集

# エソメプラゾールとアスピリンの併用は食道がんを予防する(Abstract LBA4008)

## AspECT：アスピリンとプロトンポンプ阻害薬の併用はバレット食道患者に有益である

## AspECT: Aspirin plus proton pump inhibitor benefits patients with Barrett's esophagus

ランダム化第III相試験の最新解析の結果、高用量のプロトンポンプ阻害薬（エソメプラゾール）と低用量アスピリンの併用を7年以上継続することにより、バレット食道患者の高度異形成または食道がん発症リスクが中程度減少、または総死亡を遅らせる可能性があることが示された。高用量エソメプラゾールは、標準用量エソメプラゾールに比べ複合評価項目について統計学的に有意に有益であった（p=0.0459）。最も有効な治療は、高用量エソメプラゾールと低用量アスピリンの併用であった。AspECT試験のこの結果は、2018 ASCO Annual Meetingで発表された。

## Full Text

Findings from an updated analysis from a randomized phase III trial show that taking a high dose of the acid-reducing medicine esomeprazole with low dose aspirin for at least seven years can moderately reduce the risk of developing high grade dysplasia or esophageal cancer, or delay death from any cause in people with Barrett's esophagus.

The findings were presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.

The authors estimate that development of these outcomes could be delayed by using these simple, over-the-counter medicines. Esophageal cancer is an uncommon cancer, but very difficult to screen for and treat – less than 1 in 5 (19%) of patients survive 5 years after diagnosis.

"Based on these data, we believe people with heartburn should talk with their doctor about their risk of Barrett's esophagus, but they should not self-mediate with these medications," said lead study author Janusz Jankowski, MD, PhD, Deputy Vice Chancellor, Royal College of Surgeons, Ireland and Consultant Clinical Adviser, National Institutes for Health and Care Excellence, UK. "We hope that the National Institute for Health and Care Excellence in the UK and national bodies in other countries will consider our findings when developing guidelines for esophageal cancer prevention."

Esophageal adenocarcinoma is the most common type of esophageal cancer in the West, accounting for two-thirds of all esophageal cancers. Esophageal cancer is the seventh leading cause of death from cancer in the world. Barrett's esophagus can develop in some people who have chronic gastroesophageal reflux disease (GERD) or esophagitis even when a person does not have symptoms of chronic heartburn. Damage to the lining of the esophagus causes the squamous cells in the lining of the esophagus to turn into glandular tissue. People with Barrett's esophagus are more likely to develop adenocarcinoma of the esophagus, but the risk of developing esophageal cancer is still fairly low.

It is estimated that Barrett's esophagus occurs in only 2% of adults in Western countries, but experts believe that it may be underdiagnosed. Although people with this condition have a much higher risk for esophageal cancer compared to the general population, their absolute risk is still very small – the lifetime chance of developing the disease is only 2%.

It is estimated that 80-90% of esophageal cancers are preceded by Barrett's esophagus, but most of the time cancer is diagnosed before Barrett's esophagus. Prior research has suggested that acid reduction with standard-dose proton pump inhibitors might prevent progression of Barrett's esophagus to cancer. There is also evidence from observational studies that aspirin is effective in preventing gastrointestinal cancers, including esophageal cancer.

The ASPECT trial randomly assigned 2,563 people with Barrett's esophagus to four treatment groups:

- High dose proton pump inhibitor esomeprazole
- High dose esomeprazole with low dose aspirin
- Standard dose (e.g., low dose) esomeprazole
- Standard dose (e.g., low dose) esomeprazole with low dose aspirin

The primary endpoint was time to death from any cause, diagnosis of esophageal cancer or diagnosis of high-grade dysplasia (three combined events). The analysis adjusted for patient's age and duration of Barrett's esophagus.

Patients were followed for a median of 8.9 years, and high dose esomeprazole had a statistically significant benefit on the combined endpoint compared to standard dose esomeprazole (p=0.0459). The most effective treatment was high dose esomeprazole with low dose aspirin.

Aspirin showed no benefit compared to no aspirin in the primary analysis. However, there was a weak effect when researchers censored for prior NSAID.
The treatments were safe overall, with serious side effects reported in only 1% of patients. Although both medicines are generally very safe, precautions should be taken before starting this regimen, noted Dr. Jankowski.

The most common side effect of proton pump inhibitors is diarrhea. People with heart disease should be aware that these drugs can interact with various heart medications. Other, much more rare risks include Clostridium difficile infection and osteoporosis. The most serious side effects of aspirin include allergic reactions, bleeding in the stomach, and bleeding in the brain (particularly for people with high blood pressure). In addition, people who are already taking another non-steroidal anti-inflammatory drug (NSAID), should not be taking aspirin.

"The risk of esophageal cancer weighs on patients with Barrett's esophagus. For these patients, and with little to no side effects. It's an approach that people with Barrett's should consider and discuss with their doctors," said ASCO Expert Andrew Epstein, MD.

Although this was the largest chemoprevention randomized controlled trial in Barrett's esophagus and it had the longest follow-up, more research is needed, noted Dr. Jankowski. The research was conducted in only five countries with mostly white populations, so it is not known if this chemoprevention strategy would be as effective in black and Asian people, as genetic ancestry can affect treatment efficacy. In addition, the researchers would like to follow patients on this study to see if 9-10 years of chemoprevention is even more effective and whether there is an increased risk for side effects with longer treatment.

This study received funding from Cancer Research UK.

## ASCO2018特集

# 進行扁平上皮NSCLCの予後改善 (Abstract LBA9000)

## IMpower131：化学療法にアテゾリズマブによる免疫療法を上乗せすることにより進行扁平上皮肺がんの増殖を遅らせることができる

## IMpower131: Adding atezolizumab immunotherapy to chemotherapy slows growth of advanced squamous lung cancer

第III相臨床試験の初回結果によると、進行扁平上皮非小細胞肺がん（NSCLC）患者にとって、化学療法単独による初回治療に比べ、化学療法にアテゾリズマブによるPD-L1標的免疫療法を上乗せする初回治療の方がより有益である-疾患増悪または死亡リスクが化学療法単独に比べ29%低かった（p=0.0001）。この併用療法により無増悪生存の有益性が倍になった：12か月後、がんが悪化していなかったのは、免疫療法と化学療法の併用群で24.7%、化学療法単独群では12% であった。この有益性は、PD-L1発現サブグループすべてにおいて認められた。IMpower131試験のこの結果は、2018 ASCO Annual Meetingで発表された。

## Full Text

Initial findings from a randomized phase III clinical trial show that patients with advanced squamous non-small-cell lung cancer (NSCLC) benefit more from initial treatment with PD-L1 targeted immunotherapy atezolizumab and chemotherapy than from chemotherapy alone – 29% had a reduced risk of disease worsening or death compared with those who received chemotherapy alone. At 12 months, cancer had not worsened in twice as many patients who received atezolizumab plus chemotherapy compared to those who only received chemotherapy. This benefit was observed across all PD-L1 expressing sub-groups.

The findings from the IMpower131 trial were presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.

"Until now, there have been few treatment advances for squamous non-small-cell lung cancer. Our findings may provide a new potential treatment option for this type of cancer," said lead study author Robert M. Jotte, MD, PhD, Medical Director and Co-Chair, USON Thoracic Committee, Rocky Mountain Cancer Centers in Denver, CO. "We used to think that chemotherapy just knocked down the patient's immune system and that it would be irrational to combine it with immunotherapy, but growing research, including this study, shows that chemotherapy can help trigger the immune response to the tumor, helping the immunotherapy treatment work better."

Squamous NSCLC, which accounts for 25-30% of NSCLCs, is very difficult to treat. Fewer than 15% of people with advanced squamous NSCLC survive a year after diagnosis, and less than 2% survive five years.

Recent studies have also found a benefit of combining immunotherapy with chemotherapy in non-squamous lung cancer. Given those findings, along with the results from this trial, a rapid change in clinical practice is expected, noted Dr. Jotte.

The IMpower131 trial enrolled 1,021 patients with stage IV squamous NSCLC. Tumors were tested for PD-L1 expression, but patients were included in the trial regardless of tumor PD-L1 expression level. Patients with EGFR or ALK gene changes in the tumor received targeted treatments before starting therapy on this trial. The study participants were randomly assigned to one of three treatment groups. Outcomes for only two of the groups, however, are being reported in this presentation:

- Atezolizumab plus chemotherapy (carboplatin and nab-paclitaxel), 343 patients
- Chemotherapy (carboplatin and nab-paclitaxel), 340 patients

Outcome data for the third treatment group, which received atezolizumab with a slightly different chemotherapy regimen (carboplatin and paclitaxel), are not yet available.

In this study, 29% of all patients, regardless of PD-L1 expression, had a reduced risk of disease worsening or death, compared with those who received chemotherapy alone. Importantly, there was a doubling of progression-free survival (PFS) benefit with this combination: at 12 months, cancer had not worsened in 24.7% patients receiving immunotherapy and chemotherapy, compared to 12% of those receiving chemotherapy alone.

Improved progression-free survival was observed in all groups of patients who received immunotherapy and chemotherapy, including those with PD-L1-negative tumors and liver metastases. Overall survival data are not yet mature.

This is the first phase III trial of an immunotherapy-based combined modality treatment to show a significant improvement in progression-free survival in advanced squamous NSCLC, according to the authors. Although the difference between treatment groups is modest, a statistically significant improvement shows that, overall, people with advanced squamous lung cancer can benefit when immunotherapy is added to standard treatment, according to the authors.

Although the rate of severe side effects was higher with the combined modality treatment than with chemotherapy alone (68% vs. 57%), it had a manageable safety profile, consistent with known safety risks of the individual therapies. The most common side effects of atezolizumab included skin rash, colitis, and low thyroid hormone.

At this interim analysis, a statistically significant overall survival (OS) benefit was not observed (median OS was 14 months for atezolizumab plus chemotherapy vs. 13.9 months for chemotherapy alone). Researchers are continuing to follow patients and anticipate a subsequent analysis later this year.

"This is one more example of how immunotherapy is making steady gains against a number of cancers. Immunotherapy has been shown to be effective in other types of lung cancer, and now we're seeing encouraging improvements in advanced squamous lung cancer, which historically has been very difficult to treat," said ASCO Expert David Graham, MD, FASCO.

More research is needed to determine which patients benefit the most from the addition of immunotherapy to standard chemotherapy. The researchers will explore tumor PD-L1 expression and other molecular markers, such as tumor mutational burden (TMB), that may predict whether a patient will benefit from this treatment regimen.

This study received funding from F. Hoffmann-La Roche Ltd.

## ASCO2018特集