出國報告（出國類別：開會）

會議名稱

EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

2018 CONGRESS

服務機關：行政院衛生福利部彰化醫院

姓名職稱：樊 聖　醫師

派赴國家：德 國

出國期間：107 年 10 月 17 至 24 日

報告日期：107 年 12 月 12 日

摘要

歐洲腫瘤醫學會(European Society for Medical Oncology)今年舉行之學術會議(ESMO 2018 Congress)，於 107 年 10 月 19 日至 23 日在德國慕尼黑市舉行。此一例行之年度大會係世界各國專家學者齊聚之國際性腫瘤學會議。今年最突出之主題為癌症之免疫治療、標靶治療、和精準醫學。除了介紹最新發展之教育性質演講，各個癌別領域之論文與海報發表，亦是百家齊鳴，琳琅滿目，學之不及，猶恐失之。免疫治療之主要重點，在探討腫瘤細胞逃避免疫獵殺之機制，以及克服它的方法。最新進展之學習討論，不但可以更新各個癌別的治療指引，提供臨牀服務參考，也可刺激研究創新，因此參與此類高水準會議，實為提升自己醫學實力，最有效率之途徑。

目次

本文

目的

參加歐洲腫瘤醫學會(European Society for Medical Oncology)今年舉行之學術會議(ESMO 2018 Congress)，在於聆聽吸收世界頂尖級學者專家之綜論演講和最新臨床試驗結果之發表。本報告內容即擷取本次會議中最特出精彩，具臨床實用價值之學術報告 24 頂，整理成摘要，附以圖表，匯合成一可供國內醫界參考之簡明論述，希望能對未能親自參與本次會議之本國腫瘤專家提供助益。報告內容以中文標題及英文完成，列於「會議內容」一節中。

過程(會議過程及內容)

Highlights of the ESMO 2018 Congress; Munich, Germany: October 19-23, 2018: Selected Abstract presented

肺癌 **Lung Cancer**

1. 亞洲 ALK 陽性非小細胞肺癌病人之第一線 Alectinib 療效

First-Line Alectinib Effective in Asian Patients With *ALK*-Positive Advanced NSCLC: Zhou C, et al. Primary results of ALESIA: a randomised, phase III, open-label study of alectinib vs crizotinib in Asian patients with treatment-naive ALK+ advanced NSCLC. Abstract LBA10.

Investigators of the open-label, phase 3 ALESIA trial randomly assigned 187 Asian patients with *ALK*-positive stage IIIB or stage IV NSCLC 2:1 to receive alectinib or crizotinib. All patients had not received prior systemic treatment and patients with asymptomatic central nervous system (CNS) metastases were allowed to enroll. The primary end point was PFS (assessed via investigator analysis) and the secondary end points were PFS (assessed by an independent review committee), time to CNS progression, objective response rate (ORR), duration of response (DOR), overall survival (OS), CNS ORR, quality of life, and safety.

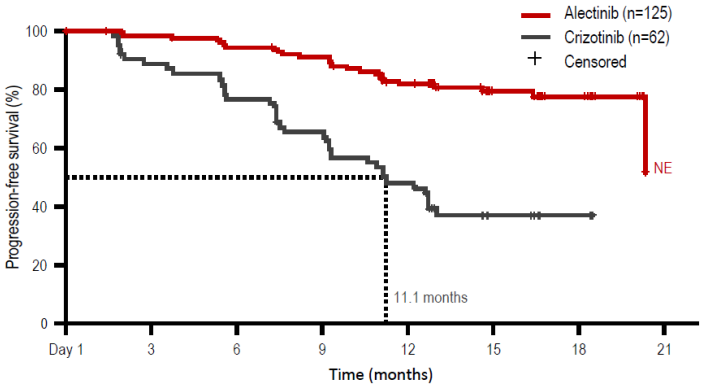
Alectinib met its primary end point, with a significant improvement in PFS with a median not yet reached compared with 11.1 months with crizotinib (HR, 0.22; 95% CI, 0.13-0.38; *P*< .0001). PFS was found to be similar when assessed by independent analysis (HR, 0.37; 95% CI, 0.22-0.61; P < .0001). The OS data are immature; the median in both arms had not yet been reached.
The ORR was higher with alectinib, at 91.2% compared with 77.4% with crizotinib (*P*= .0095). The DOR was also longer with alectinib, with a median not yet reached compared with 9.3 months with crizotinib. The time to CNS progression was also not yet reached with alectinib, but was 10.7 months with crizotinib (HR, 0.14; 95% CI, 0.06-0.30; *P*< .0001).

Grade 3 to grade 5 adverse events (AEs) were less common with alectinib, with a rate of 29% compared with 48% with crizotinib. The rate of serious AEs was 15% and 26% with alectinib and crizotinib, respectively. Discontinuation occurred in 7% and 10% of patients in the alectinib and crizotinib arms, respectively; discontinuation was due to AEs.

The authors concluded that the “ALESIA study results are consistent with the global ALEX study and confirm the clinical benefit of alectinib in Asian patients with advanced *ALK*-positive NSCLC.”

ALESIA PROGRESSION-FREE SURVIVAL (INVESTIGATOR)

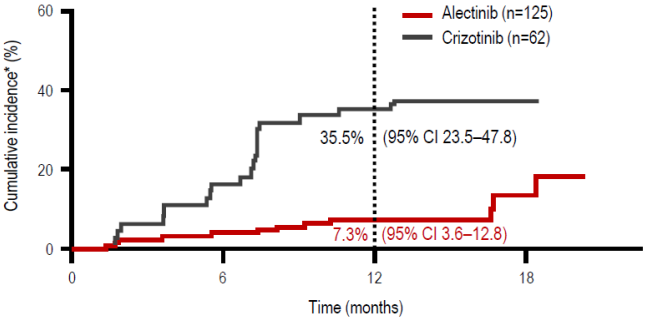
Primary endpoint



	Alectinib n=125	Crizotinib n=62
Patients with event, n (%)	26 (20.8)	37 (59.7)
Median PFS, months (95% CI)	**NE** (20.3–NE)	**11.1** (9.1–13.0)
HR (95% CI) P-value (log-rank test)	**0.22** (0.13–0.38) P<0.0001	

ALESIA TIME TO CNS PROGRESSION (IRC)

- A competing risk analysis with CNS progression, non-CNS progression and death as competing events was conducted; for each patient, only the first event was counted



Cause-specific HR (95% CI) P-value (log-rank test)	**0.14** (0.06–0.30) P<0.0001

*Cumulative incidence of CNS progression without prior non-CNS progression or death

2. 對 ALK 陽性之非小細胞肺癌之腦部轉移 Brigatinib 較 Crizotinib 更有效
Brigatinib Found More Effective for ALK-positive NSCLC Brain Mets Compared With Crizotinib: Popat S, Janne PA, et al. Intracranial efficacy of brigatinib (BRG) vs crizotinib (CRZ) in the phase 3 ALTA-1L trial. Abstract LBA58.

The next-generation ALK inhibitor brigatinib substantially delayed time to intracranial progression and prolonged interim progression-free survival (PFS) compared with crizotinib among patients with ALK-positive non-small cell lung cancer (NSCLC) with brain metastases, according to an analysis of the ALTA-1L trial.

In the phase 3 ALTA-1L trial, 275 patients with stage IIIB/IV ALK-positive NSCLC

without prior tyrosine kinase inhibitor (TKI) treatment were randomly assigned to receive brigatinib or crizotinib. The primary end point was PFS — as assessed by a blinded independent review committee (BIRC) — and the secondary end points included intracranial objective response rate (iORR) and intracranial PFS (iPFS).

Brigatinib met its primary end point in the phase 3 ALTA-1L trial of significantly prolonged PFS (hazard ratio [HR], 0.49; *P* = .0007) compared with crizotinib during its first interim analysis. This analysis evaluated outcomes of patients who had brain metastases at baseline.

A brain metastasis of any kind was present at baseline in 33% of patients, and measurable brain metastases were present in 14% of participants. In the study, 14% of patients with any brain metastases received previous treatment with brain radiotherapy.

Brigatinib significantly prolonged iPFS in the intention-to-treat (ITT) and brain metastases cohorts compared with crizotinib. The median iPFS of the ITT population was not reached in both arms, with a 1-year rate of 78% (95% CI, 68%-85%) with brigatinib compared with 61% (95% CI, 50%-71%) with crizotinib (hazard ratio [HR], 0.42; 95% CI, 0.24-0.70; log-rank *P* = .0006).

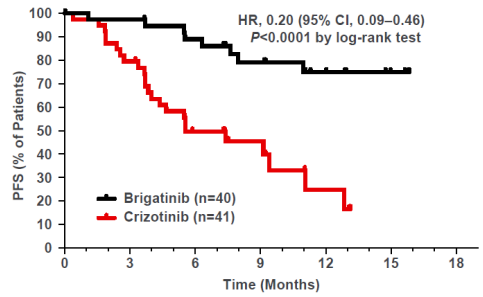
Among patients with any baseline brain metastases, the median iPFS was 6 months (95% CI, 4-9 months) with crizotinib and not yet reached with brigatinib. The 1-year iPFS was 67% (95% CI, 47%-80%) with brigatinib compared with 21% (95% CI, 6%-42%) with crizotinib (HR, 0.27; 95% CI, 0.13-0.54; log-rank *P* < .0001).

Brigatinib significantly prolonged the time to intracranial progression without prior systemic progression by 70% compared with crizotinib in the ITT population (HR, 0.30; 95% CI, 0.15-0.60; *P* < .001), with a 1-year cumulative incidence of 12% (95% CI, 6%-20%) and 23% (95% CI, 15%-31%), respectively. The brigatinib arm also demonstrated a delayed tie to systemic progression without prior intracranial progression compared with crizotinib (HR, 0.51; 95% CI, 0.30-0.86; *P* = .017).

The confirmed iORR among patients with any brain metastases at baseline was 67% and 17% with brigatinib or crizotinib, respectively (Cochran-Mantel-Haenszel test *P* < .0001). The confirmed iORR was higher among patients with measurable brain disease, with a confirmed rate of 78% and 29% with brigatinib or crizotinib, respectively (Cochran-Mantel-Haenszel test *P*= .0028).

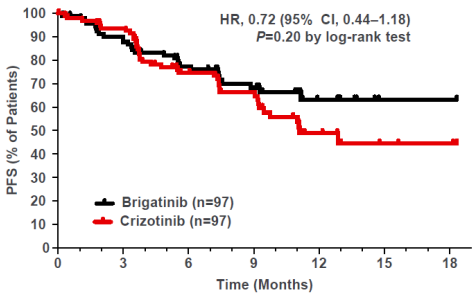
The authors concluded that these data suggest that “brigatinib has superior intracranial activity versus crizotinib in ALK TKI-naive patients with ALK-positive NSCLC.”

Patients With Brain Metastases at Baseline

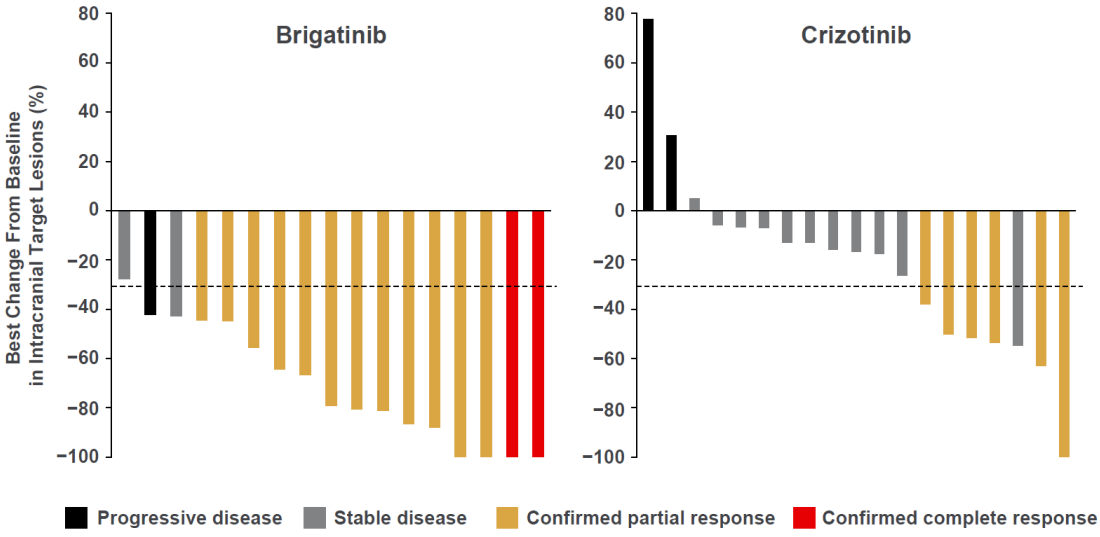


Treatment	No. (%) Patients With Events	Median PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=40)	8 (20)	NR	75 (56–87)
Crizotinib (n=41)	24 (59)	5.6 months (3.8–11.1)	25 (8–46)

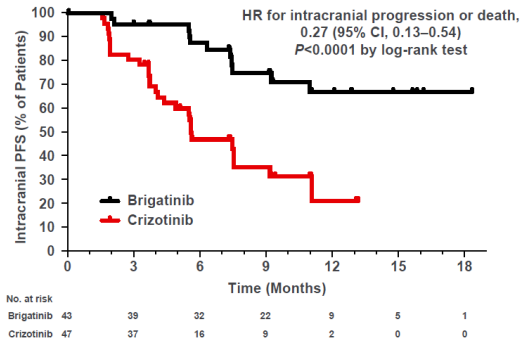
Patients Without Brain Metastases at Baseline



Treatment	No. (%) Patients With Events	Median PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=97)	28 (29)	NR	63 (50–74)
Crizotinib (n=97)	39 (40)	11.1 months (9.2–NR)	49 (36–61)

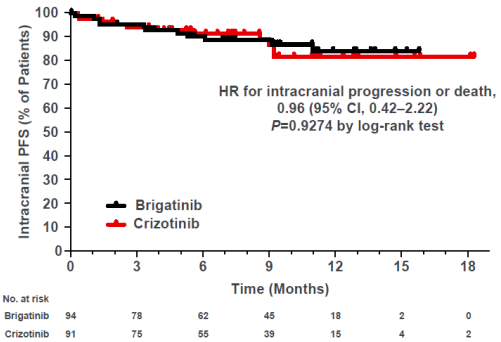


Patients With Any Brain Metastases at Baseline



Treatment	No. (%) Patients With Events: Intracranial Progression	No. (%) Patients With Events: Death	Median Intracranial PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=43)	11 (26)	0	NR (11.0–NR)	67 (47–80)
Crizotinib (n=47)	26 (55)	2 (4)	5.6 months (4.1–9.2)	21 (6–42)

Patients Without Brain Metastases at Baseline



Treatment	No. (%) Patients With Events: Intracranial Progression	No. (%) Patients With Events: Death	Median Intracranial PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=94)	2 (2)	9 (10)	NR (NR)	84 (72–91)
Crizotinib (n=91)	7 (8)	4 (4)	NR (NR)	82 (68–90)

3. 化療加上 Atezolizumab 對第 4 期之非小細胞肺癌在無惡化存活率及全體存活率上都有助益

Atezolizumab Combo Improved PFS, OS in Stage IV Non-Small Cell Lung Cancer: Cappuzzo F. Impower130: Progression-free survival (PFS) and safety analysis from a randomized phase 3 study of carboplatin + nab-paclitaxel (CnP) with or without atezolizumab (atezo) as first-line (1L) therapy in advanced non-squamous NSCLC. Abstract LBA53.

Adding atezolizumab to carboplatin plus nab-paclitaxel (CnP) as a first-line therapy significantly improved progression-free survival (PFS) and overall survival (OS) in patients with stage IV non-squamous non-small cell lung cancer (NSCLC) compared with treatment with CnP alone, according to the phase 3 IMpower130 study.

This phase 3 study tested atezolizumab plus CnP compared with CnP alone in 723 patients with stage IV disease. Patients were randomly assigned 2:1 to receive atezolizumab plus CnP (Arm A) or CnP alone (Arm B) for 4 or 6 21-day cycles and maintenance. Maintenance was treatment with atezolizumab until loss of clinical benefit for patients in arm A and best supportive care or pemetrexed for those who were in arm B.

The intent-to-treat *EGFR*-wild type ALK-negative population was 679 patients. Assignment to combination treatment resulted in a clinically meaningful improvement in OS compared with CnP alone. The median OS was 18.6 months for arm A compared with 13.9 months for arm B (hazard ratio [HR] = 0.79; 95% CI, 0.64-0.98; $P = .033$). At 12 months, 63.1% of patients in arm A were alive compared with 55.5% in arm B.

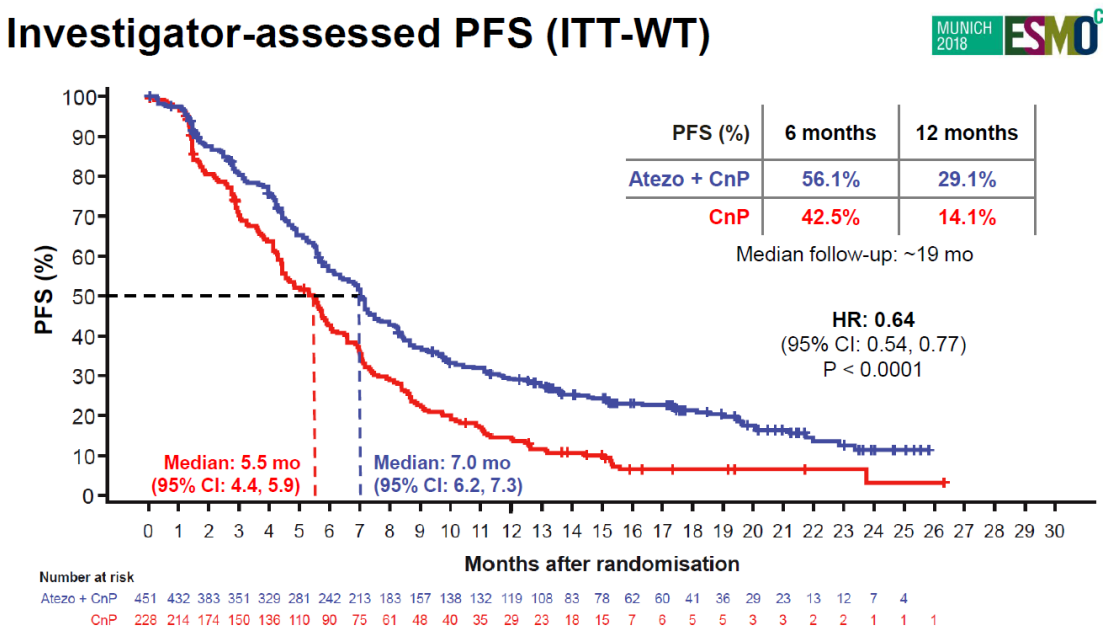
Similarly, patients assigned to arm A had significant improvements in PFS compared with those in arm B. The median PFS for the atezolizumab plus CnP arm was 7.0 months compared with 5.5 months for the CnP alone arm (HR = 0.64; 95% CI, 0.54-0.77; $P < .0001$).

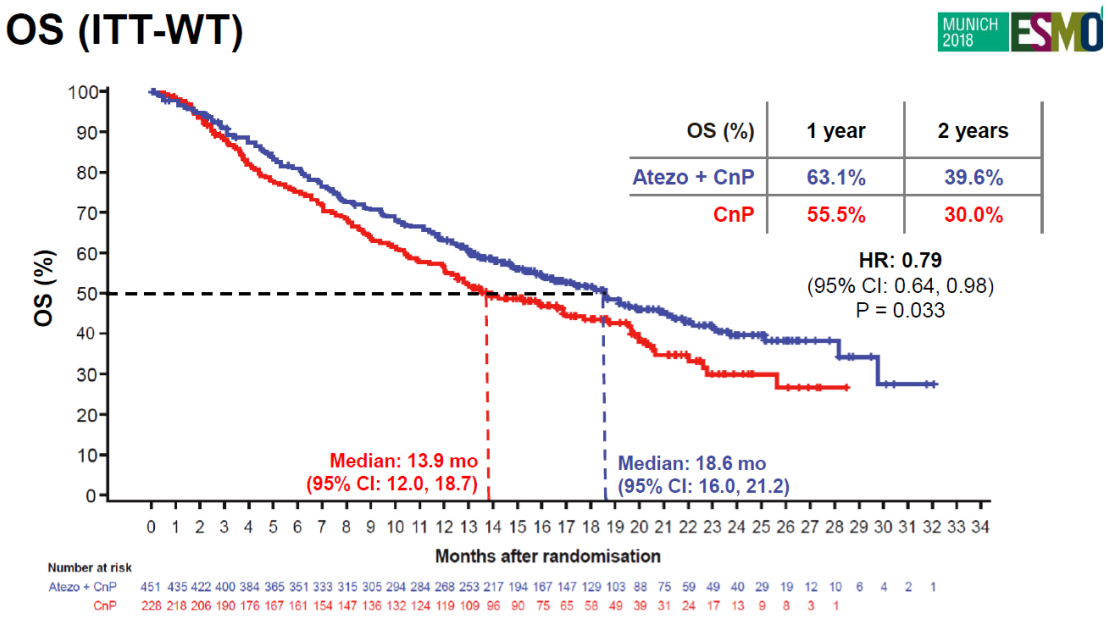
PFS and OS benefits were observed in all PD-L1 subgroups and was consistent across all subgroups, except patients with liver metastases and *EGFR*/*ALK* genomic alterations.

Median OS for patients assigned to arm A compared with arm B was 17.4 months and 16.9 months for PD-L1–high patients, respectively; 23.7 months compared with

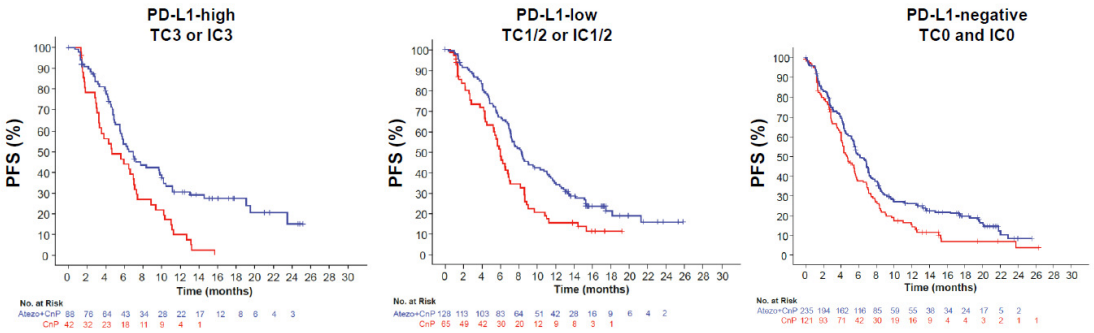
15.9 months for PD-L1–low patients, respectively; and 15.2 months compared with 12.0 months for PD-L1–negative patients, respectively.

Grade 3/4 treatment-related adverse events occurred in 73.2% of patients in arm A compared with 60.3% of patients in arm B.



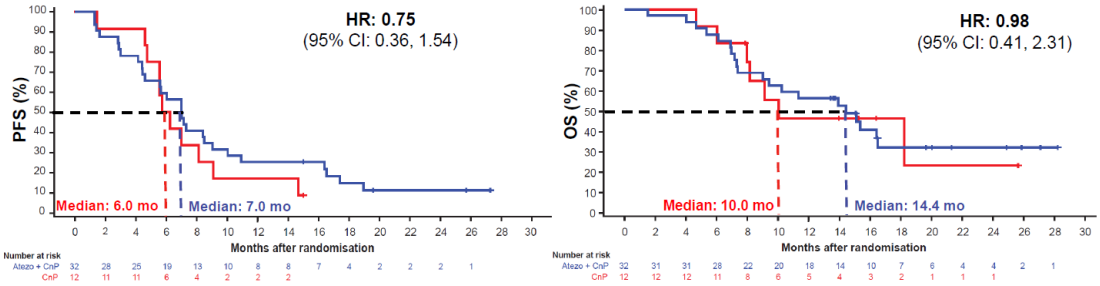


PFS by baseline PD-L1 status (ITT-WT)



	Atezo + CnP (n=88)	CnP (n=42)	Atezo + CnP (n=128)	CnP (n=65)	Atezo + CnP (n=235)	CnP (n=121)
Median PFS, mo (95% CI)	6.4 (5.49, 9.76)	4.6 (3.22, 7)	8.3 (7.16, 10.35)	6.0 (5.29, 6.93)	6.2 (5.52, 7.16)	4.7 (4.11, 5.72)
HR (95% CI)	0.51 (0.34, 0.77)		0.61 (0.43, 0.85)		0.72 (0.56, 0.91)	

Investigator-assessed PFS and OS in *EGFR/ALK*-positive subgroup



4. 以 Osimertinib 治療下產生惡化之非小細胞肺癌的抗藥機制

Resistance Mechanisms Identified for NSCLC Progression With First-Line Osimertinib: Ramalingam SS. Mechanisms of acquired resistance to first-line osimertinib: preliminary data from the phase III FLAURA study. Abstract LBA50.

Previously presented results from the main analysis of FLAURA showed that osimertinib had superior efficacy compared with standard of care EGFR tyrosine kinase inhibitors in patients with untreated *EGFR*-mutated advanced NSCLC, regardless of PD-L1 expression.

Patients (556 participants) in the study were randomly assigned to receive osimertinib or an EGFR-TKI (gefitinib or erlotinib). The researchers collected paired plasma samples at

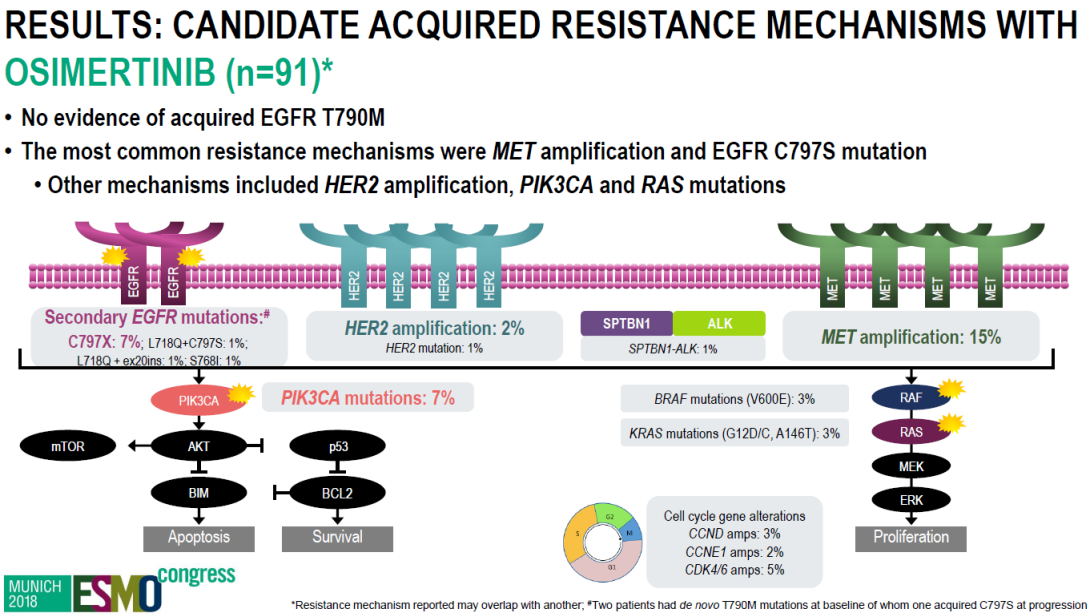
baseline and at progression or treatment discontinuation, and analyzed these samples using next-generation sequencing.

Disease progression or treatment discontinuation and plasma samples were available for 41% of patients assigned to be administered osimertinib and 57% of patients were assigned to receive a TKI. Of these patients, only those with detectable *EGFR* mutations at baseline were evaluable (91 for osimertinib and 129 for TKIs).

In the osimertinib arm, no *EGFR* T790 mutations were found.Instead, *MET* amplification was detected in 15% of patients and *EGFR*C797S mutation were found in 7% of patients. Other commonly detected resistance mechanisms were HER2 amplification, *PIK3CA*, and *RAS* mutations.

In patients assigned TKIs, T790 mutations were detected in almost one-half of this population (47%). Other mechanisms that were identified included *MET* (4%) and *HER2* gene amplification (2%).

Thus, the most commonly observed acquired resistance mechanisms in patients assigned osimertinib were *MET* amplification and *EGFR*C797S mutations.



乳癌 Breast Cancer

1. Talazoparib 在 *BRCA* 陽性之三陰性乳癌中可改善患者自覺之療效 Talazoparib Improves PROs in *BRCA*-Positive Triple-Negative Breast Cancer: Rugo HS, Fallowfield L, et al. Patient-reported outcomes (PRO) in patients (pts) with advanced

breast cancer and a germline BRCA1/2 mutation (gBRCAm) receiving talazoparib (TALA) vs physician's choice chemotherapy treatment (PCT): a focus on the EMBRACA triple negative (TNBC) subpopulation. Abstract 292O.

EMBRACA was an open-label, phase 3 trial that demonstrated that talazoparib prolonged progression-free survival compared with physician's choice chemotherapy (PCT, hazard ratio [HR], 0.60; 95% CI, 0.41-0.87; *P*= .008) among patients with TNBC who harbored a *BRCA* mutation. This post hoc analysis evaluated the PROs during the trial.

Patients reported their outcomes on day 1 of each treatment cycle, which was considered baseline, and also at the end of treatment by way of the EORTC QLQ-C30 and breast cancer module, QLQ-BR23 questionnaires. Baseline PRO scores were similar between the groups.

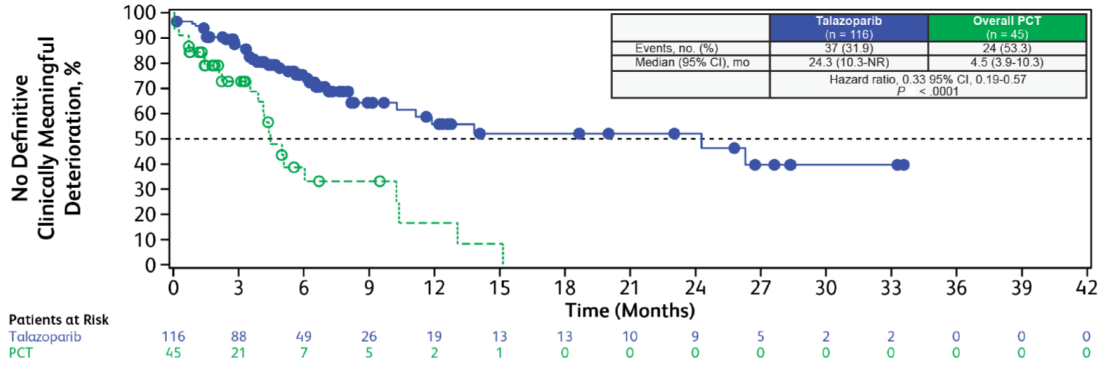
Talazoparib resulted in a significant improvement in global health status (GHS)/quality of life (QoL) compared with PCT, with an overall change of 12.5 (95% CI, 7.1-17.8; *P*< .0001). Patients who were treated with talazoparib also demonstrated a prolonged time to deterioration in GHS/QoL with a median of 24.3 months compared with 4.5 months with PCT (hazard ratio [HR], 0.33; 95% CI, 0.19-0.57; *P*< .0001). The time to deterioration for pain was also prolonged with talazoparib, at a median time of 22.7 months compared with 5.6 months with PCT (HR, 0.25; 95% CI, 0.14-0.45; *P*< .0001).

There was also a substantial improvement with talazoparib compared with PCT in the overall change from baseline for fatigue, pain, appetite loss, and breast and arm symptoms.

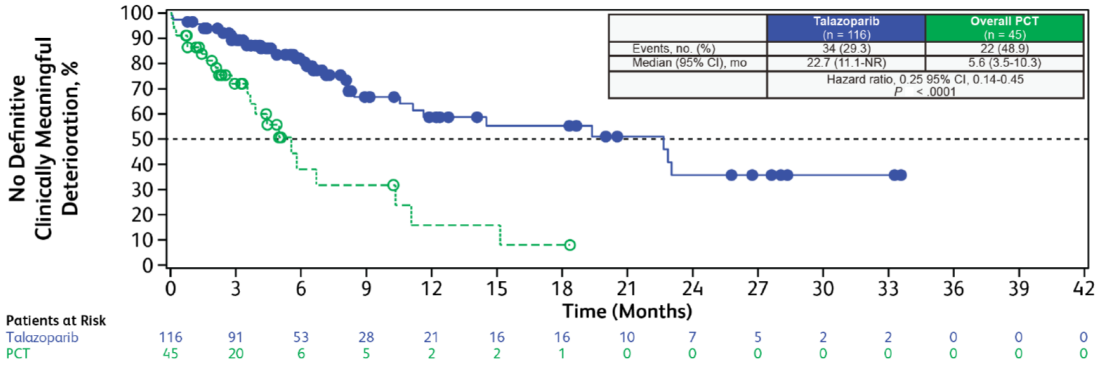
There was no significant difference between the talazoparib and PCT arms for emotional and cognitive function, nausea and vomiting, dyspnea, insomnia, constipation, diarrhea, emotions related to hair loss, or sexual enjoyment/functioning.

According to the authors, the study results suggested that “talazoparib resulted in significantly greater improvement from baseline and delayed time to deterioration in GHS/QoL and pain symptoms versus PCT.”

Time to Definitive Clinically Meaningful Deterioration[a]
EORTC QLQ-C30 GHS/QoL (TNBC PRO Evaluable Subgroup)



Time to Definitive Clinically Meaningful Deterioration[a]
EORTC QLQ-C30 Pain (TNBC PRO Evaluable Subgroup)



2. 追蹤 20 年之資料顯示在高危險早期乳癌中高劑量化療和血液幹細胞移植可增加存活 20-Year Data Link High-Dose Chemotherapy and Hematopoietic Stem Cell Transplant to Survival Benefit in High-Risk Early Breast Cancer: Steenbruggen TG, Steggink LC, Seynaeve CM. High-dose chemotherapy (HDCT) with hematopoietic stem cell transplantation (HSCT) in high-risk breast cancer (BC) patients with ≥4 involved axillary lymph nodes (ALN): 20-year follow-up of a randomized phase 3 study. Abstract 187O.

Though conventional chemotherapy is preferred over high-dose chemotherapy (HDCT) in most patients with high-risk early breast cancer due to toxicity, there may be a benefit for very high-risk patients. The aim of this study was to evaluate long-term outcomes of women who received HDCT andhematopoietic stem cell transplant (HSCT) in a phase 3 trial.

The phase 3 trial was conducted between 1993 to 1999 and randomly assigned 885 women younger than 56 with early breast cancer and at least 4 involved ALN to receive conventional chemotherapy with fluorouracil, epirubicin, and cyclophosphamide or HDCT followed by autologous HSCT. The HDCT regimen was similar to the conventional regimen, but replaced the last cycle with high-dose cyclophosphamide, thiotepa, and carboplatin.

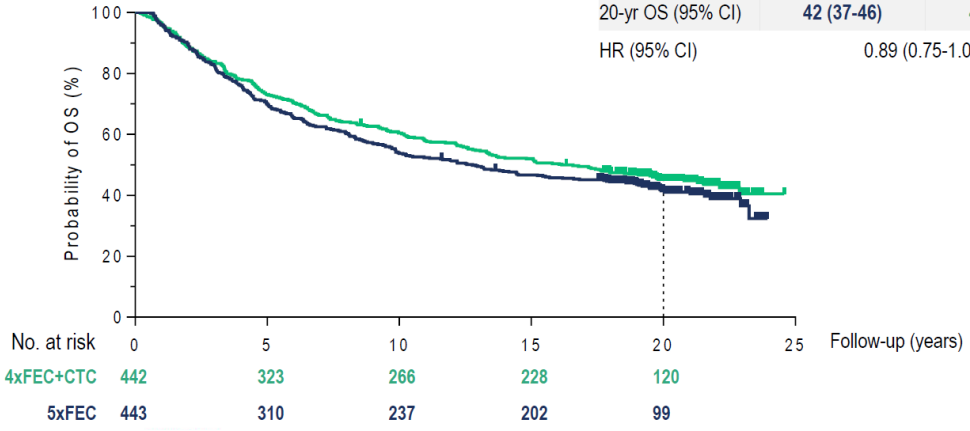
In the overall cohort, there was no difference in relapse or death between the arms, with rates of 61% and 58% in the conventional chemotherapy and HDCT arms, respectively (hazard ratio [HR], 0.88; 95% CI, 0.74-1.05) after a median follow-up of 20 years. Outcomes were also similar among patients with *ER*-positive or *HER2*-positive disease.

Among patients with more than 9 involved ALN, however, HDCT significantly improved outcomes. The relapse-free survival rate (RFS) was 39% in patients who received HDCT compared with 27% after conventional chemotherapy (HR, 0.71; 95% CI, 0.54-0.94; *P*= .02). HDCT also significantly prolonged overall survival (OS), with a 20-year survival rate of 44% compared with 30% with conventional chemotherapy (HR, 0.72; 95% CI, 0.95; *P*= .02).

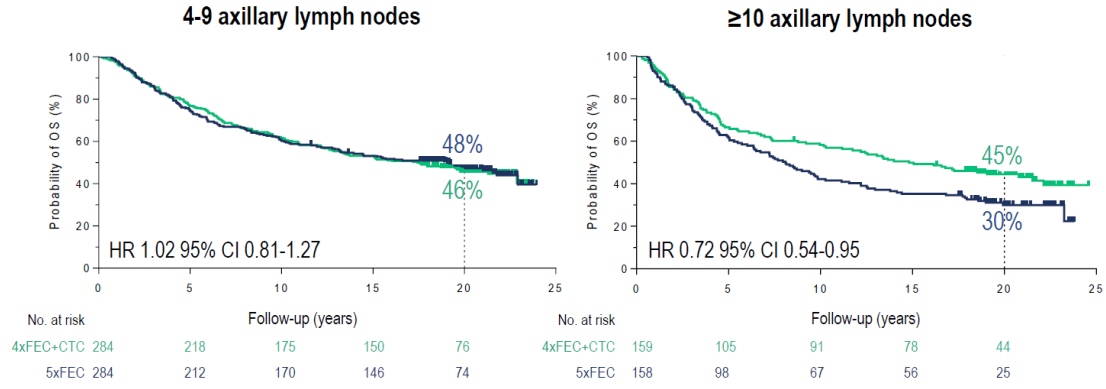
There was no significant difference in RFS or OS in the TNBC cohort, but there was a trend toward a benefit. The RFS was 51% and 34% with HDCT and conventional treatment (HR, 0.66; 95% CI, 0.42-1.03; *P*= .07). The 20-year OS was 52% and 39% with HDCT or conventional chemotherapy, respectively (HR, 0.71; 95% CI, 0.45-1.12; *P*= .14).
The authors concluded that this “long-term follow-up confirms survival benefit of HDCT in breast cancer patients with [more than] 9 involved ALN and suggests benefit in TNBC patients.”

UPDATED OS ANALYSIS
MEDIAN FOLLOW-UP OF 20 YEARS

	5xFEC (n=443)	4xFEC+CTC (n=442)
20-yr OS (95% CI)	42 (37-46)	45 (41-50)
HR (95% CI)	0.89 (0.75-1.06)	



UPDATED OVERALL SURVIVAL IN SUBGROUPS
MEDIAN FOLLOW-UP OF 20 YEARS

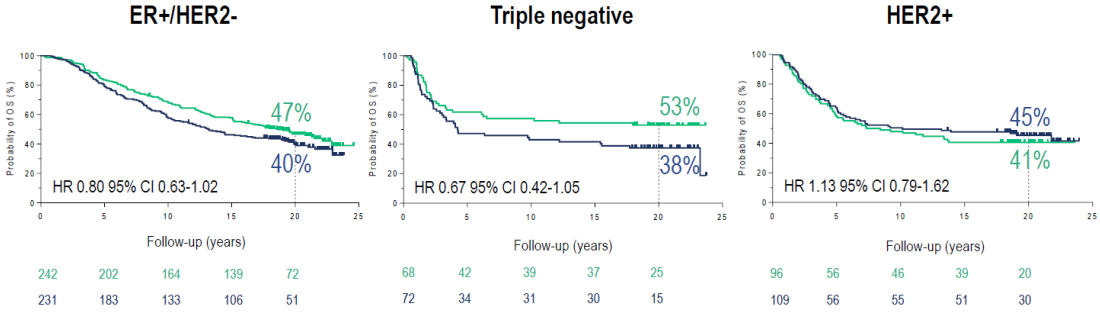


MUNICH 2018 ESMO congress

P for interaction=0.047

4xFEC+CTC
5xFEC

UPDATED OVERALL SURVIVAL IN BC SUBTYPES
MEDIAN FOLLOW-UP OF 20 YEARS



MUNICH 2018 ESMO congress

P for interaction=0.078

4xFEC+CTC
5xFEC

3. 在**HER2陽性乳癌中減少Trastuzumab使用時間可節省近100,000歐元Reducing Trastuzumab Duration Lowers Costs by Nearly £10,000 in HER2-positive Breast Cancer:** Hulme C, Hall P, et al. PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): cost effectiveness analysis results. Abstract LBA12_PR.

The 12-month duration of trastuzumab for the treatment of HER2-positive early breast cancer was adopted based on pivotal clinical trials, but given the cost of the medication, there is an interest in reducing the treatment duration. The aim of this analysis was to determine if administration of 6 months of trastuzumab is more cost-effective than 12 months of treatment.

PERSEPHONE was a phase 3 noninferiority trial comparing a 6- and 12-month duration of trastuzumab. At 6 months, a landmark analysis was conducted to evaluate costs and quality of life. This analysis included 3759 patients who were disease-free at 6 months.

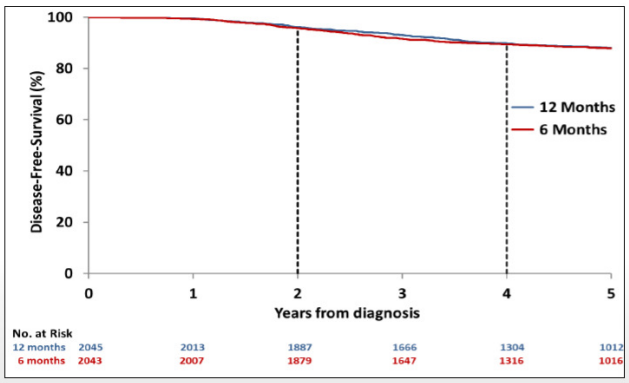
The mean cost was substantially lower per patient for 6 months of trastuzumab at £2538.64 (95% CI, £2383.38-£2700.72) compared with £12,333.83 (95% CI, £12,098.58 - £12,562.27) for 12 months, resulting in a mean savings per person of £9793.25 (95% CI, £9515.20-£9954.67). This is a cost savings of approximately $12,800 US dollars.

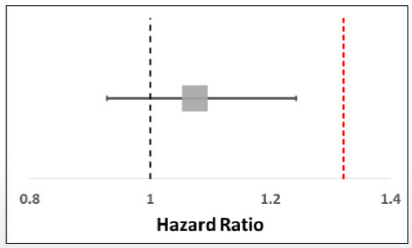
The cost savings were seen in the treatment and administration of trastuzumab itself, which accounted for £9699.58 of the savings. Costs associated with cardiac assessment and treatment and inpatient days accounted for the remaining cost savings.

The mean individual quality adjusted life years (QALYs), which were adjusted for differences at baseline, was 1.146 (95% CI, 1.131-1.61) with 6 months of trastuzumab compared with 1.128 (95% CI, 1.113-1.155) for 12 months. The difference in mean QALY was 0.018 (95% CI, -0.003 to 0.039).

The authors concluded that patients in the 6-month arm of trastuzumab had a probability of 100% for being cost-effective without decreasing quality of life.

• Median FU = 5.4 years (IQR: 3.6 – 6.7)





	6 Months (95% CI)	12 Months (95% CI)	Cost Saving (95% CI)
Average per Patient Cost	£2,538 (£2,383 - £2,700)	£12,333 (£12,098 - £12,562)	£9,793 (£9,515 - £10,071)

4. Atezolizumab 和 Nab-Paclitaxel 在轉移性三陰乳癌中可延長無病存活
Atezolizumab and Nab-Paclitaxel Prolonged PFS in Metastatic Triple-Negative Breast Cancer: Schmid P. Impassion130: Results from a global, randomized, double-blind phase 3 study of atezolizumab (atezo) = nab-paclitaxel (nab-P) vs placebo + nab-P in treatment-naïve, locally advanced or metastatic triple-negative breast cancer (mTNBC). Abstract LBA1_PR.

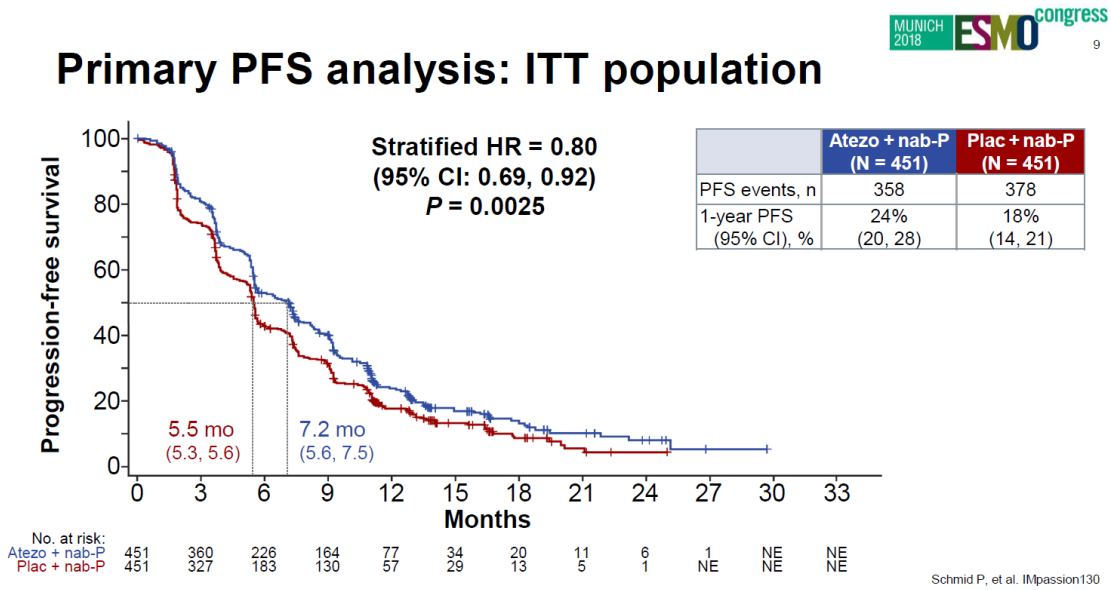
Atezolizumab plus nab-paclitaxel significantly prolonged progression-free survival (PFS) among patients with metastatic triple-negative breast cancer, with an even greater benefit observed for patients in the PD-L1–positive subgroup, according to preliminary results from the IMpassion130 trial.

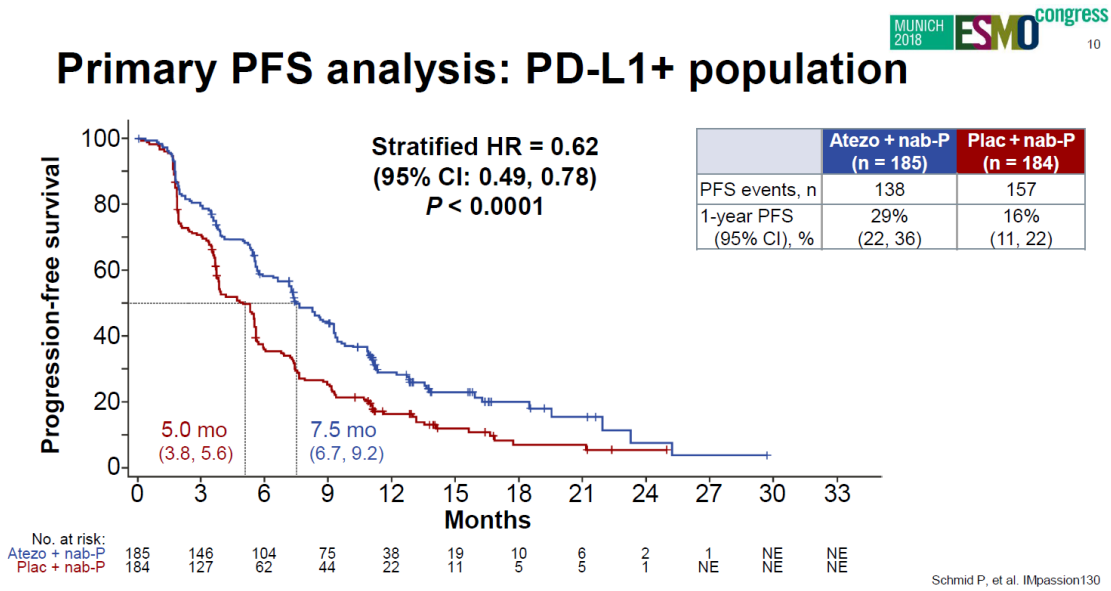
With a median follow-up of slightly more than 1 year, the median progression-free survival was 7.2 months with the combination compared with 5.5 months for placebo plus nab-paclitaxel in the intention-to-treat analysis (hazard ratio [HR] for progression or death = 0.80; *P* = .002). Patients with PD-L1–positive tumors assigned to atezolizumab plus nab-paclitaxel had a 2-month increase in PFS compared with placebo plus nab-paclitaxel (7.5 vs 5.0 months; HR = 0.62; *P* < .001).

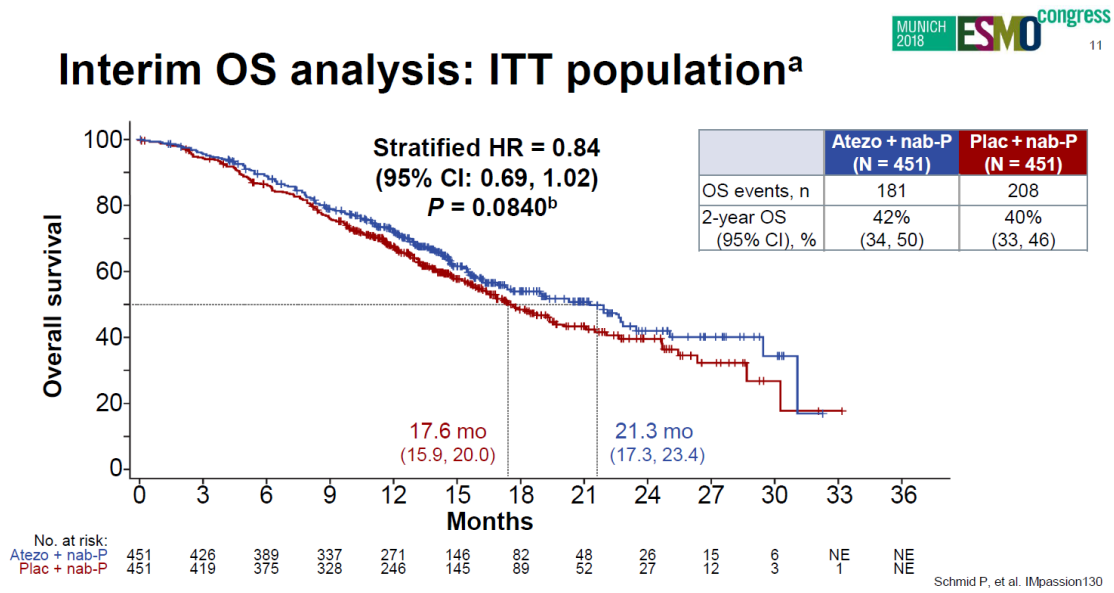
Patients with untreated, metastatic triple-negative breast cancer were randomly assigned to receive atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel. The 2 primary end points were PFS and overall survival (OS). PD-L1 positivity was defined as expression on tumor-infiltrating immune cells of 1% or greater.

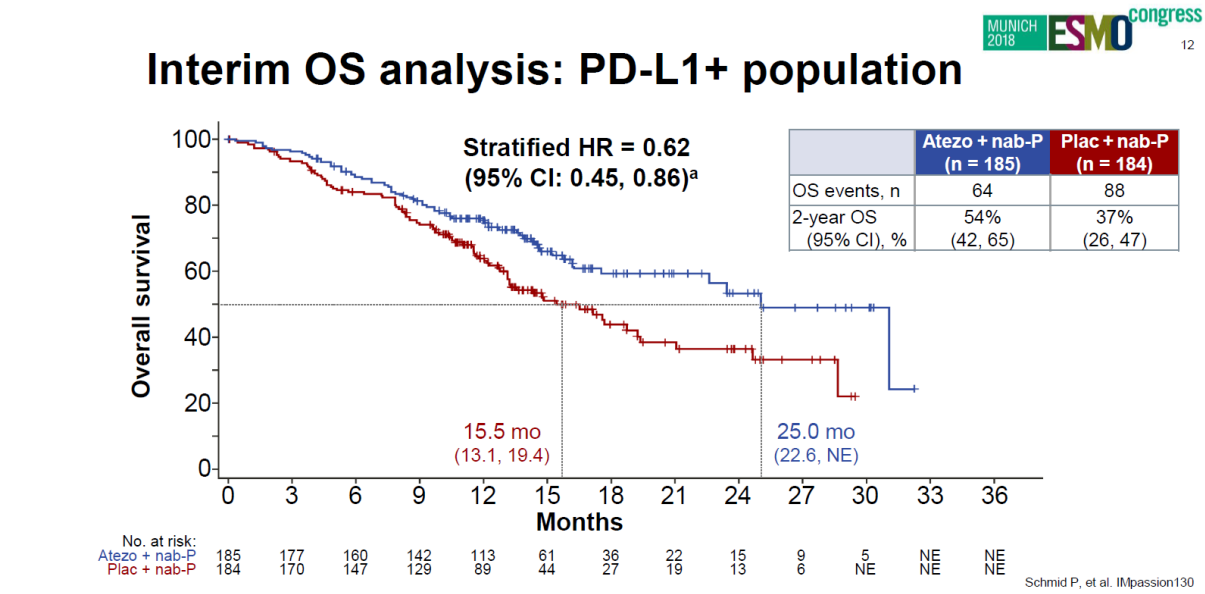
At first interim analysis, in the intent-to-treat group, median OS was 21.3 months with the combination compared with 17.6 months for placebo plus nab-paclitaxel (HR = 0.84; *P* = .08). Among those with PD-L1–positive tumors, the median overall survival was 25.0 months compared with 15.5 months, respectively.

The safety of atezolizumab plus nab-paclitaxel was consistent with the known toxic effects of each agent.









5. 4 價雙極抗體在 HER2 陽性乳癌模式中大大地有效

A Big BiTE: Tetravalent BiTE Highly Potent in HER2-positive Breast Cancer Models: Boudot A, Huang X, Murphy S, et al. ABP-100: A tetravalent bispecific T-cell engaging antibody for HER2+ solid tumors. Abstract 1170P.

Given the success of chimeric antigen T-cell (CAR-T) therapy, BiTE antibodies offer an alternative approach to directing T cells to tumor cells. This study evaluated the activity of a tetravalent BiTE, constructed to have 2 binding sites each for HER2 and CD3. Most other BiTEs are bivalent, binding only once to each target.

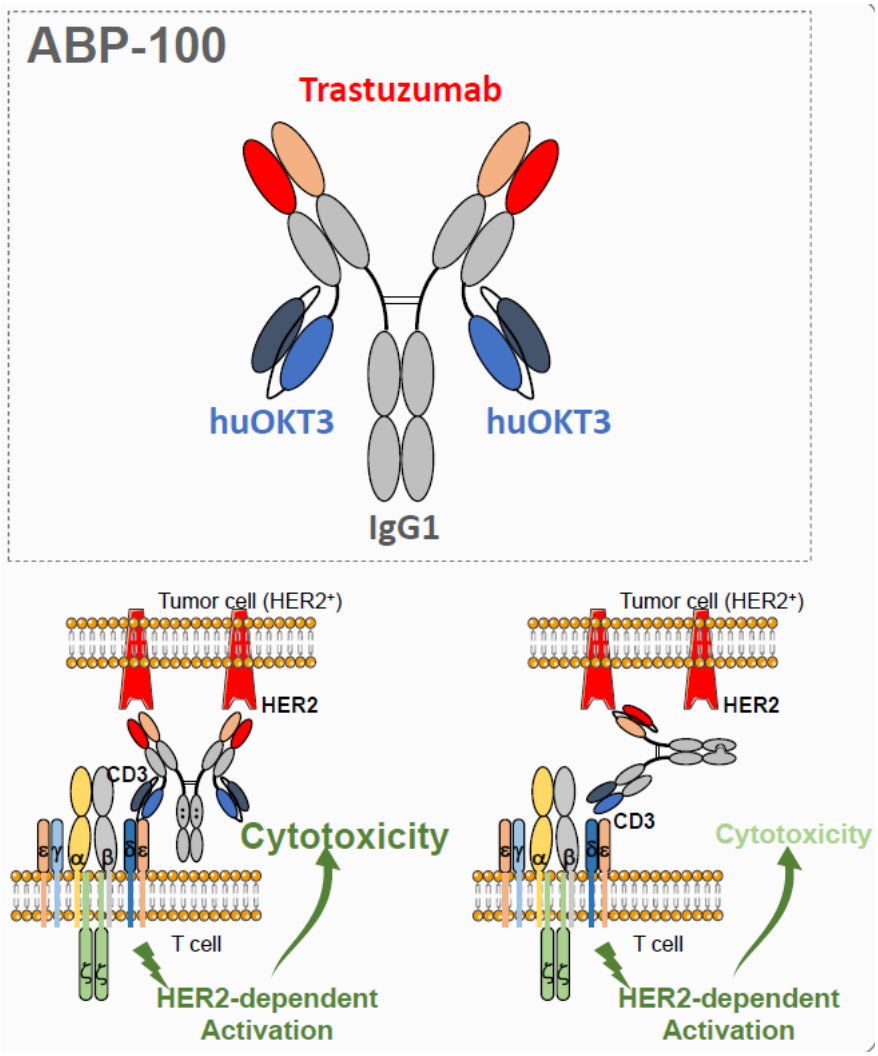
The tetravalent BiTE antibody ABP-100 demonstrated stronger binding with HER2 than the traditional monovalent approach, but the structure of ABP-100 resulted in a functionally monovalent binding of CD3.

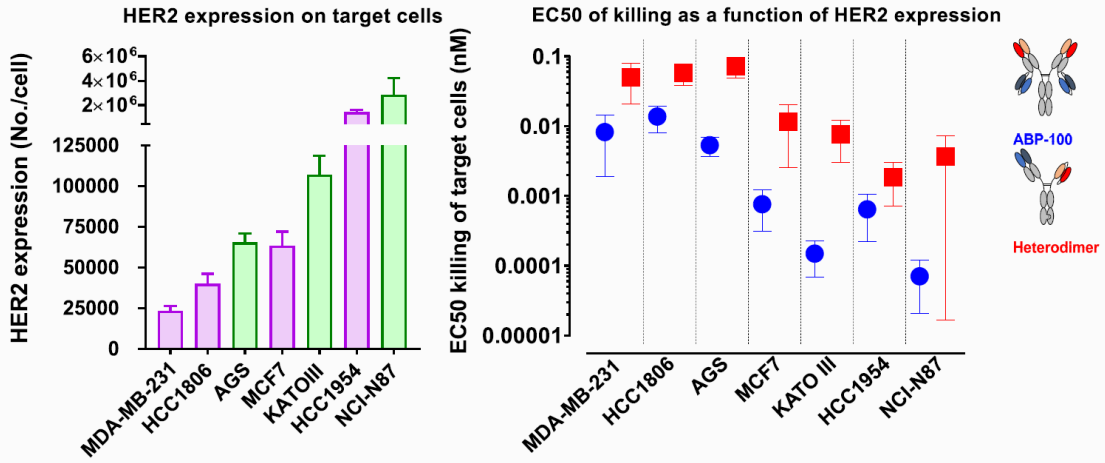
Treatment of in vitro and in vivo models of HER2-positive cancer with ABP-100 resulted in highly potent antitumor activity, with complete responses occurring at low doses, with no evidence of recurrence after treatment discontinuation.

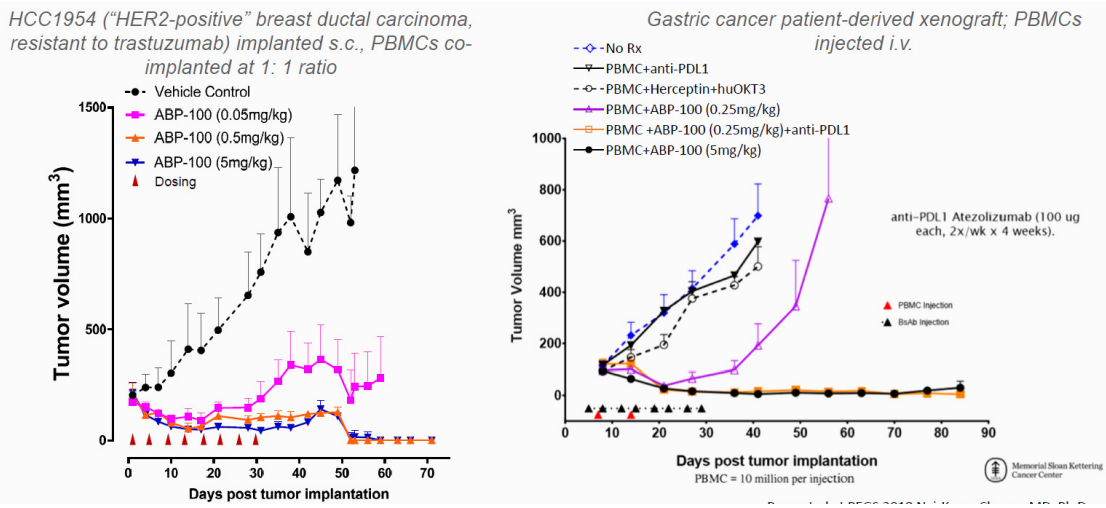
ABP-100 efficacy was dependent on HER2 expression. Combination treatment consisting of ABP-100 and an anti-PD-L1 antibody demonstrated a synergistic effect.

The safety profile of ABP-100 was similar to that of a bivalent anti-HER2 BiTE.

The authors concluded that the tetravalent structure may result in a larger therapeutic index than bivalent molecules. The authors stated that, “these data support the clinical development of ABP-100 in HER2-positive tumors.”







6. Trastuzumab 之同生物活性劑橫跨各臨床情境皆顯示相等效力 Trastuzumab Biosimilar Demonstrated Equivalent Efficacy Across Clinical Settings: Rugo HS. Settings-based efficacy comparison of trastuzumab biosimilars in breast cancer: A systematic literature review. Abstract 324P.

A biosimilar to trastuzumab, trastuzumab-dkst (Ogivri™), was recently approved by the US Food and Drug Administration based on data showing physicochemical and functional biosimilarity and phase 3 efficacy and safety data in metastatic breast cancer. Additionally, clinical trials evaluating trastuzumab biosimilars for the treatment of ERBB2-positive breast cancer have assessed bioequivalence through comparative efficacy outcomes and neoadjuvant therapy for early-stage disease or as a first-line therapy for metastatic disease.

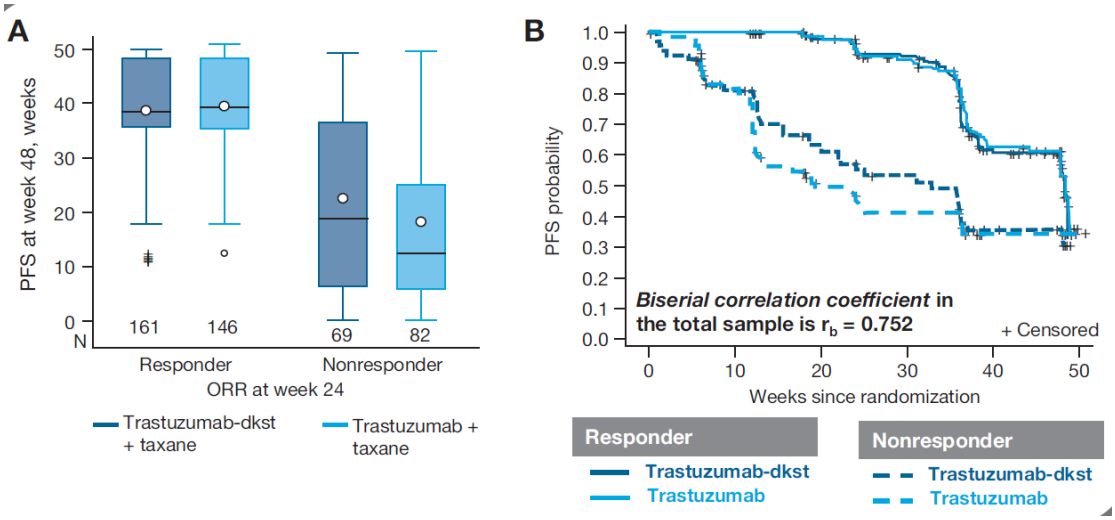
Here, researchers conducted a review to examine if demonstrating bioequivalence in terms of efficacy is different for early-stage breast cancer compared with metastatic

breast cancer. They identified abstracts and manuscripts using the terms “biosimilar” and “trastuzumab” between January 1, 2013, and March 14, 2018.

Of 84 results identified, they selected 8 phase 3 clinical trials with comparative clinical efficacy results: 4 in early-stage disease and 4 in metastatic disease. These trials included data for 6 proposed biosimilars.

In all of the trials included in the analysis, the proposed biosimilar demonstrated equivalent in terms of efficacy to the innovator product. Two of the biosimilars (CT-P6 from Celltrion and PF-05280014 from Pfizer) demonstrated efficacy equivalence in breast cancer in both the early-stage and metastatic settings.

“Although the FDA and European Medicines Agency determine biosimilarity based on totality of evidence, both the EBC and MBC settings appear to have similar sensitivity and be appropriate for determination of equivalent efficacy based on regulatory guidelines and clinical results,” the researchers wrote in the abstract. “Together, these data support extrapolation between settings.”



黑色素癌 Melanoma

1. Pembrolizumab，Dabrafenib，Trametinib 合用在黑色素癌中有效但因治療而生之副作用也大 Pembrolizumab With Dabrafenib and Trametinib Shows Efficacy, But High TRAEs, in Melanoma: Ascierto PA, Dummer R, et al. KEYNOTE-022 Part 3: Phase 2 randomized study of 1L dabrafenib (D) and trametinib (T) plus pembrolizumab (Pembro) or placebo (PBO) for BRAF-mutant advanced melanoma. Abstract 1244O.

The combination of pembrolizumab plus the BRAF inhibitors dabrafenib and trametinib showed promising antitumor activity in the phase 1 portion of the KEYNOTE-022 trial. This report was of the results from the phase 2 portion.

The double-blind, phase 2 KEYNOTE-022 trial randomly assigned 120 patients with treatment-naïve stage III or IV melanoma harboring a $BRAF^{V600E/K}$ mutation to receive pembrolizumab plus dabrafenib and trametinib or placebo plus dabrafenib and trametinib. The primary endpoint was progression-free survival (PFS) and the secondary endpoints included objective response rate (ORR), duration of response (DoR), time to response, and overall survival (OS).

The ORR was 63% with pembrolizumab plus dabrafenib and trametinib compared with 72% with the BRAF inhibitors alone, with complete response rates of 18% and 13%, respectively. The median time to response was similar between arms at 2.8 months.

During a median follow-up of 9.6 months, there was a trend toward prolonged PFS with the pembrolizumab combination, but it was not significant based on prespecified parameters that required a hazard ratio (HR) of 0.62 or less. The median PFS with the pembrolizumab combination was 16 months (95% CI, 8.6-21.5 months) compared with 10.3 months (95% CI, 7.0-15.6 months) with dabrafenib plus trametinib alone, resulting in an HR of 0.66 (P = .043). The 12-month PFS was 59% and 45% with the pembrolizumab combination or the BRAF inhibitors alone, respectively.

The median DoR was longer with the pembrolizumab combination at 18.7 months (range, 1.9+ to 22.1 months) compared with 12.5 months (range, 2.1-19.5+ months) with dabrafenib plus trametinib. Responses lasting at least 18 months was more common with pembrolizumab, occurring in 60% of patients compared with 28% of patients receiving only the BRAF inhibitors.

The 12-month OS was 80% with the pembrolizumab combination compared with 73% with dabrafenib plus trametinib.

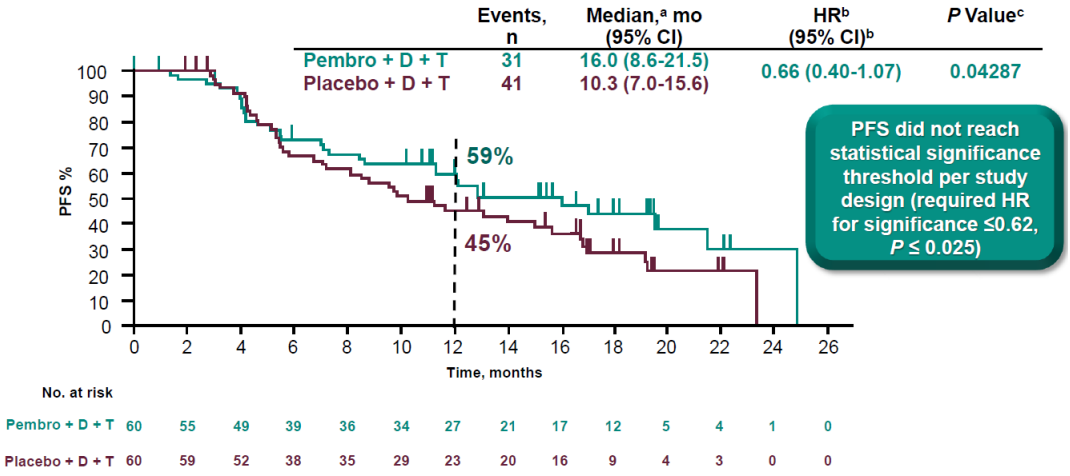
There were similar rates of any grade treatment-related adverse events (TRAEs), with 95% and 93% reported in the pembrolizumab combination and BRAF inhibitor only arms, respectively. Grade 3 to 5 TRAEs, however, occurred more frequently in the pembrolizumab combination arm at 58% compared with 27% in the dabrafenib plus trametinib arm. The discontinuation rate due to TRAEs was 40% and 20% in the pembrolizumab combination and dabrafenib plus trametinib arms, respectively.

Common grade 3 to 5 TRAEs, which occurred in at least 5% of patients, included pyrexia, elevated ALT and/or AST, increased GGT, rash, and neutropenia. There was a death in the pembrolizumab arm caused by pneumonitis, which was deemed treatment-related.

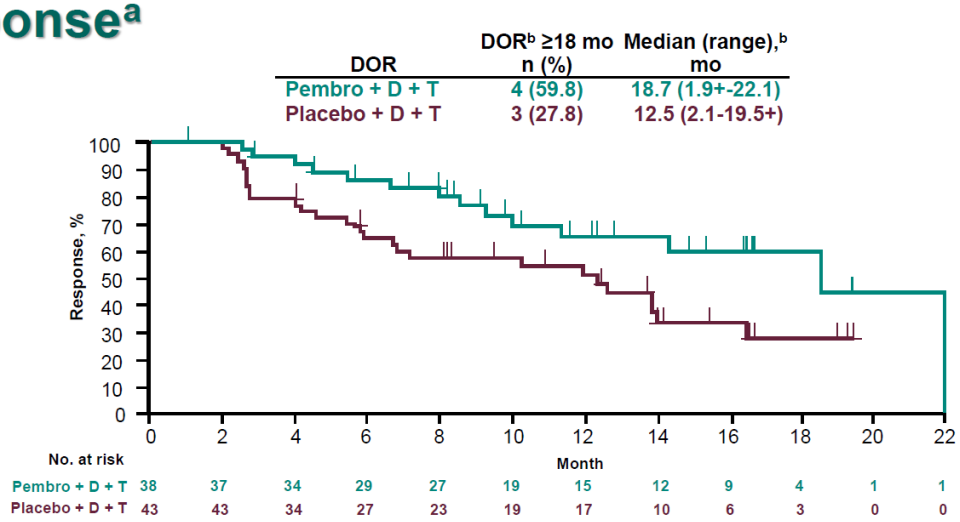
Immune-related AEs occurred in 43% of patients in the pembrolizumab group compared with 13% of patients in the BRAF inhibitor only group. The most common immune-related AEs were pneumonitis, hypothyroidism, skin disorders, hyperthyroidism, and uveitis.

The authors concluded that the pembrolizumab combination "demonstrated numerically longer PFS and DoR and a higher rate of grade 3-5 TRAEs in patients with treatment-naïve $BRAF^{V600E/K}$-mutant advanced melanoma."

Progression-Free Survival



Kaplan-Meier Analysis of Duration of Response[a]



2. 在後期黑色素癌中第一線單獨使用 Nivolumab 或與 Ipilimumab 合用持續地顯示存活助益 First-Line Nivolumab Alone or With Ipilimumab Continues to Show Durable Survival Benefits in Advanced Melanoma: Hodi FS, Dummer R, et al. Overall survival at 4 years of follow-up in a phase 3 trial of nivolumab plus ipilimumab combination therapy in advanced melanoma (CheckMate 067). Abstract LBA44.

Previously reported results from CheckMate 067 demonstrated that the first-line combination of nivolumab and ipilimumab or nivolumab alone substantially improved objective response rate, progression-free survival (PFS), and overall survival (OS) compared with ipilimumab for advanced melanoma. This analysis provides updated 4-year data with a database lock of May 10, 2018.

The phase 3 CheckMate 067 trial randomly assigned 945 patients with previously untreated, unresectable, stage III or IV melanoma with known BRAF status to receive nivolumab plus ipilimumab, nivolumab plus placebo, or ipilimumab plus placebo. The coprimary endpoints were PFS and OS.

Combination therapy or nivolumab plus placebo continued to show improved survival outcomes compared with ipilimumab plus placebo with a minimum follow-up of 48 months among the intention-to-treat population. The median OS was still not reached for nivolumab plus ipilimumab (95% CI, 38.2 months-not reached; (95% CI, 16.9-24.6) with ipilimumab (hazard ratio [HR], 0.54; 95% CI, 0.44-0.67; P < .0001) and was 36.9 months (95% CI, 28.3 months-not reached) with nivolumab (HR, 0.65; 95% CI, 0.53-0.79; P < .0001) compared with 19.9 months.

PFS was also prolonged with the combination, with a median of 11.5 months (95% CI, 8.7-19.3 months; HR, 0.42; 95% CI, 0.35-0.51; P < .0001) and a median of 6.9 months (95% CI, 5.1-10.2 months) with nivolumab (HR, 0.53; 95% CI, 0.44-0.64; P < .0001) compared with 2.9 months (95% CI, 2.8-3.2 months) with ipilimumab.

Treatment-related adverse events (TRAEs) occurred most frequently in the combination nivolumab plus ipilimumab arm among patients who received at least 1 dose of treatment. The rate of grade 3/4 TRAEs was 59%, 22%, and 28% in the combination, nivolumab, and ipilimumab arms, respectively.

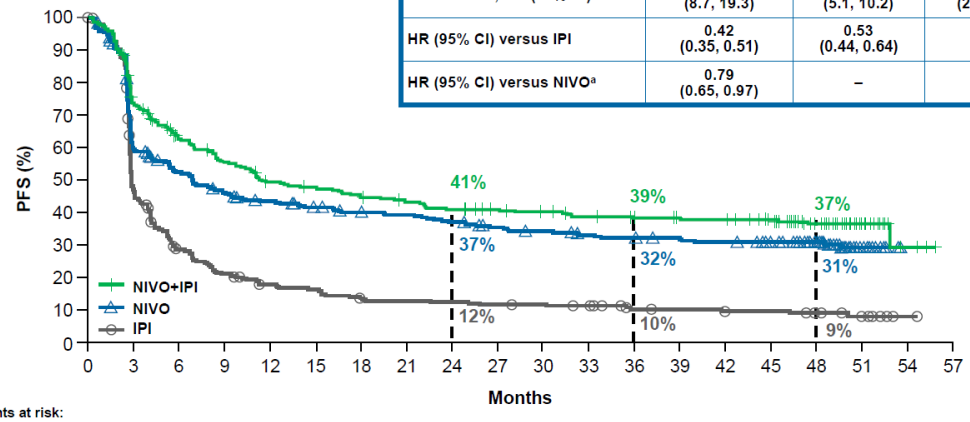
The most common grade 3 TRAEs was diarrhea with the combination or nivolumab groups and colitis in the ipilimumab group. Elevated lipase was the most common grade 4 TRAE in all groups. Serious adverse events were not evaluated in this analysis.

There were 4 treatment-related deaths, 2 of which occurred in the combination arm as a result of cardiomyopathy and liver necrosis, 1 in the nivolumab arm due to neutropenia, and 1 in the ipilimumab arm due to colon perforation. None of these deaths occurred since the 3-year update.

The authors concluded that this analysis shows “a durable, sustained survival benefit can be achieved with first-line nivolumab plus ipilimumab or nivolumab alone in patients with advanced melanoma.”

Progression-Free Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median PFS, mo (95% CI)	11.5 (8.7, 19.3)	6.9 (5.1, 10.2)	2.9 (2.8, 3.2)
HR (95% CI) versus IPI	0.42 (0.35, 0.51)	0.53 (0.44, 0.64)	–
HR (95% CI) versus NIVO[a]	0.79 (0.65, 0.97)	–	–

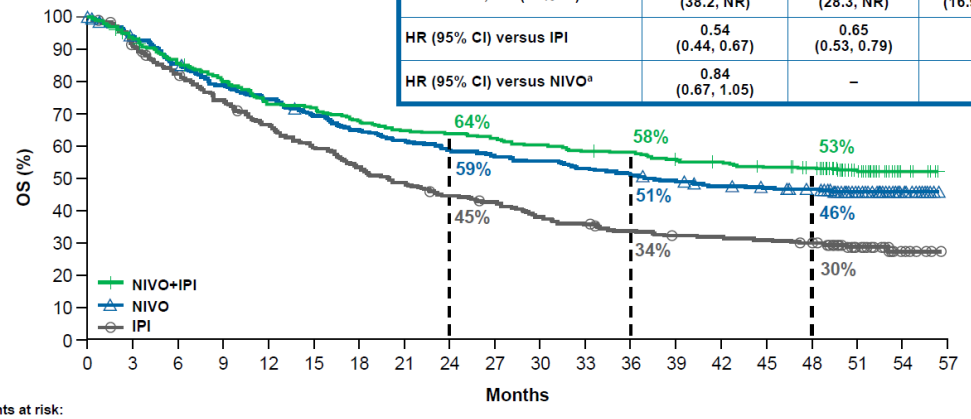


Patients at risk:

NIVO+IPI	314	218	175	155	136	131	124	117	110	104	101	95	93	89	88	81	53	19	3	0
NIVO	316	177	151	132	120	112	106	103	97	88	84	79	77	75	72	66	50	18	0	0
IPI	315	136	78	58	46	42	34	32	31	29	28	26	19	18	16	16	11	7	1	0

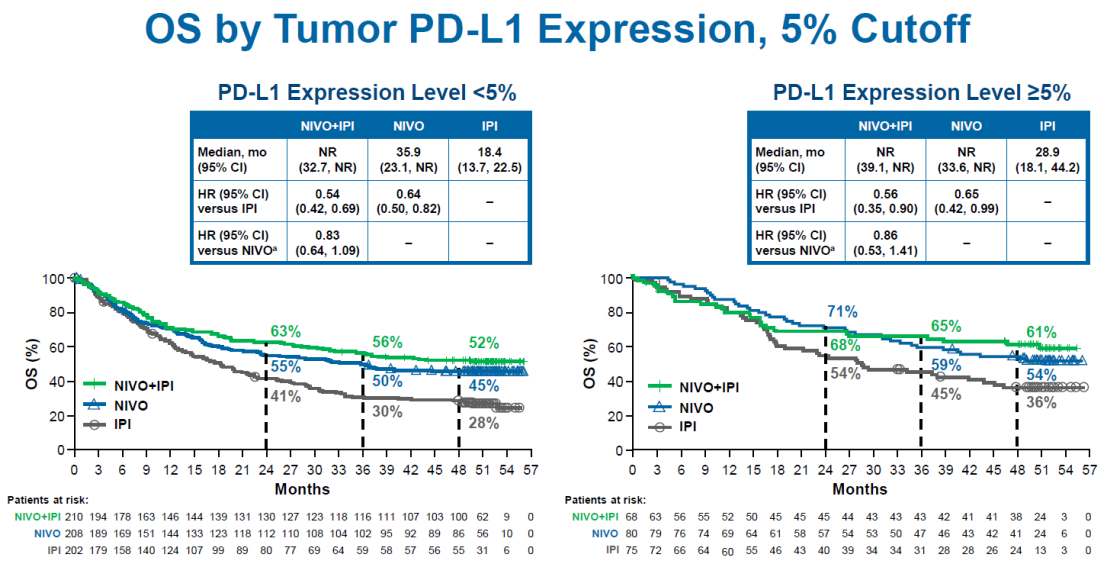
Overall Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2, NR)	36.9 (28.3, NR)	19.9 (16.9, 24.6)
HR (95% CI) versus IPI	0.54 (0.44, 0.67)	0.65 (0.53, 0.79)	–
HR (95% CI) versus NIVO[a]	0.84 (0.67, 1.05)	–	–



Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	186	180	178	171	166	160	154	96	13	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	144	140	135	85	18	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	99	94	93	90	86	50	11	0



3. 腫瘤溶解病毒 T-VEC 在真實世界中對早期轉移性黑色素瘤顯示高療效 Real-World Study Shows High Response Rates to T-VEC in Early Metastatic Melanoma: Franke V, Berger DMS, Klop WMC, et al. High response rate with T-VEC in early metastatic melanoma (stage IIIB/C-IVM1a). Abstract 1253P.

Intralesional treatment of stage IIIB/C-IVM1a unresectable melanoma with talimogene laherparepvec (T-VEC) resulted in an overall response rate (ORR) of 26% in the phase 3 OPTiM study. The purpose of this study was to evaluate the efficacy and safety of T-VEC in a real-world Netherlands population since December 2016, when the biopharmaceutical was approved there.

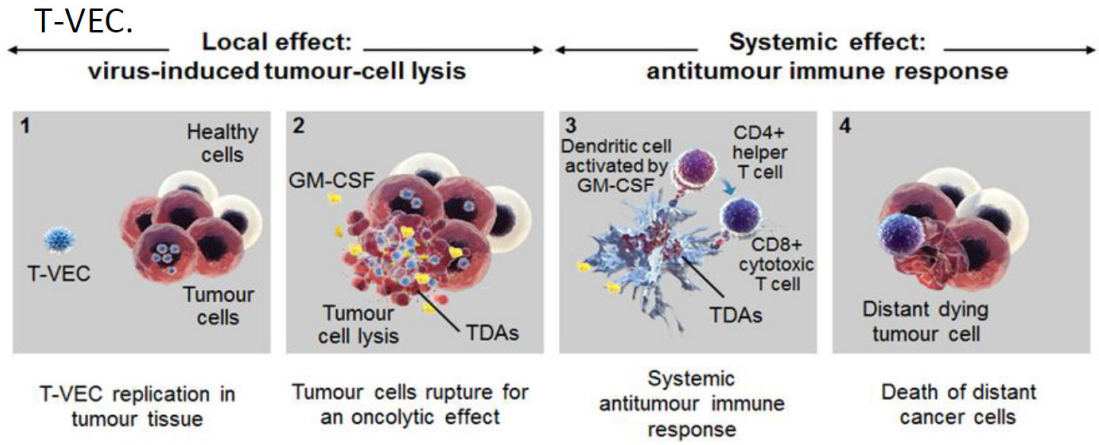
The study included 23 patients with a mean number of lesions at baseline of 5 to 50. All patients had previously undergone surgical resection, and other prior therapies included isolated limb perfusion, targeted therapy, immunotherapy, and radiotherapy.

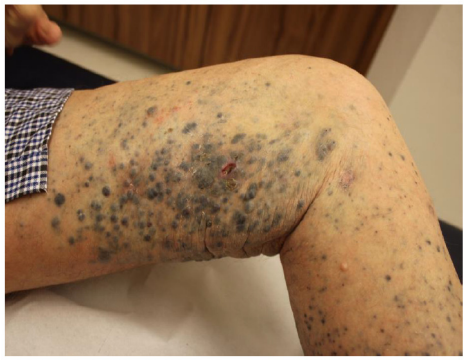
During a median follow-up of 11.3 months, the ORR was 82.6% and the disease control rate was 91.3%. Complete response was achieved by 52% of patients; all except 1 were ongoing after treatment discontinuation. The best response was a partial response in 30.4% of patients, mixed response in 8.7%, and progressive disease in 8.7%.

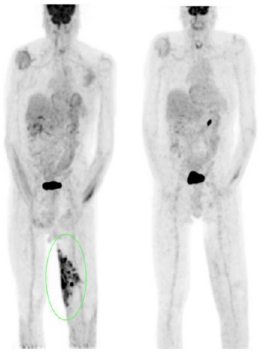
Response or toxicity to T-VEC was not affected by administration of prior therapies.

All patients experienced grade 1 to grade 2 adverse events (AEs) consisting of fatigue, influenza-like symptoms, and pain at the injection site. A case of grade 3 or higher colitis resulted in treatment interruption.

These data suggest a substantially higher ORR with T-VEC compared with its clinical trial. The authors concluded that this “confirms the role of oncolytic immunotherapy for melanoma.”



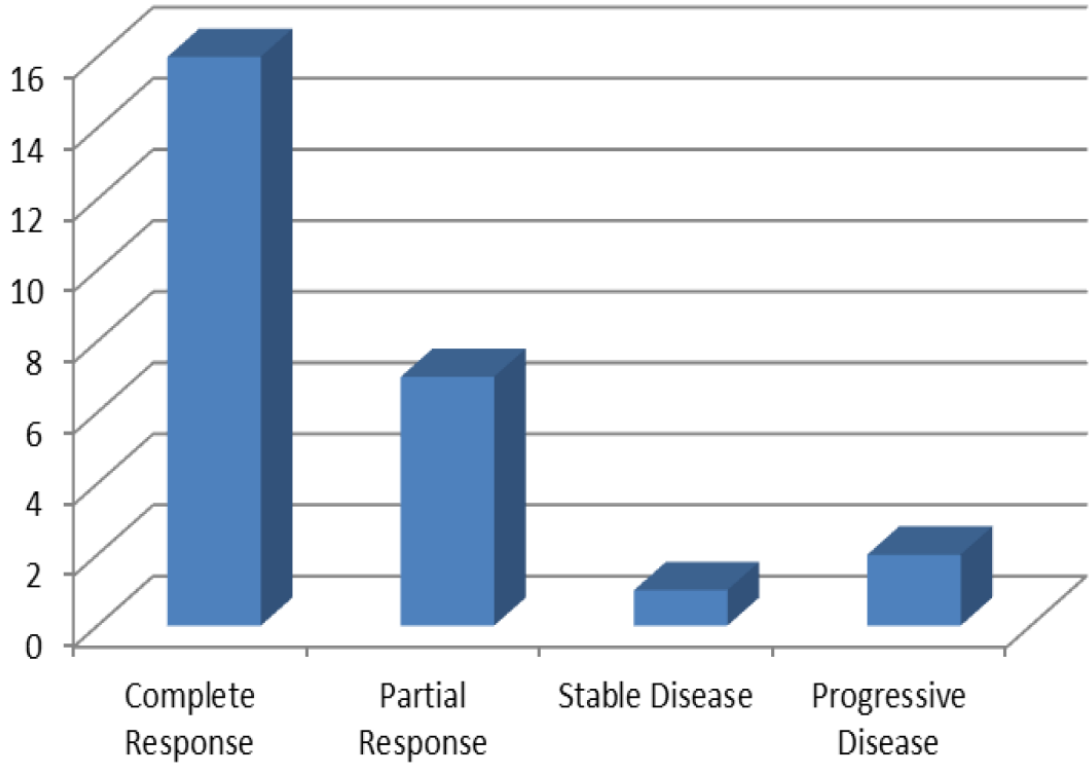




Franke V, et al. Eur J Cancer 2018;90:149–52

Baseline *After 9 cycles*

83-year-old male
Stage IIIc melanoma (left calf)
BRAF/NRAS wildtype
Severe comorbidities
Previous treatment: local excisions, LND, ILP, Imiquimod (Aldara)
Normal blood count, LDH and S100B at baseline
PET-CT response evaluation after 17 weeks of treatment (9 cycles)
Biopsy → merely melanosis with inflammation



卵巢癌 Ovarian Cancer

1. 在新診斷之後期卵巢癌中維持使用 Olaparib 比安慰劑有更好的無病存活 Olaparib Maintenance Prolongs PFS Compared With Placebo in Newly Diagnosed Advanced Ovarian Cancer: Moore KN, et al. Maintenance olaparib following platinum-based chemotherapy in newly diagnosed patients (pts) with advanced ovarian cancer (OC) and a BRCA1/2 mutation (BRCAm): phase III SOLO1 trial. Abstract LBA7_PR.

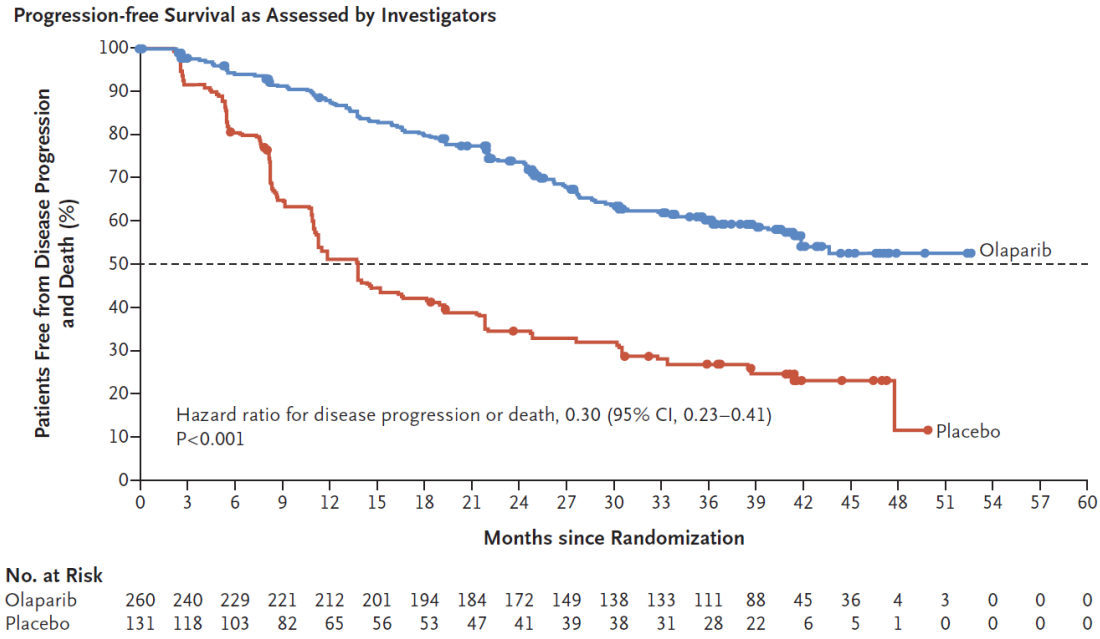
Relapse of advanced ovarian cancer commonly occurs within 3 years after standard treatment. The PARP inhibitor olaparib is effective in relapsed disease, but it is unknown whether maintenance therapy in newly diagnosed advanced ovarian cancer can improve outcomes. The purpose of this trial was to evaluate the outcomes of maintenance olaparib in this population.

In the international, double-blind, phase 3 SOLO1 trial, 391 patients were randomly assigned in a 2:1 ratio to receive 300 mg of olaparib twice daily or placebo. All patients had newly diagnosed stage III or stage IV high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian tube cancer harboring a *BRCA1/2* mutation, who had all achieved a complete or partial response

to platinum-based chemotherapy. The primary end point was progression-free survival (PFS).

Olaparib maintenance therapy significantly prolonged PFS during a median follow-up of 41 months, with a 3-year rate of 60% compared with 27% with placebo (hazard ratio, 0.30; 95% CI, 0.23-0.41; *P*< .001).
There were no new safety signals with olaparib; results were consistent with previously known toxicities.

The authors concluded that “the use of maintenance therapy with olaparib provided a substantial benefit with regard to PFS among women with newly diagnosed advanced ovarian cancer and a BRCA1/2 mutation.”



2. Niraparib 在復發性卵巢癌中的真實使用經驗迥異於臨床試驗中所見 Real-World Experience Differs from Trial Results for Niraparib in Recurrent Ovarian Cancer:
Gallagher JR. Real world occurrence of top three clinical-trial reported adverse events of PARP inhibitor niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer, a national retrospective observational study of a 200 mg/day starting-dose cohort. Abstract 986P.

In a phase 3 clinical trial of niraparib, patients initiated therapy at a 300 mg daily dose of the drug. Nausea, thrombocytopenia, and fatigue were the most commonly reported adverse events and more than 60% of patients reported experiencing these

3 events in the study. After dose adjustment in the trial, 200 mg per day was the most commonly administered dose.

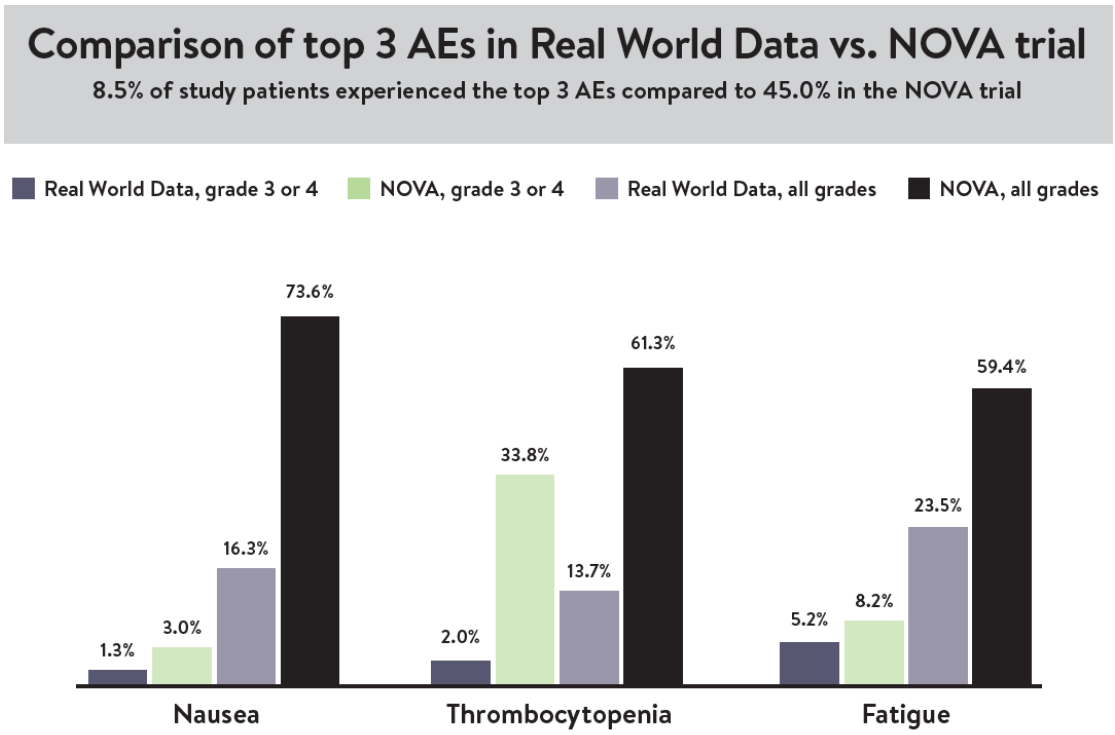
In this retrospective analysis, researchers wanted to describe adverse events among patients in a real-world setting given a 200 mg starting dose of niraparib. For the study 53 study-qualified physicians were randomly selected from a national database and were requested to extract data from the medical charts of 153 qualified patients who had received 200 mg per day niraparib for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. All patients were in complete or partial response to platinum-based chemotherapy.

In contrast to the 60% of patients in the phase 3 clinical trial, a little more than one-third (37%) of the real-world patients included experienced at least 1 of the 3 most common adverse events within the first 3 months of treatment initiation; 32% experienced only grade 1/2 events.

Overall, fatigue was reported in 24% of patients, nausea in 16% or patients, and thrombocytopenia in 14% of patients. Only 2% of patients experienced grade 3 or worse thrombocytopenia.

Very few patients had a dose interruption (4%) or had to discontinue niraparib altogether due to adverse events (2%). However, about 1 in 10 patients (11%) had to reduce their dose.

The researchers wrote that more real-world research would help to understand the effect of niraparib dosing on adverse events.



頭頸癌 Head Neck Cancer

1. Pembrolizumab 單獨使用或與化療合用在復發轉移之頭頸鱗狀上皮癌中皆可增加全體存活 Pembrolizumab Alone or With Chemotherapy Prolongs OS in Recurrent/Metastatic HNSCC: Burtness B, et al. KEYNOTE-048: Phase 3 study of first-line pembrolizumab (P) for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). Abstract LBA8_PR.

Investigators of the open-label, phase 3 KEYNOTE-048 trial randomly assigned 882 patients with recurrent/metastatic HNSCC that was not curable with local therapy (but who had not had prior systemic therapy) to receive pembrolizumab monotherapy, pembrolizumab plus chemotherapy (cisplatin or carboplatin with 5-fluorouracil), or the standard of care, which is cetuximab plus cisplatin or carboplatin for either 6 cycles, 24 months, disease progression, or until unacceptable toxicity.

The primary end point was PFS and OS in the overall population and was stratified by PD-L1 combined positive scores (CPS of ≥ 20 and ≥ 1). The data cutoff for this interim analysis was June 13, 2018, and the minimum follow-up was 17 months.

Pembrolizumab monotherapy prolonged OS among patients with PD-L1 tumor expression compared with the standard of care. In the cohort with a CPS of 20 or

higher,the median OS with pembrolizumab alone was 14.9 months compared with 10.7 months with standard chemotherapy (hazard ratio [HR], 0.61; 95% CI, 0.45-0.83; *P*= .0007). The median OS was also prolonged in the cohort with patients with a CPS of 1 or higher, albeit more modestly, with a median OS of 12.3 months with pembrolizumab compared with 10.3 months with chemotherapy (HR, 0.78; 95% CI, 0.64-0.96; *P*= .0086). In the total population, OS with pembrolizumab was noninferior to chemotherapy.
Pembrolizumab plus chemotherapy significantly prolonged OS in the overall population, but not in the PD-L1–positive cohorts. The median OS for the unselected population was 13.0 months compared with 10.7 months with standard chemotherapy (HR, 0.77; 95% CI, 0.63-0.93; *P*= .0034). The median OS with pembrolizumab was not superior to standard chemotherapy in the PD-L1 expression cohorts.

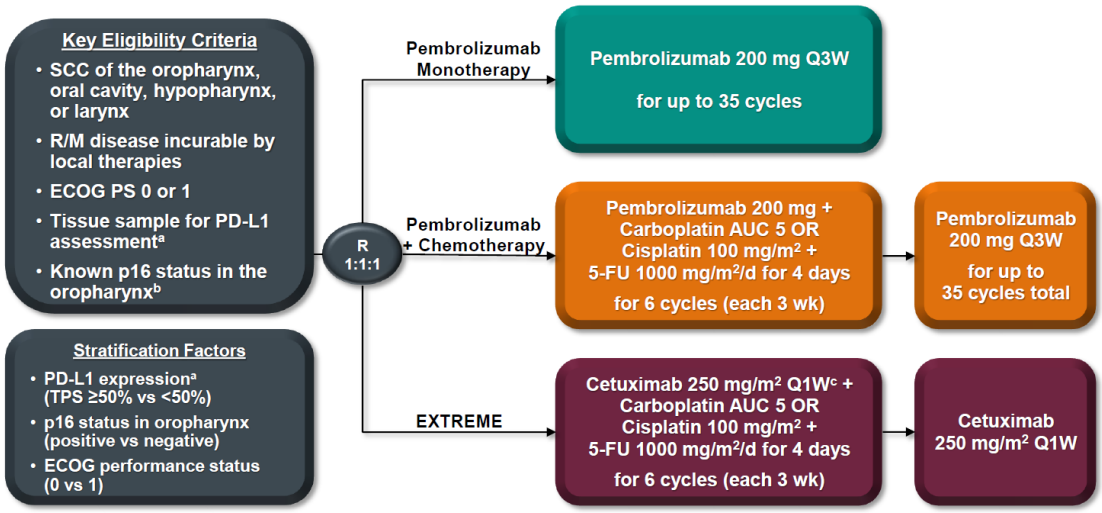
Pembrolizumab monotherapy and the pembrolizumab combination with chemotherapy did not significantly improve PFS compared with standard chemotherapy, regardless of PD-L1 expression.

The ORR was similar between the pembrolizumab plus chemotherapy and chemotherapy arms, at approximately 36% each. The ORR with pembrolizumab monotherapy was lower, at 23%. The median duration of response (DoR), however, was longer when pembrolizumab was part of the regimen. The DoR was 20.9 months with pembrolizumab monotherapy, 6.7 months with pembrolizumab plus chemotherapy, and approximately 4.3 months with standard chemotherapy, regardless of PD-L1 expression.

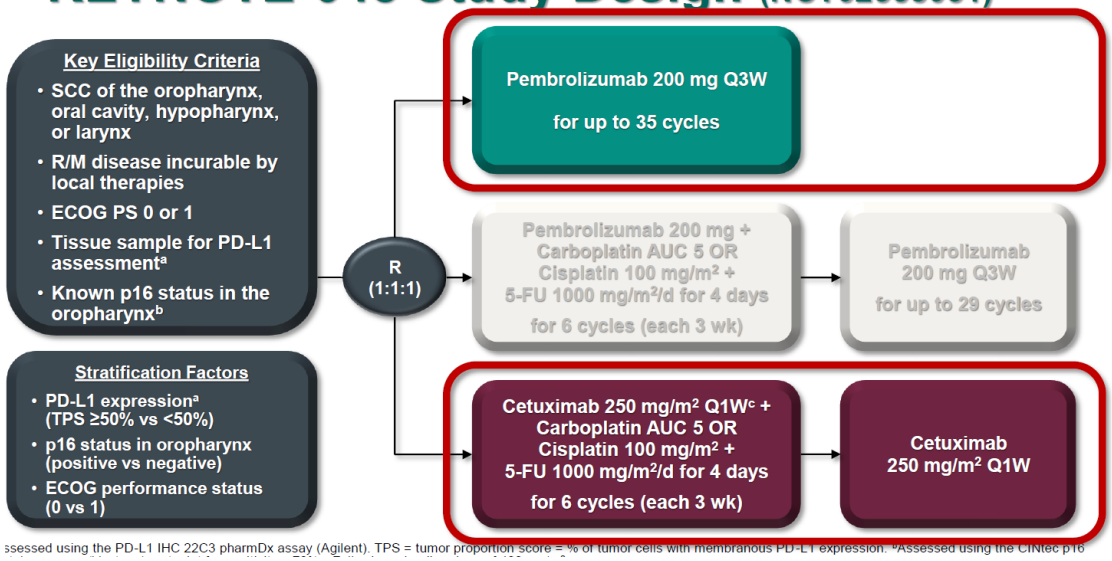
Grade 3 to grade 5 adverse events (AEs) occurred most frequently with chemotherapy-based regimens, with a rate of 69% with standard chemotherapy and 71% with pembrolizumab plus chemotherapy compared with 17% with pembrolizumab alone.

These data indicate that “pembrolizumab appears to prolong life even when the cancer continues to grow, suggesting that it should be a first-line therapy in recurrent and metastatic head and neck cancer,” according to Barbara Burtness, MD, of the Yale School of Medicine and Yale Cancer Center in New Haven, Connecticut, and an author of the study. She noted that “whether pembrolizumab is given alone or with chemotherapy may depend on PD-L1 expression.”

KEYNOTE-048 Study Design (NCT02358031)

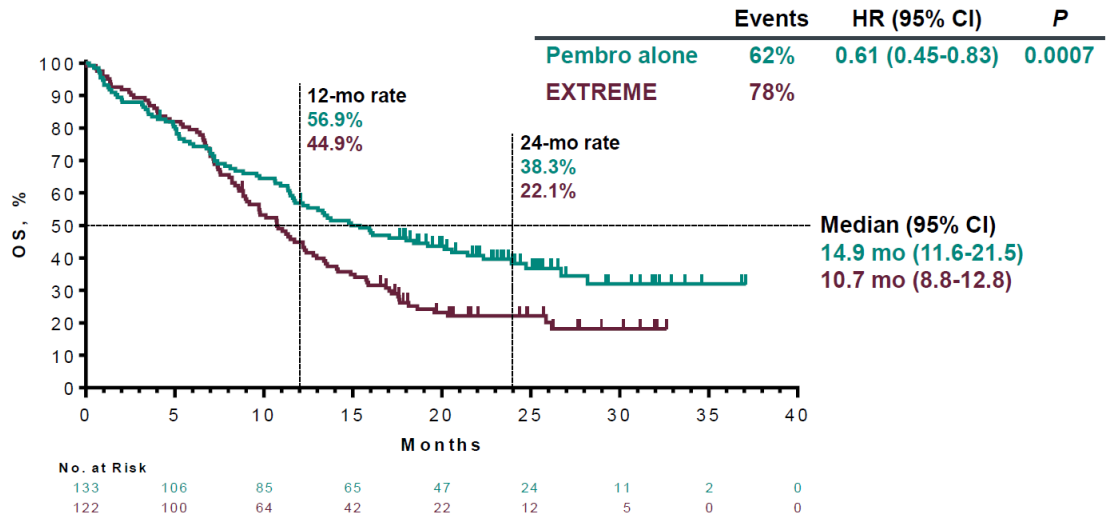


KEYNOTE-048 Study Design (NCT02358031)

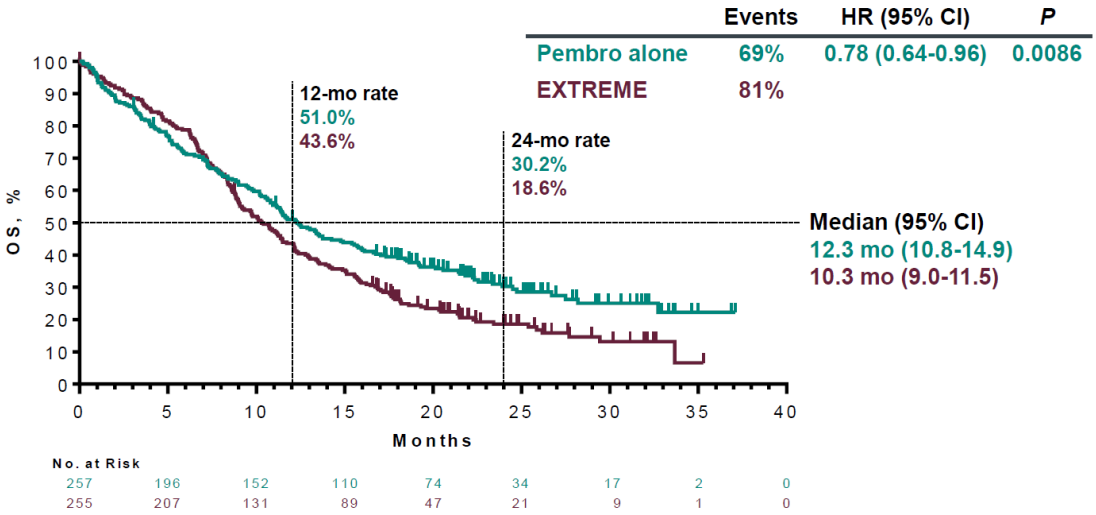


ssessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16

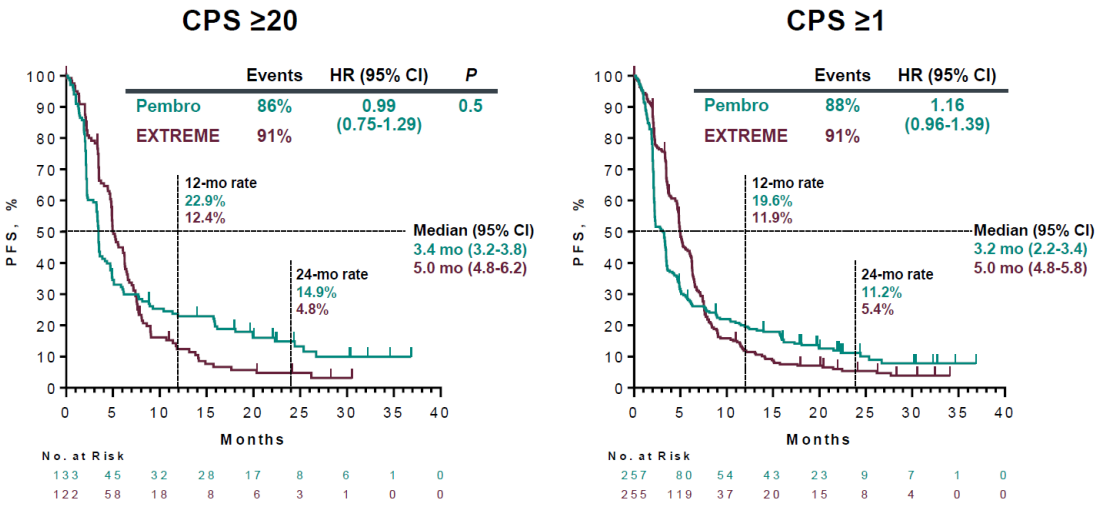
Overall Survival: P vs E, CPS ≥20 Population



Overall Survival: P vs E, CPS ≥1 Population



Progression-Free Survival: P vs E



攝護腺癌 Prostate Cancer

1. 在去勢療法失效而有骨轉移之攝護腺癌中合併使用 Abiraterone Acetate, Radium-223 不被建議 Combination Abiraterone Acetate, Radium-223 Not Recommended in CRPC With Bone Mets: Smith MR. ERA 223: A phase 3 trial of radium-223 (RA-223) in combination with abiraterone acetate and prednisone/prednisolone for the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve patients (pts) with bone-predominant metastatic castration-resistant prostate cancer (mCRPC). Abstract LBA30.

The study included 806 men with asymptomatic or mildly symptomatic disease who were randomly assigned to receive abiraterone acetate and prednisone (AAP) with (401 individuals) or without Ra-223 (405 individuals). The combination was being tested because AAP improves progression-free survival and overall survival in

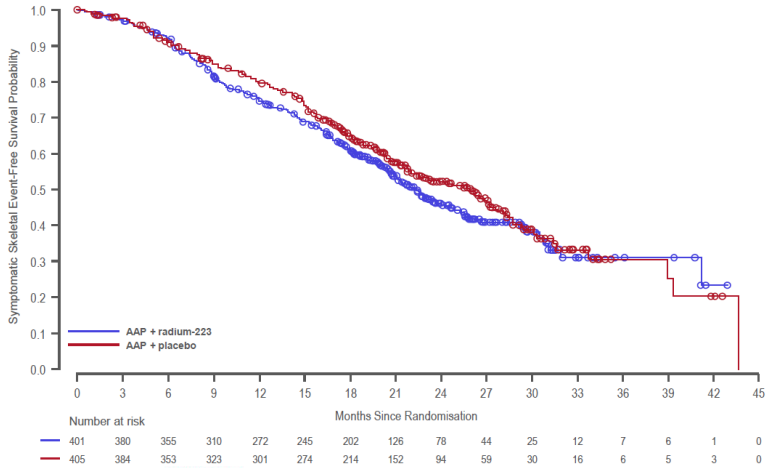
CRPC, and Ra-223 decreases symptomatic skeletal events (SSE) in CRPC with bone metastases.

An increased rate of fractures and deaths in the combination arm led to early unblinding of the study. Median SSE-free survival was similar between patients assigned AAP plus Ra-223 and those assigned to AAP alone (22.3 vs 26.0 months; HR=1.22; 95% CI, 0.917-1.374). Median overall survival was also similar between the two study arms (30.7 vs. 33.3 months; H=1.195; 95% CI, 0.950-1.505).

Although survival outcomes were similar, about one-third (29%) of patients assigned to AAP plus Ra-223 had fractures compared with 11% of patients assigned AAP alone.

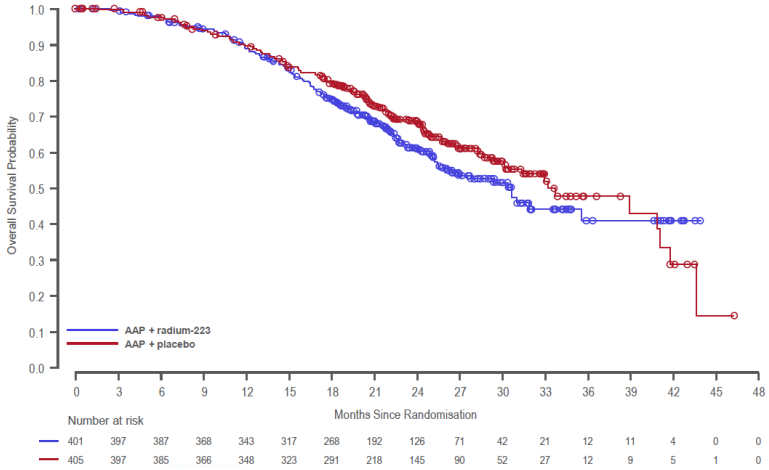
Men who were receiving bone health agents at baseline were allowed to continue taking them while on the study. Among these men, 15% assigned the combination regimen and 7% assigned to receive AAP alone had fractures compared with 37% and 15%, respectively, who were not taking bone health agents.

Symptomatic Skeletal Event-Free Survival (ITT)



SSE-FS	AAP + radium-223 N=401	AAP + placebo N=405
Events, n (%)	196 (49)	190 (47)
Median (95% CI), months	22.3 (20.4–24.8)	26.0 (21.8–28.3)
HR (95% CI)	1.122 (0.917–1.374)	
P-value (2-sided)	0.2636	

Overall Survival (ITT)



OS	AAP + radium-223 N=401	AAP + placebo N=405
Deaths, n (%)	155 (39)	141 (35)
Median (95% CI), months	30.7 (25.8–NE)	33.3 (30.2–41.1)
HR (95% CI)	1.195 (0.950–1.505)	
P-value (2-sided)	0.1280	

Final OS analysis to be performed after 500 events

Independent Review of Fracture Events*

	AAP + radium-223	AAP + placebo
Patients with ≥1 fracture, n	76	23
No bone metastasis at site of fracture, n	60	17
Type of fracture, n		
Pathological	19	6
Traumatic	27	13
Osteoporotic	37	4
Indeterminate	1	0

免疫療法 Immunotherapy

1. 檢測可助研究者發現潛藏在免疫療法效果下之因素 Assays May Help Researchers Discover Factors Underlying Immunotherapy Response: Hyland F, Looney T, Chaudhury R, Kamat A, Pankov A. Multi-dimensional immuno-oncology assays for understanding the immune system and tumor microenvironment. Abstract 137P.

Novel platforms for the analysis of the tumor microenvironment, immune system, and driver mutations could drive oncology research to better understand the determinants of response to immunotherapy.

A subset of patients treated with immune checkpoint inhibitors or other immunotherapy approaches, such as chimeric antigen receptor T-cell (CAR-T) therapies, achieve a sustained complete response. What determines this response, however, is unknown. The aim of this study was to characterize a suite of assays that could be used in oncology research to drive a greater understanding of the tumor microenvironment, immune system, and driver mutations, all of which may be determinants of response.

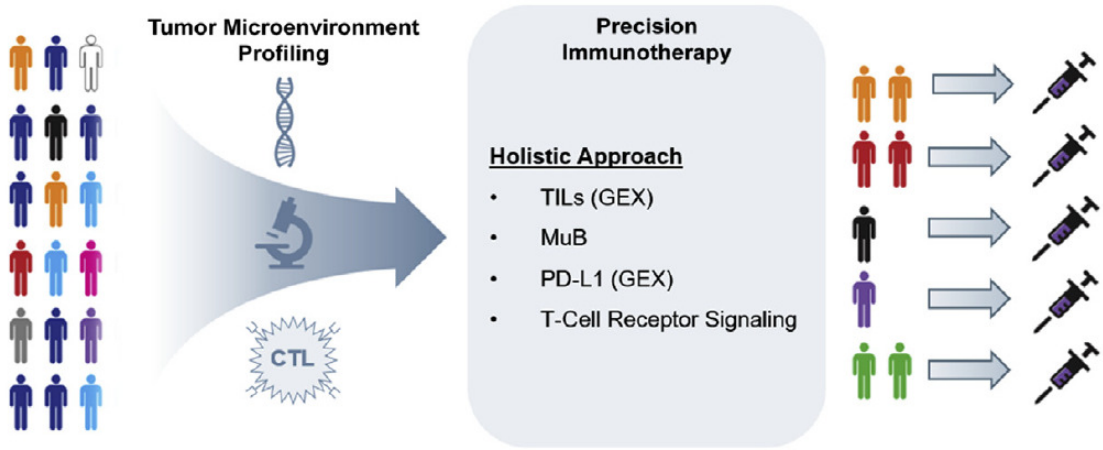
This platform uses a single software program to allow joint interpretation of a suite of 3 different Oncomine assays. These assays use a single instrument, and each assay requires 20 ng of input material.

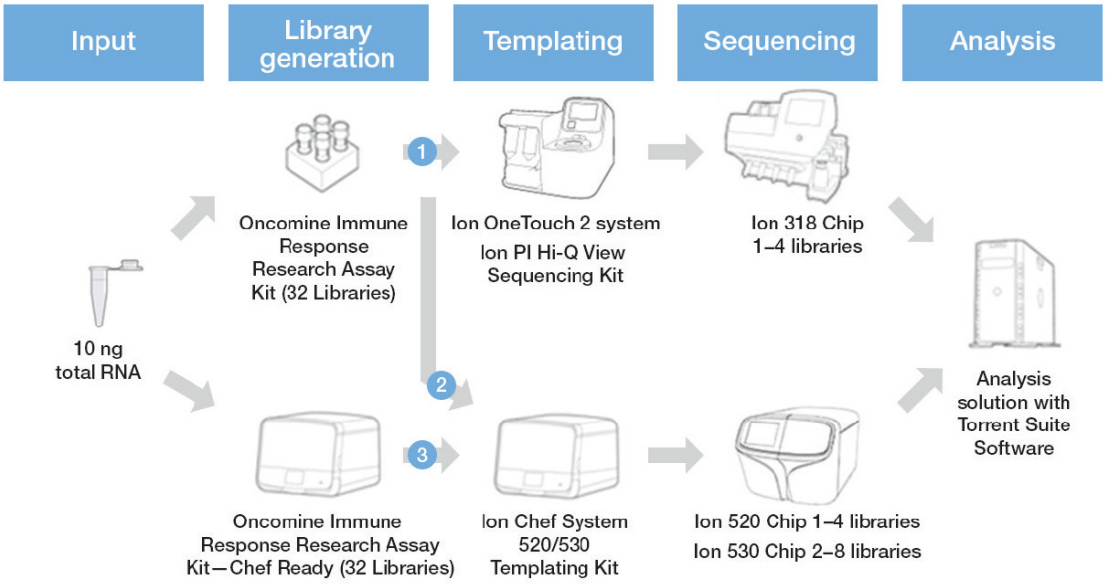
The first assays evaluated a 395-gene panel of genes involved in interferon and chemokine signaling, T- and B-cell activation, checkpoint pathways, antigen presentation, tumor proliferation, and expression markers of immune system effector cells to analyze patterns of gene expression. The study demonstrated that this assay has high sensitivity for detection, including detection of low-expressing genes that encode for interferon gamma.

The second assay sequenced the T-cell repertoire using total RNA harvested from blood to provide an estimate of T-cell diversity, among other properties. The sequencing is of the long-amplicon TCRB chain covering CDR1, CDR2, and CDR3.

The third assay is a 400-gene panel that evaluates tumor mutation load by analyzing somatic mutations per megabase using formalin-fixed paraffin-embedded tissue. This assay does not require a matched normal sample. The study demonstrated high reproducibility, concordance with matched normal tissue, correlation with exome mutation load, and accuracy on control cell lines.

The authors concluded that taken together, “These immuno-oncology assays enable deep, broad, multidimensional characterization of biomarkers to explore predictors of response, optimal combination therapy, and avoidance of adverse events, accelerating research into immunotherapy for personalized oncology.”





2. 使用節制點抑制之免疫療法所引起之副作用在黑色素癌中較非小細胞肺癌多 Immune-Related Adverse Events Due to Checkpoint Inhibition Are More Common in Melanoma Than in NSCLC: Duma N. Immune-related adverse events: Comparison of melanoma and non-small cell lung cancer patients treated with anti-PD1 therapy. Abstract 1218P.

More patients with melanoma who were treated with either nivolumab or pembrolizumab developed immune-related adverse events (irAEs) compared with patients with non-small cell lung cancer (NSCLC) treated with these same checkpoint inhibitors, suggesting differences in these events across groups.

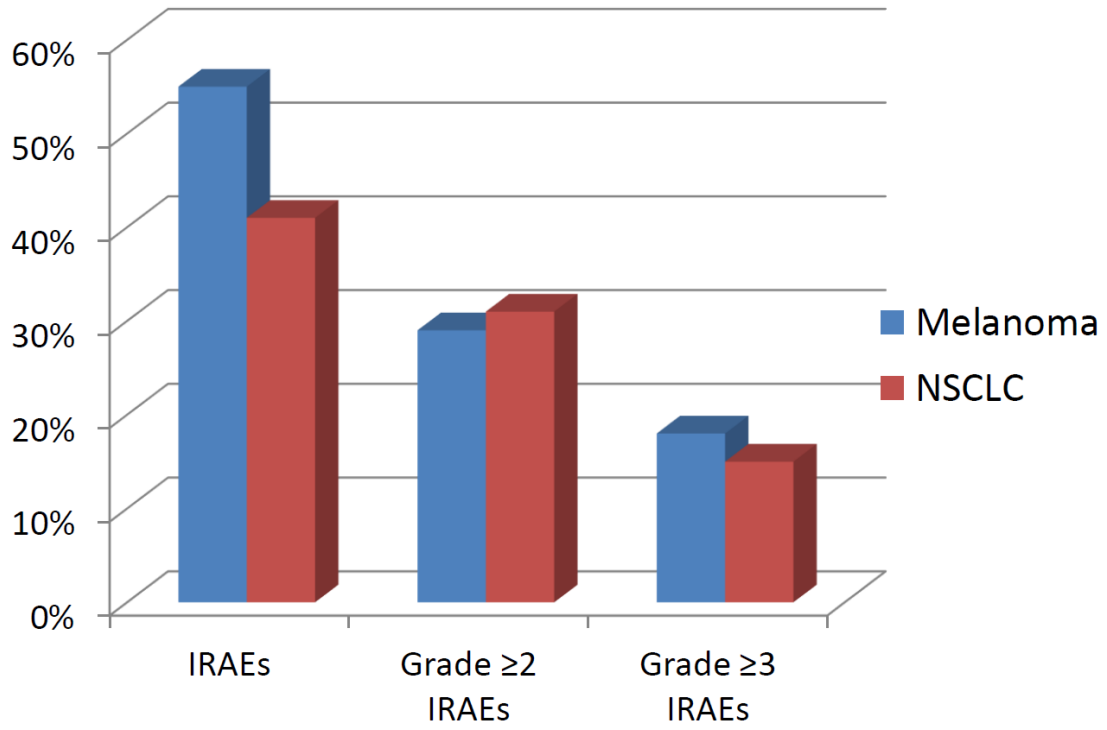
According to the abstract, irAEs are a treatment challenge of immunotherapies that could potentially limit their clinical benefit. In this study, researchers examined the

occurrence of irAEs related to treatment with an anti-PD-1 drug — nivolumab or pembrolizumab — seen in 266 patients with melanoma compared with those observed in 244 patients with NSCLC. All of the subjects were treated at the Mayo Clinic in either Rochester, Minnesota, or Jacksonville, Florida, from 2015 to 2018.

Three-quarters of patients with melanoma were treated with pembrolizumab and 66% of patients with NSCLC received nivolumab. More than one-half of patients (55%) with melanoma experienced an irAE compared with only 41% of patients with NSCLC (*P* <. 001). However, no difference in grade 3 or higher irAEs was seen between the 2 cancer types.

Specifically, patients with melanoma were more likely to develop diarrhea/colitis (19% vs 7%; *P* < .008) and endocrinopathies (33% vs 18%; *P* < .01) compared with patients with NSCLC. In contrast, patients with NSCLC were more likely to develop pneumonitis (14% vs 6%; *P* < .007).
More than half of patients with melanoma (60%) and NSCLC (57%) resumed treatment with PD-1 inhibitors after developing irAEs. However, 45% of patients with melanoma and 31% of those with NSCLC ultimately discontinued use of the immunomodulator due to toxicity.

	Melanoma % (n)	NSCLC % (n)	p value
IRAEs	55 (146)	41 (99)	0.001
Grade ≥2 IRAEs	29 (76)	31 (75)	0.66
Grade ≥3 IRAEs	18 (49)	15 (36)	0.26
Prescribed systemic steroids	66 (97)	60 (59)	0.26
Required intravenous steroids	25 (37)	27 (27)	0.75
IRAEs: Subtype (all grades)			
Diarrhea/Colitis	19 (28)	7 (7)	0.008
Dermatologic Toxicities	19 (28)	22 (22)	0.62
Endocrinopathies	33 (48)	18 (18)	0.01
Pneumonitis	6 (8)	14 (14)	0.007
Transaminitis	14 (21)	9 (9)	0.24



TRK 抑制劑 TRK inhibitor

1. 在含 *TRK* 融合之癌症中 Larotrectinib 證明有效

Larotrectinib Continues to Show Efficacy in *TRK*-Fusion Cancers: Lassen UN, Albert CM, Kummar S, et al. Larotrectinib efficacy and safety in TRK fusion cancer: an expanded clinical dataset showing consistency in an age and tumor agnostic approach. Abstract 409O.

Larotrectinib targets the protein products of *NTRK1/2/3* gene fusions and previously demonstrated an overall response rate (ORR) of 75% among 55 consecutive adult and pediatric patients with *TRK*-fusion cancers. This analysis provides updated results for those 55 patients and an additional 35 patients enrolled in larotrectinib clinical trials as of February 19, 2018.

TRK fusions were detected by molecular profiling of patients from 3 larotrectinib clinical trials. Treatment was administered until disease progression, withdrawal, or unacceptable toxicity.

Among the initial 55 patients and during a median 12.9 months of follow-up, the median duration of response (DoR) and progression-free survival (PFS) had not yet been

reached. In this cohort, responses were ongoing in 69% of patients, 58% were progression-free, and 90% were still alive at 1 year.

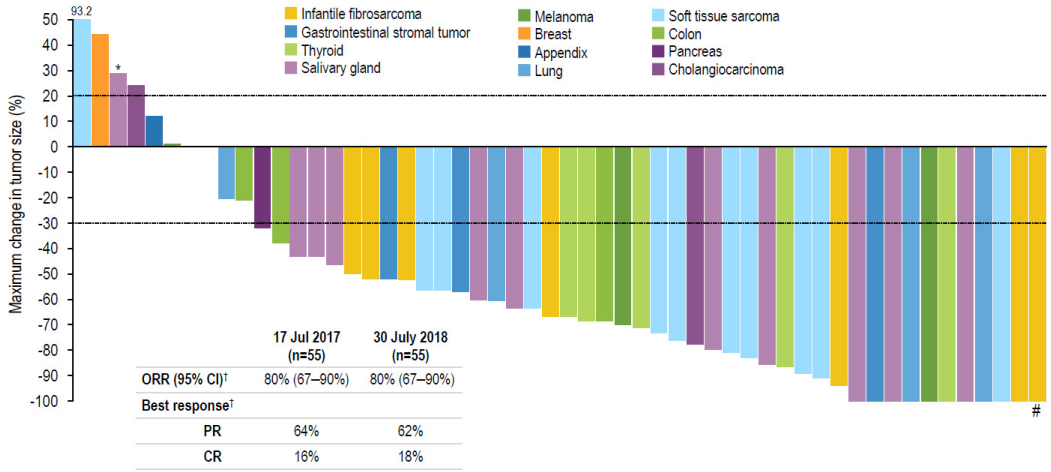
There were an additional 44 adult and pediatric patients enrolled after the primary analysis set (age range, 0.1-78 years) with various cancer types, including malignancies of the lung, colon, thyroid, salivary gland, as well as melanoma, sarcoma, congenital mesoblastic nephroma, and gastrointestinal stromal tumors.

Among the 35 evaluable patients in this cohort, the ORR was 74%, which included 5 complete and 21 partial responses, 6 stable disease, 2 with progressive disease, and 1 who was undetermined. The median DoR was not reached during a median follow-up of 5.5 months, but 88% of response were ongoing at 6 months.

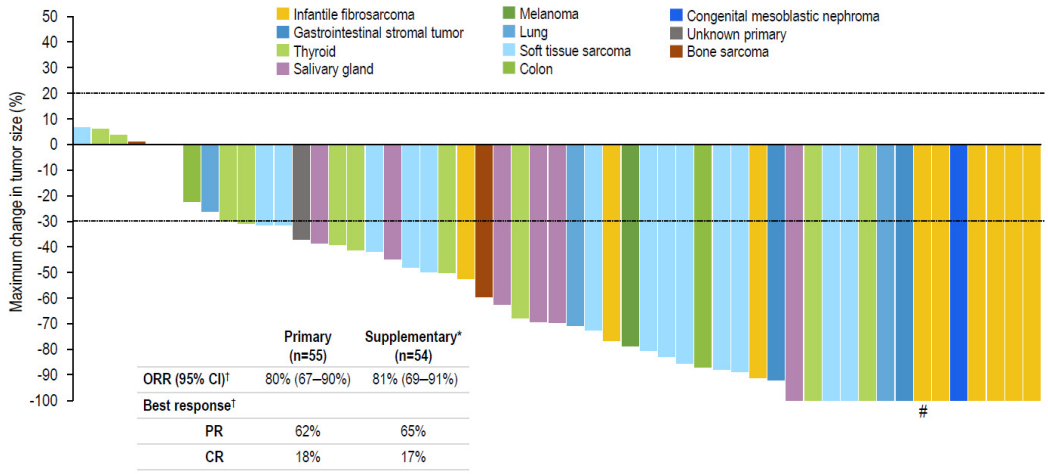
Most adverse events (AEs) were grade 1 in severity, with the most common including dizziness, elevated liver enzymes, fatigue, nausea, and constipation. Grade 3/4 AEs related to larotrectinib treatment occurred in fewer than 5% of patients.

The authors concluded that, “Larotrectinib is an effective age- and tumor-agnostic treatment for *TRK*-fusion cancer with a positive safety profile.” They noted that these results suggest that “screening patients for *NTRK* gene fusions in solid [tumors] and brain tumors should be actively considered.”

Primary dataset: Larotrectinib has proven efficacy in TRK fusion cancer

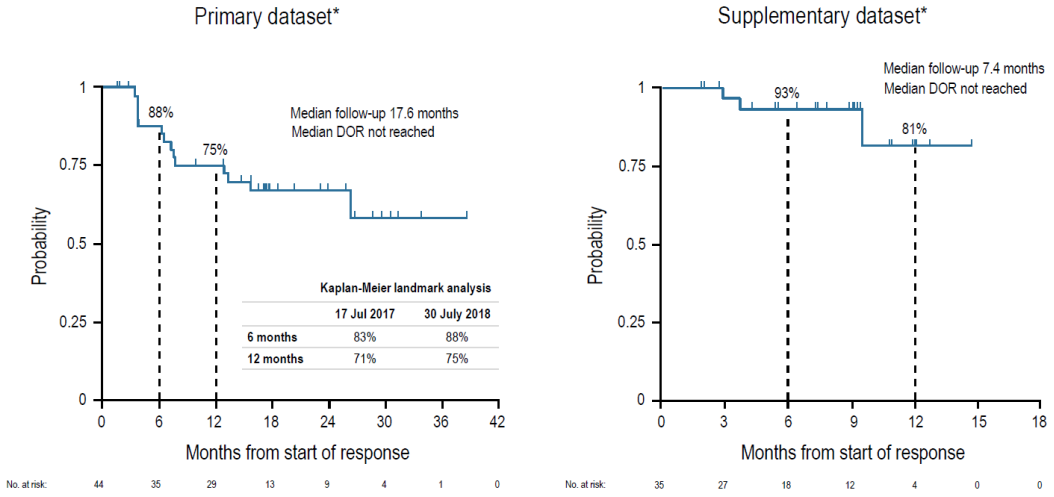


Supplementary dataset: Larotrectinib efficacy consistent with primary dataset



	Primary (n=55)	Supplementary* (n=54)
ORR (95% CI)†	80% (67–90%)	81% (69–91%)
Best response†		
PR	62%	65%
CR	18%	17%

Sustained responses with larotrectinib (DOR)



Kaplan-Meier landmark analysis	17 Jul 2017	30 July 2018
6 months	83%	88%
12 months	71%	75%

2. Entrectinib 可使 *TRK* 融合之固態腫瘤縮小

Entrectinib Shrank *NTRK* Fusion-Positive Solid Tumors: Demetri GD. Efficacy and safety of entrectinib in patients with NTRK fusion-positive (NTRK-fp) tumors: pooled analysis of STARTRK-2, STARTRK-1, and ALKA-372-001. Abstract LBA17.

The TRKA/B/C and ROS1 inhibitor entrectinib induced clinically meaningful and durable responses in patients with *NTRK*-fusion-positive solid tumors, a type of tumor with no approved therapies at this time.

The analysis included data from 3 phase 1/2 trials: ALKA, STARTRK-1, and STARTRK-2. These trials included patients with locally advanced or

metastatic *NTRK* fusion-positive tumors enrolled across 15 countries. Tumors were assessed for response at 4 weeks and then every 8 weeks thereafter.

Efficacy was evaluated in 54 patients, including some with baseline central nervous system (CNS) metastases. After 15.5 months of follow-up, the blinded independent committee review-assessed overall response rate was 57.4%, including 7.4% of patients who achieved complete response. Responses were seen in all 10 tumor types representing more than 19 histopathologies. The median duration of response was almost 1 year (10.4 months).

Median progression-free survival was 11.2 months, with a median overall survival of 20.9 months.

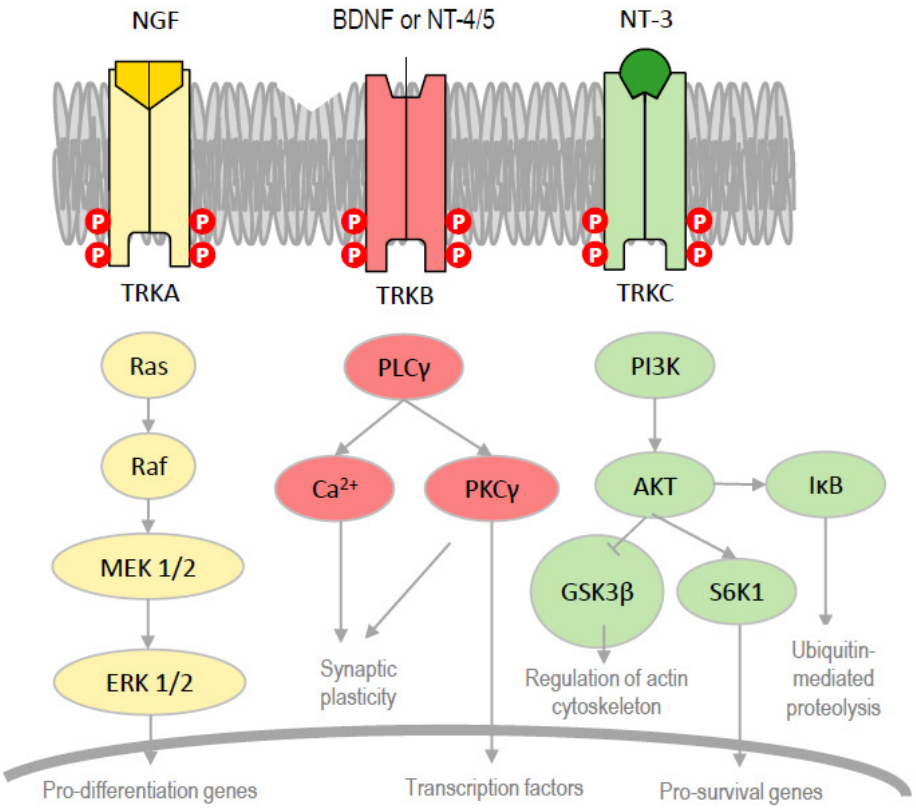
The researchers looked at outcomes among patients with or without CNS metastases. Entrectinib shrank tumors in 54.5% of patients with CNS metastases, with more than one quarter demonstrating a complete response. The median progression-free survival was 12 months in patients without metastases (42 patients) compared with 7.7 months for those with brain metastases (12 patients).

Safety was evaluated in 355 patients from the three clinical trials. The most common adverse events were grade 1/2 and were successfully managed with a dose reduction in 27.3% of patients. Only 4% of patients had to discontinue treatment do to treatment-related adverse events.

Entrectinib has been granted a breakthrough therapy designation by the US Food and Drug Administration for the treatment of *NTRK* fusion-positive, locally advanced, or metastatic solid tumors in adult and pediatric patients who have either progressed following prior therapies or have no acceptable standard therapies.

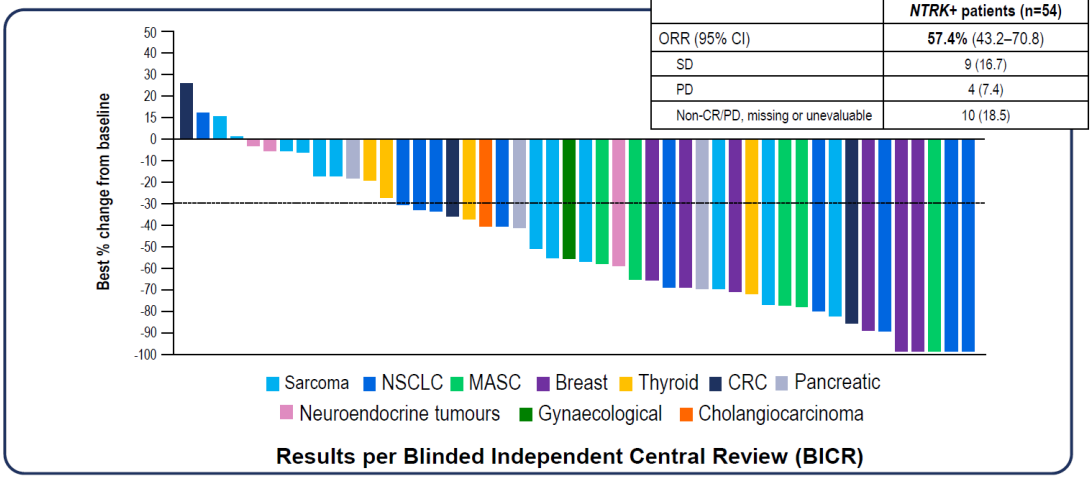
NTRK1/2/3 genes encode TRK A/B/C proteins, respectively

– ***NTRK1/2/3 gene*** **fusions are oncogenic drivers** [4]

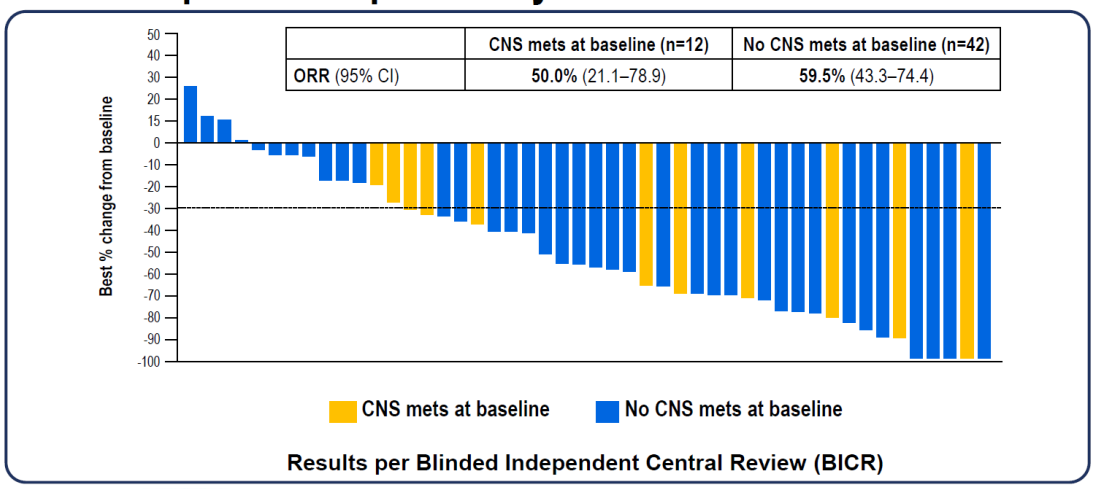


Entrectinib activity in *NTRK* fusion-positive solid tumours: individual patient responses by tumour type

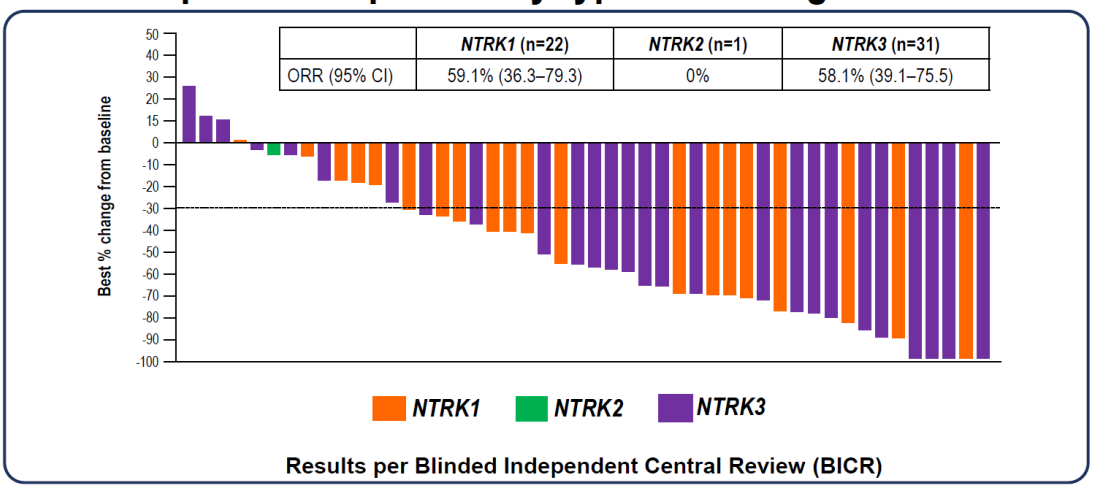
	NTRK+ patients (n=54)
ORR (95% CI)	**57.4%** (43.2–70.8)
SD	9 (16.7)
PD	4 (7.4)
Non-CR/PD, missing or unevaluable	10 (18.5)



Entrectinib activity in *NTRK* fusion-positive solid tumours: Individual patient responses by CNS mets status at baseline



Entrectinib activity in *NTRK* fusion-positive solid tumours: Individual patient responses by type of *NTRK* gene



Carbozantinib

1. Cabozantinib 在腎細胞癌中不論 PD-L1 表現如何都有效

Cabozantinib Effective Regardless of PD-L1 Expression in RCC: Choueiri TK, Suarez C. PD-L1 status and clinical outcomes to cabozantinib, sunitinib, and everolimus in patients with metastatic clear-cell RCC treated on CABOSUN and METEOR clinical trials. Abstract LBA34.

PD-L1 tumor expression is associated with better outcomes among patients with metastatic RCC treated with nivolumab and ipilimumab and may, therefore, be a biomarker

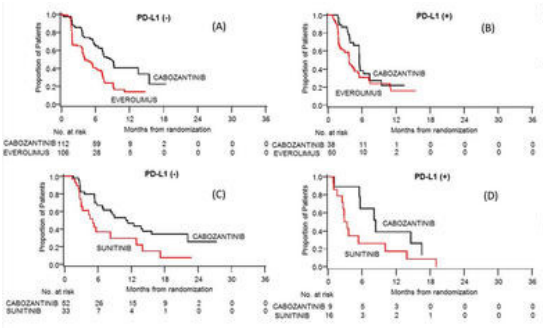
Cabozantinib is already approved for the treatment of metastatic RCC. The aim of this study was to determine if PD-L1 tumor expression could also be a predictive biomarker for cabozantinib efficacy.

In this study, tumor tissue from 416 patients enrolled in the CABOSUN and METEOR trials was analyzed by immunohistochemistry for PD-L1 and CD45/CD163 expression. PD-L1 positivity was defined as at least 1% or higher of PD-L1-positive tumor cells or immune cells.

In the METEOR and CABOSUN trials, 29% and 23% of tumors were positive for PD-L1 expression, respectively. PD-L1 positivity was significantly associated with shorter progression-free survival (PFS) and overall survival (OS), regardless of the type of treatment.

In METEOR, the median PFS was 7.2 and 5.3 months for patients who had PD-L1 negative or positive tumors, respectively (*P*= .027). Median OS was 21.3 and 15.1 months in the PD-L1–negative or –positive cohorts, respectively (*P*= .003). In CABOSUN, the median PFS was 8.3 and 5.5 months (*P*= .05) and median OS was 28.1 and 20.8 months (*P*= .05) in the PD-L1–negative or –positive groups, respectively. PD-L1 tumor expression, however, was not a predictive biomarker for cabozantinib efficacy. In both trials, cabozantinib improved PFS, OS, and objective response rate compared with everolimus or sunitinib, regardless of PD-L1 tumor positivity. There was no association between PD-L1 positivity and outcomes with cabozantinib when evaluated by immune cell expression of PD-L1, combined PD-L1 score, or using different PD-L1 positivity cutoffs.

The authors concluded that these results indicate that cabozantinib can continue to be used in a PD-L1–unselected population as a monotherapy or, potentially, in combination with immune checkpoint inhibitors.



	METEOR (N=306)					CABOSUN (N=110)				
	CABOZANTINIB (C)		EVEROLIMUS (E)		C vs E	CABOZANTINIB (C)		SUNITINIB (S)		C vs S
	N	Median Months (95%CI)	N	Median Months (95%CI)	HR (95%CI)	N	Median Months (95%CI)	N	Median Months (95%CI)	HR (95%CI)
PFS										
PD-L1(-)	112	8.5 (7.2-13.5)	106	4.1 (3.7-6)	**0.46 (0.32-0.66)**	52	11.0 (6.8-15.6)	33	5.0 (3-12.9)	**0.47** (0.26-0.86)
PD-L1(+)	38	5.6 (4.5-7.4)	50	3.7 (2-5.3)	**0.66 (0.40-1.11)**	9	8.4 (1.1-16.6)	16	3.1 (1.6-10.1)	**0.46** (0.18-1.21)
P-interaction					***0.217***					***0.998***
OS										
PD-L1(-)	112	NR	106	18.4 (15.1-NR)	**0.58 (0.38-0.88)**	52	30.3 (18.8-NR)	33	22.4 (7.6-NR)	**0.71 (0.39-1.29)**
PD-L1(+)	38	18.4 (10.4-22)	50	13.9 (8.7-18.9)	**0.82 (0.47-1.41)**	9	18.1 (1.1-35)	16	21.0 (6.4-30.8)	**0.85 (0.31-2.31)**
P-interaction					**0.359**					**0.372**

Figure. Kaplan Meier estimates of PFS according to treatment, sub-grouped by PD-L1 status in tumor cells in METEOR cohort (A,B); and in CABOSUN cohort (C,D).

2. Cabozantinib 在骨肉癌和 Ewing 肉癌中有效 Cabozantinib Shows Promising Activity in Osteosarcoma and Ewing Sarcoma: Italiano A, Katz D, et al. Cabozantinib in patients with advanced osteosarcomas and Ewing sarcomas: a French Sarcoma Group (FSG)/US National Cancer Institute phase II collaborative study. Abstract LBA67.

The outcomes for patients with relapsed and unresectable osteosarcoma and Ewing sarcoma remain poor, with no approved agents available in this setting. Preclinical studies, however, suggest that MET inhibition or antiangiogenic agents may have efficacy in these diseases. These studies sought to evaluate the efficacy and safety of cabozantinib in advanced osteosarcoma and Ewing sarcoma.

The 2 multicenter, single-arm, 2-stage phase 2 trials treated 90 adults and children with advanced osteosarcoma or Ewing sarcoma with cabozantinib once daily until progressive disease or unacceptable toxicity. The primary end points were 6-month objective response (OR) and nonprogression in the osteosarcoma cohort and OR in the Ewing sarcoma cohort.

The study is considered positive if 5 patients each with osteosarcoma or Ewing sarcoma experience an OR, or if 16 patients with osteosarcoma are free from progression at 6 months.

At baseline, the median age of study participants was 35 years and 33 years for the osteosarcoma and Ewing sarcoma cohorts, respectively, and the median lines of previous therapies was 3 and 4, respectively.

In the osteosarcoma cohort, 45.2% of patients experienced tumor shrinkage, including 11.9% who experienced partial responses (PRs) and 33.3% who saw disease stabilization. The 6-month nonprogression rate was 33.3%.

In the Ewing sarcoma cohort, tumor shrinkage occurred in 57.6% of patients, including 27.7% with PRs and 30.3% with disease stabilization. The 6-month nonprogression rate was 24.2%.

At least 1 adverse event occurred in 96% of patients.

The authors concluded that these data suggest that cabozantinib has “meaningful clinical activity in osteosarcoma and Ewing sarcoma patients with heavily pretreated advanced disease.” They noted that the primary end points were met in both cohorts.

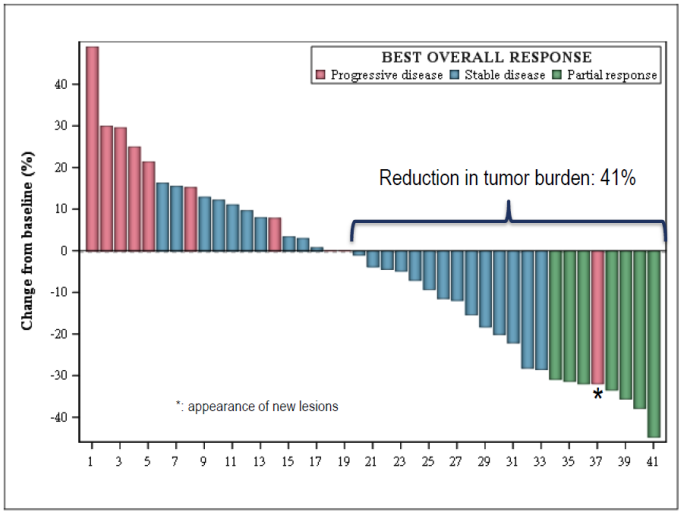
Osteosarcomas: Primary endpoint

Final analysis - 42 patients eligible and assessable for efficacy

Primary endpoint

- 5 OR (11.9%)
- 14 6-months Non Prog. (33.3%)

→ ***Conditions reached → Efficacy***



Osteosarcomas: Progression-free survival

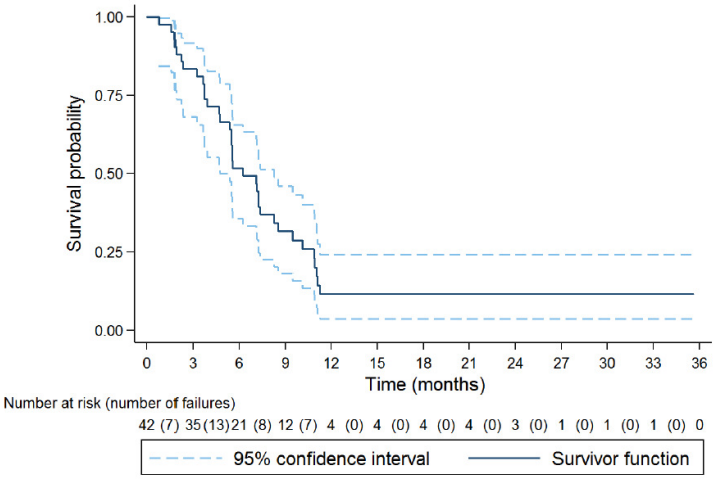
Final analysis - 42 patients eligible and assessable for efficacy

Median PFS

6.2 months $IC_{95\%}$ [5.4-8.2]

Events considered for PFS :

- Clinical progression, per investigator judgment
- radiological progression (local assessment),
- death

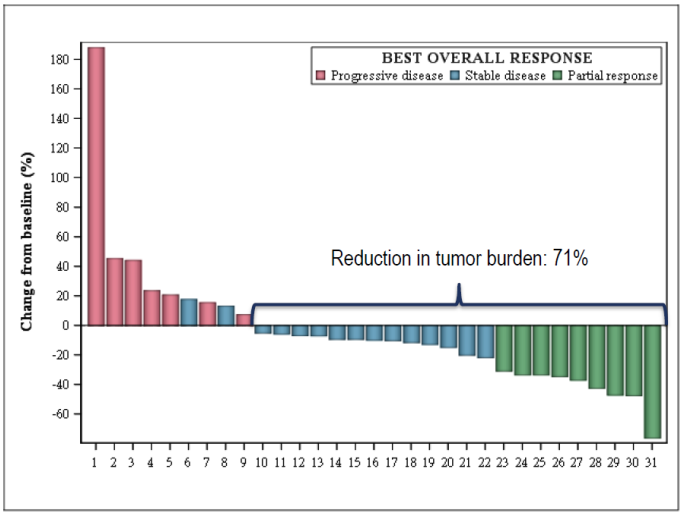


Ewing: Primary endpoint

.....Final analysis ongoing

Primary endpoint

- Stage 1 (N=21)
  - 4 OR (19%)
  - Condition reached → stage 2
- Ongoing analysis (N=32)
  - 1 pt: No tumor evaluation
  - 9 OR (28.1%)
  - Above predefined threshold → efficacy

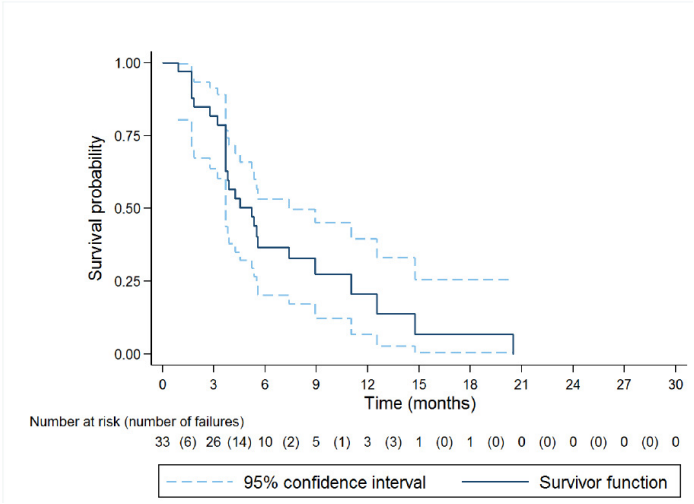


Ewing sarcomas : Progression-free survival (interim analysis)

Patients eligible and assessable for efficacy

Median PFS
5.2 months $IC_{95\%}$ [3.2-7.4]

Events considered for PFS :
- Clinical progression as per investigator judgement
- radiological progression (local assessment),
- death



3. AFP基礎質高的肝癌使用Cabozantinib效用較大Higher Baseline AFP Linked to Greater Benefit With Cabozantinib in Hepatocellular Carcinoma: Kelley RK, El-Khoueiry AB, Meyer T, et al. Outcomes by baseline alpha-fetoprotein (AFP) levels in the phase III CELESTIAL trial of cabozantinib (C) versus placebo (P) in previously treated advanced hepatocellular carcinoma (HCC). Abstract 702P.

A poor prognosis is associated with high baseline levels of AFP among patients with HCC. In the phase 3 CELESTIAL trial, cabozantinib significantly prolonged overall survival (OS) and progression-free survival (PFS) compared with placebo among patients with previously treated advanced HCC. The purpose of this analysis was to stratify the outcomes of the CELESTIAL trial by baseline AFP levels.

The phase 3 CELESTIAL trial randomly assigned 707 patients with relapsed/refractory HCC 2:1 to receive cabozantinib or placebo. All patients received prior sorafenib and up to 2 lines of systemic treatment. At baseline, all patients had a Child-Pugh score A and an ECOG performance status of 1 or less.

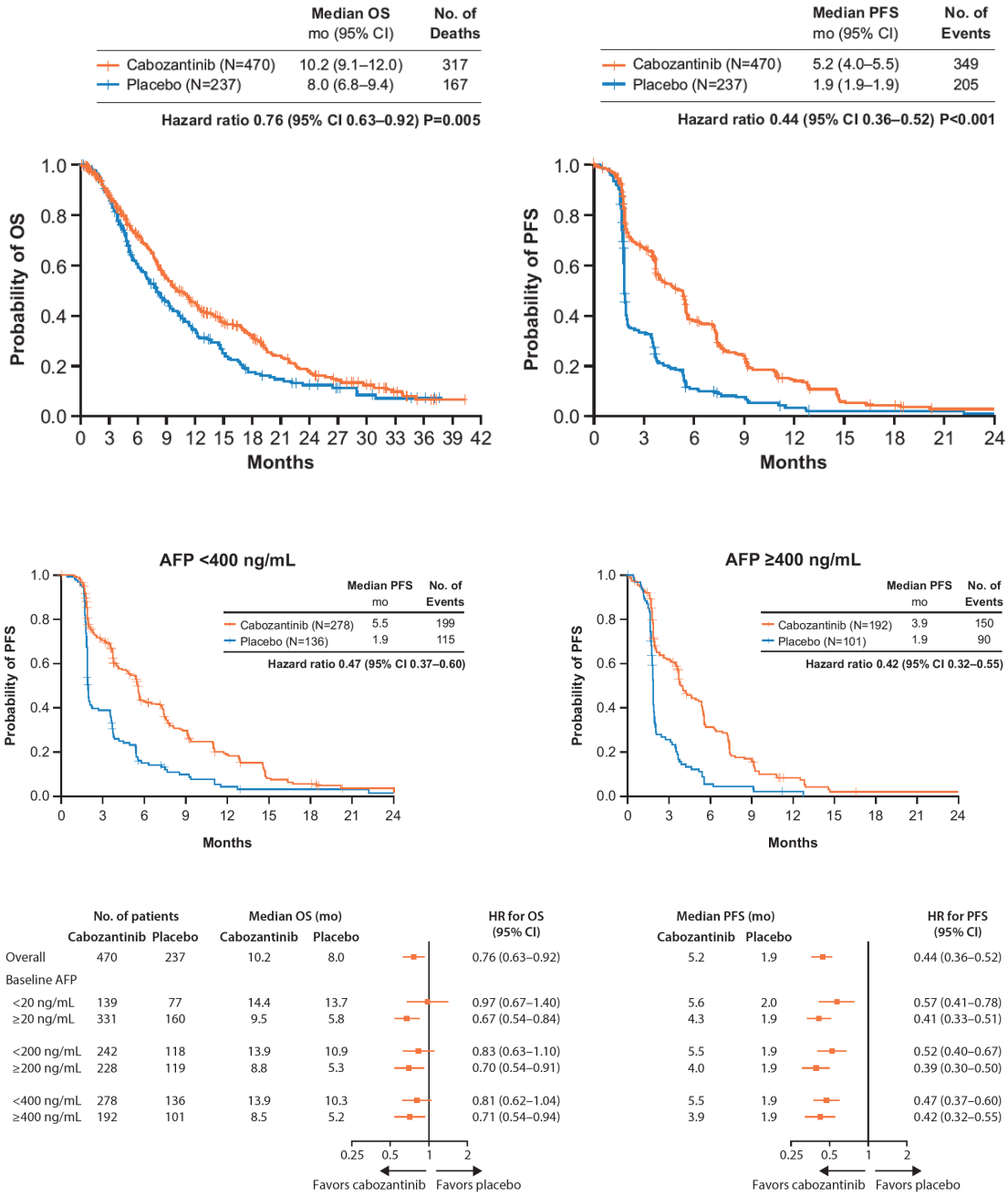
Most patients had a baseline AFP level of at least 20 ng/mL. At baseline, 69% of patients had a baseline AFP level of 20 ng/mL or more, 49% had levels of 200 ng/mL or more, and 41% had levels of 400 ng/mL or more.

Cabozantinib significantly prolonged PFS compared with placebo regardless of baseline AFP levels, with hazard ratios (HRs) ranging from 0.39 to 0.57. The median PFS was 5.5 months and 1.9 months with cabozantinib or placebo, respectively, among patients with an AFP level of less than 400 ng/mL at baseline (HR, 0.47; 95% CI, 0.37-0.60). For patients with an AFP levels greater than or equal to 400 ng/mL at baseline, median PFS was 3.9 and 1.9 months with cabozantinib or placebo, respectively (HR, 0.42; 95% CI, 0.32-0.55).

Median OS was longer with cabozantinib compared with placebo for all patients with a baseline AFP levels greater than or equal to 20 ng/mL. OS was a median 13.9 with cabozantinib compared with 10.3 months with placebo among patients with an AFP less than 400 ng/mL (HR, 0.81; 95% CI, 0.62-1.04). In the AFP greater than or equal to 400 ng/mL cohort, the median OS was 8.5 months compared with 5.2 months with cabozantinib or placebo, respectively (HR, 0.71; 95% CI, 0.54-0.94).

A high baseline AFP level was associated with an increased risk for developing high-grade transaminitis, regardless of treatment with cabozantinib or placebo. Grade 3/4 aspartate aminotransferase elevation was significantly greater with cabozantinib at 8% and 17% compared with placebo at 4% and 11% for patients with an AFP level less than 400 ng/mL or 400 ng/mL or higher, respectively.

The authors concluded that though patients with a range of baseline AFP levels experienced improved PFS and OS, “high AFP levels were associated with a larger treatment benefit with cabozantinib.”


Median OS
mo (95% CI)
No. of
Deaths
Cabozantinib (N=470) 10.2 (9.1–12.0) 317
Placebo (N=237) 8.0 (6.8–9.4) 167
Hazard ratio 0.76 (95% CI 0.63–0.92) P=0.005
Probability of OS
Months
Median PFS
mo (95% CI)
No. of
Events
Cabozantinib (N=470) 5.2 (4.0–5.5) 349
Placebo (N=237) 1.9 (1.9–1.9) 205
Hazard ratio 0.44 (95% CI 0.36–0.52) P<0.001
Probability of PFS
Months
AFP <400 ng/mL
Median PFS
mo
No. of
Events
Cabozantinib (N=278) 5.5 199
Placebo (N=136) 1.9 115
Hazard ratio 0.47 (95% CI 0.37–0.60)
Probability of PFS
Months
AFP ≥400 ng/mL
Median PFS
mo
No. of
Events
Cabozantinib (N=192) 3.9 150
Placebo (N=101) 1.9 90
Hazard ratio 0.42 (95% CI 0.32–0.55)
Probability of PFS
Months

No. of patients
Cabozantinib Placebo
Median OS (mo)
Cabozantinib Placebo
HR for OS
(95% CI)
Overall 470 237 10.2 8.0 0.76 (0.63–0.92)
Baseline AFP
<20 ng/mL 139 77 14.4 13.7 0.97 (0.67–1.40)
≥20 ng/mL 331 160 9.5 5.8 0.67 (0.54–0.84)
<200 ng/mL 242 118 13.9 10.9 0.83 (0.63–1.10)
≥200 ng/mL 228 119 8.8 5.3 0.70 (0.54–0.91)
<400 ng/mL 278 136 13.9 10.3 0.81 (0.62–1.04)
≥400 ng/mL 192 101 8.5 5.2 0.71 (0.54–0.94)
0.25 0.5 1 2
Favors cabozantinib Favors placebo
Median PFS (mo)
Cabozantinib Placebo
HR for PFS
(95% CI)
5.2 1.9 0.44 (0.36–0.52)
5.6 2.0 0.57 (0.41–0.78)
4.3 1.9 0.41 (0.33–0.51)
5.5 1.9 0.52 (0.40–0.67)
4.0 1.9 0.39 (0.30–0.50)
5.5 1.9 0.47 (0.37–0.60)
3.9 1.9 0.42 (0.32–0.55)
0.25 0.5 1 2
Favors cabozantinib Favors placebo

心得及建議

一年一度之歐洲腫瘤醫學會係世界級腫瘤醫學盛會。除了有專家學者之教育演講及研究整理，指出最新穎之發展方向，並且集合了世界各國之臨床試驗發表。今年仍以標靶治療與免疫治療為大宗。參與會議可以立即獲得最新資訊及觀念，大大有助於我們的治療水準提升。建議衛福部提供經費，每年都派本人前往學習，回來整理會議內容如此次之報告，相當於一本腫瘤醫學小書，定有益於本國學界及醫界。

附錄

・無