

ESMO Congress 2022

European Society for Medical Oncology

09–13 SEPTEMBER 2022 • PARIS • FRANCE

PEER-REVIEWED
CONFERENCE REPORT



Neoadjuvant Immune Checkpoint Inhibition in Colon Cancer

The NICHE-2 trial showed that neoadjuvant nivolumab/ipilimumab for 4 weeks achieved a major pathological response in 95% of patients with stage III colon cancer and deficient DNA mismatch repair.

read more on

PAGE

3

FGFR2 Inhibition in Cholangiocarcinoma

RLY-4008, as inhibitor of oncogenic *FGFR2* driver alterations, displayed clinical activity in patients with *FGFR* inhibitor-naïve cholangiocarcinoma harbouring an *FGFR2* fusion or rearrangement in the REFOCUS trail.

read more on

PAGE

6

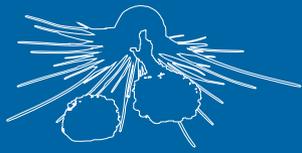
TILs Outperform Ipilimumab for Melanoma

A standing ovation was given to the second-line treatment data from tumour-infiltrating lymphocytes (TILs) extending progression-free survival compared with ipilimumab, in patients with advanced non-resectable stage III–IV melanoma.

read more on

PAGE

13



COLOPHON

Editor	Dr Stefan Rauh Centre Hospitalier Emile Mayrisch, Luxembourg
Reviewer	Prof. Guy Jerusalem CHU Liège, Belgium
Reviewer	Prof. Guy Berchem CHL Luxembourg, Luxembourg
Reviewer	Dr Joelle Collignon CHU Liège, Belgium
Reviewer	Prof. Christine Gennigens CHU Liège, Belgium

Publishing Director	Paul Willers
Editorial Operations Manager	Dr Rosalie Gadiot
Medical Science Officer	Dr Rachel Giles
Medical Project Manager	Anne van Ham
Editorial Coordinators	Dr Elke Marsch Dr Joery Goossens
Medical Writers	Dr Marten Dooper
Production Manager	Desiree Heijl
Graphic Design	MOOZ grafisch ontwerp
Graphics	Wim Kempink
Cover Photo	Unsplash, Irina Lediaeva
ISSN	2468-8762 22:24

All rights reserved.
No part of this publication may be reproduced, distributed, or transmitted in any form or by any means, including photocopying, recording, or other electronic or mechanical methods, without the prior written permission of the publisher, except in the case of brief quotations embodied in critical reviews and certain other noncommercial uses permitted by copyright law.

Copyright ©2022 Medicom Medische Uitgeverij BV

Disclaimer:
Our independent peer-reviewed Medicom Conference Reports are made possible by sponsoring. The ideas and opinions expressed in this journal or other associated publications do not necessarily reflect those of Medicom Medical Publishers. Although great care has been taken in compiling the content of this publication, Medicom is not responsible or liable in any way for the currency of the information, for any errors, omissions or inaccuracies in the original articles, or for any consequences arising from the content. Products mentioned in this report may not be covered by marketing authorisation in some countries. Product information, applicable in your country, should be reviewed before prescribing. The mention of any product, service, or therapy in this publication should not be construed as an endorsement of the products mentioned. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge of the patient, to determine drug dosages and the best treatment for the patient. Readers are advised to check the appropriate medical literature and the product information currently provided by the manufacturer of each drug to be administered to verify the dosage, method, and duration of administration, or contraindications. Readers are also encouraged to contact the manufacturer with questions about the features or limitations of any products. Medicom assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of the material contained in this publication or to any errors or omissions.

MED?COM
MEDICAL PUBLISHERS

Head Office	Postal address
Medicom Medical Publishers De Ruijterlaan 1-A 3742 AE Baarn The Netherlands	Medicom Medical Publishers PO Box 90 3740 AB Baarn The Netherlands

Telephone +31 85 4012 560
E-mail publishers@medicom-publishers.com

Contents

Letter from the Editor

3 Colorectal Cancer

- 3 High pathological responses to neoadjuvant immune checkpoint inhibition in locally advanced dMMR colon cancer
- 4 Fruquintinib: a potential new treatment for patients with refractory mCRC
- 4 Second-line avelumab is effective in patients with MSI-H/dMMR mCRC

5 Upper Gastrointestinal Cancer

- 5 Deep learning models predict relapse risk and mutational profile in GIST
- 6 Addition of pembrolizumab to lenvatinib does not improve OS in advanced HCC
- 6 New, highly selective inhibitor of *FGFR2* mutations
- 7 Chemo-immunotherapy is more effective when administered in parallel

8 Breast Cancer

- 8 TILs identify patients with immunogenic triple-negative breast cancer
- 9 OS benefit of abemaciclib in HR-positive/HER2-negative advanced breast cancer not (yet) statistically significant
- 9 OS benefit of sacituzumab govitecan in pre-treated HR-positive/HER2-negative metastatic breast cancer

10 Lung Cancer

- 10 A pathway from air pollution to lung cancer in non-smokers identified
- 11 Sotorasib demonstrates superior PFS and ORR in previously treated NSCLC
- 12 Promising clinical activity of tepotinib plus osimertinib in NSCLC with *MET* amplification after progression on first-line osimertinib
- 12 High pathological responses in borderline resectable NSCLC patients after induction with dual immunotherapy and concurrent chemoradiotherapy

13 Melanoma

- 13 Treatment with tumour-infiltrating lymphocytes for advanced melanoma outperforms ipilimumab
- 14 Neoadjuvant pembrolizumab outperforms adjuvant pembrolizumab in resectable stage III–IV melanomas
- 14 Baseline ctDNA predicts survival in resected stage III–IV melanoma
- 15 Survival-benefit of neoadjuvant T-VEC maintained over 5 years of follow-up

16 Genitourinary Cancer – Prostate Cancer

- 16 Overall survival benefit of abiraterone in mHSPC is maintained for 7 years
- 17 Limited benefit of adding long-term ADT to post-operative radiotherapy
- 18 Intensified ADT benefits biochemical PFS in biochemically relapsed prostate cancer

18 Genitourinary Cancer – Non-Prostate Cancer

- 18 Adjuvant nivolumab plus ipilimumab does not improve survival in patients with localised RCC at high risk of relapse after nephrectomy
- 19 Triple therapy improves progression-free survival in patients with advanced RCC versus dual therapy
- 20 Adjuvant atezolizumab does not improve outcomes for patients with RCC and increased risk of recurrence

20 Gynaecological cancers

- 20 OS benefit for advanced ovarian cancer treated with maintenance olaparib
- 21 Maintenance tegafur-uracil does not improve survival in locally advanced cervical cancer

22 Head and Neck Cancer

- 22 Adding first-line pembrolizumab to CRT in locally advanced HNSCC does not significantly prolong survival or event-free survival
- 23 5-FU-free chemotherapy as first-line treatment of recurrent or metastatic HNSCC
- 23 EBV-CTL do not improve survival in nasopharyngeal carcinoma

Stay up-to-date
Follow us on Twitter

MED?COM
MEDICAL PUBLISHERS



Letter from the Editor



Dear colleagues,

Have you ever seen a water-fall plot looking like a lake before? If you attended this year's Presidential Session, you did, if not: check page 3 with the amazing results of the NICHE-2 study in deficient DNA mismatch repair (dMMR) colorectal cancer.

Precision medicine provides a new option in intrahepatic cholangiocarcinoma: mFGFR2 carriers achieve significant benefits with a new, highly selective FGFR inhibitor.

Sip a "Bellini" while going through the same-named study: a high percentage of tumour infiltrating lymphocytes (TILs) is predictive of good neoadjuvant response with checkpoint blockade.

Sacituzumab govitecan may be the new standard for HR-positive HER2-negative advanced breast cancer refractory to hormonal treatment.

Also, there is amazing news in melanoma treatment: Just 3 neoadjuvant cycles can make the difference in recurrence-free survival, according to a study comparing purely adjuvant versus neoadjuvant/adjuvant pembrolizumab, in resectable stage III and IV melanoma patients.

...and reinfusing harvested and *in vitro* expanded TILs outperforms second-line checkpoint inhibition in metastatic melanoma patients.

And please check out Charles Swanton's fantastic presentation of the pathogenesis from air pollution to lung cancer: a milestone event.

As always, you'll find all of the above in detail below, and there's a lot more to digest. I hope you enjoy our ESMO 2022 congress report.

Yours, sincerely
Stefan Rauh

Biography

Dr Stefan Rauh is currently working as haematologist in the oncology department of the Centre Hospitalier Emile Mayrisch, Esch, Luxembourg. He is mainly involved in clinical work but also in research and teaching activities and is interested in public policy and international cooperation projects in oncology. He is member of the ESMO Practicing Oncologist's Working Group since 2011 (chair 2014-2018) and the ESMO Public Policy Committee, and has been an ESMO Executive Board member in 2015-2016. He is co-author of the 2017 ESMO European Cancer Patient Coalition (ECPC) Patient Survivorship Guide and an invited expert for the ECPC.

Conflict of Interest Statement:
Nothing to declare

Colorectal Cancer

High pathological responses to neoadjuvant immune checkpoint inhibition in locally advanced dMMR colon cancer

Treatment with neoadjuvant immunotherapy (nivolumab/ipilimumab) for 4 weeks achieved a major pathological response in 95% of patients with stage III colon cancer and deficient DNA mismatch repair (dMMR), as the first results of the NICHE-2 trial showed.

Approximately 10–15% of non-metastatic colon cancers demonstrate dMMR [1]. Patients with stage III dMMR tumours have recurrence rates of 20–40%, despite standard-of-care chemotherapy [2] and high-risk disease (T4- and/or N2-status) is associated with poor survival. Neoadjuvant chemotherapy in patients with dMMR colon cancer leads to a slim pathological response of 5–7% [3]. More promisingly, results from the proof-of-concept NICHE-1 trial (n=32) showed that immune checkpoint inhibition is highly effective in non-metastatic dMMR colon cancers, with 100% pathological responses and 60% pathological complete responses (pCR) [4].

Dr Miriam Chalabi (Netherlands Cancer Institute, the Netherlands) presented the first results of the subsequent (investigator-initiated) NICHE-2 study ([EudraCT 2016-002940-17](#)). The study included 112 patients (83 high-risk, stage III) with previously untreated, non-metastatic dMMR colon cancer, who were treated with one cycle nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg), followed by a second cycle nivolumab (3 mg/kg) and subsequent surgery. The primary objectives were safety/feasibility (<2 weeks delay in surgery for 95% of patients)

and 3-year disease-free survival. Secondary objectives were response rates assessed in post-treatment specimens [5].

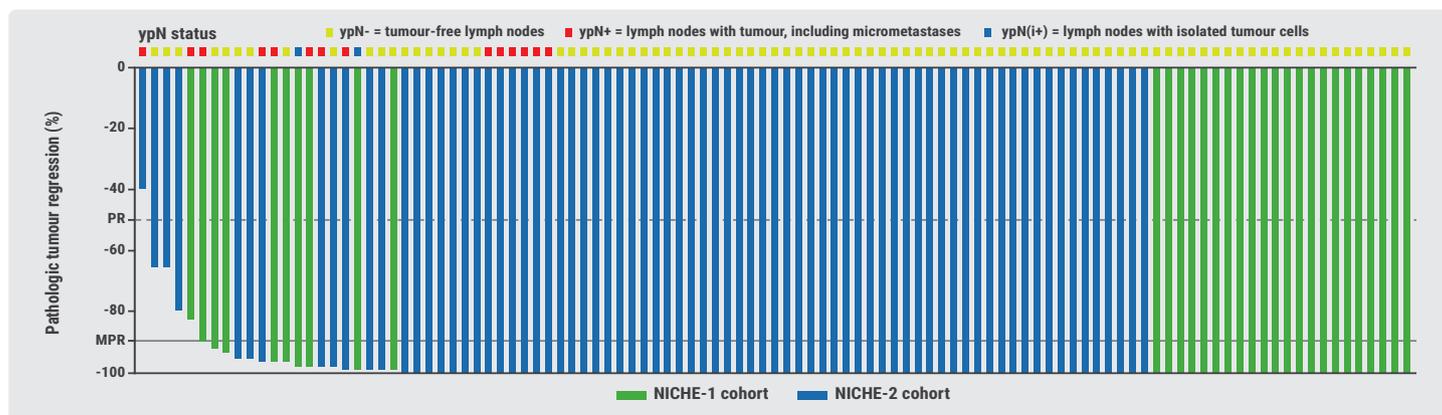
Grade ≥ 3 immune-related adverse events were observed in 4 participants and were manageable. All participants underwent surgery, resulting in 100% R0 resection. The median time from the first dose of immunotherapy to surgery was 5.4 weeks and 98% of participants underwent timely surgery. Based on these results, the primary safety endpoint was met.

Major pathological responses ($\leq 10\%$ residual viable tumour or pCR with a residual viable tumour in lymph nodes) were achieved in 95% of participants and 65% of participants achieved pCR. These results agree with the outcomes of the NICHE-1 study (see Figure). At the median follow-up of 13.1 months, none of the participants had disease recurrence.

Dr Chalabi concluded that “with only 4 weeks of neoadjuvant immunotherapy, an unprecedented major pathological response rate was achieved and the treatment was well tolerated. While we are currently acquiring the 3-year disease-free survival data, these data already show that neoadjuvant immunotherapy may have the potential to become standard-of-care for patients with dMMR colon cancer.”

1. Eikenboom EL, et al. *Clin Gastroenterol Hepatol.* 2022;20(3):e496–e507.
2. André T, et al. *J Clin Oncol.* 2015;33(35):4176–4187.
3. Seligmann JF, FOX-TROT Collaborative Group. *J Clin Oncol.* 2020;38:15_Suppl_4013–4013.
4. Chalabi M, et al. *Nat Med.* 2020;26(4):566–576.
5. Chalabi M, et al. Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: The NICHE-2 study. Abstract LBA7, ESMO Congress 2022, 09–13 September, Paris, France.

Figure: Pathological tumour regression upon neoadjuvant immune checkpoint inhibition in locally advanced dMMR colon cancer: comparison of NICHE-1 and NICHE-2 [5].



Fruquintinib: a potential new treatment for patients with refractory mCRC

Results from the phase 3 FRESCO-2 trial demonstrated a doubling of progression-free survival (PFS) and almost doubling of overall survival (OS) with VEGF-1, -2, and -3 inhibitor fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (mCRC).

The multi-TKI inhibitor regorafenib is standard-of-care in patients with (heavily) pre-treated, refractory mCRC [1]. The original phase 3 FRESCO trial ([NCT02314819](#)) showed efficacy and safety of the VEGF-1, -2, and -3 inhibitor fruquintinib in Chinese patients with mCRC in the third (or later) line setting [2]. However, standard-of-care for mCRC in China differed from global patterns when the original FRESCO trial was conducted (e.g. only 30% of participants had prior VEGF inhibition). To evaluate the efficacy and safety of fruquintinib in a globally more representative population, FRESCO-2 ([NCT04322539](#)) was conducted in the USA, Europe, Japan, and Australia. Prof. Nageshwara Arvind Dasari (MD Anderson Cancer Centre, TX, USA) presented the first results [3].

FRESCO-2 enrolled 691 patients with mCRC who had prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF therapy and –if *RAS* wildtype– anti-EGFR therapy. All participants had progressed in disease stage or were intolerant to TAS-102 and regorafenib, and had prior treatment with immune checkpoint inhibition or BRAF inhibition if indicated. 72% of participants had 3 or more prior treatment lines for metastatic disease. Participants were 2:1 randomised to fruquintinib (5 mg once daily, 3 weeks on, 1 week off) or placebo until progression or unacceptable toxicity. All participants received the best supportive care. The primary endpoint was OS and the key secondary endpoint was PFS.

Fruquintinib significantly improved median OS compared with placebo (7.4 vs 4.8 months; HR 0.662; $P < 0.001$). Fruquintinib favoured OS in all pre-specified subgroups. Of note, subsequent anti-cancer medication was balanced between the arms (29.4% in the fruquintinib arm and 34.3% in the placebo arm). PFS doubled in the fruquintinib arm (3.7 vs 1.8 months; HR 0.321; $P < 0.001$). The objective response rate was 1.5% for participants receiving fruquintinib versus 0% for placebo, whereas the disease control rate was 55.5% versus 16.1%. Grade ≥ 3 treatment-related adverse events (mainly hypertension and asthenia) were observed in 36% of participants in the fruquintinib arm versus 11.3% of participants in the placebo arm.

“The FRESCO-2 trial met its primary endpoint and the results are consistent with those of the FRESCO trial, supporting fruquintinib as a new, global treatment option for patients with refractory mCRC,” concluded Prof. Dasari.

1. [Van Cutsem E, et al. Ann Oncol. 2014; 25\(Suppl 3\):iii1–iii9.](#)
2. [Li J, et al. JAMA 2018; 319\(24\):2486–2496.](#)
3. Dasari NA, et al. FRESCO-2: A global phase III multiregional clinical trial (MRCT) evaluating the efficacy and safety of fruquintinib in patients with refractory metastatic colorectal cancer. Abstract LBA25, ESMO Congress 2022, 09–13 September, Paris, France.

Second-line avelumab is effective in patients with MSI-H/dMMR mCRC

Avelumab administration in the second line improved progression-free survival (PFS) in patients with microsatellite instability-high (MSI-H)/DNA mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC) who are naïve to immune checkpoint inhibition, results from the SAMCO-PRODIGE 54 trial demonstrated.

MSI-high/dMMR colorectal tumours are currently the only colorectal tumours sensitive to immune checkpoint inhibition with pembrolizumab improving PFS in the first-line setting [1,2]. The phase 2 SAMCO-PRODIGE 54 trial ([NCT03186326](#)), presented by Prof. Julien Taieb (Hopital European George Pompidou, France), evaluated the efficacy of avelumab in the second-line for patients with MSI-high/dMMR mCRC versus standard-of-care [3].

The open-label, phase 2 trial randomised 122 patients with MSI-high/dMMR mCRC who progressed on oxaliplatin- or irinotecan-based first-line therapy (and targeted agents if indicated) to avelumab (10 mg/kg every 2 weeks) or standard second-line chemotherapy. The primary endpoint was PFS.

Due to Kaplan-Meier PFS curves crossing at 7.3 months, the log-rank test and HR assessment of treatment were invalid. Instead, the 2-stage procedure according to Qiu and Sheng was performed [4]. Second-line avelumab improved PFS significantly versus standard-of-care ($P = 0.025$). PFS rates were 31% versus 19% at 12 months, 27% versus 9% at 18 months, and 25% versus 3% at 24 months for avelumab and standard-of-care, respectively. Objective response rates and disease control rates were similar between the treatment arms; however, disease control was maintained for 18 months with avelumab in most patients. Treatment with avelumab led to lower rates of grade ≥ 3 adverse events.

“This trial demonstrated that avelumab is safe and effective when used in the second-line in patients with MSI-high/dMMR

mCRC, confirming that immune checkpoint inhibition remains relevant beyond first-line in patients naive to immune checkpoint inhibition. However, the indirect comparison suggests that these patients should be treated with immune checkpoint inhibitors as soon as possible,” stated Prof. Taieb. Indeed, the phase 3 KEYNOTE-177 trial ([NCT02563002](#)) confirms the effects of first-line pembrolizumab for this population of MSI-H CRC [2].

1. [Eng C, et al. Lancet Oncol. 2019;20\(6\):849–861.](#)
2. [André T, et al. N Engl J Med. 2020;383\(23\):2207–2218.](#)
3. Taieb J, et al. Avelumab versus standard second-line treatment chemotherapy in metastatic colorectal cancer (mCRC) patients with microsatellite instability (MSI): The SAMCO-PRODIGE 54 randomised phase II trial. Abstract LBA23, ESMO Congress 2022, 09–13 September Paris, France.
4. [Qiu P, Sheng J. J R Stat Soc Ser B Stat Methodol. 2008;70:191–208.](#)

Upper Gastrointestinal Cancer

Deep learning models predict the risk of relapse and the mutational profile in GIST

An algorithm developed by deep learning from digitalised haematoxylin and eosin-stained whole tumour slide images outperformed classical AFIP/Miettinen relapse risk prediction in patients with gastrointestinal stromal tumours (GIST). A second algorithm predicted mutations with high accuracy.

GIST, the most frequent mesenchymal tumour of the GI tract, shows a variable clinical behaviour ranging from benign to malignant. Risk assessment according to the AFIP/Miettinen classification (high, intermediate, or low risk of relapse) and mutational profiling are major tools for patient management. The AFIP/Miettinen classification includes parameters such as the size of the tumour, localisation, and mitotic count [1]. However, the AFIP/Miettinen classification comes with subjectivity (mitotic count), costly mutational profiling and is time-consuming, and not yet available in all countries (or centres). Therefore, Dr Raul Perret (Institute Bergonié, France) and colleagues evaluated the efficacy of 2 deep learning models: 1 to predict relapse-free survival in GIST patients and 1 to predict mutational profiles [2].

Both models were based on histology, i.e. digitised haematoxylin and eosin-stained whole tumour slide images. The relapse-predicting model was trained using whole tumour slide images from 305 patients (Institut Bergonié) and validated using slide images from 286 patients (Léon Bérard Centre). Both cohorts had a similar distribution of GIST types (localisation, TKI treatment). The mutation profile-predicting model was trained using images from 1,233 patients (Institut

Bergonié) and validated on images from 238 patients (Léon Bérard Centre).

The algorithm for relapse prediction outperformed prediction based on AFIP/Miettinen classification (C-index 0.81 vs 0.76). Combining deep learning with tumour location and tumour size (Deep Miettinen), further improved C-index to 0.83. Deep Miettinen was able to stratify patients into subgroups at high or low risk for relapse-free survival. Also, the algorithm was able to split patients, characterised as ‘high risk for relapse’ according to classical AFIP/Miettinen, into 2 additional groups: high versus low risk. Likewise, the algorithm was able to split classical AFIP/Miettinen ‘intermediate risk’ patients into high-risk and low-risk groups.

The algorithm for the prediction of the presence of mutations reached an area under the receiver operating characteristic curve (AUC) for predicting *KIT* mutations of 0.80 in the training cohort and 0.85 in the validation cohort. AUC for predicting *PDGFRA* mutations was 0.92 in both cohorts. More specific, AUC for predicting *PDGFRA* exon 18^{D824V} mutation was 0.87 in both cohorts and predicting *KIT* exon 11^{del 557–558} mutation was 0.69 in the training cohort and 0.76 in the validation cohort.

“Our results strongly suggest that implementing deep learning with digitised whole slide images may represent a reproducible way to improve tailoring therapy and precision medicine for patients with GIST. However, further validation of the models is needed,” concluded Dr Perret.

1. [Miettinen M, Lasota J. Semin Diagn Pathol. 2006;23\(2\):70–83.](#)
2. Italiano A, et al. Deep learning predicts patients’ outcome and mutations from H&E slides in gastrointestinal stromal tumor (GIST). Abstract 14840, ESMO Congress 2022, 09–13 September, Paris, France.

Addition of pembrolizumab to lenvatinib does not improve OS in advanced HCC

The final analysis of the phase 3 LEAP-002 study did not demonstrate an overall survival (OS) benefit of the addition of pembrolizumab to first-line lenvatinib in patients with advanced hepatocellular carcinoma (HCC). However, the study supports the potential usefulness of lenvatinib as a standard first-line treatment for advanced HCC.

Systemic therapy options for advanced stages of HCC have rapidly expanded in the past years. The REFLECT trial ([NCT01761266](#)) demonstrated lenvatinib in first-line to be non-inferior to sorafenib regarding OS [1]. In a phase 1 study, lenvatinib plus pembrolizumab demonstrated promising anti-tumour activity as first-line therapy in unresectable HCC [2]. The current global, randomised, double-blind, phase 3 LEAP-002 trial ([NCT03713593](#)), presented by Prof. Richard Finn (David Geffen School of Medicine, CA, USA) evaluated the efficacy of lenvatinib plus pembrolizumab versus lenvatinib plus placebo as first-line therapy for advanced HCC [3].

The trial randomised 794 patients with advanced HCC, Child-Pugh class A, and without prior systemic treatment 1:1 to lenvatinib plus pembrolizumab or lenvatinib plus placebo. The dual primary endpoints were progression-free survival (PFS) and OS. Pre-specified efficacy boundaries were one-sided $P=0.002$ for PFS at the interim analysis (pre-specified final PFS analysis) and 0.0185 for OS at the final analysis.

Median OS in patients treated with lenvatinib plus pembrolizumab was 21.2 months (comparable to the phase 1 study) versus 19.0 months in patients with monotherapy lenvatinib (HR 0.840; $P=0.0227$). This difference was not statistically significant according to the pre-specified efficacy boundaries.

The median PFS at the time of the final analysis was 8.2 versus 8.1 months (HR 0.834). At 24 months, 16.7% of participants treated with lenvatinib plus pembrolizumab were progression-free versus 9.3% of patients treated with lenvatinib plus placebo. The disease control rate was 81.3% in the lenvatinib plus pembrolizumab arm (26.1% objective response rate [ORR]) versus 78.4% (17.5% ORR) in the lenvatinib plus placebo arm. The duration of response was 16.6 and 10.4 months, respectively.

Overall, 44.1% of patients treated with lenvatinib plus pembrolizumab received subsequent systemic anti-cancer treatment (34.9% tyrosine kinase inhibitor, 14.4% immunotherapy, 3.5%

chemotherapy). Of all patients treated with lenvatinib plus placebo, 52.1% received subsequent systemic therapy (40.1% tyrosine kinase inhibitor, 22.8% immunotherapy, 3.3% chemotherapy).

Based on these results, Prof. Finn concluded that “this study does not meet its pre-specified statistical significance for OS and PFS. Nonetheless, median OS in the lenvatinib monotherapy arm was longer than what was observed in REFLECT (14.5 months), which supports its role as a standard first-line treatment for advanced HCC.”

1. Kudo M, et al. *Lancet* 2018;391(10126):1163–1173.
2. Finn RS, et al. *J Clin Oncol*. 2020;38(26):2960–2970.
3. Finn RS, et al. Primary results from the phase III LEAP-002 study: Lenvatinib plus pembrolizumab versus lenvatinib as first-line (1L) therapy for advanced hepatocellular carcinoma (aHCC). Abstract LBA34, ESMO Congress 2022, 09–13 September, Paris, France.

New, highly selective inhibitor of FGFR2 driver alterations and resistance mutations

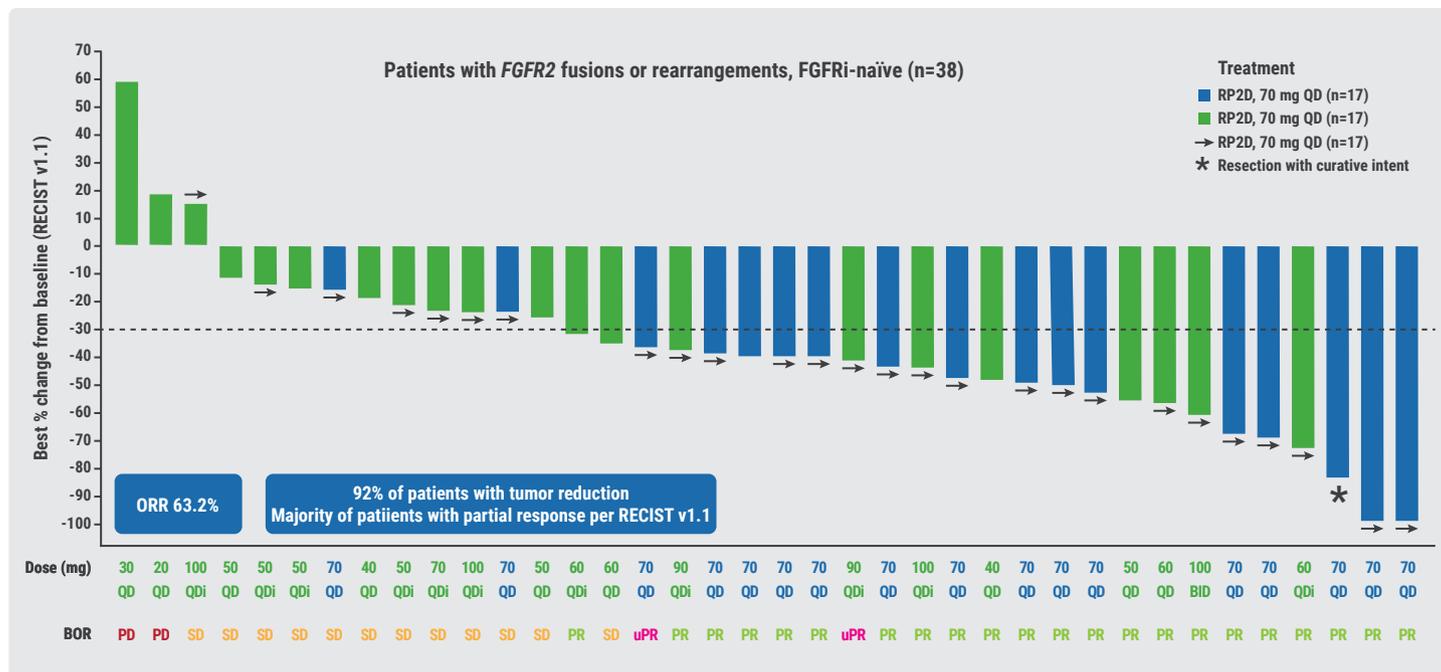
RLY-4008, a highly selective, irreversible inhibitor targeting oncogenic FGFR2 driver alterations, displayed clinical activity in patients with FGFR inhibitor-naïve cholangiocarcinoma (CCA) harbouring an FGFR2 fusion or rearrangement, results from the REFOCUS trial showed.

CCA is a rare malignancy with a dismal prognosis; the median overall survival with first-line chemotherapy is approximately 1 year [1]. *FGFR2* fusions or rearrangements drive 10–15% of intrahepatic CCR [2]. RLY-4008 is a highly selective *FGFR2* inhibitor (*FGFR2i*) and has potent *in-vivo* activity against *FGFR2* inhibitor-sensitive and resistant CCR [3]. The phase 1/2 REFOCUS trial ([NCT04526106](#)) enrolled patients with advanced solid tumours harbouring an *FGFR2* alteration who received RLY-4008. Prof. Antoine Hollebecque (Institut Gustave Roussy, France) reported the results [4].

The successful phase 1 of the REFOCUS trial resulted in a recommended phase 2 dose of 70 mg every day. 38 patients with *FGFR* inhibitor-naïve CCA were treated with RLY-4008 in phase 1 ($n=21$) or phase 2 ($n=17$). Key objectives were investigator-assessed overall response rate (ORR) per RECIST v1.1, duration of response (DOR), and safety. The radiographic ORR was 63.2% (all partial responses). The radiographic ORR in patients treated with 70 mg was 88.2% (all partial responses; see Figure). The median time to response was 1.8 months.

The most common treatment-related adverse events (all grades) were stomatitis (42%), nail toxicities (43%), palmar-plantar erythrodysesthesia syndrome (35%), and alopecia (26%).

Figure: Radiographic tumour regression and response upon RLY-4008 administration to patients with advanced solid tumours harbouring an *FGFR2* alteration [4].



RP2D, recommended phase 2 dose. QD, once daily dosing. BOR, best overall response. PR, partial response. PD, progressive disease. SD, stable disease. uPR, unconfirmed partial response. BID, twice daily dosing.

The most common grade ≥ 3 treatment-related adverse event was stomatitis (8%). Interruption of treatment occurred in 42% of patients, reduction in 27% of patients, and discontinuation in 1% of patients.

Based on these results, Prof. Hollebecque resolved that “RLY-4008 is the first highly selective, irreversible inhibitor designed to target oncogenic *FGFR2* driver alterations and resistance mutations. REFOCUS validates this novel mode of action and supports expedited development for treating patients with FGFR inhibitor-naïve CCA harbouring an *FGFR2* fusion or rearrangement.”

1. Valle J, et al. *N Engl J Med*. 2010;362:1273–1281.
2. Jusakul A, et al. *Cancer Discov*. 2017;7(10):1116–1135.
3. Casalleto J, et al. *Cancer Res*. 2021;81(13_Supplement):1455.
4. Hollebecque A, et al. Efficacy of RLY-4008, a highly selective *FGFR2* inhibitor in patients (pts) with an *FGFR2*-fusion or rearrangement (f/r). *FGFR* inhibitor (FGFRi)-naïve cholangiocarcinoma (CCA): ReFocus trial. Abstract LBA12, ESMO Congress 2022, 09–13 September, Paris, France.

Chemo-immunotherapy in gastric cancer is more effective when administered in parallel

Although associated with lower toxicity, mFOLFOX plus nivolumab and ipilimumab administered in parallel was more effective in patients with gastric cancer than mFOLFOX induction followed by nivolumab plus ipilimumab, results from the Moonlight trial showed.

In patients with HER2-negative, metastatic, or locally advanced oesophagogastric adenocarcinoma, first-line treatment with mFOLFOX plus nivolumab has become the standard-of-care [1]. However, this regimen comes with substantial toxicity (59% grade ≥ 3). One part of the phase 2 Moonlight trial (NCT03647969) compared the efficacy and safety of mFOLFOX and nivolumab plus ipilimumab administered either in parallel or sequential. Prof. Sylvie Lorenzen (Klinikum rechts der Isar, TU München, Germany) presented the results [2].

This part of the Moonlight trial enrolled 90 patients with previously untreated HER2-negative metastatic or locally advanced adenocarcinoma of the stomach or gastro-oesophageal junction. Participants were randomised 2:1 to parallel treatment with mFOLFOX, nivolumab and ipilimumab or 3 cycles of mFOLFOX induction followed by nivolumab plus ipilimumab (sequential arm). The primary endpoint was progression-free survival (PFS) at 6 months and the main secondary endpoints were overall survival, objective response rate (ORR), and safety.

After a median follow-up of 9.3 months, the median PFS was 7.29 months in the parallel arm versus 3.98 months in the sequential arm. PFS-rate at 6 months was 60% versus 30% (parallel vs sequential). In addition, parallel treatment

favoured OS, ORR and median duration of response. Grade ≥ 3 treatment-related adverse events were more common in the parallel arm compared with the sequential arm (93% vs 73%).

“Although associated with higher toxicity, mFOLFOX chemotherapy plus nivolumab and ipilimumab administered in parallel was more effective compared with mFOLFOX induction followed by nivolumab plus ipilimumab. Therefore, these results do not support the concept of chemotherapy

induction followed by immunotherapy, but should be interpreted with caution due to the small sample size and low PD-L1 expression rate in both arms (PD-L1 combined positive score [CPS] ≥ 1 in 41%; CPS_{parallel arm} 43%; CPS_{sequential arm} 40%)” closed Prof. Lorenzen.

1. [Janjigian YY et al. Lancet 2021;398\(10294\):27–40.](#)
2. Lorenzen S, et al. FOLFOX plus nivolumab and ipilimumab versus FOLFOX induction followed by nivolumab and ipilimumab in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction: Results from the randomized phase II Moonlight trial of the AIO. Abstract 12030, ESMO Congress 2022, 09–13 September, Paris, France.

Breast Cancer

Tumour-infiltrating lymphocytes identify patients with immunogenic triple-negative breast cancer

Patients with triple-negative breast cancer (TNBC) and more than 40% tumour-infiltrating lymphocytes (TIL) responded well to neoadjuvant immune checkpoint blockade, results from the phase 2 BELLINI trial showed.

High TIL levels correlate with a good prognosis in early TNBC [1,2]. In patients with early TNBC, the combination of neoadjuvant chemotherapy with PD immune checkpoint-blocking agents increased the pathological complete response (pCR) and event-free survival [3,4]. However, it is not known which TNBC patients specifically benefit from neoadjuvant PD1 inhibition, for which patients' neoadjuvant chemotherapy can be de-escalated, or whether there is an additional value of other (new generation) immune checkpoint inhibitors. Prof. Marleen Kok (Netherlands Cancer Institute, the Netherlands) presented the first stage I findings of the phase 2 basket trial BELLINI ([EudraCT 2018-004188-30](#)) testing the hypothesis that there is a subset of TNBC patients with highly immunogenic tumours and that TIL levels (at baseline) can help identify this subset [5].

BELLINI is a non-randomised window-of-opportunity study with baskets for nivolumab and nivolumab plus ipilimumab. Each basket included at least 15 participants with stage I–III TNBC (T1c–T3, N⁻/N⁺, TIL $\geq 5\%$), divided into 3 TIL categories (at least 5 participants per category): TIL-low (5–10% TIL), TIL-intermediate (11–49% TIL), and TIL-high ($\geq 50\%$ TIL).

Participants were treated with nivolumab (2 cycles, n=16) or nivolumab/ipilimumab (2 cycles nivolumab, 1 cycle ipilimumab, n=15) before the start of neoadjuvant chemotherapy or surgery. The primary endpoint was immune activation, defined as a 2-fold change in CD8-positive T cells or a 2-fold increase in *IFN- γ* expression after 4 weeks. The secondary endpoints included safety and radiological responses.

At 4 weeks, 3/19 (19%) participants treated with nivolumab and 4/15 (27%) participants treated with nivolumab/ipilimumab showed a partial radiological response. Of these 7 responders, 3 were TIL-high and 4 were TIL-intermediate. All responders had $>40\%$ TIL. No responses were observed in TIL-low participants. Most biopsies of patients with a partial radiological response were free from tumour cells, illustrating pCR, after 4 weeks. A 2-fold increase of CD8-positive T cells was observed in 53.3% of nivolumab-treated participants and 60% of nivolumab/ipilimumab-receiving participants. Both cohorts met the primary endpoint, encouraging the progression to stage II of the trial.

Radiological responders and non-responders were discriminated by a significant difference in both the levels of *IFN- γ* expression (higher in responders, $P=0.014$) and spatial distribution of CD8-positive T cells (closer to tumour cells in responders, $P=0.0014$). For all patients showing a partial response on MRI, circulating tumour DNA at 4 weeks was either cleared or $<50\%$ of baseline measurements.

“The majority of TNBC patients with TIL showed increased immune activation after only 4 weeks of immune checkpoint

blockade and a substantial fraction of these patients experienced a clinical response, highlighting the potential of immune checkpoint blockade without chemotherapy for TNBC patients,” concluded Prof. Kok.

1. [Loi S, et al. J Clin Oncol. 2019;37\(7\):559–569.](#)
2. [De Jong VMT, et al. J Clin Oncol. 2022;40\(21\):2361–2374.](#)
3. [Mittendorf EA, et al. Lancet. 2020;396\(10257\):1090–1100.](#)
4. [Schmid P, et al. N Engl J Med. 2022;386\(6\):556–567.](#)
5. Nederlof I, et al. Nivolumab and ipilimumab in early-stage triple-negative breast cancer (TNBC) with tumour-infiltrating lymphocytes (TILs): First results from the BELLINI trial. Abstract LBA13, ESMO Congress 2022, 09–13 September, Paris, France.

OS benefit of abemaciclib in HR-positive/HER2-negative advanced breast cancer not (yet) statistically significant

Results from the second interim analysis of the phase 3 MONARCH 3 showed that treatment with abemaciclib plus a non-steroidal aromatase inhibitor (NSAI) numerically increased overall survival (OS) in post-menopausal patients with HR-positive/HER2-negative advanced breast cancer compared with placebo plus NSAI in the first-line setting.

In the MONARCH 2 trial ([NCT02107703](#)), abemaciclib along with fulvestrant demonstrated significant OS benefit in pre- and post-menopausal patients with HR-positive/HER2-negative advanced breast cancer and disease progression on prior endocrine therapy [1]. The phase 3 MONARCH 3 trial ([NCT02246621](#)) investigated the efficacy of abemaciclib plus NSAI in the first-line setting in 493 post-menopausal patients with HR-positive/HER2-negative advanced breast cancer.

Previously, the MONARCH 3 trial already demonstrated a robust progression-free survival (PFS) benefit (HR 0.540; $P < 0.0001$) of abemaciclib/NSAI versus placebo/NSAI, which led to a global regulatory approval of the treatment [2,3]. As per the gold standard for efficacy assessment, a demonstration of the OS benefit of abemaciclib/NSAI was requested by the EMA. Prof. Matthew Goetz (Mayo Clinic Rochester, MN, USA) presented the results of the pre-specified second interim OS analysis (data cut-off 2 July 2021), which was scheduled after ~252 events in the intention-to-treat population (80% of planned events for final OS analysis) [4].

With 70.2 months of median follow-up, the median OS was 67.1 months for abemaciclib plus NSAI versus 54.5 months for placebo plus NSAI (HR 0.754; $P = 0.0301$). This P-value is not statistically significant due to the pre-defined statistical

analysis plan, because of multiple analyses of this endpoint, each with a specific statistical power. In the subgroup of patients with visceral disease (sVD; $n = 263$) median OS was 65.1 months versus 48.8 months in the abemaciclib plus NSAI and placebo plus NSAI arms, respectively (HR 0.708; $P = 0.0392$). This is again not statistically significant due to the statistical analysis plan. Median chemotherapy-free survival in the intention-to-treat population favoured abemaciclib plus NSAI over placebo plus NSAI (46.7 vs 30.6 months; HR 0.636). No new safety concerns were observed after prolonged exposure to abemaciclib.

“In the second interim OS analysis from MONARCH 3, a numerically longer OS was observed in both the intention-to-treat and the sVD population with the addition of abemaciclib to NSAI,” summarised Prof. Goetz. “Neither met the threshold for formal statistical significance, but data are maturing favourably.” The final OS analysis is expected in 2023.

1. [Sledge GW, et al. JAMA Oncol. 2020;6\(1\):116–124.](#)
2. [Goetz MP, et al. J Clin Oncol. 2017;35\(32\):3638–3646.](#)
3. [Johnston S, et al. NPJ Breast Cancer. 2019;5:5.](#)
4. Goetz M, et al. MONARCH 3: Interim overall survival (OS) results of abemaciclib plus a nonsteroidal aromatase inhibitor (NSAI) in patients (pts) with HR+, HER2-advanced breast cancer (ABC). Abstract LBA15, ESMO Congress 2022, 09–13 September, Paris, France.

OS benefit of sacituzumab govitecan in pre-treated HR-positive/HER2-negative metastatic breast cancer

Sacituzumab govitecan significantly improved overall survival (OS) compared with the treatment of the physician's choice (TPC) in patients with pre-treated HR-positive/HER2-negative metastatic breast cancer.

Despite new additional treatment options like CDK4/6 inhibitors, endocrine resistance in patients with HR-positive/HER2-negative metastatic breast cancer eventually develops. For endocrine-resistant disease, sequential single-agent chemotherapy is standard-of-care, however, this treatment is associated with low response rates, poor outcomes, and declining quality-of-life [1]. Sacituzumab govitecan is a first-in-class Trop-2-directed antibody-drug conjugate that has demonstrated significant improvement in progression-free survival (PFS) in pre-treated, endocrine-resistant HR-positive/HER2-negative metastatic breast cancer patients in the phase 3 TROPiCS-02 trial ([NCT03901339](#)) [2]. Prof. Hope Rugo (Helen Diller Family Comprehensive Cancer Centre, CA, USA) presented the first OS results from the TROPiCS-02 trial [3].

This randomised, phase 3 trial included 543 participants with locally advanced/metastatic, inoperable HR-positive/HER2-negative metastatic breast cancer, who's tumours progressed after at least 1 endocrine therapy, taxane, and CDK4/6 inhibitor in any setting, and who received at least 2 but not more than 4 lines of chemotherapy for metastatic disease. Participants were 1:1 randomised to receive sacituzumab govitecan (10 mg/kg, days 1 and 8, every 21 days) or TPC. OS was the key secondary endpoint.

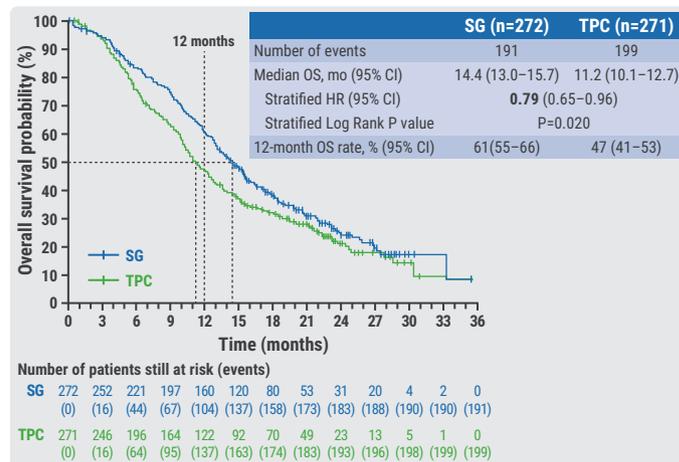
In the second interim analysis median OS for participants treated with sacituzumab govitecan was 14.4 months versus 11.2 months for TPC patients (HR 0.79; P=0.020, see Figure). The OS rate at 12 months was 61% (sacituzumab govitecan) versus 47% (TPC). The overall response rate was 57% versus 38% and the main duration of response was 8.1 months versus 5.6 months for sacituzumab govitecan and TPC, respectively. The median time-to-deterioration was 4.3 months (sacituzumab govitecan) versus 3.0 months (TPC). Grade ≥ 3 treatment-related adverse events were observed in 74% versus 60% of patients for sacituzumab govitecan and TPC, respectively.

Based on these results, Prof. Rugo concluded that "the statistically significant and clinically meaningful benefit

of sacituzumab govitecan over TPC supports the use of sacituzumab govitecan as a novel therapy for patients with pre-treated HR-positive/HER2-negative metastatic breast cancer."

1. Burstein HJ, et al. *J Clin Oncol*. 2021;39(35):3959–3977.
2. Rugo HS, et al. *J Clin Oncol*. 2022. DOI: 10.1200/JCO.22.01002.
3. Rugo HS, et al. Overall survival (OS) results from the phase III TROPiCS-02 study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with HR+/HER2- metastatic breast cancer (mBC). Abstract LBA76, ESMO Congress 2022, 09–13 September, Paris, France.

Figure: Sacituzumab govitecan treatment improves overall survival probability and overall survival rate of HR-positive/HER2-negative metastatic breast cancer patients, as per second interim analysis [3].



SG, sacituzumab govitecan. TPC, treatment of the physician's choice. OS, overall survival. mo, months.

Lung Cancer

A pathway from air pollution to lung cancer in non-smokers identified

Increasing exposure to 2.5 μm particulate matter ($\text{PM}_{2.5}$) raises the risk of non-small cell lung cancer (NSCLC) in non-smoking individuals with *EGFR* mutations. This effect is driven by an influx of macrophages and an increase in the inflammatory mediator $\text{IL-1}\beta$, which promotes carcinogenesis in airway cells, a study from the University College London showed.

Lung cancer in non-smokers is a disease with a low mutational burden, translating to up to 10-fold fewer mutations compared with lung cancer in (ever)-smokers. On the other hand, approximately half of non-smokers with lung cancer have *EGFR* mutations in their cancer cells. Evidence

links air pollution exposure to lung cancer incidence and mortality in non-smokers [1,2]. However, the molecular mechanism underlying this link has not been elucidated. Prof. Charles Swanton (University College London, UK) presented results from biobank data from 447,932 individuals [3].

Prof. Swanton and colleagues demonstrated an association between increasing exposure to airborne $\text{PM}_{2.5}$ and the risk of 7 types of cancer, including NSCLC, gastrointestinal, and head and neck cancer. In addition, they showed an association between regional $\text{PM}_{2.5}$ exposure and the incidence of *EGFR*-mutated NSCLC.

Proving causation, $\text{PM}_{2.5}$ exposure increased the number of lung tumours in 3 distinct mouse models with pre-existing

EGFR or *KRAS* mutations. Mechanistically, exposure to PM_{2.5} drives the influx of macrophages in lung tissue, releasing the inflammatory mediator IL-1 β , which drives the expansion of *EGFR*-mutated cells. Of note, *EGFR* mutations or exposure to air pollution alone were not sufficient to drive this expansion. Moreover, blockade of IL-1 β inhibited lung cancer initiation, which was consistent with data from the CANTOS trial ([NCT01327846](#)) showing a dose-dependent reduction in lung cancer incidence when people were treated with the anti-IL-1 β antibody canakinumab [4]. In addition, Prof. Charles Swanton and colleagues could show that exposure to PM_{2.5} for some hours, increased IL-1 β production by lung epithelial cells and macrophages in healthy, never-smoking humans. Finally, the researchers demonstrated that activating *EGFR* and *KRAS* mutations are present in respectively 15% and 53% of samples of lung tissue from healthy never-smokers. However, the incidence of these mutations is rare: about 1 in 600,000 cells, although their number increases with ageing.

Prof. Swanson summarised that “cancer mutations exist in normal lung tissue and their incidence increases with age. Air pollution is, via IL-1 β , likely a tumour promotor driving these mutated progenitor cells towards a ‘cancer stem cell’ kind of state, eventually resulting in lung cancer. This data could pave the way to new molecular-based prevention approaches and development of targeted therapies for non-smokers who are at risk of lung cancer, i.e. those harbouring *EGFR* mutations.”

1. [Liu X, et al. Front Med \(Lausanne\). 2021;8:742076.](#)
2. [Turner MC, et al. CA Cancer J Clin. 2020;70:460–479.](#)
3. Swanton C, et al. Mechanism of action and an actionable inflammatory axis for air pollution-induced non-small cell lung cancer: Towards molecular cancer prevention. Abstract LBA1, ESMO Congress 2022, 09–13 September, Paris, France.
4. [Ridker PM, et al. Lancet. 2017;390\(10105\):1833–1842.](#)

Selective *KRAS*^{G12C} inhibitor sotorasib demonstrates superior PFS and ORR compared to docetaxel in previously treated patients with NSCLC

Results from the phase 3 CodeBreak 200 trial showed a significant improvement in progression-free survival (PFS) and overall response rate (ORR) of the selective *KRAS*^{G12C} inhibitor sotorasib versus docetaxel in previously treated patients with *KRAS*^{G12C}-mutated non-small cell lung cancer (NSCLC).

KRAS mutations are associated with poor prognosis and occur in approximately 1 in 4 patients diagnosed with NSCLC. The specific *KRAS*^{G12C} mutation is harboured in approximately 11–16% of all *KRAS*-mutated cases [1]. Previously, the

phase 1/2 CodeBreak 100 study ([NCT03600883](#)) showed promising PFS, ORR, and overall survival (OS) in patients with *KRAS*^{G12C}-mutated NSCLC, when treated with the (oral) selective *KRAS*^{G12C} inhibitor sotorasib [2]. The current phase 3 CodeBreak 200 trial ([NCT04303780](#)) evaluated the efficacy and safety of sotorasib versus docetaxel in previously treated *KRAS*^{G12C}-mutated NSCLC patients. The results were presented by Dr Melissa Johnson (Sarah Cannon Research Institute, TN, USA) [3].

The CodeBreak 200 trial enrolled a total of 345 *KRAS*^{G12C}-mutated NSCLC patients who had undergone at least 1 prior therapy, including platinum-based chemotherapy and checkpoint inhibition. Participants were 1:1 randomised to receive sotorasib (960 mg daily) or docetaxel (75 mg/m² every 3 weeks). Cross-over to sotorasib following disease progression was allowed. The primary endpoint was PFS. The secondary endpoints were OS, ORR, time to response (TTR), duration of response, and safety.

With a median follow-up of 17.7 months, the median PFS for participants in the sotorasib arm was 5.6 versus 4.5 months for participants on docetaxel (HR 0.66; P=0.002). PFS rates at 12 months were 24.8% (sotorasib) and 10.1% (docetaxel). ORR was 28.1% versus 13.2% in participants treated with sotorasib and docetaxel, respectively. The median TTR was 1.4 versus 2.8 months, and the median duration of response was 8.6 versus 6.8 months in the sotorasib and docetaxel arm, respectively. There was no difference in OS between the two treatment arms (HR 1.01). However, due to an amendment to the study protocol, the CodeBreak 200 trial did not have enough power to detect a significant difference in OS. Of note, 34% of patients treated with docetaxel crossed over to sotorasib.

Sotorasib was well-tolerated with a lower incidence of grade ≥ 3 treatment-related adverse events compared with docetaxel. Time to deterioration in the global health status, physical functioning, and cancer-related symptoms were delayed with sotorasib compared with docetaxel.

“These findings support that sotorasib forms an important treatment option in this setting and reinforce the importance of testing for *KRAS*^{G12C} mutations,” resolved Dr Johnson.

1. [Palma G, et al. NPJ Precis Oncol. 2021;5\(1\):98.](#)
2. [Dy GK, et al. AACR Annual Meeting 2022. Abstract CT008.](#)
3. Johnson ML, et al. Sotorasib versus docetaxel for previously treated non-small cell lung cancer with *KRAS*^{G12C} mutation: CodeBreak 200 phase III study. Abstract LBA10, ESMO Congress 2022, 09–13 September, Paris, France.

Promising clinical activity of tepotinib plus osimertinib in NSCLC with *MET* amplification after progression on first-line osimertinib

Tepotinib plus osimertinib improves overall objective response versus tepotinib alone in patients with *EGFR*-mutated non-small cell lung cancer (NSCLC) with *MET* amplification after progression on first-line osimertinib in the phase 2 INSIGHT-2 trial.

About 15–30% of patients with *EGFR*-mutated NSCLC treated with osimertinib develop resistance through *MET* amplification, which is associated with poor prognosis [1]. The previous phase 1/2 INSIGHT trial ([NCT01982955](#)) already showed clinical activity of the selective, oral *MET*-inhibitor tepotinib (plus gefitinib) in patients with *MET* amplification and acquired resistance to previous *EGFR* inhibitors [2]. Prof. Julien Mazières (CHU de Toulouse, France) presented the first findings from the current open-label phase 2 INSIGHT-2 trial ([NCT03940703](#)), which evaluated the clinical activity and safety of tepotinib plus osimertinib in this population [3].

The INSIGHT-2 trial enrolled 100 patients with locally advanced/metastatic *EGFR*-mutated NSCLC who acquired resistance to first-line osimertinib and had *MET* amplification. *MET* amplification was detected by *in-situ* hybridisation in tissue biopsies (*MET* gene copy number [GCN] ≥ 5 and/or *MET*/*CEP7* ≥ 2) and/or by next-generation sequencing in liquid biopsies (*MET* GCN ≥ 2.3). A total of 88 participants were treated with tepotinib (500 mg every day) plus osimertinib (80 mg every day) and 12 participants were treated with tepotinib alone. The primary endpoint was the overall response rate (ORR).

In participants treated with tepotinib plus osimertinib, ORR was 45.8% to 56.5% depending on the time of follow-up and/or *MET* amplification detection method. The ORR was only 8.3% in participants treated with tepotinib alone. The safety profile was consistent with the known safety profiles of tepotinib and osimertinib. Grade ≥ 3 adverse events were observed in 23.9% of patients treated with tepotinib plus osimertinib. Adverse events led to the discontinuation of one or both drugs in 18.2% of participants.

“Tepotinib plus osimertinib is an active oral regimen, providing a potential chemotherapy-sparing targeted therapy option for patients with *EGFR*-mutated NSCLC with *MET* amplification after progression on first-line osimertinib,” concluded Prof. Mazières.

1. Koulouris A, et al. *Cancers (Basel)* 2022; 13: 3337.
2. Wu Y-L, et al. *Lancet Respir Med.* 2020; 8: 1132-1143.
3. Mazières J, et al. Tepotinib + osimertinib for *EGFR*m NSCLC with *MET* amplification (METamp) after progression on first-line (1L) osimertinib: Initial results from the INSIGHT 2 study. Abstract LBA52, ESMO Congress 2022, Paris, France, 09–13 September.

High pathological responses in borderline resectable NSCLC patients after induction with dual immunotherapy and concurrent chemoradiotherapy

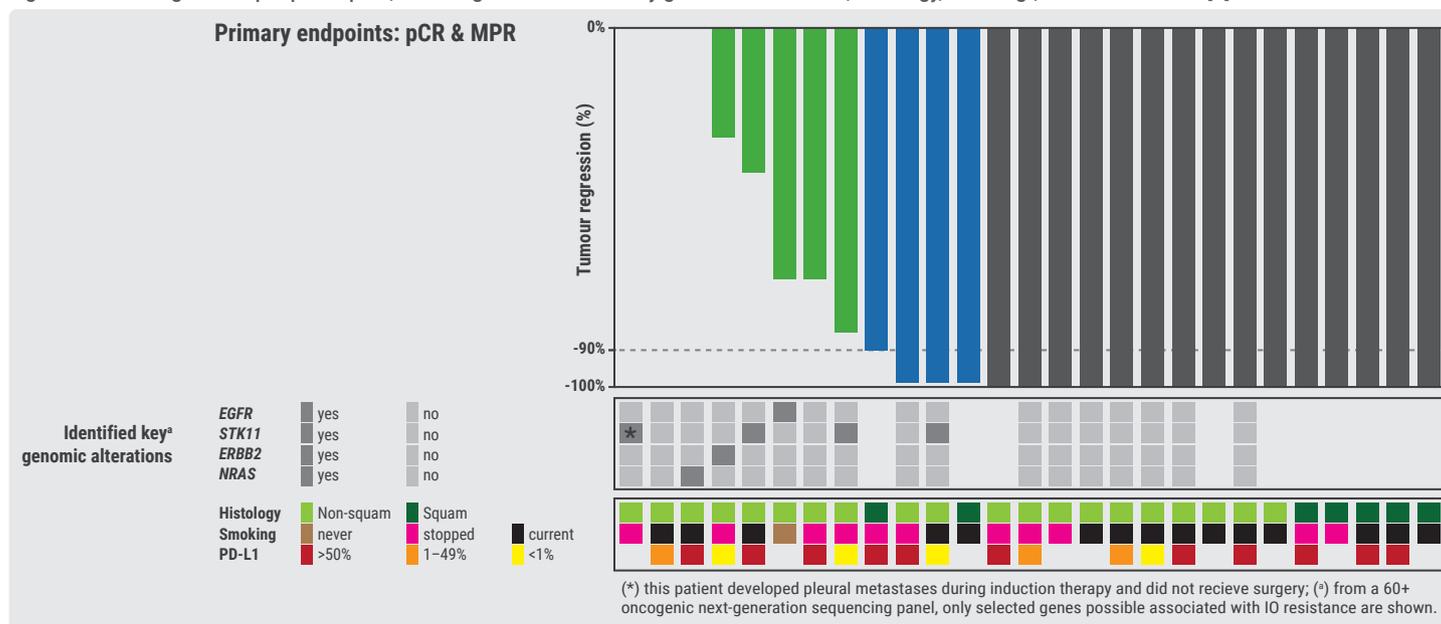
In a selected population comprising borderline operable high T- and low N-stage non-small cell lung cancer (NSCLC), neoadjuvant nivolumab/ipilimumab plus chemoradiotherapy (CRT) resulted in high pathological responses in the phase 2 INCREASE trial. Patients with high pathological responses showed increased tumour-specific cytotoxic T cells in the blood and tumour-draining lymph nodes.

A subgroup of non-metastatic high T- and low N-stage NSCLC patients are borderline resectable and may become resectable after induction with CRT. CRT using platinum-doublet is recommended [1]. Neoadjuvant chemotherapy combined with immunotherapy in resectable NSCLC has demonstrated an improved pathological complete response rate (pCR) [2]. The current INCREASE trial ([EudraCT_2019-003454-83](#)) evaluated the efficacy of pre-operative CRT combined with dual immunotherapy (nivolumab/ipilimumab) on the pCR and immunological responses in patients with borderline resectable non-metastatic NSCLC. Dr Idris Bahce (Amsterdam UMC, the Netherlands) presented the first results [3].

The single-arm, prospective, phase 2 INCREASE trial enrolled 30 patients with resectable and borderline resectable, T3–4/N0–2 NSCLC. At the time of data cut-off, 26 participants had completed neoadjuvant treatment and 24 had undergone surgery. On day 1, platinum-doublet concurrent CRT, ipilimumab (1 mg/kg) and nivolumab (360 mg flat dose) were administered, followed by nivolumab (360 mg flat dose) after 3 weeks. Radiotherapy consisted of 50–60 Gy in once-daily doses of 2 Gy, followed by a resection 6 weeks after the last dose of radiation. The primary endpoint was the pCR (a pre-specified pCR threshold of 60% was tested against the historical rate of 30% with CRT alone). Co-primary endpoints were safety and major pathological response (MPR), i.e. $\leq 10\%$ residual viable tumour cells.

Of all operated participants, 15 (63%) reached a pCR ($P < 0.001$ against historical rate) and 19 (79%) reached an MPR (see Figure on next page). The radiological objective response rate in the resected patients was 12.3%, indicating that the radiological response rate underestimates the pathological response. In patients with a pCR, the number of tumour-specific cytotoxic T cells (CD39⁺/CD8⁺) in peripheral blood and tumour-draining

Figure: Tumour regression per participant, including their identified key genomic alterations, histology, smoking-, and PD-L1 status [3].



Black bars represent full tumour regression (pCR, n=15 participants), blue illustrates partial regression (MPR, n=4 additional participants). pCR, pathological complete response. MPR, major pathological response. IO, immuno-oncology. Non-squam, non-squamous. Squam, squamous.

lymph nodes were more increased after neoadjuvant therapy than in non- and partial responders. The toxicity rates were acceptable.

Based on these results, Dr Bahce concluded that “in a selected population comprising borderline operable high T- and low N-stage NSCLC, neoadjuvant nivolumab/ipilimumab

plus CRT is safe, provides deep pathological responses and enhances T cell activation. This data supports the use of such strategies in patients presenting with an inoperable NSCLC.”

1. Eberhardt WEE, et al. *Ann Oncol.* 2015;26(8):1573–1588.
2. Forde PM, et al. *N Engl J Med.* 2022;386(21):1973–1985.
3. Bahce I, et al. Ipilimumab plus nivolumab and chemoradiotherapy followed by surgery in patients with resectable and borderline resectable lung cancer: The INCREASE trial. Abstract 9500. ESMO Congress 2022, 09–13 September, Paris, France.

Melanoma

Treatment with tumour-infiltrating lymphocytes for advanced melanoma outperforms ipilimumab

Second-line treatment with tumour-infiltrating lymphocytes (TIL) improved progression-free survival (PFS) compared with ipilimumab in patients with advanced, non-resectable stage III–IV melanoma, the results from an investigator-driven randomised phase 3 trial showed.

Although immune checkpoint inhibitors and targeted therapies have profoundly improved the outcome of patients with (advanced) melanoma, approximately 50% of patients still die from their disease within 5 years following diagnosis of stage IV

disease [1]. Adoptive cell therapy with TIL is an (elaborative and time-consuming) treatment modality with promising response rates of 36–70% in heavily pre-treated patients with advanced melanoma, observed in multiple phase 1/2 trials [2,3]. Prof. John Haanen (Netherlands Cancer Institute, the Netherlands) and colleagues performed the first investigator-driven, open-label, randomised-controlled, phase 3 clinical trial ([NCT02278887](https://clinicaltrials.gov/ct2/show/study/NCT02278887)) comparing treatments with TIL and ipilimumab [4].

In this trial, 168 participants with unresectable, stage III–IV cutaneous melanoma who had progression after 1 line of systemic treatment (no ipilimumab) were randomised to receive TIL treatment (single infusion of $\geq 5 \times 10^9$ TILs) or

ipilimumab (3 mg/kg every 3 weeks, max. 4 doses). About 90% of the participants had received prior anti-PD1 therapy. The primary endpoint of the study was PFS in the intention-to-treat (ITT) population; secondary endpoints were overall and complete response rate (RR), overall survival (OS), and safety.

The trial met its endpoint: with a median follow-up of 33 months, the median PFS was 7.2 months for the participants randomised to TIL treatment versus 2.1 months for the patients treated with ipilimumab (HR 0.50; $P < 0.001$). PFS rates at 6 months were 52.7% and 21.4% (TIL vs ipilimumab, respectively). ORR was 48.8% in the TIL-receiving participants (20.2% complete response) compared with 21.4% in the ipilimumab-treated participants (7.1% complete response). Preliminary OS data showed a trend in favour of TIL treatment; the median OS was 25.8 months in the TIL-receiving participants versus 18.9 months in participants on ipilimumab (HR 0.83; $P = 0.39$). The safety of TIL treatment was manageable and scores for health-related quality-of-life were significantly higher in TIL-treated participants during the 60 months of follow-up than in the ipilimumab-treated group ($\Delta_{\text{mean at 6 months}} 7.7$; $P < 0.01$).

“This first randomised phase 3 trial demonstrates that second-line TIL administration significantly improves PFS compared with ipilimumab in patients with unresectable, advanced melanoma. Therefore, TIL therapy could become a possible new treatment option for this population,” highlighted Prof. Haanen.

1. [Larkin J, et al. N Engl J Med. 2019;381\(16\):1535–1546.](#)
2. [Van den Berg JH, et al. J Immunother Cancer. 2020;8\(2\):e000848.](#)
3. [Sarnaik AA, et al. J Clin Oncol. 2021;39\(24\):2656–2666.](#)
4. Haanen JBAG, et al. Treatment with tumor-infiltrating lymphocytes (TIL) versus ipilimumab for advanced melanoma: Results from a multicenter, randomized phase III trial. Abstract LBA3, ESMO Congress 2022, 09–13 September, Paris, France.

Neoadjuvant pembrolizumab outperforms adjuvant pembrolizumab in resectable stage III–IV melanomas

Compared with the same treatment given entirely in the adjuvant setting, neoadjuvant pembrolizumab followed by adjuvant pembrolizumab improved event-free survival (EFS) in patients with resectable melanoma, the first results of the phase 2 SWOG S1808 trial demonstrated.

A current fundamental question for treating patients with resectable cancer is whether treatment with immunotherapy before surgery induces an enhanced anti-tumour immune response or simply delays curative surgery. In a small melanoma stage III patient cohort ($n = 20$), neoadjuvant immunotherapy

induced an immune response from a larger population of T cells compared with adjuvant immunotherapy [1].

To follow-up on this preliminary study, Dr Sapna Patel (MD Anderson Cancer Center, TX, USA) presented the first results of the phase 2 randomised SWOG S1808 trial ([NCT03698019](#)), which compared neoadjuvant pembrolizumab with adjuvant pembrolizumab in patients with resectable, stage III–IV melanoma [2].

The SWOG S1808 trial randomised 313 patients with resectable, stage III–IV melanoma to an adjuvant arm consisting of surgery followed by a maximum of 18 cycles of pembrolizumab (200 mg every 3 weeks), or a neoadjuvant arm consisting of treatment with 3 cycles of pembrolizumab followed by surgery and 15 cycles of pembrolizumab. The primary endpoint of the study was EFS. An event was defined as no surgery due to progression or toxicity, failure to start adjuvant treatment within 84 days of surgery, melanoma recurrence after surgery, or death of any cause.

With a median follow-up of 14.7 months, EFS was significantly longer in the neoadjuvant arm compared with the adjuvant arm (HR 0.58; $P = 0.004$). The 2-year EFS rate was 72% versus 49% (neoadjuvant vs adjuvant arm). Overall survival data are not yet mature. In the neoadjuvant arm, 14 of 38 events took place before surgery (compared with 1 of 67 events in the adjuvant arm). Tumour-related events occurred in 20% ($n = 31$) of participants in the neoadjuvant arm versus 40% ($n = 61$) of participants in the adjuvant arm. In the neoadjuvant arm, 9 participants achieved a radiological complete response and 59 participants achieved a radiological partial response. A central pathological review is underway. No new safety issues were observed.

“Compared with the same treatment given entirely in the adjuvant setting, neoadjuvant pembrolizumab followed by adjuvant pembrolizumab improved EFS in patients with resectable melanoma,” summarised Dr Patel.

1. [Blank CU, et al. Nat Med. 2018;24\(11\):1655–1661.](#)
2. Patel S, et al. Neoadjuvant versus adjuvant pembrolizumab for resected stage III–IV melanoma (SWOG S1801). Abstract LBA6, ESMO Congress 2022, 09–13 September, Paris, France.

Baseline ctDNA predicts survival in resected stage III–IV melanoma

Translational research on data from the CheckMate-915 trial demonstrated that baseline circulating tumour DNA (ctDNA) positivity in resected stage III–IV melanoma

predicts poorer survival. Additionally, baseline ctDNA combined with IFN γ -status and tumour mutational burden improved the predictive value.

CtDNA is tumour DNA that can be detected in the bloodstream. Both, pre- and post-resection DNA has been associated with poor clinical outcomes [1]. Recently, results from the phase 3 CheckMate 915 trial ([NCT03068455](https://clinicaltrials.gov/ct2/show/study/NCT03068455)) showed that adjuvant dual immune checkpoint inhibition with nivolumab plus ipilimumab did not improve survival in patients with completely resected stage IIIC/D–IV melanoma compared with nivolumab alone [2]. Prof. Georgina Long (University of Sydney, Australia) presented the results of her current analysis of the predictive value of pre-treatment ctDNA for disease recurrence and survival in the adjuvant immunotherapy populations of the CheckMate 915 trial [3].

CheckMate-915 randomised 1,844 participants with resected stage IIIB/D–IV 1:1 to receive adjuvant nivolumab or nivolumab plus ipilimumab. Pre-treatment ctDNA was available from 1,127 participants (61% of intention-to-treat [ITT] population) who showed no difference in baseline characteristics and efficacy from the ITT population. A trend towards a greater prevalence of ctDNA-positivity in higher stage III substages of melanoma was observed.

Additionally, an association was observed between ctDNA positivity and recurrence-free survival (HR 1.87) and distant metastases-free survival (HR 2.86) during follow-up (see Figure).

This association was particularly strong during the first months of treatment. Of note, no significant interaction between baseline ctDNA status and the treatment arm was observed.

The predictive value of baseline ctDNA improved when it was combined with baseline IFN γ -status and tumour mutational burden. Again, the association of this combined marker with early recurrence was highest in the first months of treatment.

Based on these results, Prof. Long concluded that “pre-treatment ctDNA was associated with an increased risk of early recurrence across treatment arms. ctDNA is a useful biomarker for combined analyses predicting outcome for adjuvant melanoma.”

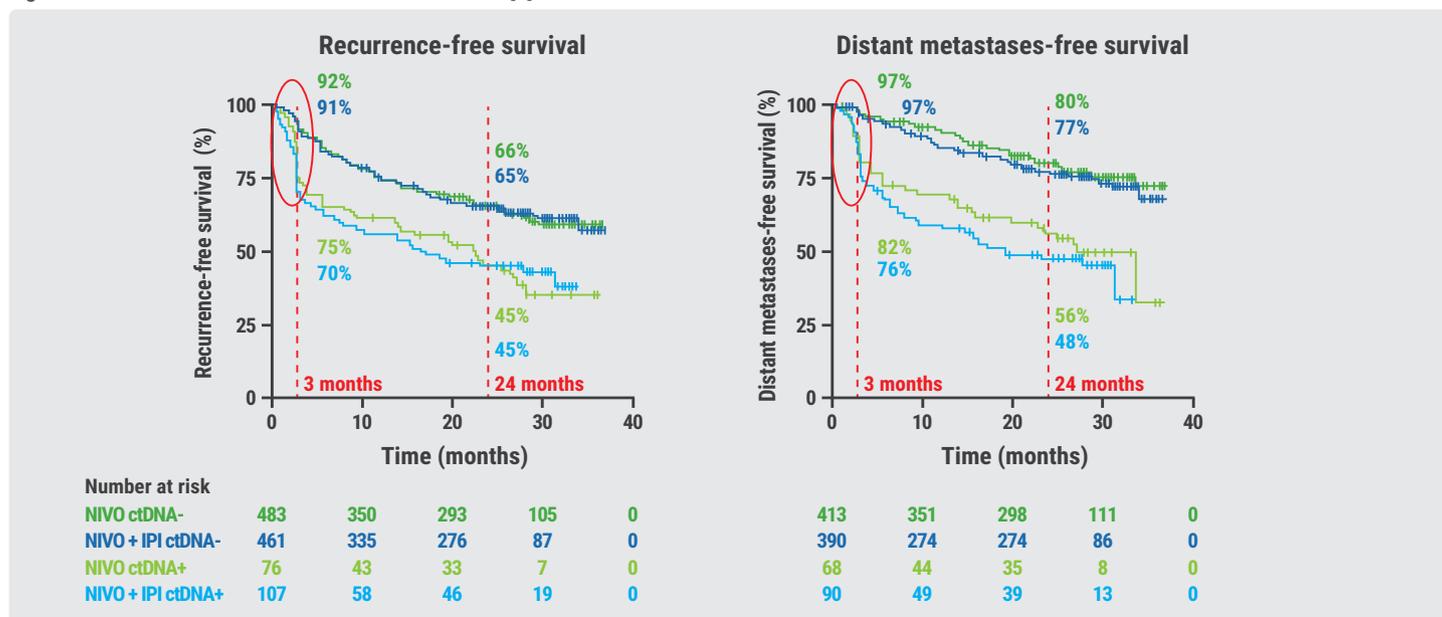
1. [Lee B, et al. Ann Oncol 2019;30\(9\):1472–1478.](https://doi.org/10.1093/annonc/mdz147)
2. [Long GV, et al. Cancer Res. 2021;81\(13_Supplement\):CT004.](https://doi.org/10.1158/1538-7443.2021.81.13.Supplement.CT004)
3. Long GV, et al. Association of pre-treatment ctDNA with disease recurrence and clinical and translational factors in patients with stage IIIB-D/IV melanoma treated with adjuvant immunotherapy (CheckMate 915). Abstract 7880, ESMO Congress 2022, 09–13 September, Paris, France.

Survival-benefit of neoadjuvant T-VEC maintained over 5 years of follow-up

Neoadjuvant talimogene laherparepvec (T-VEC) treatment in patients with resectable, stage IIIB–IVM1 melanoma resulted in a durable survival-benefit compared with surgery alone, as shown by the 5-year follow-up data of the largest randomised T-VEC trial.

T-VEC is a genetically modified herpes simplex 1 virus that, when injected into a cancer lesion, results in the lyses and

Figure: Association of baseline ctDNA with recurrence [3].



NIVO, nivolumab. IPI, ipilimumab.

release of tumour-antigens and subsequent stimulation of local and systemic immune responses [1]. The initial analysis of the large (n=150) phase 2, multicentre, randomised trial ([NCT02211131](#)) reported a significant survival benefit of neoadjuvant T-VEC compared with surgery alone after 2 years [2]. Prof. Reinhard Dummer (University of Zürich, Switzerland) presented the results of the final read-out after 5 years of follow-up [3].

The 5-year event-free survival in participants treated with neoadjuvant T-VEC was 43.7% versus 27.4% in participants with surgery alone (HR 0.57). The 5-year overall survival was 77.3% versus 62.7% (neoadjuvant T-VEC vs surgery; HR 0.54). Of note, more participants in the surgery-only arm received

systemic anti-cancer treatment compared with the T-VEC arm: 78.3% vs 54.8% (for adjuvant therapy this was 31.9% vs 13.7%). Hazard ratios for both event-free and overall survival did not change compared with the 3-year survival data.

“The results from this final analysis suggest that intratumorally administered oncolytic agents like T-VEC can elicit a meaningful long-term systemic effect. This supports neoadjuvant T-VEC followed by surgery in advanced resectable melanoma,” concluded Prof. Dummer.

1. [Ramelyte E, et al. Cancer Cell. 2021;39\(3\):394–406.](#)
2. [Dummer R, et al. Nat Med. 2021;27\(10\):1789–1796.](#)
3. Dummer R, et al. Final 5-year results of the phase II, multicenter, randomized, open-label trial of talimogene laherparepvec (T-VEC) neoadjuvant treatment (Tx) plus surgery vs immediate surgery in patients (pts) with resectable stage IIIB-IVM1a melanoma. Abstract LBA39, ESMO Congress 2022, 09–13 September, Paris, France.

Genitourinary Cancer – Prostate Cancer

Overall survival benefit of abiraterone in mHSPC is maintained for 7 years

The addition of enzalutamide to abiraterone acetate plus prednisone (AAP) did not improve overall survival (OS) of patients with metastatic hormone-sensitive prostate cancer (mHSPC), the results from the analysis of 2 phase 3 STAMPEDE platform trials demonstrated. The survival benefit of AAP, when added to androgen deprivation therapy (ADT), was maintained at 7 years.

The addition of either AAP or enzalutamide to ADT has been shown to improve mHSPC disease outcomes in men [1,2]. Combining AAP and enzalutamide improved progression-free survival (PFS), but not OS, in patients with metastatic castration-resistant prostate cancer (mCRPC) [3]. However, the benefits of combining AAP and enzalutamide in mHSPC are unknown. Additionally, survival outcomes of mHSPC patients on ADT plus AAP or AAP plus enzalutamide beyond 5 years have not been reported. The results from a comparison of 2 randomised phase 3 trials in the multi-arm, multi-stage STAMPEDE platform ([NCT00268476](#)) were presented by Prof. Gerhardt Attard (UCL Cancer Institute London, UK) [4].

The 2 trials - with no overlapping controls - randomised 1,003 mHSPC participants to ADT plus AAP and 916

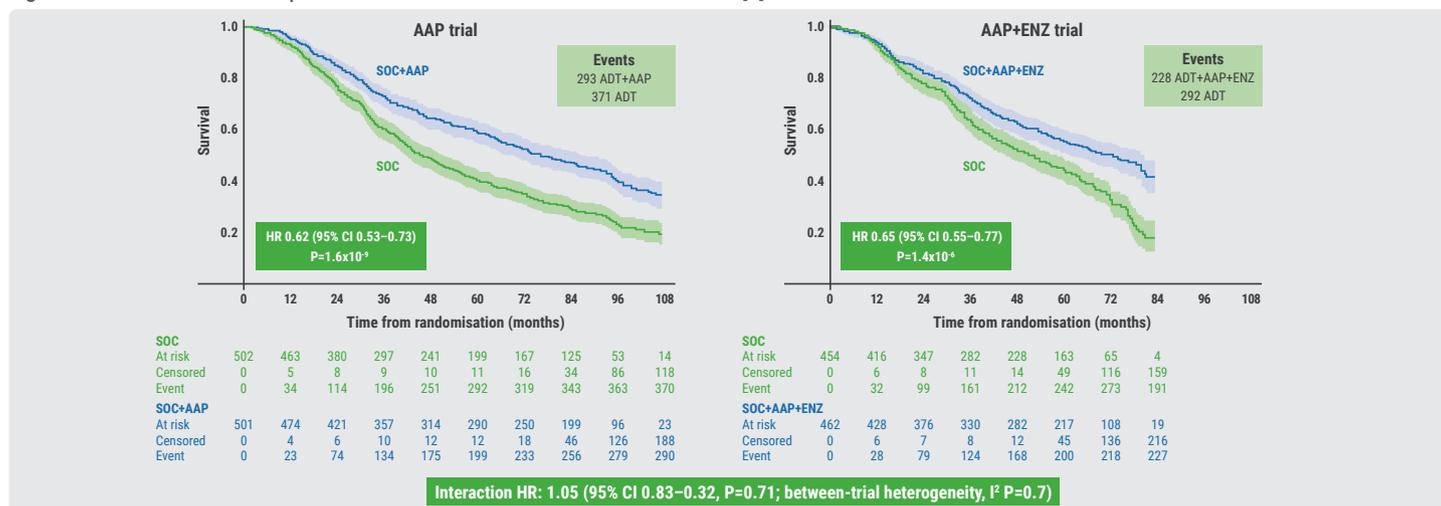
mHSPC participants to ADT plus AAP plus enzalutamide. Controls were treated with standard-of-care (SOC), namely, ADT or ADT plus docetaxel. Treatment was continued until progression. The primary outcome of the trials was OS.

The median follow-up was 95.8 months in the AAP trial and 71.7 months in the AAP plus enzalutamide trial. In both trials, the addition of second-generation hormonal agent(s) improved OS (HR 0.62 for AAP vs SOC, $P < 0.0001$; HR 0.65 for AAP plus enzalutamide vs SOC, $P < 0.0001$; see Figure on next page). No evidence was seen of a difference in the treatment effect (interaction HR 1.05; $P = 0.71$) between both trials. At 84 months of follow-up, 48% of participants treated with ADT plus AAP were still alive compared with 30% of participants treated with ADT alone.

The rates of adverse events were similar in both trials. However, adverse events occurred more frequently in patients treated with AAP plus enzalutamide compared with AAP. Grade 3–5 adverse events in the first 5 years were observed in 54.4% of patients treated with AAP and in 67.9% of patients treated with AAP plus enzalutamide.

Based on these results, Prof. Attard concluded that “enzalutamide and AAP should not be combined for treating

Figure: Overall survival curves per treatment arm: AAP and AAP + enzalutamide [4].



SOC, standard-of-care. AAP, abiraterone acetate plus prednisone. ENZ, enzalutamide. ADT, androgen deprivation therapy.

patients with mHSPC. It does not improve survival and only increases the incidence of adverse events. Additionally, these results show that the survival benefit of AAP plus ADT is maintained at 7 years.”

1. James ND, et al. *N Engl J Med*. 2017;377(4):338–351.
2. Davis ID, et al. *N Engl J Med* 2019;381(2):121–131.
3. Morris MJ, et al. *J Clin Oncol*. 2019;37(15_suppl):5008.
4. Attard G, et al. Comparison of abiraterone acetate and prednisolone (AAP) or combination enzalutamide (ENZ) + AAP for metastatic hormone sensitive prostate cancer (mHSPC) starting androgen deprivation therapy (ADT): Overall survival (OS) results of 2 randomised phase III trials from the STAMPEDE protocol. Abstract LBA62, ESMO Congress 2022, 09–13 September, Paris, France.

Limited benefit of adding long-term ADT to post-operative radiotherapy in prostate cancer

Adding long-term androgen deprivation therapy (ADT) to post-operative radiotherapy improves metastases-free survival (MFS) compared with short-term ADT in patients with non-metastatic prostate cancer, results from the RADICALS-HD trial showed. However, most patients with short-term ADT also did well.

Current key questions for treating patients with non-metastatic prostate cancer treated with radiotherapy (with or without radical prostatectomy) are: ‘Who should receive ADT added to radiotherapy?’ and ‘What is the optimum duration of ADT?’ stated Prof. Chris Parker (The Royal Marsden Hospital, UK). He presented the results from the RADICALS-HD (ISRCTN40814031), which assessed the use and duration of ADT with post-operative radiotherapy [1,2].

The trial enrolled nearly 3,000 participants who had undergone postoperative radiotherapy (adjuvant or early salvage). 1,480 of these participants were randomised 1:1 to receive short-term (6

months) versus no ADT and 1,523 participants were randomised 1:1 to receive short-term versus long-term ADT (24 months). The participants’ characteristics within the two parts of the trial were well balanced, however, participants in the ‘none versus short-term’ ADT part had less aggressive disease than those selected for the ‘short- versus long-term’ ADT part. The median follow-up was 9 years in both parts. The primary outcome was metastasis-free survival (MFS). Secondary outcomes included time to salvage ADT and overall survival (OS).

In the ‘none versus short-term’ ADT part, 6 months of ADT did not improve MFS (80% vs 79% at 10 years; HR 0.86; P=0.35,) but delayed time to salvage ADT (HR 0.54; 95% CI 0.42–0.70). In the ‘short- versus long-term’ ADT part, 24 months of ADT improved MFS compared to 6 months of ADT (78% vs 72% at 10-years; HR 0.77; P=0.03,) and delayed time to salvage ADT (HR 0.73; 95% CI 0.59–0.91). There was no interaction between the treatment effect and either the baseline prostate-specific antigen (PSA) or comorbidity score. OS data were not yet mature in either part of the trial.

“When added to post-operative radiotherapy for prostate cancer, long-term ADT improved MFS and improved time to salvage ADT, compared with short-term ADT. Short-term ADT did not improve MFS, but delayed time to salvage ADT, compared with no ADT. The effect size appeared consistent across all pre-specified subgroups,” summarised Dr Parker. Of note, the RADICALS-HD trial started 15 years ago and the management of patients has changed since then.

1. Parker CC, et al. *Clin Oncol (R Coll Radiol)*. 2022;34(9):593–597.
2. Parker CC, et al. Duration of androgen deprivation therapy (ADT) with post-operative radiotherapy (RT) for prostate cancer: First results of the RADICALS-HD trial (ISRCTN40814031). Abstract LBA9, ESMO Congress 2022, 09–13 September, Paris, France.

Intensified ADT benefits biochemical progression-free survival in biochemically relapsed prostate cancer

The addition of apalutamide to androgen deprivation therapy (ADT) for a finite duration led to a statistically significant prolongation of prostate-specific antigen (PSA) doubling time and biochemical progression-free survival without impacting testosterone recovery time, results from the phase 3 PRESTO trial showed.

Intermittent and continuous ADT are standard approaches for men with biochemically relapsed, non-metastatic prostate cancer after prostatectomy with a short PSA doubling time and a high risk of developing distant metastases and cancer-related mortality [1]. The phase 3 PRESTO trial ([NCT03009981](#)) evaluated the efficacy and safety of intensification of ADT for a finite duration on PSA doubling time suppression enabling longer treatment-free intervals within a framework of intermittent treatment. Dr Rahul Aggarwal (University of California San Francisco, CA, USA) presented the first results [2].

In the PRESTO trial, 503 participants (prior radical prostatectomy and radiotherapy, PSA doubling-time < 3 months) were randomised 1:1:1 to receive ADT, ADT plus apalutamide (APA), or ADT plus APA plus abiraterone acetate plus prednisone (AAP) for 52 weeks. The primary endpoint was biochemical progression-free survival (PFS). Secondary

endpoints included safety, patient-reported quality-of-life, time to testosterone recovery (> 50 ng/dL) (TTTR), metastasis-free survival (MFS) and time to castration resistance (TTCR).

Median biochemical PFS was improved in ADT + APA versus ADT alone (20.3 vs 24.9 months; HR 0.52; P= 0.00047). Likewise, median biochemical PFS was improved in ADT + APA + AAP versus ADT alone (20.6 vs 26.0 months; HR 0.48; P=0.00008). Biochemical PFS was independent of PSA doubling time (<3 months, 3–9 months). The addition of APA to ADT did not influence TTTR (3.9 months for ADT vs 3.8 months for ADT + APA), whereas the addition of APA + AAP to ADT led to a slight but not statistically significant prolongation of TTTR (4.8 months for ADT + APA + AAP vs 3.9 months for ADT alone). Grade ≥3 adverse events, in particular hypertension, were increased in the ADT + APA + AAP group.

Based on these results, Dr Aggarwal concluded that “the addition of APA to ADT for a finite duration leads to a statistically significant prolongation of biochemical PFS with no impact on testosterone recovery time. Therefore, this treatment regimen could be considered for high-risk patients with a short PSA doubling time. The addition of AAP to ADT + APA does not appear to further benefit the patient.”

1. Crook JM, et al. *N Engl J Med.* 2012;367(10):895–903.
2. Aggarwal R, et al. PRESTO: A phase III, open-label study of androgen annihilation in patients (pts) with high-risk biochemically relapsed prostate cancer (AFT-19). Abstract LBA63, ESMO Congress 2022, 09–13 September, Paris, France.

Genitourinary Cancer – Non-Prostate Cancer

Adjuvant nivolumab plus ipilimumab does not improve survival in patients with localised RCC at high risk of relapse after nephrectomy

Results from the phase 3 CheckMate 914 trial demonstrated that adjuvant treatment with nivolumab plus ipilimumab did not improve survival in patients with stage II–III localised renal cell carcinoma (RCC) at risk of post-nephrectomy relapse.

Patients with stage II–III localised RCC have a substantial risk of post-nephrectomy relapse [1]. Approved adjuvant therapeutic options include sunitinib (USA only) and pembrolizumab [2].

Previously, dual immune checkpoint blockade with nivolumab and ipilimumab improved long-term survival versus sunitinib in patients with untreated advanced RCC [3]. The current analysis of the CheckMate 914 trial ([NCT03138512](#)) evaluated the clinical outcomes of adjuvant nivolumab plus ipilimumab in the setting of resected stage II–III clear-cell RCC with a high risk of recurrence. Prof. Robert Motzer (Memorial Sloan Kettering Cancer Center, NY, USA) presented the results [4].

A total of 816 patients were randomised 1:1 to receive nivolumab (240 mg every 2 weeks, 12 doses) plus ipilimumab (1 mg/kg every 6 weeks, 4 doses) or a placebo after radical

of partial nephrectomy with negative surgical margins. The primary endpoint was disease-free survival (DFS); secondary endpoints were overall survival (OS) and safety. In the case of non-significant DFS endpoints, no formal analysis of OS was to be performed.

With 37.0 months of median follow-up, the primary endpoint of DFS was not met (HR 0.92; P=0.53). DFS rates at 24 months were 76.4% in the nivolumab plus ipilimumab arm versus 74.0% in the placebo arm. Of note, 43% of participants discontinued treatment in the nivolumab plus ipilimumab arm versus 11% in the placebo arm. The incidence of grade ≥ 3 treatment-related adverse events was 28% and 2% for the nivolumab plus ipilimumab and placebo arms, respectively.

Based on these results, Prof. Motzer concluded that “adjuvant treatment with nivolumab plus ipilimumab does not improve survival in patients with stage II–III localised clear-cell RCC. The safety of nivolumab/ipilimumab in this population is consistent with the known profile of this combination in patients with advanced RCC.”

1. Motzer RJ, et al. *J Clin Oncol*. 2017;35(35):3916–3923.
2. Powles T, et al. *Ann Oncol*. 2021;32(12):1511–1519.
3. Motzer RJ, et al. *Cancer* 2022;128(11):2085–2097.
4. Motzer RJ, et al. Adjuvant nivolumab plus ipilimumab (NIVO+IPI) vs placebo (PBO) for localized renal cell carcinoma (RCC) at high risk of relapse after nephrectomy: Results from the randomized, phase III CheckMate 914 trial. Abstract LBA4, ESMO Congress 2022, 09–13 September, Paris, France.

Triple therapy improves progression-free survival in patients with advanced RCC versus dual therapy

The first results of the phase 3 COSMIC-313 trial demonstrated that triple therapy (nivolumab plus ipilimumab plus cabozantinib) improved progression-free survival (PFS) versus dual checkpoint inhibition (nivolumab plus ipilimumab) in patients with previously untreated advanced renal cell carcinoma (RCC).

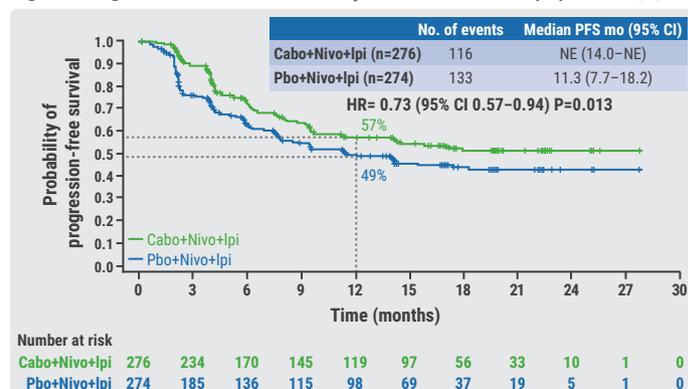
Dual immune checkpoint inhibition with nivolumab plus ipilimumab is the first-line standard-of-care for patients with advanced RCC of IMDC intermediate or poor risk [1]. However, approximately 20% of patients deteriorate to progressive disease as the best response, representing an unmet medical need. Additionally, first-line cabozantinib plus nivolumab has demonstrated clinical effectiveness in patients with advanced RCC [2]. In a phase 1 trial, triplet therapy (nivolumab plus ipilimumab plus cabozantinib) showed clinical activity and manageable toxicity [3]. Based

on this background, the COSMIC-313 ([NCT03937219](https://clinicaltrials.gov/ct2/show/study/NCT03937219)) evaluated the efficacy and safety of first-line triple therapy (nivolumab plus ipilimumab plus cabozantinib) in patients with advanced RCC of poor or intermediate IMDC risk. Prof Toni Choueiri (Dana-Farber Cancer Institute, MA, USA) presented the first results [4].

The COSMIC-313 trial randomised 855 previously untreated advanced RCC patients with poor (25%) or intermediate IMDC (75%) risk to receive cabozantinib (40 mg once daily) or placebo plus standard-of-care 4 cycles of nivolumab (3 mg/kg every 4 weeks) and ipilimumab (1 mg/kg every 3 weeks), followed by nivolumab (480 mg every 3 weeks) up to 2 years. The primary endpoint of the study was PFS in the 550 first randomised patients. Secondary endpoints were overall survival (OS) in the total intention-to-treat (ITT) population, objective response rate (ORR), duration of response, and safety.

Triple therapy significantly improved median PFS versus dual therapy (not reached vs 11.3 months; HR 0.73; P=0.013, see Figure). PFS rates at 12 months were 57% and 49% for triple and dual therapy, respectively. Triple therapy favoured PFS in all pre-specified subgroups, except participants with IMDC poor risk (HR 1.04). ORR was 43% (3% complete response, 40% partial response) in participants treated with triple therapy versus 36% (3% complete, 33% partial) in participants treated with dual therapy. The median duration of response was not reached in either study arm. The safety profile of the triple therapy was generally manageable and consistent with the profiles of the treatment components.

Figure: Progression-free survival analysis of the total ITT population [4].



Cabo, cabozantinib. Nivo, nivolumab. Ipi, ipilimumab. NR, not reached. NE, not estimatable. mo, months. Pbo, placebo.

“This first study to use dual immune checkpoint inhibition as the control demonstrated a significant benefit in PFS for triple therapy consisting of nivolumab plus ipilimumab plus cabozantinib in previously untreated patients with IMDC

intermediate risk,” concluded Prof. Toni Choueiri. Follow-up for assessing the OS is ongoing.

1. [Motzer RJ, et al. *New Engl J Med.* 2018;378\(14\):1277–1290.](#)
2. [Choueiri TK, et al. *N Eng J Med.* 2021;384\(9\):829–841.](#)
3. [Apolo AB, et al. *J Clin Oncol.* 2020;38\(31\):3672–3684.](#)
4. Choueiri TK, et al. Phase III study of cabozantinib (C) in combination with nivolumab (N) and ipilimumab (I) in previously untreated advanced renal cell carcinoma (aRCC) of IMDC intermediate or poor risk (COSMIC-313). Abstract LBA8, ESMO Congress 2022, 09–13 September, Paris, France.

Adjuvant atezolizumab does not improve outcomes for patients with RCC and increased risk of recurrence

Atezolizumab as adjuvant therapy after resection for patients with renal cell cancer (RCC) who have an increased risk of recurrence did not improve clinical outcomes versus placebo, results from the phase 3 IMmotion010 trial showed.

The standard-of-care for patients with locoregional or oligometastatic RCC is radical nephrectomy with or without metastasectomy [1,2]. Adjuvant treatment with pembrolizumab significantly improved disease-free survival (DFS) compared with placebo after surgery among patients with RCC who were at high risk for recurrence [3]. The phase 3 IMmotion010 trial ([NCT03024996](#)) evaluated the safety and efficacy of adjuvant therapy with atezolizumab for patients with RCC and increased risk of recurrence. Dr Axel Bex (The Royal Free London NHS Foundation Trust, UK) presented the results [4].

The IMmotion010 trial enrolled 778 participants with resected intermediate to high-risk RCC (T2 Grade [Gr] 4, T3a Gr 3/4,

T3b/c or T4 any Gr, TxN+ any Gr or M1 resected with no evidence of disease). Participants were 1:1 randomised to atezolizumab (1,200 mg every 3 weeks for 16 cycles or 1 year) or placebo. The primary endpoint was investigator-assessed DFS; key secondary endpoints were independent review facility-assessed DFS in the intention-to-treat population and DFS in participants with PD-L1 immune cell expression $\geq 1\%$, overall survival and safety.

Adjuvant atezolizumab did not improve DFS versus placebo: median investigator-assessed DFS was 57.2 versus 49.5 months; 2-year investigator-assessed DFS was 67% versus 65% (HR 0.93; P=0.5). Exploratory analyses showed that atezolizumab improved DFS in patients (n=34) with PD-L1 immune cell expression of $\geq 5\%$: HR 0.57) and in patients (n=104) with a sarcomatoid component (HR 0.77). Atezolizumab was well tolerated and the safety results were consistent with the known safety profile of atezolizumab.

“Atezolizumab as adjuvant therapy after resection for patients with RCC who have increased risk of recurrence did not improve clinical outcomes compared with placebo. Further studies are needed to clarify the role of immunotherapy in the adjuvant setting for RCC,” summarised Dr Bex.

1. [Ingels A, et al. *Nat Rev Urol.* 2022;19\(17\):391–418.](#)
2. [Ljunberg B, et al. *Eur Urol.* 2022;82\(4\):399–410.](#)
3. [Choueiri TK, et al. *N Engl J Med.* 2021;385\(8\):683–694.](#)
4. Bex A, et al. IMmotion010: Efficacy and safety from the phase III study of atezolizumab (atezo) vs placebo (pbo) as adjuvant therapy in patients with renal cell carcinoma (RCC) at increased risk of recurrence after resection. Abstract LBA66, ESMO Congress 2022, 09–13 September, Paris, France.

Gynaecological cancers

OS benefit for advanced ovarian cancer patients treated with maintenance olaparib

The addition of maintenance olaparib to bevacizumab provided a clinically meaningful overall survival (OS) benefit in homologous recombination deficiency (HRD)-positive patients, results from the final analysis of the phase 3 PAOLA-1/ENGOT-ov25 trial showed.

Earlier analyses from the PAOLA-1/ENGOT-ov25 trial ([NCT02477644](#)) showed significant benefits in progression-free survival (PFS) of maintenance olaparib plus bevacizumab therapy in patients with newly diagnosed advanced ovarian cancer who had received first-line standard-of-care treatment including bevacizumab [1]. Prof. Isabelle Ray-Coquard (Centre Léon Bérard, France) presented the final PAOLA-1/ENGOT-ov25

trial analysis, which investigated whether the PFS advantages observed in the primary analysis translated to an OS benefit at 5 years [2].

The PAOLA-1/ENGOT-ov25 trial randomised 806 participants with newly diagnosed, advanced, high-grade ovarian cancer who had a response after first-line platinum-taxane chemotherapy plus bevacizumab 2:1 to receive olaparib (300 mg twice daily) or placebo for 2 years. All participants received bevacizumab (15 mg/kg every 3 weeks) for up to 15 months.

The median OS in the intention-to-treat population was 56.5 months in the olaparib plus bevacizumab arm versus 51.6 months in the placebo plus bevacizumab arm (HR 0.92; P=0.4118). At 5 years of follow-up, 47.3% versus 41.5% of participants were still alive in the olaparib plus bevacizumab and placebo plus bevacizumab arm, respectively. A total of 45.7% of participants in the placebo plus bevacizumab arm received a PARP inhibitor during any subsequent treatment versus 19.6% of participants in the olaparib plus bevacizumab arm.

In HRD-positive patients, the median OS was 75.2 months for olaparib plus bevacizumab-treated participants (n=255) compared with 57.3 months in the placebo plus bevacizumab (n=133) arm (HR 0.62, see Figure). No OS benefit was observed in HRD-negative patients (36.8 months for olaparib vs 40.4 months for placebo; HR 1.19). The updated median PFS in the HRD-positive group was 46.8 months and 17.6

months for olaparib plus bevacizumab- and placebo plus bevacizumab-treated participants respectively (HR 0.41). No new safety signals were observed.

“This data shows that, despite a high proportion of patients in the control arm receiving a PARP inhibitor post-progression, the addition of maintenance olaparib to bevacizumab provided a clinically meaningful OS benefit in HRD-positive patients,” concluded Prof. Ray-Coquard.

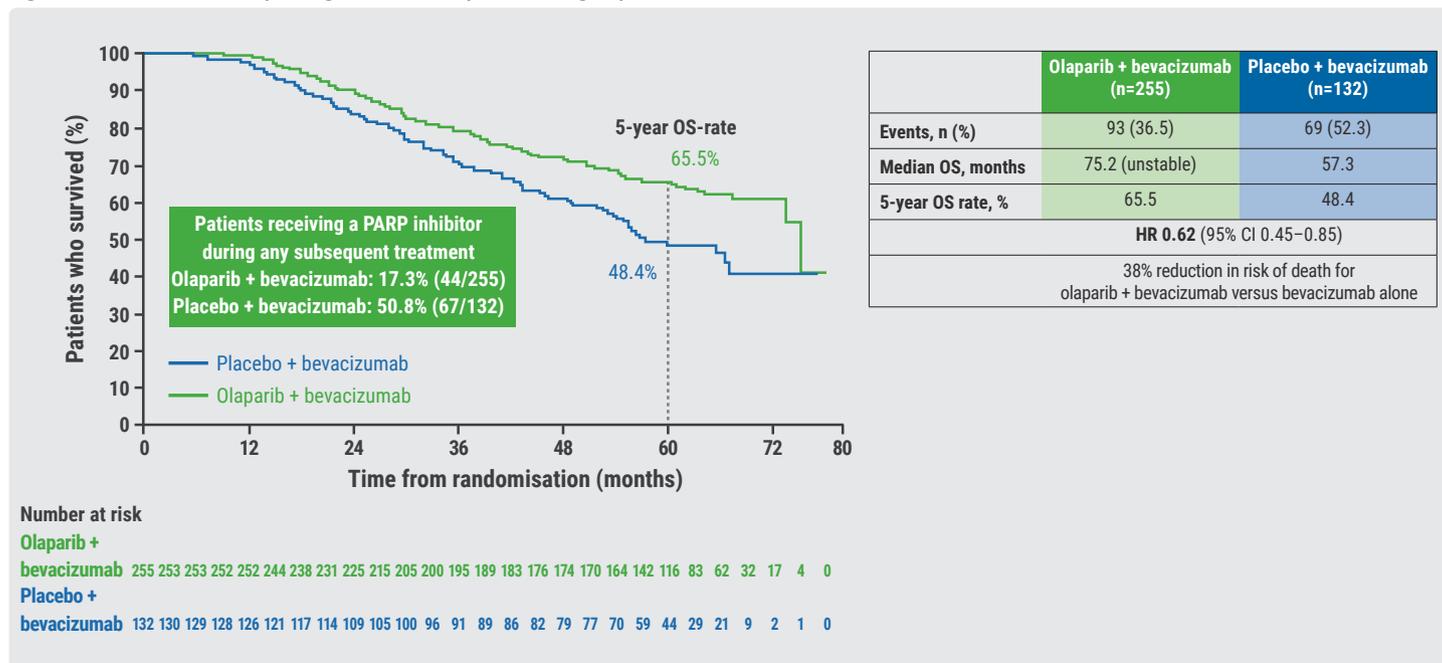
1. Ray-Coquard IL, et al. N Engl J Med 2019;381(25):2416–2428.
2. Ray-Coquard IL, et al. Final overall survival (OS) results from the phase III PAOLA-1/ENGOT-ov25 trial evaluating maintenance olaparib (ola) plus bevacizumab (bev) in patients (pts) with newly diagnosed advanced ovarian cancer (AOC). Abstract LBA29, ESMO Congress 2022, 09–13 September, Paris, France.

Maintenance tegafur-uracil does not improve survival in locally advanced cervical cancer

Continuous administration of low-dose tegafur-uracil (UFT) for 2 years after curative concurrent chemoradiotherapy (CCRT) did not improve median progression-free survival (PFS) or median overall survival (OS), results of the GOTIC-002 LUFT trial demonstrated.

The current standard therapy for locally advanced cervical cancer (LACC) is CCRT followed by brachytherapy. However, there is room to improve survival, e.g. by giving maintenance chemotherapy after CCRT. Maintenance with UFT improves survival in gastric, lung, colon, and breast cancer [1–5].

Figure: Overall survival was prolonged in the HRD-positive subgroup [2].



OS, overall survival.

The GOTIC-002 LUFT trial ([jRCTs031180174](#)) evaluated the efficacy and safety of low-dose UFT for 2 years as maintenance chemotherapy after curative CCRT for patients with LACC. Prof. Keiichi Fujiwara (Saitama Medical University, Japan) presented the results [5].

During 8 years, the study enrolled 351 participants with LACC (FIGO 1B2–IVa) with a partial or complete response after curative CCRT. Participants were 1:1 randomised to maintenance UFT (300 mg or 400 mg every day for 2 years) or observation. The primary endpoint was PFS; secondary endpoints included OS, safety and quality-of-life. Maintenance UFT did not improve median PFS over observation (62.0% vs

61.3%; HR 0.92; P=0.634) or median OS (76.1% vs 77.6%; HR 1.04; P=0.869). Maintenance UFT was well tolerated, with grade ≥ 3 adverse events observed in 22.6% of participants in the UFT arm compared with 15.9% of observed participants.

Based on these results, Prof. Fujiwara acknowledged that “continuous administration of low-dose UFT for 2 years after curative CCRT does not improve PFS or OS.”

1. Nakajima T, et al. *Br J Surg*. 2007;94(12):1468–1476.
2. Kato H, et al. *N Engl J Med*. 2004;350(17):1713–1721.
3. Akasu T, et al. *Jpn J Clin Oncol*. 2006;36(4):237–2344.
4. Kasumi F, et al. *Oncology*. 2003;64(2):146–153.
5. Fujiwara K, et al. Randomized phase III trial of maintenance chemotherapy with tegafur-uracil versus observation following concurrent chemoradiotherapy for locally advanced cervical cancer, GOTIC-002 LUFT trial. Abstract LBA31, ESMO Congress 2022, 09–13 September, Paris, France.

Head and Neck Cancer

Adding first-line pembrolizumab to CRT in locally advanced HNSCC does not significantly prolong survival or event-free survival

The primary endpoint of a study comparing first-line pembrolizumab plus chemoradiotherapy (CRT) to CRT alone failed to meet its primary endpoint (even though there was a strong trend for improvement of event-free survival (EFS) in patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC), the first results of the phase 3 KEYNOTE-412 trial suggested.

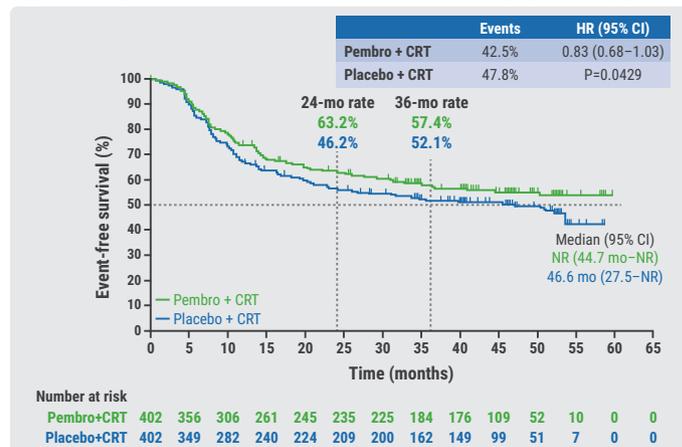
Standard-of-care for patients with unresected LA-HNSCC is concurrent chemoradiotherapy (CRT) with high-dose cisplatin [1]. However, less than 50% of patients remain free of disease after 3 years and the 5-year overall survival (OS) rate is about 50% [2]. Pembrolizumab (with or without chemotherapy) was recently shown to improve survival in patients with recurrent or metastatic HNSCC [3]. The phase 3 KEYNOTE-412 trial ([NCT03040999](#)) investigated the efficacy of pembrolizumab plus CRT versus placebo plus CRT in patients with LA-HNSCC. Prof. Jean-Pascal Machiels (Cliniques Universitaires Saint-Luc, Belgium) presented the first results [4].

In the KEYNOTE-412 trial, 804 participants with newly diagnosed, treatment-naïve LA-HNSCC were randomised 1:1 to receive pembrolizumab (200 mg every 3 weeks) plus CRT (70 Gy/35F plus cisplatin 100 mg/m² every 3 weeks) or placebo plus CRT.

A pembrolizumab or placebo priming dose was given 1 week before CRT, followed by 2 doses during CRT and 14 doses of maintenance therapy after CRT, for a total of 17 doses. The primary endpoint was EFS (efficacy boundary, one-sided P=0.0242). OS and safety/tolerability were secondary endpoints.

After a median follow-up of 47.7 months, median EFS for participants treated with pembrolizumab plus CRT was not reached versus 46.6 months for participants treated with placebo plus CRT (HR 0.83; P=0.0429, CI 0.68-1.03). Hence, the primary endpoint was not met (see Figure).

Figure: EFS per treatment arm in the intention-to-treat population [4].



Pembro, pembrolizumab. CRT, chemoradiotherapy. EFS, event-free survival. NR, normal range. Mo, month.

EFS rates at 24 months were 63.2% versus 56.2% and 57.4% vs 52.1% at 36 months for pembrolizumab plus CRT and placebo plus CRT participants, respectively. Median OS was also not significantly different between the study arms (HR 0.90). The difference in median EFS between the arms was somewhat more pronounced in patients with PD-L1 CPS ≥ 1 (n=685; HR 0.80) and patients with PD-L1 CPS ≥ 20 (n=291; HR 0.73). No new safety signals were observed.

Based on these results, Prof. Machiels concluded that “pembrolizumab plus CRT is associated with a favourable trend towards improved EFS versus placebo in patients with LA-HNSCC. PD-L1 expression may be an informative biomarker. However, LA-HNSCC remains a challenging disease to treat.”

1. Machiels J-P, et al. *Ann Oncol.* 2020;31(11):1462–1475.
2. Braakhuis BJM, et al. *Ann Oncol.* 2012;23 Suppl 10:x173–7.
3. Burtneß B, et al. *Lancet.* 2019;394(10212):1915–1928.
4. Machiels J-P, et al. Primary results of the phase III KEYNOTE-412 study: Pembrolizumab (pembro) with chemoradiation therapy (CRT) vs placebo plus CRT for locally advanced (LA) head and neck squamous cell carcinoma (HNSCC). Abstract LBA5, ESMO Congress 2022, 09–13 September, Paris, France.

5-FU-free chemotherapy combination as an alternative for first-line treatment of recurrent or metastatic HNSCC

Pembrolizumab combined with 5-FU-free paclitaxel and carboplatin was effective and tolerable as a first-line treatment for patients with recurrent or metastatic head and neck squamous cell cancer (R/M HNSCC) and may be an alternative for standard 5-FU containing regimen, preliminary results from the phase 4 KEYNOTE B10 trial demonstrated.

Standard-of-care treatment for patients with R/M HNSCC is pembrolizumab combined with 5-FU and platinum chemotherapy [1]. However, alternatives to 5-FU are needed based on their toxicities, patient inconvenience and complications [2]. The phase 4 KEYNOTE B10 trial ([NCT04489888](#)) evaluated the efficacy and safety of pembrolizumab in combination with 5-FU-free carboplatin plus paclitaxel as first-line treatment for R/M HNSCC patients. Dr Marcin Dzienis (Gold Coast University Hospital, Australia) presented the first results of this ongoing study [3].

The KEYNOTE B10 trial enrolled all patients with previously untreated R/M HNSCC of the oral cavity, oropharynx, larynx, or hypopharynx. Participants were treated with pembrolizumab (200 mg every 3 weeks) for ≤ 35 cycles, paclitaxel (100 mg/m²

every week on days 1 and 8; or 175 mg/m² every 3 weeks on day 1) for 6 cycles, plus carboplatin (AUC 5 mg/mL/min every 3 weeks) for 6 cycles. The primary endpoint is the objective response rate (ORR). Results from the first 92 participants were presented.

After a median follow-up of 8.2 months, 51 participants had discontinued treatment: 31 due to disease progression, and 10 due to adverse events. ORR was 42.7% (4.9% complete responders). ORR was irrespective of age, sex, HPV status, and PD-L1 expression. The median time-to-response was 1.5 months and the median duration of response was 5.5 months.

Grade ≥ 3 treatment-related adverse events (AE) were observed in 70.7% of patients and serious treatment-related AEs in 17.4% of patients. The most common grade ≥ 3 treatment-related AEs were neutropenia, anaemia, and leukopenia.

Based on these (preliminary) results, Dr Dzienis concluded: “Efficacy and safety results of this trial suggest that this 5-FU-free combination may be an alternative to the current standard-of-care.”

1. Burtneß B, et al. *Lancet.* 2019;394(10212):1915–1928.
2. Guigay J, et al. *Front Oncol.* 2019;9:668.
3. Dzienis M, et al. Pembrolizumab (pembro) + carboplatin (carbo) + paclitaxel (pacli) as first-line (1L) therapy in recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): Phase VI KEYNOTE-B10 study. Abstract 6510, ESMO Congress 2022, 09–13 September, Paris, France.

Epstein Barr virus-specific autologous cytotoxic T lymphocytes do not improve survival in nasopharyngeal carcinoma

Results from the phase 3 VANCE trial showed that the addition of Epstein Barr virus-specific autologous cytotoxic T lymphocytes (EBV-CTL) to chemotherapy (gemcitabine plus carboplatin) in patients with recurrent but incurable and metastatic advanced nasopharyngeal carcinoma (R/M NPC) did not improve survival.

The first-line treatment for EBV-associated R/M NPC is gemcitabine plus carboplatin [1]. EBV-CTL is an autologous T-cell immunotherapy generated from patients' blood that has shown promising efficacy in combination with standard first-line chemotherapy in patients with R/M NPC [2].

The VANCE trial ([NCT02578641](#)) evaluated the efficacy and safety of gemcitabine plus carboplatin followed by EBV-CTL versus gemcitabine plus carboplatin alone. Dr Han Chong

Toh (National Cancer Centre, Singapore) presented the first results [3].

A total of 330 participants were enrolled in 5 countries worldwide (R/M NPC predominantly occurs in people with [South East] Asian ethnicity) and 1:1 randomised to receive 6 cycles of chemotherapy alone (1,000 mg/m² gemcitabine, AUC 2 carboplatin on days 1 and 8) or 4 cycles of chemotherapy followed by up to 6 cycles of EBV-CTL. The primary endpoint was overall survival (OS); secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and safety.

The median OS did not differ significantly between the 2 treatment arms: 25.0 months in the chemotherapy plus EBV-CTL

arm versus 24.9 months in the chemotherapy alone arm (HR 1.19; P=0.942). However, there was a trend towards improved OS in patients from USA, Taiwan, and Singapore. The addition of EBV-CTL to the standard chemotherapy regimen did not improve median PFS or ORR. The safety profile was identical in both treatment arms.

“EBV-CTL treatment is well tolerated, but does not improve survival in patients with R/M NPC,” concluded Dr Toh.

1. [Bossi P, et al. *Ann Oncol.* 2020;32\(4\):452–465.](#)
2. [Chia W-K, et al. *Mol Ther.* 2014;22\(1\):132–139.](#)
3. Toh HC, et al. Randomized phase III VANCE study: Gemcitabine and carboplatin (GC) followed by Epstein Barr virus-specific autologous cytotoxic T lymphocytes (EBV-CTL) versus the same chemotherapy as first-line treatment for advanced nasopharyngeal carcinoma (NPC). Abstract 6520, ESMO Congress 2022, 09–13 September, Paris, France.