

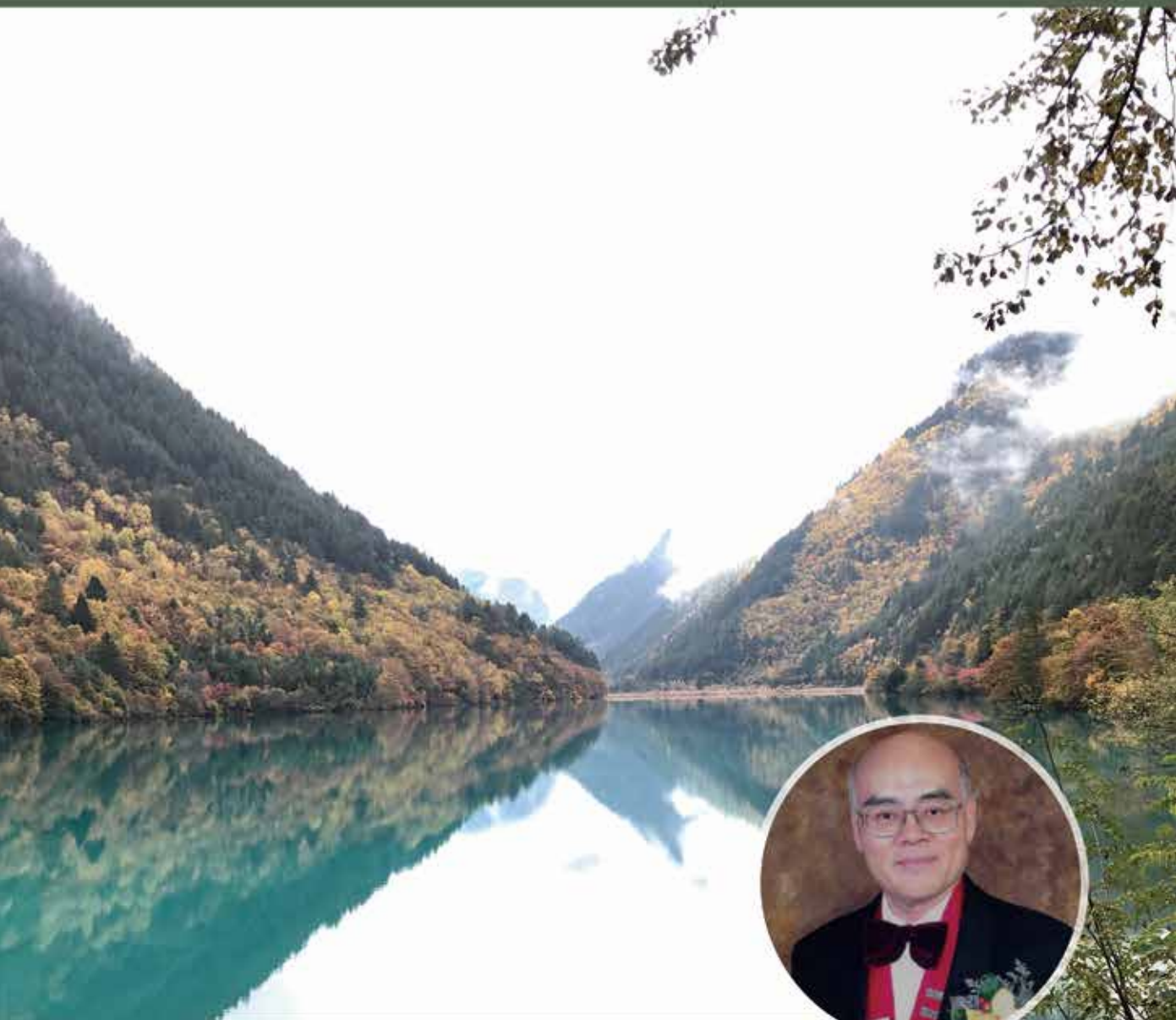


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Oncology



In Memoriam: Dr CHAN Chok-wan



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A Key to More Possibilities for Treating Your Women's Cancer Patients

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For detailed precautions and adverse events, please consult the full prescribing information.

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KEYTRUDA
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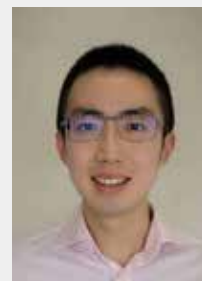
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The Cover Shot



This photo was taken at Mirror Lake, Jiuzhaigou, in the autumn of 2023. The pristine lake reflects images of the sky and surrounding mountains, drawing our eyes to the vanishing point. What lies beyond? One can find out only by venturing forward and changing perspectives, not by standing still. I find this to be an apt representation of the ever-evolving field of oncology.



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Editorial

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Dr Thomas YAU

Issue Editor

It is my pleasure to introduce this issue of The Hong Kong Medical Diary on Oncology, five years after the last issue. During this period, there have been numerous advancements in the field, with immuno-oncology continuing to play an important role in cancer management, as well as targeted therapy for oncogene addiction entering the therapy arena for some cancer types of which chemotherapy used to be the cornerstone of treatment.

Lung cancer remains the commonest cancer and the leading cause of cancer deaths worldwide. It accounts for more than one-fourth of all cancer deaths in Hong Kong. Fortunately, both molecular targeted drugs and immunotherapy can offer promising benefits in disease control and meaningful extension in survival depending on the molecular characterisation. In this issue, Dr Roland Leung, Dr Chan Hoi-wai, Dr Lam Yim-kwan and Dr Anthony Lam will highlight the recent advances in the use of targeted therapy for oncogene-driven metastatic non-small cell lung cancer (NSCLC), and the use of perioperative immunotherapy and targeted therapy for early-stage NSCLC.

In Hong Kong, colorectal cancer ranked second in both incidence and cancer deaths. Systemic chemotherapy has been the backbone therapy in the treatment of metastatic disease for decades. Targeted therapies, including anti-VEGF (vascular endothelial growth factor) agents and anti-EGFR (epidermal growth factor receptor) antibodies are routinely employed to enhance the treatment efficacy. Yet advances in the treatment of metastatic CRC were slow. In the past few years, the integration of molecular profiling and immunotherapy has opened new avenues for personalised treatment approaches. Dr Josephine Tsang will review the recent treatment advancements in colorectal cancer.

Pancreatic ductal adenocarcinoma, or (exocrine) pancreatic cancer, remains one of the most lethal cancers, with annual incidence being almost equal to mortality. Until very recently, only cytotoxic chemotherapy was shown to be effective. Dr Jenny Lo and Dr Gerry Kwok will give an account of the current and upcoming therapeutic landscape of metastatic pancreatic cancer.

Patients with advanced urothelial cancer have a dismal prognosis. In general, urothelial cancer is chemo-sensitive, but chemotherapies are associated with significant toxicity and only provide a modest improvement in survival. In recent years, immunotherapy and precision medicine have been widely used in advanced urothelial cancer. Dr Karen Li and Dr Bryan Li will discuss the progress in the systemic management of this once deadly disease, which is transformed forever with the development of novel therapies.

Dr Jeffrey Wong will review systemic treatment for advanced biliary tract cancer, which is a heterogeneous entity comprising gallbladder cancer, intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma, and with divergent etiologies and cancer biology. The author will discuss the available upfront and subsequent treatments, with a particular focus on recent advances.

Finally, I would like to express my gratitude to all the contributing authors for their effort and support. It happens that November is Lung Cancer Awareness Month as well as Pancreatic Cancer Awareness Month. I hope this issue of the Hong Kong Medical Diary will provide good insights and useful information to readers, not only on lung cancer and pancreatic cancer but also on other cancers.



Systemic Treatment for Advanced Biliary Tract Cancer-light at the End of the Duct?

Dr Jeffrey SL WONG

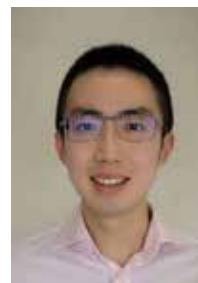
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INTRODUCTION

Biliary tract cancer (BTC) is a heterogeneous entity which encompasses gallbladder cancer (GBC) and cholangiocarcinoma (CCA), with CCA being further divided into intrahepatic (IHCCA) or extrahepatic (EHCCA) types. BTC is endemic in China, where the incidence is up to 40 times higher than in the rest of the world (up to 4 - 6 cases per 100,000)¹. Unfortunately, the majority of patients are inoperable at presentation. Furthermore, advanced BTC generally has an aggressive disease course with a distal prognosis in historical series¹. However, recent breakthroughs in the understanding of disease biology, immuno-oncology and molecular-directed therapy have greatly improved survival for a proportion of advanced BTC patients. Here, we review the landscape of systemic treatment for advanced BTC, with a particular focus on recent advances.

GENETIC LANDSCAPE AND MOLECULAR FEATURES

The heterogeneity of BTCs is reflected in their divergent causes and molecular features. GBCs are mainly attributable to chronic irritation of the gallbladder due to gallstone disease, primary sclerositis cholangitis (PSC), or anatomical variations in the pancreaticobiliary duct junction, causing reflux of pancreatic juice into the biliary tree¹. CCAs are associated with hepatitis B or C infections and PSC. In addition and particularly notable locally, parasitic infections by liver flukes such as *Clonorchis sinensis*, which are acquired through ingestion of undercooked freshwater fish, are strong risk factors for CCA(1). Several recurrent targetable mutations have been identified, albeit at varying frequencies for different subtypes. HER2 amplification/overexpression is found in all types of BTCs, but occurs much more commonly in GBC (19 - 31 %) and EHCCA (17 - 29 %) compared to IHCCA (4 - 5 %)². Fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement occurs almost exclusively in IHCCA (in around ~ 15 % of IHCCA)³, and causes perturbations in MAPK-ERK, PI3K-AKT and JAK-STAT pathways, leading to aberrant cell proliferation, survival, invasion and angiogenesis⁴. Also related to the MAPK-ERK pathway are BRAF mutations, which are found in 5 - 7 % of BTCs and portend higher staging as well as worse survival⁵. Isocitrate dehydrogenase 1/2 (IDH1/IDH2) mutations occur in ~ 25 % of IHCCA, and are oncogenic

through suppressing liver progenitors cells from undergoing hepatocyte differentiation and hepatocyte quiescence⁶. Finally, NTRK fusions are uncommonly found (< 1 %) but are nevertheless important drivers as they are highly targetable⁷. Overall, a significant portion of BTCs harbours actionable mutations. Thus, next-generation sequencing is crucial in all patients to ensure the matching of optimal treatment.

No less importantly, some BTCs have been found to be immunogenic. These include both a subset of tumours which is hypermutated, such as those associated with microsatellite-instability or deficient mismatch repair (MSI-H/dMMR); as well as tumours which express immune checkpoints such as PD-L1 or infiltrated by CD8+ cytotoxic T-cells^{8,9}. These findings form the basis of immune-oncological approaches towards BTCs.

CLINICAL DATA

First-line Treatment

The backbone of first-line treatment is chemotherapy. Its role was first established in the 1990s when 5-fluorouracil(5FU) with etoposide was shown to improve overall survival (OS) and quality of life compared to best supportive care (BSC)¹⁰. In the subsequent decade, a series of small phase II trials demonstrated clinical activities for fluoropyrimidines, gemcitabine and platinum-based agents, with the best responses found in gemcitabine and platinum containing regimens¹¹. The contemporary standard was established by the ABC-02 trial, in which gemcitabine plus cisplatin (Gem-Cis) was compared to gemcitabine only and demonstrated significantly superior OS (median OS 11.7 vs 8.1 months, hazard ratio (HR) 0.64, $p < 0.001$) and progression-free survival (PFS) (median PFS 8.0 vs 5.0 months, $p < 0.001$) with similar adverse events¹². Other regimens, such as gemcitabine or fluoropyrimidines plus oxaliplatin and gemcitabine plus capecitabine or nab-paclitaxel, have also demonstrated clinical activities and are reasonable alternatives in patients unfit for Gem-Cis¹³⁻¹⁶. Combining Gem-Cis and nab-paclitaxel was initially shown to be numerically superior to historical control with Gem-Cis alone in a single arm phase 2 trial¹⁷. However, in the subsequent SWOG S1815 phase 3 trial comparing the two regimens, there was no significant improvement in median OS (14 vs 12.7 months, $p = 0.58$) or median PFS (8.2 vs 6.4 months, $p = 0.47$) for triplet vs Gem-Cis¹⁸.



The most exciting advance in first-line treatment is the incorporation of immune checkpoint inhibitors (ICIs). As mentioned above, a subset of BTCs are immunogenic. Furthermore, chemotherapy synergises with ICIs by inducing tumour cell death and neoantigen release, and by modulating the tumour microenvironment through depleting immunosuppressive cells. The phase 3 TOPAZ-1 trial evaluated durvalumab compared to placebo in combination with Gem-Cis, and showed significantly improved OS (median OS 12.8 vs 11.5 months, HR 0.8, $p = 0.021$) and PFS (median PFS 7.2 months vs 5.7 months, HR 0.75, $p = 0.001$), as well as better landmark survival (24.9 % vs 10.4 % at 24 months) and a numerically higher objective response rate (ORR) (26.7 vs 18.7 %)(19). Safety was comparable, with 75.7 and 77.8 % of patients experiencing grade 3 - 4 adverse events, respectively. Subsequently, pembrolizumab also showed significant improvement in OS (median OS 12.7 vs 10.9 months, HR 0.83, $p = 0.0034$) but not PFS (6.5 vs 5.6 months, HR 0.86, not reaching pre-specified statistical significance) or ORR (29 vs 29 %) in the phase 3 KEYNOTE-966 trial²⁰. In these 2 trial, PD-L1 positivity (> 1 %) was demonstrated in around 58 - 68 % of patients^{19, 20}. However, patients benefitted from ICI regardless of PD-L1 positivity, suggesting that there is no need to select patients based on PD-L1 status. Accordingly, ICI + Gem-Cis represents the new standard-of-care for all first-line BTC patients. Currently, durvalumab has been approved by the Food and Drug Administration, while the indication for pembrolizumab is under review.

Two important exceptions to the ICI-chemotherapy paradigm exist. Firstly, patients who are MSI-H/dMMR tend to respond well to ICIs alone, with a significant portion attaining long-term response. In the KEYNOTE-158 trial, pembrolizumab demonstrated an overall ORR of 34 % and median OS of 23.5 months for patients with MSI-H/dMMR non-colorectal tumours progressing on other therapies²¹. In the 22 patients with CCA, the ORR was 40.9 %, the median DOR was not reached and the median OS was 24.3 months. Given its efficacy, pembrolizumab alone can be used upfront for MSI-H/dMMR advanced BTC. Secondly, for patients with NTRK fusions, the two licensed NTRK inhibitors, lanrotectinib and entrectinib, each showed activities towards cholangiocarcinoma in their registration trials^{22, 23}. As their indications for NTRK-fusion tumours are tumour-type agnostic, either can be used in the first-line for NTRK-fusion BTCs.

Second-line or Beyond

For patients who progressed on gemcitabine-based therapy and have no targetable mutations, treatment options remain limited and prognosis is unfortunately guarded. The ABC-06 trial established 5-FU-oxaliplatin (FOLFOX) as the standard treatment for patients who progressed on Gem-Cis by showing the superiority of the regimen over BSC²⁴. However, the median OS was only 6.2 months (vs 5.3 months in BSC arm, HR 0.59, $p = 0.031$) and ORR was 5 %. Nivolumab demonstrated some activity in a single-arm phase 2 trial, with an ORR of 11 % and a median OS of 14 months²⁵. Other regimens, such as liposomal irinotecan plus 5-FU²⁶, as well as agents not used in the first-line, may also be considered.

For patients with targetable mutations, the clinical approach in gemcitabine-treated disease is instead driven by biomarker-selected treatment, which outcomes are numerically superior to historical controls achieved by chemotherapy alone.

Strategies to target HER2 amplification/overexpression across different tumour types have increasingly been diversified, and this holds true for BTCs as well. In patients with pretreated BTC and HER2 amplification/overexpression, dual blockade by pertuzumab and trastuzumab (PH), antibody drug conjugates such as trastuzumab deruxtecan (T-DXd), small molecular inhibitors such as tucatinib and bispecific antibodies such as zanidatamab have all been evaluated in phase 2 studies. In the BTC cohort of the MyPathway basket study, PH demonstrated an ORR of 23 %, median PFS of 4.0 months and median OS of 10.9 months²⁷. T-DXd was evaluated in the HERB trial and showed an ORR of 36.4 %, median PFS of 4.4 months and median OS of 7.1 months²⁸. Tucatinib combined with trastuzumab was evaluated in the SGNTUC-019 study, in which ORR was 46.7 %, median PFS was 5.5 months and median OS was 15.5 months²⁹. Last but not least, zanidatamab, a bispecific antibody which novelly binds to two different HER2 domains (dimerisation and extracellular juxtamembrane domains), demonstrated an ORR of 41.3 %, median PFS of 5.5 months and overall survival at nine months of 69.9 % in the HERIZON-BTC-01 study³⁰.

For patients with IDH1 mutations, the IDH1 inhibitor ivosidenib has been approved. In the phase 3 ClarIDHy trial, ivosidenib was compared to placebo in patients with IDH1-mutant BTC progressing on two or more lines of treatment^{31, 32}. In the experimental arm, both the PFS (median PFS 2.7 vs 1.4 months, HR 0.37, $p < 0.0001$) and OS (median OS 10.3 vs 5.1 months, HR 0.49, $P < 0.001$, when adjusted for crossover) were significantly improved. Treatment-related adverse events mainly consisted of gastrointestinal disturbance and fatigue, and was rarely serious.

Recently, multiple agents for FGFR fusion or rearrangement disease have been debuted. Three FGFR inhibitors, futibatinib, pemigatinib and infigratinib, have been shown to be active in IHCCA pretreated with at least 1 line of therapy. In the single-arm, phase 2 FOENIX-CCA2 trial, futibatinib achieved an ORR of 42 % with a median duration of response (DOR) of 9.7 months, a median PFS of 9.0 months and median OS of 21.7 months³³. Meanwhile, in the FIGHT-202 trial, pemigatinib showed an ORR of 35.5 %, median DOR of 7.5 months, median PFS of 6.9 months and median OS of 21.1 months³⁴. Lastly, infigratinib demonstrated an ORR of 23.1 %, median DOR of 5.0 months, median PFS of 7.3 months and median OS of 12.2 months³⁵. Side effects mainly consisted of hyperphosphatemia, an on-target toxicity as renal phosphate transport is mediated by FGFR, as well as dermatological and gastrointestinal disturbances, most of which are grade 1 - 2.

Finally, patients with BRAF V600E mutations may be treated with combined BRAF and MEK blockade. In the BTC cohort of the ROAR basket trial, patients with pretreated BRAF V600E mutant disease were given dabrafenib and trametinib³⁶. The ORR was 51 %, the



median PFS was nine months, and the median OS was 14 months.

CONCLUSIONS

Large strides have been made towards characterising and improving the treatment of advanced BTCs. Despite these developments, the majority of patients do not respond to available treatments and prognosis, in general, remains poor. Further breakthroughs in discovering novel targets, augmenting anti-tumour immunity and enhancing treatment potency are desperately needed and eagerly awaited.

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Treatment of Non-small-cell Lung Carcinoma - Are We Reaching the Crossroads?

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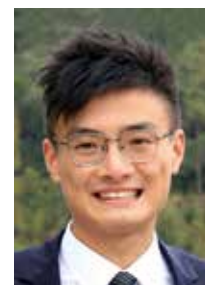
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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 December 2023.

Lung cancer is the most common cancer and the leading cause of cancer deaths worldwide¹. In 2020, there were 5,422 new cases of lung cancer and a total of 4,037 lung cancer patient deaths in Hong Kong, accounting for 26.7 % of all cancer deaths².

Non-small-cell lung cancer (NSCLC) constitutes more than 80 % of all lung cancers and comprises two major histological subtypes: squamous cell carcinoma and adenocarcinoma.

The treatment of NSCLC has become the paradigm of precision medicine with the use of tyrosine kinase inhibitors (TKIs). The advent of immune-checkpoint inhibitors (ICIs) harnessing the immune system to eliminate tumour cells has provided yet another successful treatment strategy by targeting the PD-L1-PD-1 axis or in combination with anti-CTLA4 to 'release the brake' on the T-cell mediated anti-tumour immune response^{3,4}.

In this review, we would like to highlight the recent advances in the use of targeted therapy for oncogene driven metastatic NSCLC and the use of perioperative immunotherapy and targeted therapy for resectable NSCLC.

TARGETED THERAPY FOR ONCOGENE-ADDICTED METASTATIC NSCLC

Most patients with NSCLC present late with metastatic and incurable disease. Treatment with systemic therapy is of palliative intent and aims to prolong survival and improve the quality of life.

Molecular characterisation of tumours has refined the classification and treatment of NSCLC and is now a key to decision-making in initiating therapy. Use of a targeted therapy is now often the preferred option up front in the presence of an activating driver mutation. The rationale is a superior tumour response rate to chemotherapy and significantly less toxicity. Mutated driver oncogenes typically encode receptors and kinases. When mutated, they constitutively activate signalling pathways that promote cancer cell survival and proliferation. These pathways also influence the

local tumour microenvironment and systemic immune landscape, which in turn contribute to tumour evasion of immunosurveillance.

The prototypical activation mutation of EGFR is observed in up to 62 % of lung adenocarcinoma in Asian populations (Fig. 1) and 15 per cent worldwide⁵⁻⁷. EGFR exon 19 in-frame deletions and the L858R point mutation in exon 21 account for up to 90 % of EGFR mutations detected in NSCLC⁸. These mutations are biomarkers for the effectiveness of EGFR TKIs. The use of specific TKIs targeting this mutation has revolutionised the landscape of the treatment of metastatic NSCLC. It was the first example of a targeted therapy that resulted in better outcomes than standard platinum-based chemotherapy in NSCLC in terms of response rate, duration of response and overall survival⁹⁻¹⁷.

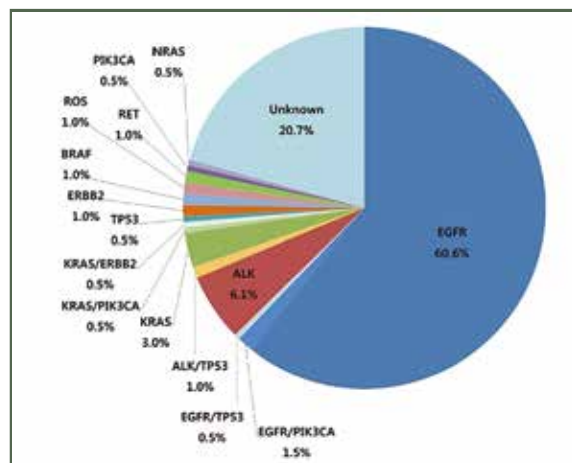


Fig. 1: Frequency of driver gene mutations in lung adenocarcinomas from East Asian never-smoker females. (Ha et al. 2015)⁷

Among the available TKIs, namely osimertinib, erlotinib, gefitinib, afatinib and dacomitinib, the third-generation TKI osimertinib, in particular, has demonstrated superior therapeutic effect and is now the recommended first-line treatment. It was compared with the first-generation TKIs in the randomised FLAURA trial published in 2018¹⁸. Osimertinib had a superior progression free survival (PFS) of 18.9

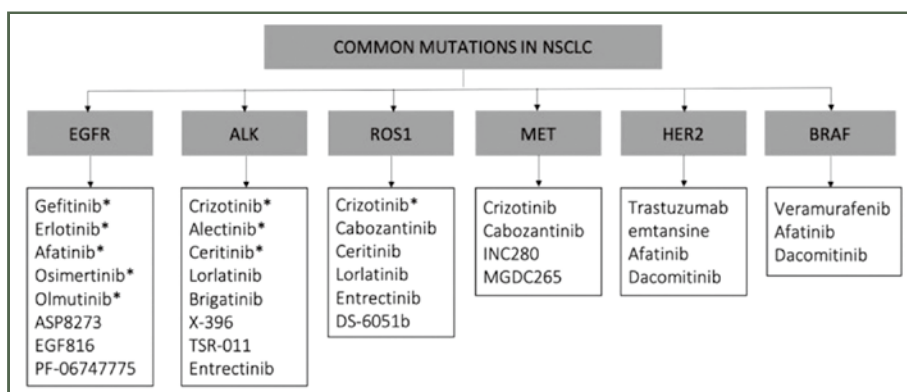


Fig. 2: Available molecular targeted drugs for NSCLC. * FDA-approved drugs for NSCLC. (García-Fernández et al. 2020)²⁵

months compared with 10.2 months in the control arm (hazard ratio (HR) 0.46). Duration of response was greater with osimertinib (17.2 versus 8.5 months). With longer follow-up, a survival advantage was seen with osimertinib (HR 0.80), where the median survival was 38.6 months compared with 31.8 months with erlotinib or gefitinib¹⁹.

Following the breakthrough in targeting the EGFR mutation, ALK fusion, ROS1 fusion, MET exon 14 skipings, RET fusion, BRAF, NTRK1-3, HER2 kinase domain mutations, and even the long deemed undruggable KRAS mutations, have all become therapeutically actionable (Fig. 2). Gene fusions involving ALK and ROS1 are associated with sensitivity to ALK/ROS1 TKIs. Crizotinib, ceritinib, alectinib, brigatinib and lorlatinib are all approved in various lines of treatment in preference to chemotherapy for tumours harbouring ALK/ROS1 fusions²⁰⁻²⁴.

There is currently research investigating the other driver mutations and their respective inhibitors for metastatic NSCLC against the traditional chemotherapy.

KRAS mutation is a common mutation in NSCLC but was known to be difficult to be targeted. But KRAS G12C is now. G12C KRAS mutation is now a clinically actionable target following the FDA approval of sotorasib for patients with previously treated advanced-stage NSCLC in 2021, although this agent has a modest overall response rate of 37% only²⁶. In the phase 2 KRYSTAL-1 registration trial, another KRAS G12C inhibitor, adagrasib, showed an ORR of 43 % and a median PFS of 6.5 months^{27, 28}. Novel agents are under investigation for G12C KRAS-mutant solid tumours. A phase I study in 137 patients with advanced KRAS-mutant cancers published in August 2023 showed that among the 60 patients with NSCLC, the ORR to the KRAS G12C inhibitor divarasib was 53 per cent and the median PFS was 13.1 months²⁹.

Meanwhile, squamous cell carcinoma is driven by the loss of tumour suppressor genes, such as TP53, PTEN or LKB1, which precludes the use of targeted therapies³⁰. Potentially actionable activating mutations in the FGFR, PI3K or EGFR signalling pathways exist, but the efficacy of targeted therapies has not yet been proven³¹. A clinical trial of the pan-FGFR TKI erdafitinib preliminarily suggests promising activity against several

FGFR-altered tumour types, including both squamous and non-squamous subtypes of NSCLC, with ORRs of 27 % and 14 %, respectively³².

THE TRANSFORMATIVE POWER OF ICI IN NSCLC

The other groundbreaking development in the treatment of NSCLC has been the combination of chemotherapy with ICIs. During the initial wave of studies, the patients were recruited based on the absence of driver mutations in EGFR, ALK and ROS-1 fusions since these have effective first line therapy with TKIs. The studies include anti-PD1 antibody (pembrolizumab), anti-PDL1 antibody (atezolizumab) and a combination of anti-CTLA-4 and anti-PDL1 antibody (ipilimumab and nivolumab)³³⁻³⁵. All the studies showed encouraging enhancement in doubling the response rate, a significant increase in duration of disease control, and most importantly, extended overall survival in the first line setting in both squamous cell carcinoma and adenocarcinoma. This has transformed the upfront treatment of NSCLC in the first line setting.

The more difficult question remains - what is the optimal frontline treatment for those rarer driver mutations? Should they be treated with chemotherapy with ICI or should they be given their corresponding specific inhibitors? Due to the low prevalence, this question may remain unanswered in the foreseeable future.

REVOLUTION IN THE PERIOPERATIVE THERAPY FOR RESECTABLE NSCLC

Although most lung cancers present late at an advanced stage, there are still 30 % of patients who are diagnosed early with stage I to III disease³⁶. Curative surgery is still the aim of these patients. However after complete surgical resection, these patients are still at substantial risk for recurrence and death at up to 50 percent after five years from surgery³⁷. The use of adjuvant chemotherapy aims to reduce the risk of recurrence of death. The role of adjuvant chemotherapy for completely resected stage IB and IIIA NSCLC with a cisplatin-based regimen was demonstrated in the LACE meta-analysis, but it confers only a modest 5-year



overall survival benefit of 5 % over surgery alone³⁸. Over the last three years, significant progress has been made in the application of preoperative and adjuvant (chemo)immunotherapy in lung cancer. In the adjuvant setting, both atezolizumab and pembrolizumab are approved as adjuvant treatment following resection and platinum-based chemotherapy for patients with stage II to III NSCLC, based on the phase III IMpower010 and PEARLS/KEYNOTE-091 trials.

On the other hand, the application of neoadjuvant immunotherapy has already been proven successful in patients with numerous solid tumour types, and the feasibility of such in NSCLC has been confirmed in four randomised phase III clinical trials: CheckMate 816, AEGEAN, Neotorch and KEYNOTE-671. This is also supported by the great advances ICIs have delivered in the metastatic setting.

In Checkmate 816, patients with stage IB to IIIA resectable NSCLC and no known EGFR/ALK genetic mutation were subjected to chemotherapy with or without nivolumab. The addition of Nivolumab to standard chemotherapy improved pathologic complete response (pCR) rates (24.0 % versus 2.2 %; HR 13.9, 99 % CI 3.5 - 55.8) and median event free survival (EFS) durations (31.6 months versus 20.8 months, HR 0.63; 97.38 % CI 0.43 - 0.91), without decreasing the percentage who underwent definitive surgery (83 % versus 75 %) or increasing grade ≥ 3 adverse events (34 % versus 37 %)³⁹. In an updated report, the 3-year EFS was 57 % versus 43 % in the neoadjuvant nivolumab plus chemotherapy and chemotherapy arms, respectively, with an immature 3-year OS of 78 % versus 64 %⁴⁰.

In KEYNOTE-671, 797 patients with stage II–IIIB NSCLC received four cycles of cisplatin-based chemotherapy in combination with pembrolizumab 200 mg every three weeks for four cycles or placebo, followed by surgery and pembrolizumab or placebo for a maximum of 13 cycles⁴¹. Those who received pembrolizumab achieved significantly longer event free survival versus placebo (not reached (NR) versus 17.0 months; HR 0.58, 95 % confidence interval (CI) 0.46 - 0.72), regardless of histology, PD-L1 expression or stage of disease. Interim results showed a trend toward improved OS with this treatment regimen at a median follow-up of 25.2 months (HR 0.73, 95 % CI 0.54 - 0.99), although the significance boundary was not met at this time point. This study provides additional supportive evidence regarding the benefit of checkpoint inhibition in resectable NSCLC.

For those patients who have locally advanced disease who received definitive chemoradiotherapy when surgery is not deemed to be feasible, the addition of 1 year of maintenance durvalumab is associated with EFS and OS benefit, as shown in the phase 3 PACIFIC study^{42,43}.

Taken together, with the emergence of fundamental clinical benefits of using ICI in treating metastatic NSCLC, time is ripe to transform how resectable NSCLC can be treated. The markedly improved response rate and improvement in disease free survival with perioperative ICI and chemotherapy argue this is the new standard of care. Obviously to deliver this

improvement, the multi-disciplinary approach for assessment and patient management must be adopted to select the best approach for individual patients.

Lastly, there is also a breakthrough in oncogene driven tumours in the adjuvant setting. The randomised phase III ADAURA trial randomly assigned patients with completely resected stage IB, II, or III NSCLC harbouring a sensitising mutation in EGFR to 3 years of the third-generation EGFR TKI osimertinib versus placebo⁴⁴. Of 682 patients who underwent randomisation, 339 received osimertinib and 343 received a placebo. Among patients with stage II to IIIA disease, the 5-year overall survival was 85 % in the osimertinib group and 73 % in the placebo group (HR 0.49; 95.03 % CI, 0.33 - 0.73; $P < 0.001$). In the overall population (patients with stage IB to IIIA disease), the 5-year overall survival was 88 % in the osimertinib group and 78 % in the placebo group (HR 0.49; 95.03 % CI, 0.34 - 0.70; $P < 0.001$).

SUMMARY

Since the last Hong Kong Medical Diary on Oncology published five years ago in 2018, there have been numerous advances in the field of lung cancer, among other cancer types. With that, we are looking forward to further improving the outcome of patients with NSCLC, whether they present early or late or advanced stage disease.

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Radiology Quiz



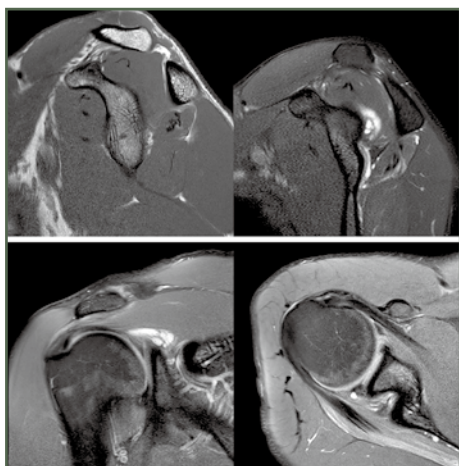
Radiology Quiz

Dr Thomas WL YIP

MBChB, FRCR



Dr Thomas WL YIP



A 24-year-old volleyball player complained of progressive shoulder weakness.

Questions

1. Which muscle is atrophied?
2. Can you spot the pathology that is responsible for said muscle atrophy?

(See P.36 for answers)

ATTR-CM, a life-threatening and progressive disease that is widely and frequently underdiagnosed^{1,2}

25% of adults aged 80 years or older were found to have significant myocardial TTR amyloid deposition at autopsy²

What is ATTR-CM?²

- A type of cardiac amyloidosis
- Can occur as either wild type or hereditary type
- Progressive and life-threatening
- When the protein transthyretin misfolds, fibril deposits build up in the heart causing ATTR-CM

Please click the link below or scan the QR code to learn more about ATTR-CM and how you can save the lives of potential ATTR-CM patients
www.vyndamax.com.hk



The following warrant your immediate attention²⁻⁴:

Red Flags

Cardiac:



HFpEF²



HF therapy intolerance³

³The standard therapies for HF, including ACEI, ARB, and BB³



LVH on Echo²



Imaging and ECG discrepancy^{**2}

^{**}Imaging finding of LVH and normal/low QRS voltage on ECG²

Non-cardiac:



Orthopaedic syndromes

(e.g. carpal tunnel syndrome, lumbar spinal stenosis and bicep tendon rupture)²



Polyneuropathy²



Family history of TTR amyloidosis⁴

Abbreviations: ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin-receptor blockers; ATTR-CM: Transthyretin amyloid cardiomyopathy; BB: Beta blockers; ECG: Electrocardiogram; Echo: Echocardiography; HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; LVH: Left ventricular hypertrophy; TTR: Transthyretin
References: 1. Rapezzi C et al. *Nat Rev Cardiol.* 2010;7(7):398-408. 2. Witteles RM et al. *JACC Heart Fail.* 2019;7(8):709-16. 3. Castano A et al. *Heart Fail Rev.* 2015;20(2):163-78. 4. Kittleson MM. *Circulation.* 2020;142(1):e7-e22.

VYNDAMAX ABBREVIATED PRESCRIBING INFORMATION

1. TRADE NAME: Vyndamax™ capsules (Tafamidis 61 mg) **2. PRESENTATION:** 61mg soft capsules **3. INDICATIONS:** Vyndamax is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM). **4. DOSAGE:** The recommended dose is one capsule of Vyndamax 61 mg (tafamidis) orally once daily. **5. CONTRAINDICATIONS:** Hypersensitivity to the active substances or to any of the excipients of the drug (Please refer to the full prescribing information for details). **6. WARNINGS & PRECAUTIONS:** Women of childbearing potential should use appropriate contraception when taking tafamidis and continue to use appropriate contraception for 1-month after stopping treatment with tafamidis. Tafamidis should be added to the standard of care for the treatment of patients with transthyretin amyloidosis. Physicians should monitor patients and continue to assess the need for other therapy, including the need for organ transplantation, as part of this standard of care. Tafamidis should be discontinued in patients who undergo organ transplantation. **7. INTERACTIONS:** Substrates of efflux transporter BCRP (breast cancer resistant protein; e.g., methotrexate, rosuvastatin, imatinib); substrates of uptake transporters OAT1 and OAT3 (organic anion transporters; e.g., non-steroidal anti-inflammatory drugs, bumetanide, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, ganciclovir, adefovir, cidofovir, zidovudine, zalcitabine). **8. PREGNANCY AND LACTATION:** Tafamidis is not recommended during pregnancy and in women of childbearing potential not using contraception. Tafamidis should not be used during breast-feeding. **9. SIDE EFFECTS:** Flatulence and liver function test increased. A causal relationship has not been established. Reference: Prescribing Information HK PI (Version Jul 2020) Date of preparation: Nov 2020 Identifier number: VYNX1120 **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**



MCHK CME Programme Self-assessment Questions

Please read the article entitled "Treatment of Non-small-cell Lung Carcinoma - Are We Reaching the Crossroads?" by Dr Roland CY LEUNG and Dr Alvin HW CHAN and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 December 2023. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary. (Address: Duke of Windsor Social Service Bldg., 4/Fl., 15 Hennessy Rd., Wan Chai. Enquiry: 2527 8898)

Questions 1-10: Please answer T (true) or F (false)

1. Most patients with NSCLC present late at an advanced stage.
2. The most common activating mutation of EGFR in NSCLC is exon 20 insertion.
3. Crizotinib, ceritinib, alectinib, brigatinib and lorlatinib are all approved in various lines of treatment in preference to chemotherapy for NSCLC harbouring ALK/ROS1 fusions.
4. The third-generation TKI osimertinib was compared with first-generation TKIs in the randomised phase III FLAURA2 trial.
5. KRAS G12C mutation is now druggable.
6. Divarasil targets the HER2 kinase domain mutation.
7. Patients with stage I to III NSCLC have approximately a 50 per cent chance of recurrence and death five years after complete surgical resection of curative intent.
8. Atezolizumab and pembrolizumab are approved as adjuvant treatment following resection and platinum-based chemotherapy for patients with stage II to III NSCLC.
9. The efficacy of nivolumab in the neoadjuvant setting for stage IB to IIIA resectable NSCLC was demonstrated in the randomised phase III KEYNOTE-671 trial.
10. The efficacy of osimertinib in the adjuvant setting for completely resected stage IB, II, or III NSCLC harbouring a sensitising mutation in EGFR was demonstrated in the randomised phase III ADAURA trial.

ANSWER SHEET FOR DECEMBER 2023

Please return the completed answer sheet to the Federation Secretariat on or before 31 December 2023 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Treatment of Non-small-cell Lung Carcinoma - Are We Reaching the Crossroads?

Dr Roland CY LEUNG

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Resident, Department of Medicine, Queen Mary Hospital

1 2 3 4 5 6 7 8 9 10

Name (block letters): _____ HKMA No.: _____ CDSHK No.: _____

HKID No.: ____ - ____ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.: _____ MCHK No. / DCHK No.: _____ (must fill in)

Answers to November 2023 Issue

Recent Advances in Lipid Therapy

1. T 2. T 3. T 4. F 5. T 6. T 7. F 8. F 9. F 10. T

7356-HK-2300022 6/10/2023



Targeted Therapy for a Less Common Epidermal Growth Factor Receptor Mutation in Non-small Cell Lung Cancer: Focus on Exon 20 Insertions

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Dr Anthony CY LAM

According to the Hong Kong Cancer Registry, lung cancer is ranked first among males and third among females in terms of disease incidence among different types of malignancies¹. Up to 81 % of lung cancers diagnosed in Hong Kong in 2020 belonged to the non-small cell lung cancer (NSCLC)¹. In particular, adenocarcinoma comprises nearly half of lung cancer around the world and in Hong Kong¹⁻³.

Normally, cell survival and proliferation are sustained by the presence of functional signalling proteins. However, mutations in the genes encoding for these signalling proteins will cause uncontrolled activation of cellular growth, leading to cancer formation. These are known as driver mutations⁴. The detection of these mutations may be performed through analysis of the tumour cells, body fluid or plasma samples. Testing can be performed by polymerase chain reaction (PCR) or next generation sequencing (NGS) in the laboratory setting.

Among the various genetic alterations identified, relatively more prevalent mutations had been identified, namely those affecting the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1), and proto-oncogenes such as B-Raf, MET and RET⁵. Data from our locality in 2020 regarding genetic mutations for NSCLC had demonstrated EGFR, ALK, and ROS1 mutations in 44.8 %, 4 % and 2.8 % of cases, respectively¹.

According to retrospective studies, up to 80 - 85 % of EGFR mutations in NSCLC belonged to L858R substitution or exon 19 deletion⁶⁻⁸. In the meantime, exon 20 insertion is the third most often encountered mutation, with a proportion ranging around 4 - 12 % among EGFR mutation positive NSCLC⁶⁻⁸. They are associated with a worse prognosis than other types of EGFR-mutant NSCLC^{9, 10}. Fig. 1 illustrates the breakdown of EGFR mutations in a pie chart⁶.

EGFR exon 20 insertions have represented an unmet need in managing genomically altered NSCLC^{9, 10}. The scope of this article will cover the clinical significance and implications of EGFR exon 20 insertions among patients with metastatic NSCLC.

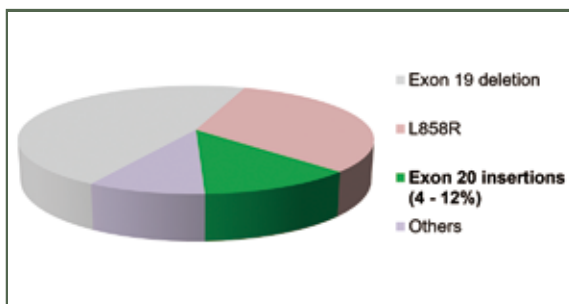


Fig. 1: Breakdown of the epidermal growth factor receptor (EGFR) mutations identified in non-small cell lung cancer (adapted from Riess JW, Gandar DR, Frampton GM, Madison R, Peled N, Bufill JA, et al. Diverse EGFR Exon 20 Insertions and Co-Occurring Molecular Alterations Identified by Comprehensive Genomic Profiling of NSCLC)

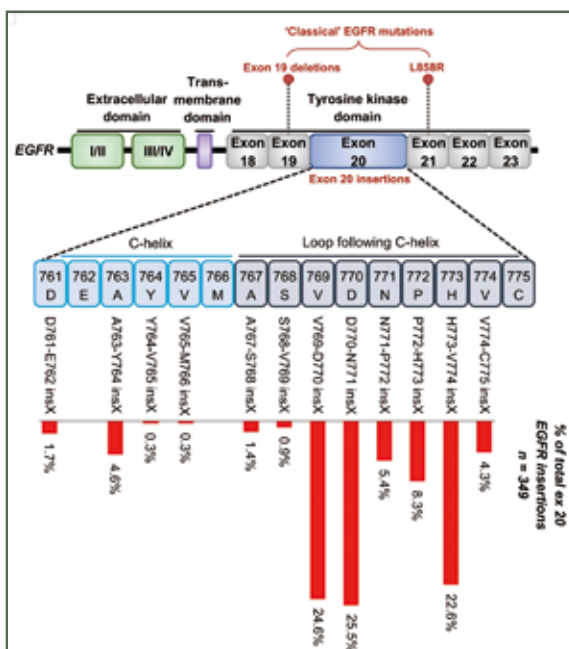


Fig. 2: Structure of EGFR exon 20 and its insertion mutations (Excerpted from Vyse S, Huang PH. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. Signal Transduct Target Ther. 2019;4:5.)



SPECTRUM OF EGFR EXON 20 INSERTIONS

Exon 20 insertions are not just one mutation. They are a range of mutations that happen in a span of exon 20 known as the C-helix and the loop following the C-helix as illustrated in Fig. 2¹⁰. There are at least 20 or 30 different exon 20 insertions. There are a few commoner ones in positions 769, 770 and 773.

Exon 20 insertions are not equal in terms of drug resistance. The insertions on the C-helix side, especially the A763 Y764 type, remain sensitive to some first-generation EGFR inhibitors such as gefitinib, erlotinib, or even afatinib. On the contrary, insertions in the loop following the C-helix are predominantly resistant to prior generations of EGFR inhibitors.

DETECTING AND TARGETING EGFR INSERTIONS

It is important to identify these driver mutations because of the effective therapies that have been developed. NGS was recommended to ensure that the different variants of EGFR exon 20 insertion mutations are detected when performing biomarker testing in NSCLC.

PCR-based assays can detect the most common types of EGFR mutations, but they often miss the less common mutations, such as EGFR exon 20 insertion mutations, as well as different variants of those mutations. NGS is the preferred testing approach, as recent research has shown that a wide variety of unique variants of EGFR exon 20 insertion mutations can be identified via NGS, while PCR methods are projected to miss approximately 50 % of those variants^{11, 12}. By sequencing, one can detect all of these different mutations and not miss any one of them, which is therapeutically important.

CHEMOTHERAPY AS FIRST LINE TREATMENT

Targeted therapies are drugs that specifically inhibit the activity of the signalling proteins that are pertinent to cancer growth. It is of note that activation of these proteins may be caused by different mutations within the same genome. For instance, the commonest EGFR mutations encountered are L858R substitution in exon 21, and deletion in exon 19, for which targeted therapy with tyrosine kinase inhibitors (TKIs) is available with established effectiveness in prolonging survival. First generation TKIs include gefitinib and erlotinib, while second generation TKIs include afatinib and dacomitinib^{13 - 16}.

There have been multiple trials in search of effective treatment for exon 20 insertion positive advanced NSCLC^{10, 17}. However, a limited response rate was observed among different generations of TKIs when prescribed to this group of patients. It has been shown that there was only a 27 % response rate with progression free survival (PFS) of three months for first generation TKI erlotinib¹⁸. Afatinib and Osimertinib, being second and third generation TKIs, respectively,

also had low activity against this type of EGFR mutation^{19, 20}. The Exon 20 insertions comprise a diverse group of mutations that add additional amino acids that heavily restrict drug access to the ATP-binding pocket. This explains why the first-generation drugs do not work very well because the drug binding pocket is less accessible.

Currently, the United States National Comprehensive Cancer Network guidelines recommend first line treatment with platinum-based chemotherapy for this type of NSCLC³.

NEW DEVELOPMENTS

Until recently, two new drugs, Amivantamab and Mobocertinib, have been approved by the United States Food and Drug Administration (FDA) for the treatment of metastatic NSCLC with EGFR exon 20 insertional mutations, after progression from initial treatment³. Owing to their different mechanisms of action, if a patient progresses on either drug therapy, they may consider switching to the other drug as next line treatment³.

AMIVANTAMAB

Amivantamab is a monoclonal antibody that is bispecific to EGFR and MET receptors²¹. Its mechanism of action is two-fold - on the one hand, it inhibits the binding of ligands to the extracellular domain of EGFR, and on the other hand, it promotes the destruction of tumour cells by interacting with macrophages and natural killer cells²¹.

The phase 1 study of the drug recruited eighty-one patients with disease progression after initial treatment of metastatic NSCLC with exon 20 insertion EGFR mutation²². The study concluded with a 40 % overall response rate (ORR) with a median PFS of 8.3 months and a median overall survival of 22.8 months²². Interestingly, three patients were found to have attained complete disease response²².

Common adverse drug reactions reported were rash (86 %), infusion-related reactions (66 %), paronychia (45 %), hypo-albuminaemia (27 %), constipation (24 %), stomatitis (21 %) and diarrhoea (12 %)²³. Furthermore, 5 % of participants developed severe hypokalemia, 4 % developed pulmonary embolism, and also 4 % had severe neutropenia²².

MOBOCERTINIB

Mobocertinib is a TKI which inhibits a range of EGFR exon 20 insertion mutations²³. A total of 114 patients were enrolled into a phase 1/2 trial studying its efficacy as next line treatment after standard platinum-based chemotherapy²⁴. The study achieved a 28 % ORR with a median PFS of 7.3 months and a median overall survival of 24 months²⁴.

Common adverse drug reactions reported were diarrhoea (91 %), rash (45 %), paronychia (38 %), decreased appetite (35 %), nausea (34 %), vomiting (30 %), and stomatitis (24 %)²⁴. In addition, a fifth of the



participants (21 %) developed at least grade 3 severe diarrhoea²⁴.

It is important to consider the different safety profiles of these agents when discussing them as treatment options with patients and individualise treatment selection based on each patient's needs and preferences, as well as other key clinical and patient-related factors.

It is worth noting that studies of both drugs had acknowledged their limitations - they were early phase trials in which there was no randomisation, and there was no control group included^{22, 24}. Regarding technical limitations, the quality and quality tumour tissue collected may occasionally be insufficient for analysis, and it was not possible to detect all kinds of EGFR exon 20 insertions with their analytic methods^{22, 24}. Moreover, patients with untreated or active brain secondaries were excluded from both studies; therefore, the activities of the drugs against intracranial disease cannot be adequately assessed^{22, 24}.

At the time of writing, phase 3 clinical trials for both drugs are in progress, for evaluation of their effectiveness as first-line therapy when combined with conventional chemotherapy, compared with chemotherapy alone^{25, 26}.

FURTHER RESEARCH

Two new TKIs, Sunvozertinib and Ziplertinib, received breakthrough therapy designation by the FDA for investigation of potential next line treatments.

In a phase 2 study abstract published in May 2023, among 104 recruited Chinese patients for next line therapy, it was stated that Sunvozertinib had an ORR of 60 %²⁷. Meanwhile, a response rate of 48 % was reported for patients who had brain metastasis²⁷. Details of drug related adverse effects were not mentioned in the abstract, although it was claimed to be similar to prior studies of the drug and other EGFR inhibitors²⁷. Side effects of diarrhoea, rash, anaemia and cardiac arrhythmia had been reported from a phase 1 trial previously²⁸.

In a phase 1/2a study published in June 2023, Ziplertinib was used in seventy-three patients as subsequent line treatment and demonstrated an ORR of 38 % with a median PFS of 10 months. The most frequent side effects reported were rash (80 %), paronychia (32 %), diarrhoea (30 %), fatigue (21 %), anaemia (19 %) and dry skin (18 %). Six patients (8 %)

had to discontinue treatment due to conditions such as pneumonitis, hepatotoxicity and fatigue²⁹.

OUTLOOK

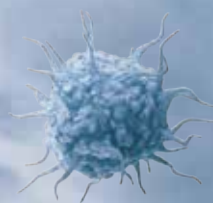
In summary, there is ongoing development relating to newer treatments of NSCLC possessing exon 20 insertion EGFR mutations. The new drugs introduced are summarised in Table 1³⁰. Results from newer clinical trials may become available in the near future, and it could be possible that they may provide more insights and benefits to our patients.

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Table 1. New drugs targeting EGFR exon 20 insertions (Adapted from Lau S, Velcheti V. Recent Developments in Targeting EGFR Exon 20 Mutations in Non-Small Cell Lung Cancer. [Internet] 2023 [Updated 2023 Jan 19] Available from: <https://dailynews.ascopubs.org/doi/recent-developments-targeting-egfr-exon-20-mutations-non-small-cell-lung-cancer>)

Drug	Mechanism of action	Subjects	ORR (%)	Median PFS / median DOR (months)	Key toxicities	Dose reduced / discontinued (%)
Amivantamab	EGFR / MET Antibody	81	40	8.3 / 11.1	Rash, infusion reactions	13 / 4
Mobocertinib	EGFR/ HER2 TKI	114	28	7.3 / 17.5	Diarrhoea, rash	25 / 17
Sunvozertinib	EGFR / HER2 TKI	104	60	–	Diarrhoea, rash	–
Ziplertinib	EGFR TKI	73	38	10 / 10	Rash, diarrhoea, paronychia	14 / 8



Strike now with **XTANDI**[®] (enzalutamide) in men with mHSPC

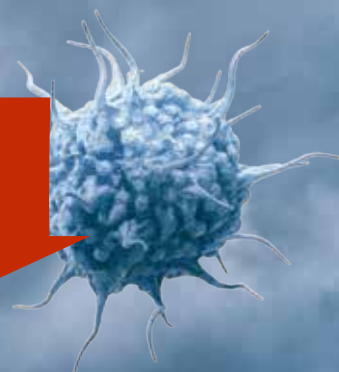
The phase III ARCHES study* established
adding **XTANDI** to ADT for treating men
with mHSPC:^{1,2}

61%
reduction

in the risk of radiographic
progression or death
vs ADT alone¹

34%
reduction

in the risk of death
vs ADT alone²



XTANDI (enzalutamide) is indicated for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy, the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer, the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated, the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy³

* ARCHES was a multinational, double-blind, randomised, placebo-controlled phase III study comparing the efficacy and safety profile of XTANDI + ADT vs placebo + ADT in 1,150 men with mHSPC. The primary endpoint was rPFS and OS was a key secondary endpoint.^{1,2}

ADT=androgen deprivation therapy; AE=adverse event; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; nmCRPC=non-metastatic castration-resistant prostate cancer; OS=overall survival; PSA=prostate-specific antigen; rPFS=radiographic progression-free survival.

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IN LOCALLY ADVANCED OR METASTATIC UROTHELIAL CANCER

PADCEV: Take Off Towards Better Horizons

An innovative Nectin-4–targeted treatment, **PADCEV extended median overall survival to 12.9 months** in patients who previously received platinum chemotherapy and a PD-1 or PD-L1 inhibitor

30%

Reduction in risk of death
vs chemotherapy

mOS¹**12.9 vs 9.0 months**

(HR= 0.70; 95% CI: 0.56, 0.89; p=0.00142)

38%

Reduction in risk of disease
progression vs chemotherapy

mPFS¹**5.6 vs 3.7 months**

(HR= 0.62; 95% CI: 0.51, 0.75; p<0.00001)

>2x

Objective response rate
vs chemotherapy

ORR¹**41% vs 18%**

(p< 0.001)

Locally advanced or metastatic urothelial cancer patients pre-treated with platinum-based chemotherapy and PD-1/PD-L1 therapies can initiate PADCEV treatment with **no biomarker testing required²**

Abbreviations:
CI: confidence interval; mOS: median overall survival; mPFS: median progressive-free survival; ORR: objective response rate; PD-1: programmed death receptor-1; PD-L1: programmed death ligand 1

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Abbreviations: 1L: First-line; HCC: Hepatocellular carcinoma; OS: Overall survival; PFS: Progression-free survival.
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Navigating the Metastatic Pancreatic Cancer Treatment Landscape in 2023

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Pancreatic adenocarcinoma (PC) is the 12th most common cancer worldwide, accounting for more than 2 % of all cancer cases and the 7th leading cause of cancer mortality¹. According to the National Program of Cancer Registries database, age-standardised incidence rates of PC have been increasing more rapidly among individuals younger than 55 than those 55 years or older. Pancreatic cancer has a poor prognosis, with a 5-year survival rate of 10 %. Up to 80 % of patients are diagnosed with inoperable or metastatic disease at presentation. Cytotoxic chemotherapy is effective, but primary and secondary chemoresistance remains difficult to overcome. Novel therapies are urgently needed.

CYTOTOXIC CHEMOTHERAPY FOR METASTATIC PANCREATIC CANCER

Over the past decade, treatment of metastatic and locally advanced PC has been standardised. Twenty-five years ago, gemcitabine was approved as a standalone treatment with a modest median OS of 5.6 months compared with placebo¹. The development of a combination therapy required an additional 10 years with a median OS of 6.2 months but with an addition increased in toxicity². The year 2011 marked the transition point for better patient outcomes as a landmark trial demonstrated that FOLFIRINOX, compared to the standard of care, gemcitabine alone achieved a doubling of median OS of 11.1 months³. Two years later, gemcitabine and nab-paclitaxel were introduced, with a median OS of 8.5 months⁴. Since then, oncologists have been weighing the decision of whether to prescribe FOLFIRINOX or gemcitabine nab-paclitaxel combination for patients. Although there has not been a study directly comparing the two treatments in first-line setting, it is evident that the three drug regimen FOLFIRINOX is more toxic, with around 45 % of the patients experiencing grade 3 or 4 neutropenia.

We added to our armamentarium with the NAPOLI-1 trial in 2016 that showed an improved PFS and OS of 3 months and 6.2 months, respectively, with two drug regimens liposomal irinotecan and fluorouracil after progression on gemcitabine⁵. Liposomal irinotecan comprises irinotecan that is a free base encapsulated in liposome nanoparticles. The liposome is designed to increase and prolong blood and intratumoral levels of irinotecan up to a doubling time of 11.7 hours and sheltered it from converting to its active metabolite SN38 and was approved by the FDA in 2015⁶. As a result of the study, sequencing has become a challenge depending on what oncologists choose as first-line therapy for patients.

The latest update in the world of pancreatic cancer is the

NAPOLI-3 trial with a brand new regimen. The study uses a combination of liposomal irinotecan, oxaliplatin (dosage of 60 mg/m² instead of 80 mg/m²), leucovorin and fluorouracil- NALIRIFOX with a high threshold comparator arm- gemcitabine nab-paclitaxel in the first-line setting. The overall survival curves separated persistently throughout the study follow up. The study achieved a median OS of 11.1 months with Nalirifox vs 9.2 months with gemcitabine-nab-paclitaxel. Objective response rates were also higher with Nalirifox- 41.8 % vs 36.2 % with nab-paclitaxel-gemcitabine. Currently, Nalirifox is not FDA approved and it is cost-limiting. The toxicity of Nalirifox was consistent, with grade 3/4 treatment related diarrhoea up to 20 % but decreased neurotoxicity.⁷

MULTIPLE PATHWAYS TO CHEMOTHERAPY RESISTANCE

Despite advances in chemotherapeutic regimens, the median overall survival of metastatic PC remained a dismal 12 months. Stromal fibrosis in the PC tumour microenvironment (TME) not only impairs drug delivery and efficacy, but also allows persistent clones to acquire drug resistance⁸. Gemcitabine resistance, for example has been linked to diverse proteomic changes and phenotypic rewiring in the tumour cell, and cell extrinsic mechanisms that involve TME macrophages which provide growth factors such as insulin-like growth factor^{9, 10, 11}. The multiplicity of chemo resistant pathways calls for alternative avenues to tackle PC.

CURRENT LIMITATIONS OF IMMUNE-BASED STRATEGIES

The immunosuppressive PC TME poses a significant challenge to facilitating and sustaining a robust cytotoxic T-cell (CTL) response against tumour cells, and has been reviewed elsewhere¹². While tumour infiltration of CTL, Th1 helper cells, and an abundance of neoantigens predict favourable PC prognosis, early studies to target immune checkpoints such as PDL1-PD1 and CTLA4-CD80/86 interaction have largely failed in the clinic¹³. Report of a successful, highly personalised immune strategy such as adoptive T-cell receptor therapy against tumour neoantigens raises issues of cost, broad applicability, and manufacturing expertise¹⁴. Further preclinical studies to target immunosuppressive myeloid cell populations, or monoclonal antibodies to activate antibody-dependent cellular cytotoxicity may hold promise in the future^{12, 15}.

KRAS INHIBITORS FOR PANCREATIC CANCER



Since KRAS hotspot mutations occur in up to 90 % of tumours, molecular inhibitors of the oncogenic driver may be effective¹⁶. Thus, the approval of sotorasib and adagrasib for KRAS G12C mutant NSCLC brought much hope to PC in 2021. In the G12C space accounting for 1 - 2 % of PC, Amgen's sotorasib binds the switch II pocket of the KRAS active site by forming a covalent bond with the C12 residue and traps inactive GDP-KRAS to decrease GTP-KRAS and signalling¹⁷. The inhibitor was investigated in the Phase 1 - 2 CodeBreak 100 trial and showed a 21 % response rate, a PFS of 4.0 months, and an overall survival of 6.9 months in 38 patients that were heavily pretreated¹⁸. Adagrasib, on the other hand, showed a 50 % response rate and a median PFS of 6.6 months in 12 PC patients in the phase 2 cohort of the Krystal-1 study¹⁹.

Fortunately, both inhibitors' specificity for mutant KRAS led to tolerable side effects, with common adverse events being nausea and vomiting, diarrhoea, and fatigue^{18, 19}. For the more common G12D mutation, numerous G12D specific inhibitors are currently in preclinical development¹⁷. MRTX1133, for example, was reported to show high specificity for the mutant, along with promising in-vivo activity in murine xenograft models. It has been granted an investigational new drug application by the US FDA in early 2023²⁰ and has entered phase 1/2 clinical trials for refractory solid tumours with G12D mutations (NCT05737706).

EXPLOITING HOMOLOGOUS RECOMBINATION DEFICIENCY (HRD) IN PANCREATIC CANCER

In 2019, the POLO trial showed that after platinum-based combination chemotherapy, olaparib maintenance prolongs PFS by 50 % in BRCA1/2 mutant PC²¹. This showed that the paradigm of poly-adenosine diphosphate ribose polymerase (PARP) inhibition in BRCA1/2 mutant ovarian cancer can also yield clinical benefit in PC. Important preclinical experiments showed that cells with HR deficiency, an error free pathway to repair double stranded breaks, be exquisitely sensitive to PARP1 inhibition²². PARP inhibitors impair base excision repair and alternative end-joining in HRD cells and trap PARP on DNA, increasing double stranded breaks during replication to cause catastrophic damage.

Accurate detection of HRD is clinically important, as germline testing for BRCA1/2 mutations showed a mere 5 % detection rate in the POLO study, yet increases to 7.7 % when HR associated proteins undergo germline and somatic testing for deleterious mutations²³. Critically, PARP inhibitors are no less efficacious in tumours with somatic HRD, as reported in ovarian cancer and in PC^{24, 25}. Surrogate HRD assays, such as the detection of genomic scarring have shown HRD detection in up to 40 % of cases, thus expanding the relevance of PARP inhibition to a greater number of PC patients²³.

CONCLUSIONS

While chemotherapy remains the cornerstone of management in metastatic PC, other strategies are available in selected patients to combat chemo-resistant disease. Targeted small molecules against KRAS G12C and G12D mutations are fast coming to the clinic, while PARP inhibition offers an orally available agent for

HRD tumours with manageable side effects. In patients with adequate tumour tissue, timely molecular testing is critical to select patients who may benefit from these novel therapies. Immune based strategies are promising, but the formidable challenge in translational research is to overcome an immunosuppressive environment innate to PC. With dedication and collaborative efforts, we strive towards a future where metastatic pancreatic cancer becomes manageable and chronic.

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Review on Recent Advancements of Colorectal Cancer

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Colorectal cancer (CRC) remains a significant global health burden, representing one of the most frequently diagnosed malignancies and a leading cause of cancer-related mortality worldwide¹. In Hong Kong, CRC ranked second in both the incidence and cancer related mortality in both sexes². In recent years, there have been remarkable advancements in our understanding of the molecular underpinnings, prognostic markers, and therapeutic strategies for colorectal cancer. These breakthroughs have the potential to revolutionise the diagnosis, treatment, and outcomes of patients with this devastating disease.

RISK FACTORS

Colorectal cancer (CRC) risk factors include age (risk increases with age), family history of CRC or certain genetic conditions (Lynch syndrome, FAP)³⁻⁵, personal history of polyps or CRC, inflammatory bowel disease, unhealthy lifestyle factors (a poor diet low in fibre, high in red/processed meats, obesity, physical inactivity, smoking, heavy alcohol consumption), type 2 diabetes, racial/ethnic background (African Americans, Ashkenazi Jews), previous radiation therapy to the abdomen/pelvis, and certain hereditary factors^{3, 6-10}. While having one or more risk factors increases the likelihood of CRC, many cases occur in individuals without identifiable risk factors.

EARLY DETECTION AND SCREENING

Early detection and screening play a crucial role in the management of colorectal cancer (CRC). Regular screening allows for the identification of precancerous polyps or early-stage cancers when treatment is most effective. Several screening methods are available:

1. Colonoscopy: Considered the gold standard, colonoscopy allows for direct visualisation of the entire colon and rectum, enabling the detection and removal of precancerous polyps and early-stage cancers¹¹.
2. Fecal occult blood test (FOBT): This test detects hidden blood in stool samples. It is a non-invasive and cost-effective screening option. Positive FOBT results are followed by a colonoscopy¹².
3. Fecal immunochemical test (FIT): Similar to FOBT, FIT detects blood in stool samples. It has higher specificity and sensitivity and does not require dietary restrictions¹³.

4. Stool DNA testing: This test detects DNA changes in stool samples, including genetic mutations associated with CRC. It can help identify high-risk individuals needing further evaluation¹⁴.
5. Flexible sigmoidoscopy: This procedure examines the rectum and lower part of the colon. While it does not assess the entire colon, it can detect abnormalities in the lower region. Early detection through these screening methods allows for the prompt diagnosis and treatment of CRC, leading to improved outcomes and increased survival rates^{11, 15}.

Screening recommendations may vary based on individual risk factors, age, and medical history.

GENOMIC AND EPIGENOMIC ALTERATIONS IN COLORECTAL CANCER

Biomarkers play a crucial role in predicting prognosis and guiding treatment decisions in colorectal cancer. Several biomarkers have been identified and extensively studied for their prognostic significance. Commonly studied biomarkers include KRAS and NRAS mutations, which are associated with resistance to anti-EGFR therapies^{16, 17}. Microsatellite instability (MSI) and mismatch repair deficiency (dMMR) indicate a defective DNA repair system, and also high tumour mutational burden (TMB) are associated with a better prognosis and potential response to immune checkpoint inhibitors¹⁸⁻²¹. The presence of the BRAF V600E mutation is associated with a poorer prognosis, while TP53 mutations indicate a worse prognosis²². HER2 mutations in metastatic colorectal cancer are associated with HER2 protein overexpression or gene amplification. It accounts for approximately 2 - 5 % of colorectal cancer. Circulating tumour DNA (ctDNA) analysis provides non-invasive monitoring of tumour burden, treatment response, and disease recurrence.

Additionally, gene expression signatures like Oncotype DX and ColoPrint analyse multiple gene expression patterns to provide risk scores correlating with disease recurrence and patient survival²³. These biomarkers, when combined with clinicopathological factors, enhance prognostic assessment. However, the clinical utility of biomarkers may vary depending on the tumour stage and other clinical factors.



THE DIVERSE APPROACHES FOR MANAGING COLORECTAL CANCER

Metastatic colorectal cancer (mCRC) requires a multimodal treatment approach that combines different treatment modalities to improve patient outcomes. Commonly utilised treatment modalities for metastatic colorectal cancer include:

1. **Systemic Chemotherapy:** Systemic chemotherapy is the backbone of treatment for mCRC. Combinations of chemotherapy drugs, such as fluoropyrimidines (e.g. 5-fluorouracil, capecitabine), oxaliplatin, and irinotecan, are used to target cancer cells throughout the body. Different chemotherapy regimens, such as FOLFOX (5-fluorouracil, leucovorin, oxaliplatin) and FOLFIRI (5-fluorouracil, leucovorin, irinotecan), are commonly employed^{24, 25}.
2. **Targeted Therapies:** Specific molecular targets in cancer cells can be exploited using targeted therapies. For mCRC, targeted therapies include anti-EGFR (epidermal growth factor receptor) antibodies like cetuximab and panitumumab, which are effective in patients with wild-type RAS genes²⁶, and anti-VEGF (vascular endothelial growth factor) agents like bevacizumab and aflibercept, which inhibit tumour blood vessel formation²⁷.
3. **HER-2 directed therapies:** HER-2 positive colorectal cancers account for approximately 2 - 5 % of the metastatic colorectal cancer population. Clinical trials investigating HER2-positive colorectal cancer have explored the efficacy of HER2-targeted therapies. Trials such as HERACLES and MyPathway demonstrated promising results with trastuzumab, pertuzumab, and lapatinib, showing disease control and prolonged progression-free survival^{28, 29}. DESTINY-CRC01 trial is evaluating trastuzumab deruxtecan, an antibody-drug conjugate, in patients who progressed on standard therapies³⁰. It results in an overall response rate (ORR) of 45.3 % in cohort A ((the HER2 positive, defined as immunohistochemistry (IHC) staining 3+ or in-situ hybridization (ISH) positive) patients)³¹. These trials provide insights into the potential of HER2-targeted treatments. Recently tucatinib, another HER2 directed tyrosine kinase inhibitor (TKI) had, received accelerated approval from the FDA base on the Mountaineer trial, the confirmed objective response rate per blinded independent central review (BICR) was 38.1 % (95 % CI 27.7 - 49.3; three patients had a complete response and 29 had a partial response)³².
4. **Immunotherapy:** Immune checkpoint inhibitors (ICIs) are a type of immunotherapy that target proteins on immune cells or cancer cells, known as checkpoints, to enhance the immune response against cancer. In mCRC, ICIs such as pembrolizumab and nivolumab have shown efficacy in patients with tumours that exhibit microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR)^{33, 34}. These molecular features result in an increased tumour mutation burden and a higher likelihood of response to immunotherapy. ICIs can be used as monotherapy or in combination with other agents.

THE ERA OF IMMUNOTHERAPY

1. **Pembrolizumab, an anti-PD-1 (programmed death-1) antibody,** was approved by the Food and Drug Administration (FDA) as a first-line treatment in patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer. The approval was based on the Keynote-177 trial, which was a multicentre, international, open-label, active-controlled randomised trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR colorectal cancer. At final analysis, with a median follow-up of 44.5 months, the median overall survival (OS) was not reached (NR; 95 % CI 49.2 - NR) with pembrolizumab vs 36.7 months (27.6 - NR) with chemotherapy (hazard ratio [HR] 0.74; 95 % CI 0.53 - 1.03; $p = 0.036$). The superiority of pembrolizumab versus chemotherapy for overall survival was not demonstrated because the prespecified α of 0.025 needed for statistical significance was not achieved. At this updated analysis, median progression-free survival was 16.5 months (95 % CI 5.4 - 38.1) with pembrolizumab versus 8.2 months (6 - 10.2) with chemotherapy (HR 0.59, 95 % CI 0.45 - 0.79)³⁵.
2. **Nivolumab and Ipilimumab:** Nivolumab, another anti-PD-1 antibody, and ipilimumab, an anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) antibody, have demonstrated efficacy when used in combination for MSI-H or dMMR mCRC that has progressed after prior treatment. This combination has shown higher response rates compared to single-agent immunotherapy, leading to FDA approval for this indication³⁵.

Biomarker Testing for MSI-H or dMMR status is crucial to identify patients who are likely to benefit from immunotherapy. It includes PCR-based assays or immunohistochemistry, which is performed to assess the molecular characteristics of the tumour and determine eligibility for immunotherapy³⁶. Ongoing clinical trials are investigating the use of immunotherapy in combination with other treatment modalities, such as chemotherapy, targeted therapies, and radiation therapy, to enhance response rates and improve outcomes in mCRC^{37, 38}. These combination approaches aim to overcome resistance mechanisms and enhance the immune response against cancer cells. Although immunotherapy has shown promising results in a subset of mCRC patients, it is important to note that the majority of patients with mCRC do not exhibit MSI-H or dMMR tumours and may not benefit from immunotherapy as a stand-alone treatment. Therefore, careful patient selection and biomarker testing are essential in identifying those who are most likely to respond to immunotherapy.

NEOADJUVANT APPROACHES IN COLORECTAL CANCER

Neoadjuvant therapy refers to the administration of treatment before the primary treatment, which is typically surgery, in the management of colorectal cancer (CRC). The goal of neoadjuvant therapy is to shrink

tumours, improve surgical outcomes, and potentially increase the likelihood of a complete response or cure. In particular, neoadjuvant immunotherapy has emerged as a promising treatment approach for patients with dMMR/MSI-H colorectal cancer (CRC). This unique molecular profile makes them more susceptible to immunotherapy³⁹. Neoadjuvant checkpoint inhibitors, such as pembrolizumab and nivolumab, have demonstrated high response rates and significant tumour regression in dMMR/MSI-H CRC patients. Dorstimab has emerged as a notable luminary in recent times. In a recent phase 2 study with MMR-d stage II or III rectal adenocarcinoma, followed by standard chemoradiotherapy and surgery, 12 patients completed the treatment, and all patients, 100 % had a clinical complete response with no evidence of tumour on clinical examination, imaging and endoscopies⁴⁰. This example demonstrates the potential for neoadjuvant immunotherapies to improve outcomes by increasing the likelihood of complete tumour eradication and reducing the risk of disease recurrence. Furthermore, neoadjuvant immunotherapy may provide an opportunity to assess treatment response and identify potential biomarkers for predicting response and resistance.

BARRIERS TO SUCCESSFUL IMMUNOTHERAPY

Immune-related adverse events (irAEs) are a significant consideration in the use of immunotherapy. While immunotherapy has shown great promise in treating various cancers, it can also lead to unintended effects on the immune system, resulting in irAEs. IrAEs can affect different organs and systems in the body, and their severity can range from mild to severe. Common irAEs include dermatological reactions like rashes and pruritus (itching), gastrointestinal issues such as diarrhoea and colitis, endocrine disorders like thyroid dysfunction, and hepatic (liver) abnormalities. Other less common irAEs may involve the lungs, kidneys, nervous and cardiovascular systems. The onset of irAEs can vary, with some occurring early in treatment while others may manifest after months of therapy. Prompt recognition and management of irAEs are critical to minimise their impact and ensure patient safety. Healthcare providers closely monitor patients undergoing immunotherapy, regularly assessing for symptoms and conducting appropriate diagnostic tests to detect and manage irAEs promptly. The management of irAEs typically involves a multidisciplinary approach, with oncologists, dermatologists, endocrinologists, gastroenterologists, and other specialists collaborating to provide comprehensive care. Treatment strategies may include the administration of corticosteroids or other immunosuppressive medications to suppress the immune response and alleviate symptoms. In severe cases, immunotherapy may need to be temporarily or permanently discontinued⁴¹. It's important to note that while irAEs can pose challenges, the overall benefit of immunotherapy in treating cancer often outweighs the risks. Close monitoring, early detection, and effective management of irAEs are key to optimizing patient outcomes and ensuring the safe and successful use of immunotherapy.

CONCLUSION

Recent advancements in CRC research have revolutionised our understanding and management of the disease. The integration of molecular profiling, targeted therapies, immunotherapies, and precision medicine has opened new avenues for personalised treatment approaches. Furthermore, improvements in screening methods and preventive measures offer opportunities for early detection and reduced disease burden. Continued research and collaboration between clinicians, scientists, and patients are essential to further enhance CRC outcomes and decrease the global burden of this devastating disease.

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Presentation: Budesonide/Formoterol Turbuhaler. **Indications:** In adults and adolescents (12 years and older), for the treatment of asthma, to achieve overall asthma control, including the relief of symptoms and the reduction of the risk of exacerbations. Symptomatic treatment of moderate to severe COPD in adults. **Dosage & Administration:** 1) Symbicort anti-inflammatory reliever therapy (patients with mild disease) 160/4.5 mcg Turbuhaler Adult & Adolescent ≥ 12yr: 1 inhalation as needed in response to symptoms. If symptoms persist after a few minutes, 1 additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion. A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. 2) Symbicort maintenance and reliever therapy Adult & Adolescent ≥ 12yr: Patients should take 1 inhalation of Symbicort Turbuhaler 160/4.5 mcg as needed in response to symptoms to control asthma. If symptoms persist after a few minutes, 1 additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion. Recommended maintenance dose is 1 inhalation b.i.d. and some may need 2 inhalations b.i.d. A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. 3) Symbicort maintenance therapy 160/4.5 mcg Turbuhaler Adult & Adolescent ≥ 12yr: 1-2 inhalations b.i.d. Max daily dose is 4 inhalations. **Contraindications:** Hypersensitivity to budesonide, formoterol or lactose. **Precautions:** Should be used for the shortest duration of time required to achieve control of asthma symptoms. Should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications. Not to be used to initiate treatment with inhaled steroids in patients being transferred from oral steroids. It is recommended that the maintenance dose be tapered when long-term treatment is discontinued. Potential systemic effects of ICS: HPA axis suppression and adrenal insufficiency, bone density, growth, visual disturbance, infections/tuberculosis, sensitivity to sympathomimetic amines, cardiovascular disorders, hypokalaemia, diabetes, pneumonia, lactose, pregnancy & lactation. Not recommended for children below 12 years of age. Incidence of candidiasis can be minimized by having patients rinse their mouth out with water after inhaling their maintenance dose. **Interactions:** CYP3A4 inhibitors, beta-receptor blocking agents, other sympathomimetic agents, Xanthine derivatives, mineralocorticosteroids and diuretics. Monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines and anticholinergics. **Undesirable effects:** Palpitations, Candida infections in the oropharynx, headache, tremor, mild irritation in the throat, coughing, hoarseness. **Full local prescribing information is available upon request.** API HK SYM021

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The Evolution of Treatments for Metastatic Urothelial Carcinoma: From Limited Options to Biomarker-Guided Therapies

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INTRODUCTION

Bladder cancer is the tenth most common cancer worldwide¹. In Hong Kong, an estimated 400 people are diagnosed with bladder cancer yearly. The incidence increases with age and peaks between 55 and 70 years old. The incidence of urothelial carcinoma is more common in men than in women². The 5-year survival rate for metastatic urothelial carcinoma remains poor, at 8% only³. Smoking is the most important risk factor for the development of urothelial carcinoma⁴. Increased understanding of metastatic urothelial carcinoma through identifying predictive biomarkers and immunotherapy has enabled the development of promising therapeutic options. Here, we summarise the journey of achievements and lessons learnt to build the current and future treatment of metastatic urothelial carcinoma.

THE EARLY DAYS: CHEMOTHERAPY

Before the advent of effective chemotherapy for metastatic urothelial cancer, patients rarely survive more than six months⁵. Like many other solid tumours, urothelial cancer is chemo-sensitive. Cisplatin-based combination chemotherapy is the standard first-line treatment for metastatic urothelial cancer. Two cisplatin-based regimens are commonly used for first-line therapy for metastatic bladder cancer: MVAC (methotrexate/vinblastine/doxorubicin/cisplatin) and GC (gemcitabine/cisplatin). A phase III study demonstrated a statistically comparable survival rate between MVAC and GC (14.8 vs. 13.8 months; HR 1.04; $p = 0.75$), with GC showing fewer toxicities. Common toxicities of these regimens include neutropenia, nausea/vomiting and alopecia⁶. In EORTC 30924, dose-dense MVAC (shortened two weeks-per-cycle schedule with G-CSF support) produced better complete response rates and median progression-free survival (mPFS) than MVAC, while overall survival (OS) is similar⁷. Over 50 % of patients with metastatic urothelial carcinoma are ineligible for cisplatin due to comorbidities or frailty. According to the Galsky criteria, patients are eligible for cisplatin-based combination chemotherapy if they meet all the criteria: Eastern Cooperative Oncology Group (ECOG) performance status 0-1, eGFR ≥ 60 , audiometric hearing loss $<$ grade 2, peripheral neuropathy grade $<$ 2 and cardiac insufficiency $<$ New York Heart Association (NYHA) class III⁸. A combination of Gemcitabine with Carboplatin or Taxanes is an option for patients who are cisplatin-ineligible, which appears to be inferior⁹. Vinflunine is approved in Europe for second-line

treatment of platinum-refractory metastatic urothelial cancer¹⁰. Overall, chemotherapies are associated with significant toxicity and only provide a modest improvement in survival.

THE ADVENT IMMUNOTHERAPY: A PARADIGM SHIFT

Urothelial tumour cells escape from host immune responses by expressing PD-L1. The binding of PD-L1 to PD-1 on T cells hampers the activation and proliferation of T cells¹¹. Checkpoint inhibition against the PD-L1/PD-1 is a therapeutic target in urothelial carcinoma.

FRONTLINE IMMUNOTHERAPY

Pembrolizumab has shown promising activity in the frontline treatment of cisplatin-ineligible metastatic urothelial carcinoma. In KEYNOTE-052, patients receiving first-line pembrolizumab have a median duration of response of 33 months and a median overall survival (mOS) of 11 months. The overall response rate (ORR) was higher in patients with a combined positive score (CPS) > 10 compared with those with CPS ≤ 10 (47 vs. 21 %) ^{12,13}.

Chemotherapy, followed by maintenance immunotherapy, is the standard of care for metastatic urothelial carcinoma. In the JAVELIN Bladder 100 trial, patients with locally advanced or metastatic bladder cancer who achieved complete or partial response after four to six cycles of cisplatin or carboplatin combined with gemcitabine were randomised to receive maintenance avelumab and best supportive care (BSC) or BSC alone. mOS were 23.8 months in the avelumab group vs 15.0 months in the control group (HR = 0.76; $P = 0.0036$). mPFS was 5.5 months in the avelumab group vs 2.1 months in the control group (HR = 0.54; $P < 0.0001$) ¹⁴.

SECOND LINE IMMUNOTHERAPY

Immunotherapy is the standard of care for patients who progress during or after first-line platinum-based chemotherapy. Among the five PD-L1/PD1 inhibitors studied in the second line, Pembrolizumab has the most robust survival data. In KEYNOTE-045, Pembrolizumab demonstrates a clinically meaningful OS benefit versus chemotherapy (10.1 vs. 7.2 months; HR 0.70) in patients with locally advanced or metastatic urothelial carcinoma in the second-line setting. Patients who responded to Pembrolizumab also experienced a durable response



(median > 2 years). The toxicity profile favoured Pembrolizumab¹⁵. Other agents include Nivolumab¹⁶ and Avelumab¹⁷, Durvalumab¹⁸ and Atezolizumab¹⁹.

ONGOING IMMUNOTHERAPY TRIALS

There are a number of ongoing immunotherapy trials for metastatic urothelial carcinoma. CheckMate 901 investigates Nivolumab in combination cisplatin-based chemotherapy or chemotherapy alone for previously untreated cisplatin-eligible and -ineligible patients²⁰. The result will be presented in 2023 ESMO European Society of Medical Oncology meeting. We are expecting positive results that we eagerly await.

THE ERA OF PRECISION MEDICINE: BIOMARKER-GUIDED THERAPY AND ANTIBODY-DRUG CONJUGATES

Despite the success of immunotherapy for the treatment of metastatic bladder cancer, most patients ultimately progress, and we need more effective therapies along the line. Predictive biomarkers are used to identify patients who are likely to respond to a particular therapy. In 2014, the Cancer Genome Atlas project (TCGA) identified that 69 % of metastatic urothelial carcinoma have potential druggable mutations. It also suggests APOBEC3B may be a potential predictive biomarker for response to immunotherapy²¹. Approximately 20 % of patients with advanced urothelial carcinoma have fibroblast growth factor receptor (FGFR) alterations²². Activation of FGFR signalling leads to activation of the mitogen-activated protein kinase and may contribute to oncogenesis. Erdafitinib is an oral pan-FGFR tyrosine kinase inhibitor (TKI) for treating metastatic urothelial carcinoma following progression on platinum chemotherapy and immunotherapy. A phase II trial shows promising efficacy with an objective response rate of 40 % (3 % with a complete response (CR)), mOS 13.8 months²². Common treatment-related adverse events of Erdafitinib include hyperphosphatemia, diarrhoea, dry mouth, and decreased appetite²². Erdafitinib is suggested for patients with advanced or metastatic urothelial carcinoma with an FGFR2 or FGFR3 alteration who progress on chemotherapy and immunotherapy. Based on these data, the phase 3 trial THOR assesses whether Erdafitinib improved survival over chemotherapy in patients with FGFR alteration and progressed on or after one prior treatment that included immunotherapy. Preliminary results show that erdafitinib had superior OS and PFS relative to chemotherapy^{23, 24, 25}. FGFR mutations and fusions need to be checked for all patients with metastatic urothelial cancer.

Antibody-drug conjugates (ADCs) consist of a cytotoxic agent covalently linked to an antibody via a chemical linker²⁶. For patients who progressed after platinum chemotherapy and immunotherapy and are FGFR mutation negative, antibody-drug conjugates Enfortumab vedotin and Sacituzumab govitecan are the standards of care. Enfortumab vedotin targets nectin-4, while Sacituzumab govitecan targets trophoblast cell surface antigen 2 (Trop 2)^{26, 27}. Both are highly expressed

in urothelial tumours and do not require biomarker testing prior to initiation of therapy. In EV-301, enfortumab vedotin, as compared with chemotherapy, improved mOS (13 versus 9 months; HR 0.70), PFS (6 versus 4 months; HR 0.62) and ORR (41 versus 18 %). Common side effects include rash, peripheral neuropathy and hyperglycaemia²⁶. In a phase II trial TROPHY-U-01, which led to the FDA approval of Sacituzumab govitecan, the ORR was 27 % including CR of 5 %, the mPFS was 5.4 months and the mOS was 19.9 months, respectively²⁷.

Novel combinations are also being evaluated. Pembrolizumab, combined with enfortumab vedotin, is now FDA approved for the initial treatment of patients with metastatic urothelial carcinoma who are cisplatin-ineligible but fit to receive combination systemic therapy. In EV-103 Cohort K, the addition of pembrolizumab to enfortumab vedotin yielded an exciting ORR of 65 % versus 45 % for EV alone, although this difference was statistically insignificant²⁸.

In the Chinese population, HER2 is overly expressed in 9.2 % - 61.1 % of urothelial carcinoma²⁹. HER2-targeted agents have demonstrated promising efficacy in the treatment of metastatic breast and gastric cancer. Therefore, the role of HER2-targeted agents is of interest in the treatment of metastatic urothelial carcinoma. Yet, there is so far no obvious survival benefit of Trastuzumab, Trastuzumab emtansine and Lapatinib^{30 - 33}.

CONCLUSION

The treatment landscape of metastatic urothelial carcinoma has made significant achievements over the past decade. From the early days of chemotherapy, we have moved to targeted therapies with impressive efficacy and tolerability. The advent of immunotherapy marked a significant revolution, but the true triumph has come with the advent of precision medicine, with biomarker-guided therapies to improve patient selection. The survival of patients of this once deadly disease is transformed forever with the development of novel therapies. However, many questions remained unanswered. What are the best sequencing of treatments? What is the best duration of treatment when we achieve complete remission? What is the best maintenance strategy in the first line setting? Many more active researchers will shed light on them in the years to come.

Understanding these developments can help manage patients with metastatic urothelial carcinoma, facilitate discussions with patients and their families, and liaise with oncologists to ensure the most effective treatment strategies are pursued. The future of metastatic urothelial carcinoma treatment looks promising, with new therapeutic options and combinations likely to bring further advances for this aggressive disease.

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Tributes to Honorary President Dr CHAN Chok-wan 1945 - 2023

Dr Dawson FONG

Honorary President, Federation of Medical Societies of Hong Kong



Dr Dawson FONG

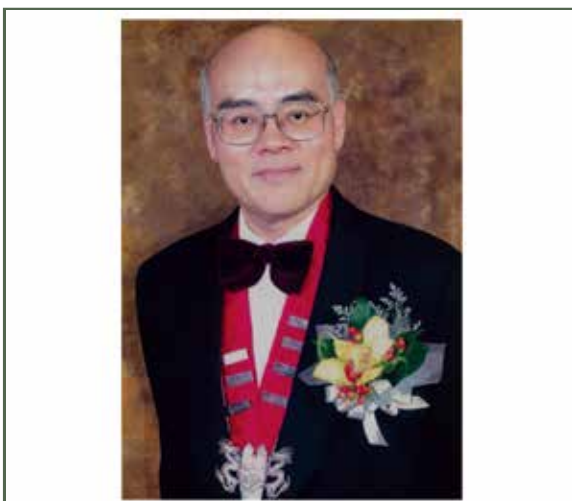


Fig. 1: Dr CHAN Chok-wan, the President of FMSHK 1991 - 2003

One day during my Paediatric Clerkship in the late 70's, I was looking for cases to study in a paediatric ward at Queen Mary Hospital. Suddenly, I heard, ascending crystal clear above the crying and screaming of the infants, a strong baritone voice. The voice led me to a 'senior' doctor standing in the far corner of the cubicle chatting with his colleagues who apparently could only listen. From his guise of authority, I truly believed that he was one of the Senior Lecturers, if not a young Professor. That impression stayed for a while until eventually I realised that although he was not a professor, Dr Chan Chok-wan was a rising star in Paediatrics. In more than a decade that followed, because of my interests in paediatric neurosurgery, our paths crossed occasionally. But I really got to know the man only when I started to serve at the Executive Council of the Federation of the Medical Society (FMSHK) under his presidency in the mid-90's.

As a gifted leader, he was a man of vision. At the time, Hong Kong was going through the transition in 1997. As a big organisation like the FMSHK encompassing nearly all walks of life in the medical and health sectors, it is, in itself, a sizeable community, constantly involved in political and professional issues arising from within and without. As closer ties were developing between Hong Kong and the mainland, Dr Chan led us into regular bilateral scientific meetings with the Chinese Medical Association held in various major cities and, of course, in Hong Kong. These interactions that opened up communications between member societies and

counterparts on the mainland were priceless. His vast connections locally and abroad help the executives greatly in aligning all the logistics in bringing these meetings into reality. I still remember the hard work we went through and in the process, I, for one, learned a great deal.

We had spent numerous evenings in the Board Room of the FMSHK, having Executive Committee and Council Meetings. Dr Chan would guide us through the well-studied, usually lengthy agenda with his masterly attention to detail. When it got late, he would invite us to go to dinner together afterwards. On a few occasions, by the time we came out of the restaurant, it was close to midnight. Some of our spouses probably would grumble but I have to admit those occasions were not bad as an opportunity to cultivate comradeship.

He was a charismatic leader. Delegation of jobs among various already busy members of the Executive Committee may not be easy and yet Dr Chan was excellent in his persuasion with a big smile and yet we all felt the force behind the beam. It was from his encouragement that many of us were able to step out of our comfort zone, achieving the unlikely. In return, he would award us most generously with his heart-felt gratitude. That may explain why colleagues would stay on as Executive Committee members term after term, well expecting more daunting tasks ahead.

Dr Chan was a man of inexhaustible energy. As the Federation President for 12 years between 1990 and 2002, he was extremely efficient and productive. He had strengthened the FMSHK from a mere social club for the medical, dental and health societies into a hub for professional exchanges among different specialists highlighted by regular scientific meetings and the monthly publication Medical Diary, sharing with all members the latest in specific facets of the clinical fields.

But that was just one of his many roles and achievements. He was a paediatrician, a paediatric neurologist, one who was in love with the specialty and totally committed to children. This was exemplified by his seminal work on child development leading to the launching of free universal developmental screening for all preschool children at the Hong Kong Maternal and Child Health Centres back in 1978.

He had since the early 80's, been the President of the Hong Kong Paediatric Society, the Hong Kong Paediatric Foundation and the Hong Kong Society of Child Neurology and Developmental Paediatrics. With the advent of the Hong Kong Academy of Medicine, he



was instrumental in consolidating a distinct College for Paediatricians and subsequently an accreditation system for paediatric subspecialties in the Hong Kong College of Paediatrics. For the community, he was the key figure on many HKSAR policy work groups, notably the Committee for a Comprehensive Child Development Service (CCDS) and the Committee on the Centre of Excellence in Paediatrics that later on became the Hong Kong Children Hospital as we know now.

He launched the Hong Kong Journal of Paediatrics in 1983 and he was the editor of numerous paediatric journals, publications and guidebooks on child health and child care.

Hong Kong could not contain him. He served the world. He was the Outstanding Paediatrician of Asia Pacific in 2000 and subsequently the President of Asia Pacific Paediatric Association and the President of the International Paediatric Association 2007 - 2010.

In the early hours of 19th November 2023, Dr Chan passed away peacefully after a gallant and arduous fight with ill health, surrounded by his family members. He was survived by his daughters, Emily, Josephine, Purdy and Angie.

The FMSHK has lost a stellar President, the Paediatric Community an outstanding leader and the children in Hong Kong a strong and capable advocate. He will always be remembered for the strong voice, his authoritative speeches and his magnanimity!

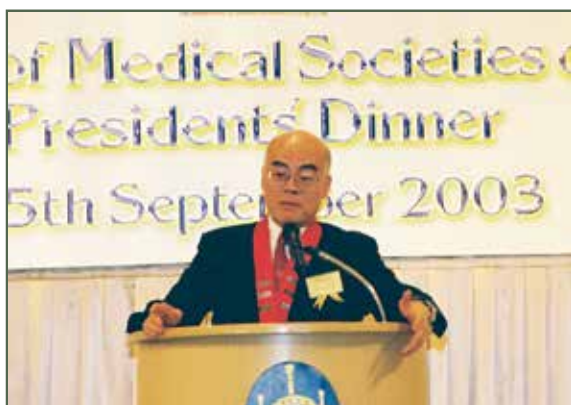


Fig. 4: Dr CHAN at the President Dinner 2003.



Fig. 5: Dr CHAN at the President Dinner 2003 (6th from left)



Fig. 2: Prof DC ANDERSON President of BMA(HK) (left) and Dr CHAN at the Federation Annual Dinner in 1997.



Fig. 3: Dr CHAN at the President Dinner 2002 (1st roll, 5th from left)



Fig. 6: The memorable occasion of Honorary President Conferment in 2021.
From left: Prof Bernard CHEUNG, Dr Mario CHAK, Dr Dawson FONG, Dr CHAN Chok-wan, Dr Raymond LO, Dr Demsond NGUYEN, Dr Samuel FUNG and Dr Peggy CHU



Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					*In-person The HKMA District Health Network (Kowloon West) CME Lecture Topic: Navigating the Landscape: Advances in Prostate Cancer Diagnosis and Treatment	2
3	4	*In-person / Zoom Live HKMA-HKSH CME Programme 2023-2024 Topic: Advances in Proton Therapy for Cancer Treatment	*Certificate Course in Cardiology 2023	*Certificate Course in Ophthalmology 2023 - Module 2	*Zoom Live Topic: What's New in Hypertension Management?	9
10	11	*In-person The HKMA District Health Network CME Lecture Topic: To-be-confirmed	*In-person / Zoom Live HKMA-CUHK Medical Centre CME Programme 2023 Theme: Women's Health Topic: Breast Health and Breast Surgery *Certificate Course in Cardiology 2023	*In-person / Zoom Live HKMA-HKSTP CME Programme 2023 Topic: To-be-confirmed	15	16
17	18	*In-person / Zoom Live HKMA-GHK CME Programme 2023 Topic: Cataract/ Glaucoma	*In-person The HKMA District Health Network (Kowloon West) CME Lecture Topic: Lipid Management in High-risk Patients - What Else from LDL Reduction?	*Zoom Live Topic: Updates in Management of Lipid Disorders *FMSHK Executive Committee Meeting	22	23
24	25					
31		26	27	28	29	30
* FMSHK Annual Dinner 2023						



Date / Time	Function	Enquiry / Remarks
1 FRI 2:00 PM	In-person The HKMA District Health Network (Kowloon West) CME Lecture Topic: Navigating the Landscape: Advances in Prostate Cancer Diagnosis and Treatment Organiser: The HKMA District Health Network Speaker: Dr Thomas Yiu-chung LAM Venue: Greater China Club, Unit A, 10/F, D2 Place ONE, 9 Cheung Yee Street, Lai Chi Kok, Kowloon	Mr Peter HO 3108 2514 1 CME Point
5 TUE 2:00 PM	In-person / Zoom Live HKMA-HKSH CME Programme 2023-2024 Topic: Advances in Proton Therapy for Cancer Treatment Organiser: The Hong Kong Medical Association and the Hong Kong Sanatorium & Hospital Speaker: Dr Amy Tien-ye CHANG Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept. 2527 8452 1 CME Point
6 WED 7:00 PM	Certificate Course in Cardiology 2023 Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Raymond Chi-yan FUNG	Ms Vienna LAM Tel: 2527 8898
7 THU 7:00 PM	Certificate Course in Ophthalmology 2023 - Module 2 Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Sunny Chi-lik AU, Dr Nancy Shi-yin YUEN	Ms Vienna LAM Tel: 2527 8898
8 FRI 2:00 PM	Zoom Live Topic: What's New in Hypertension Management? Organiser: The Hong Kong Medical Association Speaker: Dr Stanley Shek-yin AU	HKMA CME Dept. 2527 8452 1 CME Point
11 MON 2:00 PM	Zoom Live Topic: Antiplatelet Therapy in 2023: From Guidelines to Clinical Practice Organiser: The Hong Kong Medical Association Speaker: Dr LAU Chun-leung	HKMA CME Dept. 2527 8452 1 CME Point
12 TUE 2:00 PM	In-person The HKMA District Health Network (Tai Po) CME Lecture Topic: To-be-confirmed Organiser: The HKMA District Health Network Speaker: Dr Pierre CHAN Venue: Jade Garden (Tai Po Mega Mall), Shop 136-150, 1/F, Zone B, Tai Po Mega Mall, 8&10 On Pong Road, Tai Po	Mr Peter HO 3108 2514 1 CME Point
13 WED 2:00 PM	In-person / Zoom Live HKMA-CUHK Medical Centre CME Programme 2023 Theme: Women's Health Topic: Breast Health and Breast Surgery Organiser: The Hong Kong Medical Association and the CUHK Medical Centre Speaker: Dr Yolanda Ho-yan CHAN Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept. 2527 8452 1 CME Point
13 WED 7:00 PM	Certificate Course in Cardiology 2023 Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr David Ka-yip LO	Ms Vienna LAM Tel: 2527 8898
14 THU 2:00 PM	In-person / Zoom Live HKMA-HKSTP CME Programme 2023 Topic: To-be-confirmed Organiser: The Hong Kong Medical Association and the Hong Kong Science and Technology Park Speaker: To-be-confirmed Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept. 2527 8452 1 CME Point
19 TUE 2:00 PM	In-person / Zoom Live HKMA-GHK CME Programme 2023 Topic: Cataract/ Glaucoma Organiser: The Hong Kong Medical Association and the Gleneagles Hong Kong Hospital Speaker: Dr Jonathan Cheuk-hung CHAN Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept. 2527 8452 1 CME Point
20 WED 2:00 PM	In-person The HKMA District Health Network (Kowloon West) CME Lecture Topic: Lipid Management in High-risk Patients - What Else from LDL Reduction? Organiser: The HKMA District Health Network Speaker: Dr LUK Ngai-hong Venue: The HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Mr Peter HO 3108 2514 1 CME Point
21 THU 2:00 PM	Zoom Live Topic: Updates in Management of Lipid Disorders Organiser: The Hong Kong Medical Association Speaker: Dr Canice Lok-hang NG	HKMA CME Dept. 2527 8452 1 CME Point
21 THU 7:00 PM	FMSHK Executive Committee Meeting Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
31 SUN 8:00 PM	FMSHK Annual Dinner 2023 Organiser: The Federation of Medical Societies of Hong Kong; Venue: Run Run Shaw Hall, 1/F, Hong Kong Academy of Medicine Jockey Club Building Theme: Federation, Sing and Shine Dress code: Black Tie	Ms. Lucy LAU Tel: 2527 8898



Answers to Radiology Quiz

Answers:

1. Infraspinatus muscle is atrophied with denervation changes. (yellow arrow)
2. Labral cysts present at the spinoglenoid notch compress on the suprascapular notch, which cause infraspinatus denervation. (green arrow)

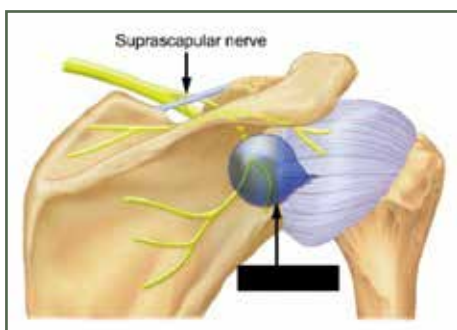
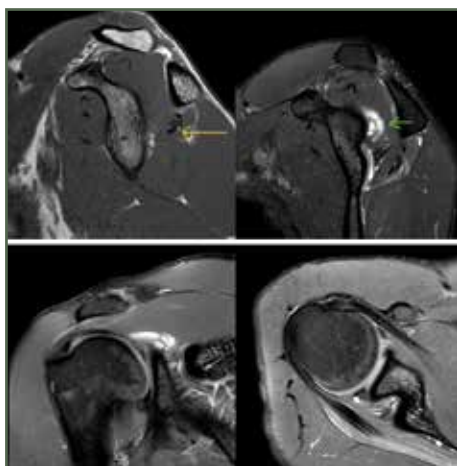


Photo reference: Suprascapular Neuropathy in Overhead Athletes: A Systematic Review of Aetiology and Treatment Options. Pratham Surya, Rahul Pankhania, Saif Ul Islam

Dr Thomas WL YIP
MBChB, FRCR

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The Federation of Medical Societies of Hong Kong
香港醫學組織聯會

The Federation Annual Dinner 2023

31 December 2023 (Sunday)

Run Run Shaw Hall, 1/F, Hong Kong Academy of Medicine Jockey Club Building



Federation, Sing and Shine

Subscribe a table to participate in the singing contest/ be our panel of judges!
OR simply book your tickets to join the Annual Dinner!

Rules of the Game (Singing Contest):

- Solo Contest / Group Contest
- Language of Songs: Cantonese/ Mandarin/ English
- Genres: Pop/ classics/ musical

Awards will be presented to the best singers!

Time: Dinner starts from 20:00 (Reception at 19:00)
Dress code: Black Tie
Ticket Price: HK\$1,688/ person OR HK\$18,568/ table
(Early Bird Offer: HK\$1,488/ person, valid until 8 December)
Special Offer for Member Societies: HK16,368/ table
(1 person FREE for a table of 12)



Performer:

Mr Ramon LO 羅啟豪先生
2nd Runner up of
'Midlife, Sing & Shine!'
《中年好聲音》第一季季軍

Enquiries:

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DESTINY-Breast03, the **first and only head-to-head** study vs
trastuzumab emtansine (T-DM1), demonstrated

UNPARALLELED PFS

THE NEW STANDARD OF CARE FOR 2L HER2+
METASTATIC BREAST CANCER¹



~4X
longer
mPFS[†]

ENHERTU demonstrated:

36%
reduction

in risk of death vs T-DM1 (HR: 0.64, 95% CI: 0.47, 0.87; P=0.0037) in a Phase 3 superiority trial^{*††}

~4X
longer
mPFS

as assessed by investigator:
28.8 vs 6.8 months mPFS in
TDM-1 (HR: 0.33, 95% CI: 0.26, 0.43; P<0.000001)^{†††}

**Consistent
OS benefit**

across key prespecified subgroups^{§1}

>2X
confirmed
ORR

vs TDM-1 (**78.5 vs 35.0%**; P<0.0001)[†]
• Around 1 in 5 patients achieved complete response in the ENHERTU arm¹

International Clinical Practice Guidelines recommend ENHERTU (trastuzumab deruxtecan) as the preferred regimen for 2L HER2+ metastatic breast cancer^{2,3}

*The P value for OS crossed the prespecified boundary (P=0.013) and was statistically significant; †Two-sided from stratified log-rank test; ††Nominal P value; †††Including those based on hormone-receptor status, previous pertuzumab treatment, baseline visceral disease, baseline brain metastases, and prior lines of systemic therapy (not including hormone therapy)

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen.¹

DESTINY-Breast03 is a Phase 3, multicenter, open-label, randomized, head-to-head study to compare efficacy and safety of ENHERTU vs T-DM1 of 524 adults with HER2+ unresectable and/or mBC who received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy. ENHERTU patients received 5.4 mg/kg IV Q3W until unacceptable toxicity or disease progression. Primary endpoint was PFS (BICR) according to RECIST v1.1. Secondary endpoints included OS, ORR, DOR, and PFS (investigator).¹⁻⁴

2L, second line; BICR, blinded independent central review; CI, confidence interval; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IV, intravenous; mBC, metastatic breast cancer; mDOR, median duration of response; mPFS, median progression-free survival; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; T-DM1, ado-trastuzumab emtansine

References: 1. Hurvitz SA, Hogg R, Chung WP, et al; on behalf of the DESTINY-Breast03 investigators. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: Updated results of the randomized, phase 3 study DESTINY-Breast03. Presented at: San Antonio Breast Cancer Symposium, December 6-10, 2022. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for Breast Cancer V.4.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed 17 November 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 3. Gennari A, Andre F, Barrios CH, et al. ESMO clinical practice guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol* 2021;32:1475-1495. 4. Trastuzumab deruxtecan Prescribing Information. Daiichi Sankyo Hong Kong Ltd. Inc. and AstraZeneca Hong Kong. Version: Aug 2022.

Enherthu abbreviated PI

Presentation: Enherthu powder for concentrate for solution for infusion 100 mg. **Active ingredient:** Trastuzumab deruxtecan. **Indication:** as monotherapy indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens. **Dosage:** 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Precautions:** Patients should be monitored for signs and symptoms of ILD/pneumonitis; neutropenia; left ventricular ejection fraction decrease; embryo-fetal toxicity to a pregnant woman; moderate and severe hepatic impairment. **Undesirable effects:** (Very Common ≥10%) Upper respiratory tract infection, neutropenia, anaemia, leukopenia, lymphopenia, thrombocytopenia, hypokalaemia, decreased appetite, headache, dizziness, interstitial lung disease, dyspnoea, cough, epistaxis, nausea, vomiting, diarrhoea, abdominal pain, constipation, stomatitis, dyspepsia, alopecia, transaminases increased, musculoskeletal pain, fatigue, pyrexia, ejection fraction decreased, weight decreased. (Common ≥1 - <10%) pneumonia, febrile neutropenia, dehydration, dysgeusia. Vision blurred, rash, skin hyperpigmentation, pruritus, oedema peripheral, blood alkaline phosphatase increased, blood bilirubin increased, blood creatinine increased, infusion-related reactions. **Full local prescribing information is available upon request.**

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