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Oncology

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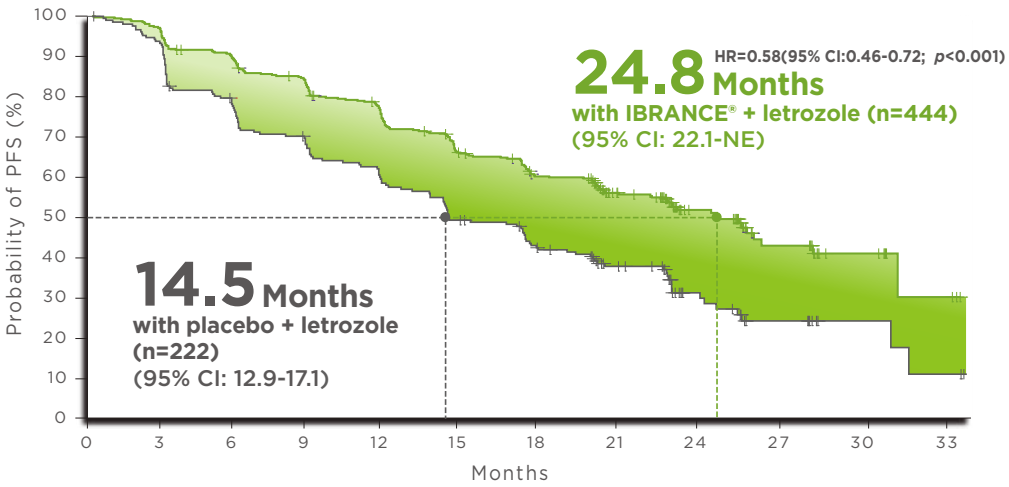
JOINING FORCES

INTRODUCING

IBRANCE®
palbociclib

The first-in-class CDK4/6 inhibitor[1] for postmenopausal women with ER+/HER2- metastatic breast cancer (mBC), in combination with letrozole as initial endocrine-based therapy.[2]

IBRANCE® + letrozole : mPFS>2 years in first-line setting[3]



RECOMMENDED AS A FIRST-LINE ENDOCRINE THERAPY OPTION BY THE NCCN GUIDELINES FOR POSTMENOPAUSAL PATIENTS WITH ER+/HER2- METASTATIC BREAST CANCER[4]

Study design: In PALOMA-2 , a double-blind, phase 3 study, 666 postmenopausal women with ER-positive, HER2-negative breast cancer, who had not had prior treatment for advanced disease, were randomly assigned in a 2:1 ratio to receive 125 mg of IBRANCE® per day, administered orally in 4-week cycles (3 weeks of treatment followed by 1 week off), or matching placebo. All the patients received 2.5 mg of letrozole per day, administered orally (continuous treatment). The primary end point was progression-free survival and the secondary end points were overall survival, objective response, clinical benefit response, patient-reported outcomes, pharmacokinetic effects, and safety.[3]

CDK4/6=cyclin-dependent kinases 4 and 6; ER=estrogen receptor; HER2=human epidermal receptor 2; CI=confidence interval; HR=hazard ratio; mPFS= median progression-free survival; NE=not estimable

Reference : 1. McCain J. First-in-Class CDK4/6 Inhibitor Palbociclib Could Usher in a New Wave of Combination Therapies for HR+, HER2- Breast Cancer. *P T.* 2015;40(8):511-20. **2.** IBRANCE® (palbociclib) Prescribing Information. Pfizer. Hong Kong. Version:Jul 2016. **3.** Finn RS, Martin M, Rugo HS, *et al.* Palbociclib and Letrozole in Advanced Breast Cancer. *N Engl J Med.* 2016; 375:1925-1936. **4.** NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. National Comprehensive Cancer Network (NCCN). Version 2.2016.

Abbreviated prescribing information
TRADE NAME: IBRANCE® (Palbociclib) **PRESENTATION:** Capsules 75 mg, 100 mg or 125 mg. **INDICATIONS:** Palbociclib is indicated in combination with Letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. **DOSAGE:** 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days. Palbociclib should be taken with food in combination with Letrozole 2.5 mg once daily given continuously. Management of some adverse reactions may require dose modification. Refer to the Package insert for complete recommendation. **CONTRAINDICATIONS:** Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. **WARNINGS & PRECAUTIONS:** Palbociclib should be prescribed and managed by a qualified physician who is experienced in the use of anti-cancer agents. **Effects on ability to drive and use machines:** Patients should exercise caution when driving or operating machinery because fatigue and dizziness have been reported with the use of Palbociclib. **Neutropenia and other Hematological Toxicities:** Monitor complete blood count before starting treatment and at the beginning of each cycle, on Day 14 of the first two cycles and as clinically indicated. Dose modification in starting treatment is recommended for patients who develop grade 3 or 4 neutropenia. Refer to the Package insert for complete recommendation. **QT Interval Prolongation:** Palbociclib may induce QT prolongation. **Infections:** Monitor patients for signs and symptoms of infection and treat as medically appropriate. Physicians should be aware of the increased risk of infection with Palbociclib and should inform patients to promptly report any episodes of fever. **Pulmonary Embolism:** Monitor patients for signs and symptoms of pulmonary embolism and treat as medically appropriate. (Please refer to the full prescribing Information for details) **INTERACTIONS:** Proton pump inhibitors under fasted conditions. CYP3A inhibitors, substrates and inducers; Antacids; Grapefruit, grapefruit juice, and products containing grapefruit extract; St. John's wort (Please refer to full prescribing information for details) **PREGNANCY AND BREAST FEEDING:** Palbociclib may cause fetal harm when administered to a pregnant woman. Palbociclib should not be used during pregnancy and is indicated for use in postmenopausal women. If females of childbearing potential are receiving this drug they should use adequate contraceptive methods during therapy and for at least 21 days after completing therapy. It is unknown whether Palbociclib is excreted in human milk. **SIDE EFFECTS:** Neutropenia; leukopenia; anemia; thrombocytopenia; upper respiratory infection; decreased appetite; peripheral neuropathy; dysgeusia; epistaxis; stomatitis; nausea; diarrhea; vomiting; alopecia; fatigue; asthenia; pyrexia. (Please refer to the full prescribing Information for details)
Reference: IBRANCE Hong Kong Prescribing Information (Version Jul 2016) Date of Preparation: October 2016 Identifier Number: IBRA1016
Full Prescribing Information is available upon request.

Pfizer Oncology

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Disclaimer

The Cover Shot

This is aerial photo taken by drone in June, 2018 in Muskoka, central Ontario.

Muskoka extends from Georgian Bay in the west, to the northern tip of Lake Couchiching in the south, to the western border of Algonquin Provincial Park in the east. Located approximately a two-hour car drive north of Toronto. Muskoka is spectacular at all times of the year, it is particularly renowned for its beautifully rugged landscape, it explodes with color during September and October, bursting with vibrant reds, yellows and oranges.

Dr Victor HSUE

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Editorial

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Editor

Dr Victor HSUE

It has been some time since the last issue on Clinical Oncology in The Hong Kong Medical Diary. During this period there have been tremendous changes in this field and the most encouraging progress is the birth and development of an era of immuno-oncology (IO). IO revolutionises the whole arena of treatment and prognosis in the management of both solid tumours and also haematological malignancies.

Lung cancer mortality in Hong Kong remains the highest among all cancers at more than 4,000 deaths in 2015. However, with the use of new targeted agents and immuno-oncology drugs, both the disease-free survival and quality of life of the patients have been much improved. In this issue, Dr Victor HF Lee will illustrate the latest management of non-small cell lung cancer including the new targeted agents and IO drugs.

Hormonal treatment of breast cancer has been around for more than a century since Beatson performed a bilateral oophorectomy on a woman with advanced disease on June 15, 1895. Tamoxifen has been in use for more than half a century. Since the development of aromatase inhibitors about 25 years, further advances in hormonal treatment have been slow. Fortunately, in the past few years, various studies on the use of m-Tor inhibitors and CDK 4/6 inhibitors on metastatic breast cancer have been published. Different combinations of hormonal treatment have now become the new standard of treatment. Dr Joyce SY Wong will review the most recent treatments, which can spare many patients with advanced disease from chemotherapy.

In Hong Kong there has been continuous increase in the incidence of prostate cancer in the last four decades. It is now the third commonest cancer with more than 1,800 new cases in 2015. Like breast cancer, it is hormonal sensitive and there are new advances and major studies published in the last few years showing improved survival. Dr Darren MC Poon will have a detailed discussion on these issues, incorporating novel treatments on advanced-stage disease.

Finally, there will be a discussion of advanced-stage gastric cancer by Dr Lam Ka-On and Dr Chan Wing-Lo. This is a difficult condition to treat, as most patients will have poor performance. The authors will lead us through the several lines of treatment that can be offered nowdays. This will include some new chemotherapeutic, targeted therapy and to immunotherapeutic agents, all serving to extend the patients survival and improve their quality of life.

While there are many new developments in treatment, myths about food and cancer persist. There will be a brief update on these issues. Unfortunately there are too many scams in the media particularly on the internet, which makes it difficult even for health care workers to find the truth. A good resource of information can be found in the third edition of Diet, Nutrition, Physical Activity and Cancer: a Global Perspective released in 2018. It is available on Internet on the World Cancer Research Fund web site: https://www.wcrf.org.

I hope it will not be too long before we update you again on the advancing edge of treatment options for various malignant conditions.

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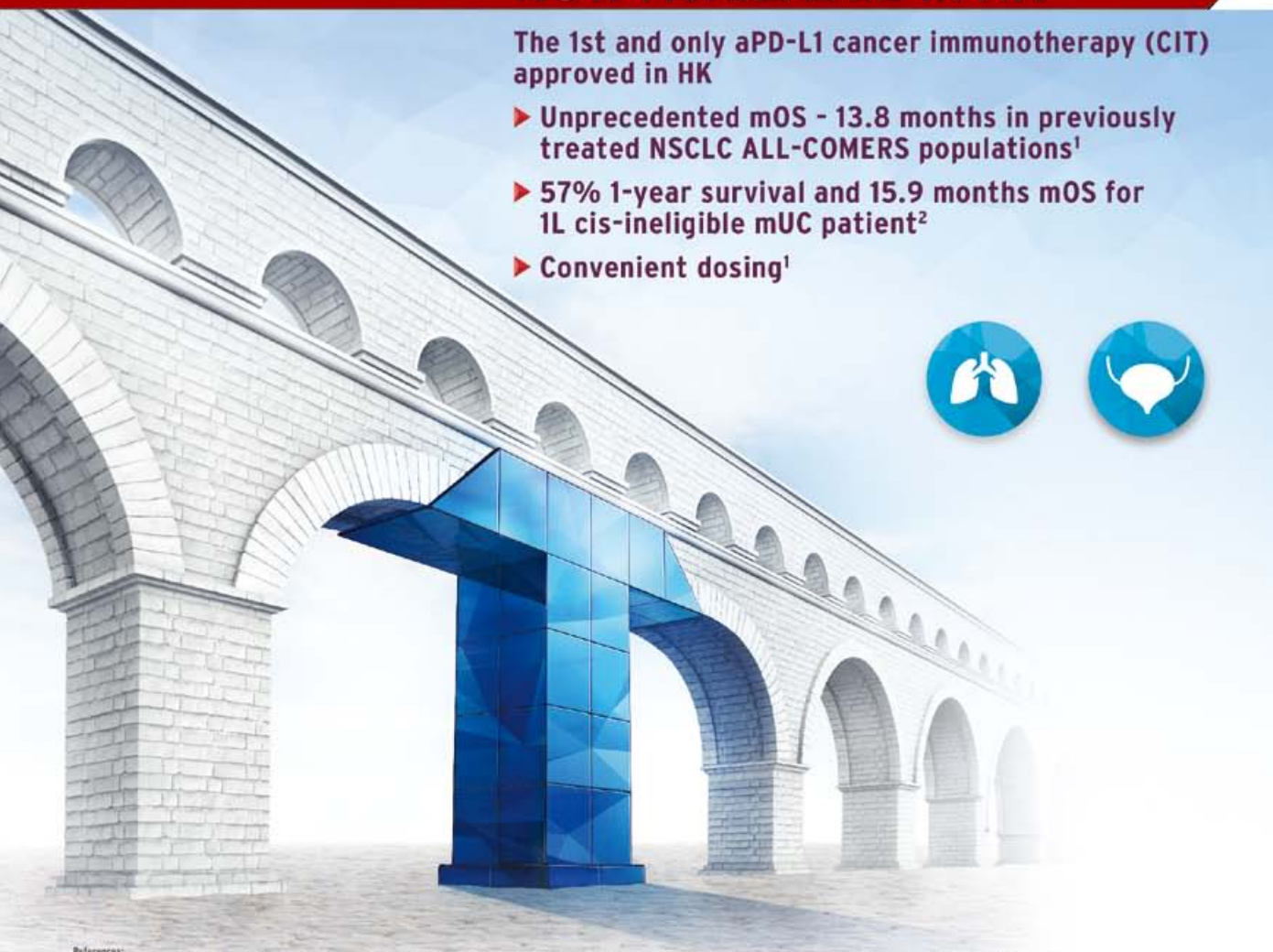

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References:
1. Rittmeyer A, Barlesi F, Waterkamp D, et al. OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389:255-265.
2. Balar AV, Galsky MD, Rosenberg JE, et al; IMvigor210 Study Group. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet*. doi: 10.1016/S0140-6736(16)32455-2.

Abbreviated Product Information

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Please refer to the full prescribing information for the management of immune-related adverse reactions.

Contraindications: None.

Adverse Effects: Patients experienced immune-related adverse effects, infections and infusion-related reactions. Refer to Warnings and Precautions section of the full prescribing information for more details. Adverse effects ≥ 10%: Pyrexia, pneumonia, decreased appetite, arthralgia, back pain, insomnia, dyspnea and cough. Laboratories abnormalities include hyponatremia, hypoalbuminemia, increased alkaline phosphatase, increased AST, increased ALT, increased creatinine, hypokalemia, hypercalcemia and increased total bilirubin. Immunogenicity is observed in study and did not appear to have a clinically significant impact on pharmacokinetics, safety or efficacy.

Full prescribing information should be consulted prior to prescribing.

Date of preparation: April 2018

PM-HK-0416-07-2018 Valid until 28/2/2020 or until change is required in accordance with the regulatory requirements, whichever comes first.

aPD-L1=anti-programmed death-ligand 1; 1L cis-ineligible=first-line cisplatin-ineligible; mOS=median overall survival; NSCLC=non-small-cell lung cancer; mUC = metastatic urothelial carcinoma

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Objectives:

To have more understanding on Clinical Cytogenetics and Genetics

Date	Topics	Speakers
12 Oct	Human Chromosomes and their identification	Dr. SIU Lai Ping , Lisa Scientific Officer, Queen Elizabeth Hospital
19 Oct	Genetic diseases, genetic ethics and genetic counselling	Dr. Lam Tak Sum, Stephen Cytogenetic Specialist, Hong Kong Sanatorium & Hospital
26 Oct	Cytogenetics in Prenatal Diagnosis	Mr. Chan Wing Kwong Consultant Clinical Geneticist, Hong Kong Sanatorium & Hospital
2 Nov	New Genetic Methods in IVF	Dr. Chan Tsun Leung, Chris Molecular Geneticist, Hong Kong Sanatorium & Hospital
9 Nov	Cytogenetics in Blood Cancers	Dr. WONG Wai Shan Haematology Consultant, Queen Elizabeth Hospital
16 Nov	Genetic tests and personalized medicine	Dr. MA Shiu Kwan, Edmond Haematology Consultant and Pathology Lab In-Charge Hong Kong Sanatorium & Hospital

Date : 12, 19, 26 October & 2, 9, 16 November 2018 (Every Friday)
Time : 7:00 pm – 8:30 pm
Venue : Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
Language Media : Cantonese (Supplemented with English; course materials are in Chinese / English)
Course Fee : HK$750 (6 sessions)
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Recent Advances in the Management of Advanced/Metastatic Non-small-cell Lung Cancer

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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 30 September 2018.

Introduction

Lung cancer is the most common cancer worldwide and the second most common in Hong Kong,[1] of which, non-small-cell lung cancer (NSCLC) constitutes about 80% of all cases of lung cancer while the rest includes small-cell lung cancer, lymphepithelioma-like carcinoma, neuroendocrine tumours, primary lymphoma and sarcoma, etc. Within NSCLC, adenocarcinoma is the predominant histology, followed by squamous cell carcinoma and large cell neuroendocrine carcinoma. Histological typing is crucial as the treatment of choice varies based on the different genetic aberrations within each histological phenotype. Twenty years ago, systemic platinum-based doublet chemotherapy was the only drug of choice for stage IV NSCLC.[2] The clinical benefit unfortunately was meagre if not none, let alone the chemotherapy-related toxicities and the detriment to quality of life. The median overall survival in that era was just between 6 and 9 months despite aggressive treatment. For the past 20 years, treatment for metastatic stage IV NSCLC has gone through enormous breakthrough. Discovery of driver and actionable mutations has led to the rapid development of tyrosine kinase inhibitors, which have been proven to result in significant improvement of progression-free survival (PFS), overall survival (OS) and probably as importantly, quality of life as compared to traditional systemic chemotherapy as first-line or subsequent line therapy for patients whose tumours harbour driver mutations. More recently, the unravelling of the intricate interplay between the host immune system and tumour cells has prompted the development of immune checkpoint inhibitors which are shown to be more beneficial when used alone, or in combination with systemic chemotherapy when compared to systemic chemotherapy as first-line treatment for stage IV disease. Similarly, treatment options for stage III locally advanced NSCLC have become more diversified, from the traditional 2-dimensional radiotherapy concurrent with the toxic chemotherapy, to concurrent chemoradiation with the contemporary radiation technique and the use of immune checkpoint inhibitors as consolidation therapy following concurrent chemoradiation.

All these major milestones of achievement in customised and personalised therapies have successfully preserved the quality of life and prolonged the median survival of these patients to more than three years nowadays. In this article, an overview of the latest management paradigm this once-thought deadly malignancy is presented.

Overview

For the past 20 years, treatment outcomes and survival of stage IV NSCLC have tremendously improved, mainly attributed by the discovery of gene/receptor mutations including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS-1, MET, BRAF, etc and the identification of the immune checkpoints responsible for tumour evasion from the host immune system.[2] The discovery and presence of these somatic driver genetic aberrations/mutations is definitely more clinically important and relevant to Asian patients, since half of the never-smoking patients with pulmonary adenocarcinoma have such actionable mutations as compared to only one fourth of patients in the Western countries (Fig 1).[3] EGFR mutations particularly on exon 19 (presented as

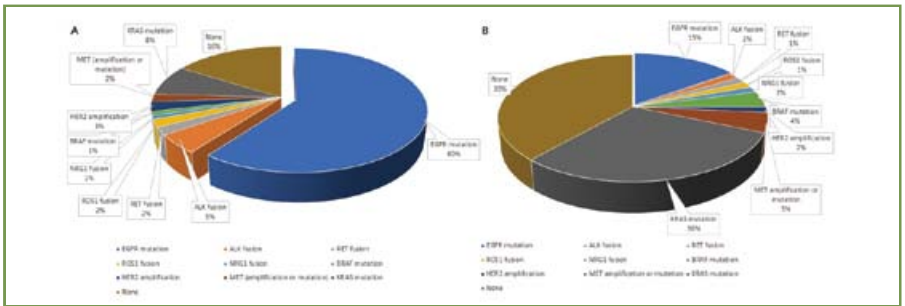

Fig 1. Incidence of oncogene-driven mutations of non-small-cell lung cancer in Asian (A) and Western countries (B) (adapted and modified from Saito M, Shiraishi K, Kunitoh H, et al. Gene aberrations for precision medicine against lung adenocarcinoma. Cancer Sci 2016;107(6):713-720)

deletional mutation) and exon 21 (presented as L858R point mutation) are present in half of the Asian patients with pulmonary adenocarcinoma, whose uncontrolled autophosphorylation of the tyrosine kinase in the intracellular domain can be effectively halted by the customised tyrosine kinase inhibitors (TKIs) leading to tumour cell death. Likewise, the identification of the ALK gene rearrangement in about 5-7% of the lung cancer population has also prompted the emergence of effective TKIs as well.[4] The clinical benefits and safety of these TKIs against EGFR and ALK mutations are further elaborated below.

Treatment for stage IV NSCLC with the epidermal growth factor receptor (EGFR) mutation

EGFR mutation is the most common actionable mutation in this locality and various generations of TKI have been evaluated extensively (Table 1).[5-15] Gefitinib and erlotinib, as first generation TKIs, have once been regarded as the standard first-line treatment for EGFR-mutant NSCLC as shown in international and regional phase III randomised-controlled trials (RCT). The pivotal IPASS (Iressa Pan-Asia Study) trial which was led by Hong Kong and other Asian countries, was the first one showing the preferential benefits of improved PFS with gefitinib compared to systemic chemotherapy with paclitaxel and carboplatin for advanced EGFR-mutated pulmonary adenocarcinoma. Gefitinib and erlotinib were proven comparably effective in both Asian and Western populations in the respective phase III RCT with a median PFS between 9 and 13 months as compared to 5 to 6 months brought by chemotherapy. The objective response rate up to 70% with TKIs in contrast to about 40% with chemotherapy is definitely another advantage of TKIs in patients who wish to derive a rapid response for their symptomatic bulky tumours. The side effect profiles are also in favour of TKIs over chemotherapy: easier administration as oral agents together with less immunosuppression, anorexia, vomiting and constipation, at the expense of more but manageable acneiform rash, stomatitis, diarrhoea and liver function derangement.

Table 1. Selected phase II/III randomized-controlled trials on efficacy of various generations of EGFR TKI as first-line treatment for EGFR-mutant stage IV NSCLC

Trial	Reference	Drug	Number of patients	Objective response (%)	Median progression-free survival (months)
IPASS	5	Gefitinib	1217	71.2	9.5
NEJSG	6	Gefitinib	230	73.7	10.8
WJTOG3405	7	Gefitinib	177	62.1	9.2
OPTIMAL	8	Erlotinib	165	83.0	13.1
EURTAC	9	Erlotinib	174	61.0	9.7
LUX-Lung6	10	Afatinib	910	66.9	11.0
LUX-Lung7	11	Afatinib	319	70.0	11.0
ARCHER 1050	12	Dacomitinib	452	75.0	14.7
FLAURA	14	Osimertinib	556	80.0	18.9

Recently second-generation TKIs (classified as such because of their irreversible binding to the tyrosine kinase domain as compared to the reversible binding in the first generation TKIs) including afatinib and dacomitinib were also found superior to chemotherapy and probably first-generation TKIs as first-line treatment for metastatic EGFR-mutated NSCLC as shown in combined analysis of LUX-Lung3 and LUX-Lung6 studies led by Asian institutions.[10] The latest phase IIB LUX-Lung7 study comparing afatinib to gefitinib as first-line treatment showed a meagre improvement of PFS by 0.1 month (median 11.0 vs. 10.9 months, p=0.017).[11] Similarly, a very recent phase III RCT comparing dacomitinib to gefitinib exhibited an improvement of PFS (median 14.7 months vs. 9.2 months, p<0.0001) and OS (median 34.1 months vs. 26.8 months, p=0.044) in the updated analysis.[12,13] However such survival improvement is also accompanied by an increased incidence of treatment-related grade 3-4 adverse events including more acneiform rash, diarrhoea and liver function derangement when compared to the first-generation TKIs, leading to a higher and earlier need of treatment interruption and subsequent dose reduction.

Though long-term responders to these first- and second-generation TKIs may be occasionally noticed, acquired drug resistance eventually develops, which is believed to originate from the emergence of clones with the ability of generating genetic alterations leading to clonal survival under the selective pressure of the current TKI treatment. The most common mechanism of acquired resistance is the presence of somatic T790M mutation on exon 20 of EGFR, accounting for about 50–60% of known mutations of acquired TKI resistance.[16-18]

Third-generation TKIs are specially designed to curb the acquired T790M mutation. Of them, osimertinib has been so far the only approved TKI for T790M-mutant NSCLC after initial failure to earlier generations of TKI. The AURA3 phase III RCT, comparing osimertinib to platinum-based chemotherapy, showed an overwhelming PFS advantage (median 10.1 months vs. 4.4 months, p<0.001) as further treatment in those who developed T790M mutation after progression to gefitinib, erlotinib or afatinib.[14]

A more encouraging result is the release of FLAURA study, a phase III RCT comparing osimertinib with first-generation TKI as first-line treatment for stage IV EGFR-mutant NSCLC. This is first study demonstrating the superiority of osimertinib over the first-generation TKI as first-line treatment even in the absence of T790M mutation.[15] This advantage was represented by an improvement of PFS from 10.2 months to 18.9 months (p<0.001). Of equal importance, osimertinib lacks the activity against wild-type EGFR, resulting in fewer rashes, diarrhoea and dry skin. One caution to note is the slightly increased incidence of non-fatal grade 1-3 prolonged QTc interval with osimertinib. To date, first-line treatment for stage IV EGFR-mutant NSCLC can be either first or second generation TKIs followed by osimertinib if T790M resistant mutation develops or upfront treatment with osimertinib, albeit meanwhile higher financial burden.

Other mechanisms of acquired resistance to TKIs include MET amplification, HER amplification/mutation, small cell transformation and rarely secondary mutations for instance BRAF mutation have been implicated.[14,19-24] Re-

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biopsy of growing tumours or more recently plasma/fluid biopsy for whole-exome/whole genome sequencing by next-generation sequencing platforms to detect other novel/rare acquired mutations after progression despite TKI therapy has caught rising attention recently which can guide the oncologists and patients for the most appropriate subsequent therapy.[16,25]

Treatment for stage IV NSCLC with rearrangement of ALK gene

The second most important mutation for NSCLC is ALK gene rearrangement. They were first discovered and described in Japan that about 7% of their patients who harboured echinoderm microtubule associated protein like-4 (EML4) rearrangement with ALK forming a fusion oncogene (EML4-ALK), as a result of an inversion rearrangement from inv(2) (p21;p23).[26,27] EML4 thus substitutes the extracellular and intramembranous parts of ALK and fuses with the juxta-membranous part.

ALK-directed targeted therapy has dramatically evolved for the past decade (Table 2). The first approved ALK inhibitor, crizotinib, has demonstrated promising anti-tumour activity against ALK-rearranged metastatic NSCLC in second-line setting after failure to first-line chemotherapy, producing a response rate of 65% and a median PFS of 7.7 months.[28] Soon it was also proven effective in first-line setting in PROFILE 1014, producing a response rate of 74% for crizotinib versus 45% for chemotherapy and longer median PFS of 10.9 months (versus 7.0 months for chemotherapy).[29] Furthermore, it was recently published as a planned subgroup analysis that the intracranial disease-control rates at 12 weeks (85% vs. 45%; p<0.001) and 24 weeks (56% vs. 25%; p=0.006) were significantly higher with crizotinib than with chemotherapy for patients with treated brain metastases.[30] Nevertheless, crizotinib was found to have low penetration to the central nervous system compared to the more novel generations of ALK inhibitors as described below. Intriguingly, crizotinib was found to be active against MET and ROS-1 rearrangement, which occurs in about 1% of NSCLC.[29-33] Therefore, it was FDA-approved for its use in ROS-1 rearranged metastatic NSCLC, as represented by its objective response rate of 72% and median PFS of 19.2 months in an expansion cohort of phase I study.[33] Another caveat associated with crizotinib is the development of acquired drug resistance within 1 to 2 years of treatment despite an initial promising objective response.

Ceritinib as second-line treatment after failure to crizotinib has evolved rapidly. A phase I study (ASCEND-1) including 122 patients who had advanced ALK-positive NSCLC investigated the efficacy and safety of ceritinib.[34] Among the 80 patients who failed crizotinib, ceritinib produced an objective response rate of 56%. The median PFS was 7.0 months for those who received ceritinib with daily dose 400 mg or higher. Furthermore, the intracranial disease control rate was 79% (15 out of 19 patients) in those without prior treatment with ALK inhibitor and 65% (49 out of 75 patients) in those previously pretreated with ALK inhibitor. Later it was also shown more efficacious than chemotherapy as first-line treatment with a median PFS of 16.6 months versus 8.1 months (p<0.00001) in ASCEND-4 study.[35] However it also brings significant toxicities including gastrointestinal side effects (nausea, vomiting, diarrhoea), liver function derangement, photopsia and others which lead to frequent treatment suspension and subsequent dose reduction, when taken as a full dose (750 mg daily) in a fasting status. A recent randomised study comparing a lower dose of ceritinib (450mg daily) taken with a low-fat meal attained a similar plasma concentration but fewer gastrointestinal toxicities as compared to a full dose of 750 mg daily in a fasting status.[36]

Alectinib is another selective ALK TKI with high CNS penetration compared to crizotinib and active against many secondary mutations which confer resistance to crizotinib. A phase II trial demonstrated an objective response of 48% and a median PFS of 8.1 months in patients who received alectinib for their ALK-positive crizotinib-resistant NSCLC.[37] The recent J-ALEX (using alectinib 300 mg twice daily dosing conducted in Japan) and ALEX (using alectinib 600 mg twice daily dosing conducted in countries outside Japan) trials all revealed a progression-free survival advantage (not reached for alectinib) over crizotinib (around 11 months) as first-line treatment, leading to approval by Food and Drug Administration (FDA) in the United States in this setting.[38,39] Moreover, the side effects are much fewer and more tolerable with alectinib.

The patterns of drug resistance after failure to crizotinib are less predictable compared to that seen after TKIs for EGFR-mutant NSCLC, though many resistant mutations can be effectively tackled by newer generations of ALK TKIs. Other novel potent ALK inhibitors including brigatinib, lorlatinib, ensartinib (X-396) have been comprehensively investigated as subsequent therapy following crizotinib failure and first-line therapy and the study results are highly awaited.

Table 2. Selected phase III randomized-controlled trials on efficacy of various generations of ALK TKI as first-line treatment for ALK-rearranged stage IV NSCLC

Trial	Reference	Drug	Number of patients	Objective response (%)	Median progression-free survival (months)
PROFILE 1014	29	Crizotinib	343	74.0	10.9
ASCEND-4	35	Ceritinib	376	72.5	16.6
J-ALEX	38	Alectinib (300mg twice daily)	207	92.0	Not reached
ALEX	39	Alectinib (600mg twice daily)	303	82.9	Not reached

Treatment for stage IV NSCLC without actionable mutations

Platinum-based doublet chemotherapy has been the standard treatment for non-targetable stage IV NSCLC. Platinum combined with the newer agent pemetrexed in the induction phase followed by pemetrexed alone in the maintenance setting was proven better than with the older chemotherapeutic agents in non-squamous NSCLC.[40] Addition of anti-vascular endothelial

growth factor monoclonal antibody bevacizumab to chemotherapy in both induction and maintenance phase results in further improvement in PFS in non-squamous NSCLC.[41,42]

Immunotherapy for stage IV NSCLC

Immunotherapy has gradually emerged as a new hope of treatment for advanced NSCLC. The greatest breakthrough is the discovery of immune checkpoints which play an important role of immune evasion of tumour cells from T-cell surveillance in the host immune system. Of these immune checkpoint inhibitors, programmed death-1 (PD-1) on the cytotoxic T-cells and the programmed death-ligand 1 (PD-L1) on the tumour cells have been recently catching the oncologist's attention, since their binding with each other can allow the tumour cells escape from the immune surveillance leading to tumour escape. The development of the monoclonal antibodies against these immune checkpoints can restore the immune surveillance which enhances tumour killing by the cytotoxic T-cells. Up to now, pembrolizumab (anti-PD1), nivolumab (anti-PD1) and atezolizumab (anti-PDL1) are approved immunotherapeutic agents for stage IV NSCLC. In particular, pembrolizumab was shown to confer both PFS (10.3 months vs. 6.0 months, p<0.001) and OS (median not reached for both arms, p=0.005) benefit as first-line treatment in patients with advanced NSCLC whose PD-L1 expression on at least 50% of tumour cells and had no sensitising EGFR mutation and ALK translocation, compared to standard chemotherapy in KEYNOTE-024 trial.[43] Very recently, pembrolizumab alone, or in combination with platinum-based chemotherapy as first-line treatment was shown to offer OS benefit across all PD-L1 expression categories for non-squamous metastatic NSCLC (KEYNOTE-042 & KEYNOTE-189), as presented in the Annual Meeting of American Society of Clinical Oncology (ASCO) this year.[44] It is also superior to chemotherapy in terms of PFS and OS improvement for squamous metastatic NSCLC (KEYNOTE-407).

Nivolumab together with ipilimumab (a monoclonal antibody against another immune checkpoint called CTLA-4) also brought a prolongation of PFS in patients whose tumours showed high tumour mutation burden as confirmed by next-generation sequencing, compared to chemotherapy alone as first-line treatment (CheckMate227).[45] Finally another PD-L1 inhibitor atezolizumab, when combined with bevacizumab and chemotherapy also significantly lengthened PFS and OS (19.2 months vs. 14.7 months, p=0.02) compared to bevacizumab and chemotherapy as first-line treatment (IMpower150).[46] Therefore, the choices of immunotherapy as first-line treatment for stage IV NSCLC without actionable mutations have become diversified. They can also be used as second-line or later settings if not administered earlier. Though the common side effects are usually mild, serious grade 3-4 immune-related adverse events in less than 5% of patients including interstitial lung disease, hepatitis, colitis, nephropathy and hypopituitarism can occur, and require urgent attention, treatment interruption and appropriate medical intervention.

Treatment for stage III NSCLC

Management of stage III NSCLC has been always diversified and evolving. Adjuvant chemotherapy with or without radiation therapy is the standard post-operative treatment for pathological stage III disease. Treatment choices for unresectable stage III NSCLC include concurrent chemoradiation with or without induction/adjuvant chemotherapy, preoperative chemotherapy followed by surgery, preoperative chemoradiation followed by surgery. New agents with pemetrexed in combination with cisplatin as the concurrent backbone with radiation therapy brings few toxicities compared to the traditional etoposide and cisplatin doublets.[47] Modern radiation techniques with intensity-modulated radiation therapy (IMRT) can better spare the lungs and the heart from unnecessary irradiation resulting in better treatment efficacy and safety.[48] However, further radiation dose escalation from the standard 60 Gy to 74 Gy and the use of anti-EGFR monoclonal antibody could not be translated to a better survival.[49]

Adjuvant targeted therapy as post-operative treatment for resected stage III NSCLC with actionable mutations is being evaluated and the results will be available within a couple of years (ADJUVANT/CTONG1104 for gefitinib, ALCHEMIST for erlotinib and ADAURA for osimertinib).[50]

Recently, the use of immune checkpoint inhibitor durvalumab (a PD-L1 monoclonal antibody) as consolidation therapy for 1 year following radical concurrent chemoradiation was shown to offer PFS benefit compared to concurrent chemoradiation alone (median 16.8 months vs. 5.6 months, p<0.0001). Mature data on OS and toxicity profile especially radiation pneumonitis/fibrosis are needed to confirm its long-term efficacy and safety.[51]

Summary

There has been an epoch-making breakthrough in managing locally advanced and metastatic NSCLC for the past two decades. The management paradigm becomes more personalised and it is hopeful that patients can derive a tailor-made management plan with their oncologists and families in the very near future.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Recent Advances in the Management of Advanced/Metastatic Non-small-cell Lung Cancer" by Dr Victor Ho-fun LEE 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 30 September 2018 Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

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

1. Non-small-cell lung cancer is the most common type of lung cancer.
2. Among non-small-cell lung cancers in Hong Kong, squamous cell carcinoma is the most common histological type.
3. The incidence of epidermal growth factor receptor (EGFR) mutation in Asian populations is much higher than that in Western countries.
4. Re-arrangement of the anaplastic lymphoma kinase (ALK) gene is the most common actionable mutation of non-small-cell lung cancer in Asian populations.
5. BRAF is one of the actionable mutations in stage IV non-small-cell lung cancer.
6. Osimertinib is the most potent tyrosine-kinase inhibitor with the longest progression-free survival against EGFR-mutant stage IV non-small-cell lung cancer.
7. Crizotinib has better penetration into the central nervous system compared to systemic chemotherapy as first-line treatment for ALK-rearranged stage IV non-small-cell lung cancer.
8. Crizotinib has better penetration into the central nervous system compared to alectinib as first-line treatment for ALK-rearranged stage IV non-small-cell lung cancer.
9. Alectinib has worse toxicity profiles compared to crizotinib as first-line treatment for ALK-rearranged stage IV non-small-cell lung cancer.
10. Concurrent chemoradiation is one of the standard treatments for physically fit patients who have unresectable stage III non-small-cell lung cancer.

ANSWER SHEET FOR SEPTEMBER 2018

Please return the completed answer sheet to the Federation Secretariat on or before 30 September 2018 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Recent Advances in the Management of Advanced/Metastatic Non-small-cell Lung Cancer

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Answers to August 2018 Issue

Managing Lower Urinary Tract Symptoms with Special Attention to Overactive Bladder in the Primary Care Setting

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

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Contemporary Management of Metastatic Prostate Cancer

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Introduction

The incidence of prostate cancer has dramatically increased in Hong Kong over the last decade. According to the 2015 Hong Kong Cancer Registry, prostate cancer is currently ranked the third commonest male cancer. The clinical management of patients with metastatic prostate cancer is challenging and the primary goals are extending their survival with symptoms alleviation and maintaining quality of life. The treatment paradigm of metastatic prostate cancer has been revolutionarily changed and the androgen-deprivation treatment (ADT) alone is no longer the standard of care currently. Enormous efforts in improving the treatment outcome in this group of patients have been rewarded with significant improvement in survival in the last 5 to 10 years. In this article, the latest advancement in the management of metastatic prostate cancer will be reviewed.

Metastatic prostate cancer without prior systemic treatment

Upfront chemotherapy and ADT

Continuous androgen-deprivation therapy (ADT), either in the form of surgical or medical castration, had been the gold standard for newly found metastatic prostate cancer from 1941 until 2015, when 2 landmark clinical trials (CHAARTED and STAMEPED) showed that ADT combined with 6 courses of docetaxel improved survival. Docetaxel is a taxane that binds tubulin and stabilises microtubules, thereby inhibiting mitosis and androgen-receptor signalling by disrupting nuclear transport of the receptor. In 2005, the Eastern Cooperative Oncology Group (ECOG) initiated a trial comparing standard ADT with or without 6 cycles of docetaxel in patients with metastatic hormone-sensitive prostate cancer (mHSPC; the CHAARTED study)[1]. In a recent updated analysis with a median follow-up time of 53.7 months, the group reported a median overall survival (OS) for the combined treatment arm of 57.6 months compared with 47.2 months for ADT alone (hazard ratio [HR], 0.72; 95% CI, 0.59–0.89; p=0.0018). Subgroup analysis indicates that this survival benefit is significant primarily in the group of patients (513 patients) with high-volume disease, defined by the presence of visceral metastases and/or 4 or more bone lesions (≥ 1 appendicular lesions) (51.2 months for the combined arm vs 34.4 months for ADT alone; HR, 0.63; 95% CI, 0.50–0.79; p<0.001). The combined arm was superior with regard to secondary study endpoints, including time to the development of castration resistance (either by prostate-specific antigen or clinical progression) and time to clinical progression.

The STAMPEDE trial was started in 2005 to test the same chemo-hormonal hypothesis, and the results reported were similar to those of CHAARTED[2]. With a median follow-up of 43 months for 2,962 patients, the latest published report from STAMPEDE showed a significant OS difference in favour of the combined ADT + docetaxel arm (HR, 0.78; 95% CI, 0.66–0.93; p=0.006). The median OS was 81 months (range, 30 months to not reached) for the combined arm vs 71 months (range, 32 months to not reached) for the ADT-alone arm. The combination arm also showed significantly improved failure-free survival. Toxicities observed in both CHAARTED and STAMPEDE included those previously reported with docetaxel and were mostly reversible.

These robust data have led to the incorporation of the upfront chemo-hormonal therapy as one of the treatment options for mHSPC in various treatment guidelines, including NCCN, EAU, NICE, etc. In Hong Kong, the chemo-hormonal therapy was introduced in early 2015. In a retrospective study conducted by the Hong Kong Society of Uro-Oncology (HKSUO), the preliminary efficacy, i.e. the time to castration-resistance, of chemo-hormonal therapy among patients with mHSPC in Hong Kong was comparable to the pivotal study (median time to castration-resistance: HKSUO vs CHAARTED, 19.5 vs 20.2 months). However, the high frequency of haematologic toxicities in Asian patients (the rates of grade 3 or 4 febrile neutropenia, neutropenia and anaemia were 12.5%, 40.6% and 3.1% respectively) highlights the importance of proper patient selection and pre-emptive use of granulocyte colony-stimulating factor[3].

Upfront abiraterone and ADT

Abiraterone, a potent and irreversible inhibitor of cytochrome-P (CYP)-17 that blocks androgen synthesis, has been shown in large scale randomised trials to confer significant survival advantage over placebo in both chemo-naïve metastatic castration-resistant prostate cancer (mCRPC) patients and mCRPC patients with prior chemotherapy. We will present these trials in a subsequent section below. Similar to the success story of docetaxel, investigators attempted to push abiraterone more forward in the newly diagnosed metastatic prostate cancer setting, and to investigate the upfront combination abiraterone and ADT versus ADT alone in mHSPC in 2 large clinical trials, namely LATITUDE and STAMPEDE.

LATITUDE was a multicentre, double-blind, randomised, phase III trial conducted in 34 countries that compared abiraterone plus prednisone (5 mg once daily) with dual placebos in men with high-risk metastatic prostate cancer at the time of diagnosis. "High-risk" disease was defined in this trial as two or more of the following three features: Gleason score ≥ 8, ≥ 3 bone metastases, and/or visceral disease. The coprimary endpoints were overall survival and radiographic progression–free survival (rPFS)[4].

STAMPEDE is a multi-arm, multi-stage trial in men being given long-term ADT. As such, the trial has included multiple interventions in a group of men, which includes not only men presenting with metastatic disease, but also men with high-risk locally advanced and recurrent prostate cancer. The abiraterone comparison of STAMPEDE (arm G vs arm A) was an open-label trial comparing abiraterone plus prednisolone (5 mg once daily) with ADT alone. The primary endpoint was overall survival[5].

Both trials have yielded striking and similar results, with 38% and 39% reductions in the risk of death in LATITUDE and STAMPEDE respectively, in men with metastatic disease. Neither trial has achieved sufficient follow-up to enable an estimate of the median survival gain, but informal extrapolation of the survival curves leads to an estimated median survival gain in excess of 20 months. The true magnitude of the survival gain in LATITUDE may be compromised by crossover after unblinding for those men who were still progression-free and receiving placebo.

Comparison between upfront abiraterone and docetaxel in combination with ADT in mHSPC

Up to now, there is no direct head-to-head randomised study to compare abiraterone versus docetaxel in combination with ADT in mHSPC. In the STAMPEDE study, there was an overlapping time from November 2011 to March 2013 when the patients receiving ADT could either be randomized into abiraterone or docetaxel. Using the data in this period of time, the direct and randomised comparative analysis of these two treatments in mHSPC showed no evidence of a difference in overall or prostate cancer-specific survival. Despite the similar effectiveness in these 2 promising treatment approaches, there remains a distinct difference. Firstly, the treatment with docetaxel, albeit having chemotherapy-related side effects, only takes 6 courses of 3-weekly treatment. In contrary, the abiraterone-prednisolone treatment will be continued until disease progression, implicating prolonged drug exposure. Secondly, there is a huge cost difference between abiraterone and docetaxel, which may bring in important considerations as far as financial burden is concerned.

In conclusion, from 2018, the androgen-deprivation therapy (ADT)should no longer be the standard of care for newly diagnosed metastatic prostate cancer, in particular to those with high volume disease (visceral metastasis, or ≥4 bone metastases) or high risk features (2 out of 3 features: GS ≥8, visceral metastasis or ≥3 bone metastases). Abiraterone or docetaxel should be considered and offered to these patients in order to prolong the overall survival and delay the time to develop symptomatic disease or skeletal events.

Metastatic castration-resistant prostate cancer (mCRPC)

Despite the initially high response rate to androgen deprivation therapy (ADT), the majority of prostate cancers will develop castration resistance inevitably over time, mostly within the first year of ADT in men with metastatic disease. Docetaxel was the first life-prolonging drug in men with mCRPC, and therefore, it has been the standard therapy for mCRPC in combination with prednisone since 2004. In the last few years, several new options for the treatment of metastatic castration-resistant prostate cancer (mCRPC) have been approved: the CYP17 inhibitor abiraterone, the androgen receptor (AR) antagonist enzalutamide, the taxane cabazitaxel, and the alpha-emitter radium-223 for men with bone metastases. All these therapeutic agents have proven survival benefit for mCRPC in clinical phase III studies (Fig. 1).

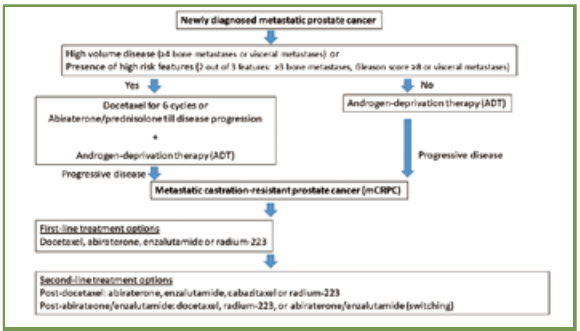

Fig. 1. Treatment algorithm for mCRPC

Abiraterone

Abiraterone acetate is an inhibitor of CYP17A1 and targets both 17a-hydroxylase and 17,20-lyase activities, thereby inhibiting residual androgen biosynthesis. In the COU-AA-301 study, abiraterone (1000 mg po) and prednisolone (5 mg BD) were shown to prolong overall survival (OS) in mCRPC patients who had prior docetaxel (OS; 15.8 vs 11.2 months; hazard ratio [HR] 0.74; p<0.0001)[6]. In chemo-naïve asymptomatic or mildly symptomatic mCRPC patients, abiraterone significantly prolonged the median OS in the abiraterone acetate group than in the placebo group (34.7 vs 30.3 months; HR 0.81; p=0.0033)[7]. Concurrent administration of low-dose prednisone (5 mg twice a day) with abiraterone is required to prevent hypertension, hypokalemia, and fluid retention resulting from adrenocorticotropic-generated mineralocorticoid excess. In the HKSUO's retrospective study, OS after abiraterone in Hong Kong chemo-naive patient cohort (18.1 months) was considerably shorter than that reported in the COU-AA-302 trial (34.7 months), and the OS was particularly short in those with visceral metastases (2.8 months)[8]. Conversely, abiraterone was efficacious in post-chemo patients. Abiraterone resulted in comparable pain control in both groups of patients and the most common grade 3 or above toxicities were hypertension (6.9/5.8 %) and hypokalaemia (3.4/3.8 %) in our chemo-naive/post-chemo patients.

Enzalutamide

Enzalutamide is a second-generation, nonsteroidal

androgen-receptor (AR) inhibitor that affects the AR pathway in three ways: it binds to the AR with greater relative affinity than bicalutamide, reduces the efficiency of AR nuclear translocation, and impairs both DNA binding to androgen response elements and recruitment of coactivators. The AFFIRM trial (n = 1,199) evaluated enzalutamide 160 mg po vs. placebo after chemotherapy, with overall survival (OS) as the primary endpoint. The median OS with 95% confidence interval (CI) was 18.4 (17.3 – not reached) vs. 13.6 (11.3 – 15.8) months, with a resulting hazard ratio (HR) of 0.63 (95% CI: 0.53-0.75, p<0.001)[9]. The PREVAIL trial (n = 1,717) evaluated enzalutamide vs. placebo in chemo-naïve patients, with radiographic progression-free survival (rPFS) and OS as co-primary endpoints[10]. The resulting HR for enzalutamide vs. placebo for rPFS was 0.19 (95% CI: 0.15–0.23, p<0.001) and for OS was 0.71 (95% CI: 0.60 – 0.84, p<0.001). In the HKSUO's retrospective study, we confirmed that earlier lines of enzalutamide treatment were associated with longer PFS and OS, more frequent PSA response, and less fatigue. The observed incidence of any fatigue (grade 1 or 2: 54.7%; grade 3 or 4: 9.4%) in the Hong Kong's cohort was much higher than those reported in the AFFIRM and PREVAIL trials. Physicians should be vigilant in detecting and managing enzalutamide-associated fatigue in the real-life setting.

Chemotherapy

Docetaxel (75 mg per square metre administered intravenously every 3 weeks) in combination with prednisolone, was the first life-prolonging drug in men with mCRPC since 2004. Two landmark clinical studies, TAX-327 and SWOG 9916, showed a significant survival benefit with docetaxel/prednisolone compared to the old-fashioned chemotherapy (mitoxantrone or estramustine) in mCRPC[11,12]. Since then, docetaxel/prednisolone had become the first-line treatment option for mCRPC patients. A retrospective study by Poon et al. evaluated the clinical efficacy and tolerability of docetaxel treatments for mCRPC patients in Hong Kong. It was shown that the median overall survival and progression-free survival were 20.8 months and 5.8 months respectively, which was comparable to the aforementioned TAX-327 and SWOG 9916 studies. The incidence of febrile neutropenia in this cohort is slightly higher than in previous reports (14% in the Poon et al. study vs. 3-5% in TAX 327 and SWOG 9916 studies). This is in concordance with the findings that Asians are susceptible to chemotherapy-induced myelosuppression. Preemptive primary G-CSF should be considered in Chinese mCRPC patients when docetaxel-based chemotherapy is initiated[13].

Cabazitaxel (at a dose of 25 mg per square metre administered intravenously every 3 weeks) , a second-generation semi-synthetic tubulin-binding taxane, led to significantly improved OS compared with mitoxantrone (both in combination with prednisone/ prednisolone) in men with mCRPC whose disease has progressed during or after docetaxel-based therapy in the TROPIC phase III trial (median survival 15.1 months in the cabazitaxel group and 12.7 months in the mitoxantrone group; HR 0.70; p < 0.0001)[14]. Febrile neutropenia and diarrhoea were significantly more frequent in the cabazitaxel group than in the control group.

Radium-223

Prostate cancer is well-known of its high propensity of bone metastases among other cancers, and up to 90% of patients with mCRPC developed bone metastases. Radium-223, an alpha-particle–emitting radionuclide, mimics calcium and carries a higher biological efficacy in causing tumour cell damage (dsDNA breaks) with more localised effects in bone as a result of the very short range of alpha radiation, and less penetration of the surrounding tissue and subsequently less bone marrow damage. In the ALSYMPCA study, the overall survival was significantly better for patients with mCRPC treated with radium-223 compared with placebo (median OS 14.0 vs 11.2 mo; HR 0.70; p = 0.002)[15]. Patients who had symptomatic bone metastases without visceral metastasis and without nodal metastases larger than 3 cm in the short-axis diameter were eligible for this study and the benefit of radium-223 in these patients remains uncertain. Adverse events with radium-223 were generally infrequent and included diarrhoea and a small number of cases of thrombocytopenia.

Sequencing of treatments in mCRPC

There are currently five approved systemic life-prolonging therapies for use in mCRPC, with yet little data to guide sequencing. Clinical factors such as the presence or absence of symptoms or visceral metastases, prior treatments and clinical response, potential side effects and preexisting toxicity, patient's preference, co-morbidities, life expectancy, quality of life, progression dynamics, tumour burden and eligibility for chemotherapy, should help to determine the best therapeutic choice at each treatment node. Those with asymptomatic bone-only disease could be considered for abiraterone, enzalutamide, or docetaxel in the first-line setting. For symptomatic disease, docetaxel could be used while radium-223 is another option if the disease is only present in the bone. In the second-line setting, radium-223 can be used in the appropriate clinical setting. Taxane chemotherapy could be used if a novel androgen-directed therapy was used in the first-line setting. Cabazitaxel, if docetaxel was previously used, should be considered. There are scarce data on the best treatment options in the third-line setting. In general, we recommend alternating between androgen-targeting agents and taxane chemotherapy. Finally, studies had shown AR-V7–encoding RNA expression in circulating tumour cells is associated with a poor prognosis and resistance to abiraterone and enzalutamide but not to taxanes[16,17]. The testing for the androgen receptor splice-variant AR-V7 may be a relevant treatment-specific biomarker to aid in the selection of androgen-targeting therapy versus chemotherapy in the future.

Conclusion

ADT alone should be no longer the standard of care for patients with metastatic prostate cancer from 2018 onwards. Consideration should be given to the use of upfront chemotherapy or abiraterone together with ADT in patients with newly diagnosed metastatic prostate cancer with high risk features or high volume disease in order to prolong their overall survival. It is a luxury dilemma for uro-oncologists on the optimal selection and sequencing of various life-prolonging therapies, including abiraterone, cabazitaxel, docetaxel,

enzalutamide, and radium 223, in patients who had progressive disease despite androgen-deprivation (mCRPC). Further clinical trials in evaluating the application of biomarkers, e.g AR-V7 splice variant, in treatment decisions are eagerly awaited.

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Kyprolis® (carfilzomib) for Injection

For relapsed/refractory multiple myeloma patients with at least 1 prior treatment,

RESPOND WITH KYPROLIS®

Two phase 3 studies supporting the efficacy and safety of Kyprolis® combined with lenalidomide and dexamethasone, and Kyprolis® with dexamethasone alone.[1,2]

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With KRd, almost 1 out of 3 patients reached complete response or better (31.8%)[3]	KYPROLIS® doubled the rate of complete response or better versus bortezomib (12.5% vs. 6.2%, $p<0.0001$)[3]	DEEP RESPONSE
Median PFS of 26.3 months with KRd in first relapse patients (vs. 17.6 months with Rd; HR=0.69, 95% CI: 0.57-0.83, $p<0.0001$)[3]	KYPROLIS® doubled the median progression-free survival versus bortezomib (18.7 vs. 9.4 months; HR=0.533, 95% CI: 0.44-0.65, $p<0.0001$)[3]	SUSTAINABLE EFFICACY
A favourable overall risk-benefit profile[1]	Significantly less peripheral neuropathy vs. Vd[4]	ACCEPTABLE RISK PROFILE

Kd: Kyprolis with dexamethasone; **KRd:** Kyprolis with lenalidomide and dexamethasone; **PFS:** Progression-free survival; **Rd:** Lenalidomide with dexamethasone; **Vd:** Bortezomib with dexamethasone

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Kyprolis® (Carfilzomib) Abbreviated Prescribing Information
Kyprolis® for injection 30 mg Kyprolis® for injection 60 mg
INDICATIONS Kyprolis in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. **DOSAGE AND ADMINISTRATION** The dose is calculated using the patient's baseline body surface area (BSA). Patients with a BSA greater than 2.2 m² should receive a dose based upon a BSA of 2.2 m². Dose adjustments do not need to be made for weight changes of less than or equal to 20%. *Kyprolis in combination with lenalidomide and dexamethasone:* When combined with lenalidomide and dexamethasone, Kyprolis is administered intravenously as a 10 minute infusion, on two consecutive days, each week for three weeks (days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (days 17 to 28). Each 28-day period is considered one treatment cycle. Kyprolis is administered at a starting dose of 20 mg/m² (maximum dose 44 mg) in cycle 1 on days 1 and 2. If tolerated, the dose should be increased on day 8 of cycle 1 to 27 mg/m² (maximum dose 60 mg). From cycle 13, the day 8 and 9 doses of Kyprolis are omitted. Treatment with Kyprolis combined with lenalidomide and dexamethasone for longer than 18 cycles should be based on an individual benefit-risk assessment, as the data on the tolerability and toxicity of carfilzomib beyond 18 cycles are limited. In combination with Kyprolis, lenalidomide is administered as 25 mg orally on days 1–21 and dexamethasone is administered as 40 mg orally or intravenously on days 1, 8, 15, and 22 of the 28 day cycles. Appropriate dose reduction for the starting dose of lenalidomide should be considered according to the recommendations in the current lenalidomide summary of product characteristics, for example for patients with baseline renal impairment. Dexamethasone should be administered 30 minutes to 4 hours before Kyprolis. *Kyprolis in combination with dexamethasone:* When combined with dexamethasone, Kyprolis is administered intravenously as a 30-minute infusion on two consecutive days, each week for three weeks (days 1, 2, 8, 9, 15, and 16) followed by a 12-day rest period (days 17 to 28). Each 28-day period is considered one treatment cycle. Kyprolis is administered at a starting dose of 20 mg/m² (maximum dose 44 mg) in cycle 1 on days 1 and 2. If tolerated, the dose should be increased on day 8 of cycle 1 to 56 mg/m² (maximum dose 123 mg). Treatment may be continued until disease progression or until unacceptable toxicity occurs. When Kyprolis is combined with dexamethasone alone, dexamethasone is administered as 20 mg orally or intravenously on days 1, 2, 8, 9, 15, 16, 22, and 23 of the 28 day cycles. Dexamethasone should be administered 30 minutes to 4 hours before Kyprolis. *Recommended dose modifications:* Dosing should be modified based on Kyprolis toxicity. Recommended actions and dose modifications are needed. See Prescribing Information for details. Special populations: *Renal impairment:* Appropriate dose reduction for the starting dose of lenalidomide in patients with baseline renal impairment should be considered. No starting dose adjustment for Kyprolis is recommended in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis based on available pharmacokinetic data. Renal function should be assessed at treatment initiation and monitored at least monthly or in accordance with accepted clinical practice guidelines, particularly in patients with lower baseline creatinine clearance (CrCL < 30 mL/min). Appropriate dose modifications based on toxicity should be made. There are limited efficacy and safety data on patients with baseline creatinine clearance < 30 mL/min. *Hepatic impairment:* The pharmacokinetics of Kyprolis has not been evaluated in patients with severe hepatic impairment. No starting dose adjustment is recommended in patients with mild or moderate hepatic impairment based on available pharmacokinetic data. Liver enzymes and bilirubin should be assessed at treatment initiation and monitored monthly during treatment with carfilzomib, regardless of baseline values, and appropriate dose modifications based on toxicity should be made. *Elderly patients:* Overall, the subject incidence of certain adverse events (including cardiac failure) in clinical trials was higher for patients who were ≥ 75 years of age compared to patients who were < 75 years of age. *Paediatric population:* The safety and efficacy of Kyprolis in paediatric patients have not been established. Method of administration: Kyprolis is to be administered by intravenous infusion The 20/27 mg/m² dose is administered over 10 minutes. The 20/56 mg/m² dose must be administered over 30 minutes. Kyprolis must not be administered as a bolus. **CONTRAINDICATIONS** • Hypersensitivity to the active substance or to any of the excipients • Women who are breast-feeding. As Kyprolis is administered in combination with other medicinal products, refer to their summaries of product characteristics for additional contraindications. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** As Kyprolis is administered in combination with other medicinal products, the summary of product characteristics of these other medicinal products must be consulted prior to initiation of treatment with Kyprolis. As lenalidomide may be used in combination with Kyprolis, particular attention to the lenalidomide pregnancy testing and prevention requirements is needed. Cardiac disorders: New or worsening cardiac failure (e.g. congestive cardiac failure, pulmonary oedema, decreased ejection fraction), myocardial ischaemia and infarction have occurred following administration of Kyprolis. Death due to cardiac arrest has occurred within a day of Kyprolis administration and fatal outcomes have been reported with cardiac failure and myocardial infarction. While adequate hydration is required prior to dosing in cycle 1, all patients should be monitored for evidence of volume overload, especially patients at risk for cardiac failure. Stop Kyprolis for grade 3 or 4 cardiac events until recovery and consider whether to restart Kyprolis at 1 dose level reduction based on a benefit/risk assessment. Electrocardiographic changes: There have been cases of QT interval prolongation reported in clinical studies. An effect of Kyprolis on QT interval cannot be excluded. Pulmonary toxicity: Acute respiratory distress syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in patients receiving Kyprolis. Some of these events have been fatal. Evaluate and stop Kyprolis until resolved and consider whether to restart Kyprolis based on a benefit/risk assessment. Pulmonary hypertension: Pulmonary hypertension has been reported in patients treated with Kyprolis. Some of these events have been fatal. Stop Kyprolis for pulmonary hypertension until resolved or returned to baseline and consider whether to restart Kyprolis based on a benefit/risk assessment. Dyspnoea: Dyspnoea was commonly reported in patients treated with Kyprolis. Stop Kyprolis for grade3 and 4 dyspnoea until resolved or returned to baseline and consider whether to restart Kyprolis based on a benefit/risk assessment. Hypertension: Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with Kyprolis. Some of these events have been fatal. If the hypertension cannot be controlled, the Kyprolis dose should be reduced. In case of hypertensive crises, stop Kyprolis until resolved or returned to baseline and consider whether to restart Kyprolis based on a benefit/risk assessment. Acute renal failure: Cases of acute renal failure have been reported in patients who received Kyprolis. Renal function should be monitored at least monthly or in accordance with accepted clinical practice guidelines, particularly in patients with lower baseline creatinine clearance. Reduce or stop dose as appropriate. Tumour lysis syndrome: Cases of tumour lysis syndrome (TLS), including with fatal outcome, have been reported in patients who received Kyprolis. Patients with a high tumour burden should be considered to be at greater risk for TLS. Ensure that patients are well hydrated before administration of Kyprolis in cycle 1, and in subsequent cycles as needed. Uric acid lowering medicinal products should be considered in patients at high risk for TLS. Evidence of TLS during treatment should be monitored for, including regular measurement of serum electrolytes, and managed promptly. Stop Kyprolis until TLS is resolved. Infusion reactions: Infusion reactions, including life-threatening reactions, have been reported in patients who received Kyprolis. These reactions can occur immediately following or up to 24 hours after administration of Kyprolis. Dexamethasone should be administered prior to Kyprolis to reduce the incidence and severity of reactions. Haemorrhage and thrombocytopenia: Cases of haemorrhage (e.g. gastrointestinal, pulmonary and intracranial haemorrhage) have been reported in patients treated with Kyprolis, often associated with thrombocytopenia. Some of these events have been fatal. Platelet counts should be monitored frequently during treatment with Kyprolis. Reduce or stop dose as appropriate. Venous thrombosis: Cases of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism with fatal outcomes, have been reported in patients who received Kyprolis. Patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Thromboprophylaxis should be considered based on an individual benefit/risk assessment. Hepatic toxicity: Cases of hepatic failure, including fatal cases, have been reported. Kyprolis can cause elevations of serum transaminases. Reduce or stop dose as appropriate. Liver enzymes and bilirubin should be monitored at treatment initiation and monthly during treatment with carfilzomib, regardless of baseline values. Thrombotic microangiopathy: Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome (TTP/HUS) have been reported in patients who received Kyprolis. Some of these events have been fatal. Signs and symptoms of TTP/HUS should be monitored for. If the diagnosis is suspected, stop Kyprolis and evaluate patients for possible TTP/HUS. If the diagnosis of TTP/HUS is excluded, Kyprolis can be restarted. The safety of reinitiating Kyprolis therapy in patients previously experiencing TTP/HUS is not known. Posterior reversible encephalopathy syndrome: Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving Kyprolis. Kyprolis should be discontinued if PRES is suspected. The safety of reinitiating Kyprolis therapy in patients previously experiencing PRES is not known. Contraception: Female patients of child bearing potential (and/or their partners) must use effective contraception measures during and for one month following treatment. Male patients must use effective contraception measures during and for 3months following treatment if their partner is pregnant or of childbearing potential and not using effective contraception. Carfilzomib may decrease the efficacy of oral contraceptives. Sodium content: This medicinal product contains 0.3 mmols (7 mg) of sodium per mL of reconstituted solution. This should be taken into consideration for patients on a controlled sodium diet. **UNDESIRABLE EFFECTS** The most serious adverse reactions that may occur during Kyprolis treatment include: cardiac toxicity, pulmonary toxicities, pulmonary hypertension, dyspnoea, hypertension including hypertensive crises, acute renal failure, tumour lysis syndrome, infusion reactions, thrombocytopenia, hepatic toxicity, PRES and TTP/HUS. In clinical studies with Kyprolis, cardiac toxicity and dyspnoea typically occurred early in the course of Kyprolis therapy. The most common adverse reactions (occurring in > 20% of subjects) were anaemia, fatigue, diarrhoea, thrombocytopenia, nausea, pyrexia, dysgeusia, respiratory tract infection, cough and peripheral oedema. **INTERACTIONS** Carfilzomib is primarily metabolised via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers. Caution should be observed when carfilzomib is combined with substrates of P-gp (e.g. digoxin, colchicine). **FERTILITY, PREGNANCY AND LACTATION** Women of childbearing potential/Contraception in males and females: Female patients of child bearing potential (and/or their partners) must use effective contraception measures during and for one month following treatment. Male patients must use effective contraception measures during and for 3 months following treatment if their partner is pregnant or of childbearing potential not using effective contraception. Pregnancy: There are no data from the use of carfilzomib in pregnant women. Studies in animals have shown reproductive toxicity. Kyprolis should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected. Please refer to the current lenalidomide summary of product characteristics. Breast-feeding: It is unknown whether carfilzomib or its metabolites are excreted in human milk. Based on its pharmacological properties, a risk to the suckling child cannot be excluded. Consequently, as a precautionary measure, breast-feeding is contra-indicated during and for at least 2 days after treatment with Kyprolis. Fertility: No fertility studies have been performed in animals. Please read the full prescribing information prior to administration and full prescribing information is available upon request. Kyprolis® is a registered trademark of Amgen Inc.

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Management of Advanced Gastric Cancer

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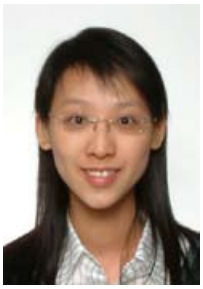


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Background

Gastric cancer is the sixth commonest cancer in Hong Kong and remains as the fifth leading cause of cancer mortality[1]. Surgery is the mainstay of curative treatment in stage I to III gastric cancer. However, gastric cancer at diagnosis in more than half of the patients is already too advanced and inoperable. Even for the cancer which is resectable upfront, the recurrence rate is still high at round 40-80%[2,3]. This article gives an overview on the latest development of systemic therapy for advanced/ metastatic gastric cancer. Fig. 1 shows the current treatment algorithm for advanced gastric cancer.

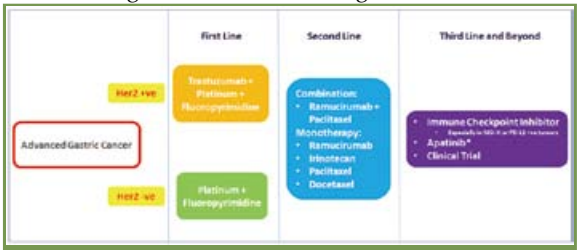

*Fig. 1. Simplified treatment algorithm for advanced gastric cancer. *Apatinib is not currently available in Hong Kong.*

First-line treatment

In the last decade, palliative chemotherapy has become the standard of care in patients with advanced/ metastatic gastric cancer. A Cochrane review and meta-analysis performed by Wagner et al demonstrated a significant survival benefit in favour of palliative chemotherapy compared with best supportive care (BSC) (HR 0.37; 95% CI 0.24-0.55, p<0.0001)[4]. This could be interpreted as an improvement in median survival (OS) from 4.3 months (BSC) to 11 months (with chemotherapy). Combination chemotherapy is superior to monotherapy (HR 0.83, 95% CI 0.74-0.93, p=0.001). Doublet chemotherapy with 5-fluorouracil (5FU) and platinum-based agents is the standard in Asian countries whilst the triplet chemotherapy with the addition of anthracycline is more commonly used in Western countries.

The newer oral fluoropyrimidines, capecitabine and S-1 (or more known as TS-1 in Hong Kong), have been investigated extensively in advanced gastric cancer, as monotherapy and as substitutions for infusional 5FU in combination regimens. The REAL-2 trial evaluated the role of oxaliplatin and capecitabine in chemotherapy-naive metastatic gastric cancer patients[5]. This phase III trial randomised over 1000 patients into four epirubicin-based regimens: 1) epirubicin, cisplatin, fluorouracil (ECF), 2) epirubicin, oxaliplatin, fluorouracil (EOF), 3) epirubicin, cisplatin, capecitabine (ECX), and 4) epirubicin, oxaliplatin, capecitabine (EOX). The efficacy of oral oxaliplatin and capecitabine were non-inferior to cisplatin and fluorouracil respectively, with manageable toxicity profiles, suggesting the more convenient capecitabine and oxaliplatin can safely replace the conventional infusional 5-FU and cisplatin respectively.

S-1 is another oral fluoropyrimidine and is commonly used as first-line regimen in Japan and Korea. The randomised phase III SPIRITS trial including 298 advanced gastric cancer patients showed a longer median OS and progression-free survival (PFS) in patients assigned to S-1 plus cisplatin than in those assigned to S-1 alone (OS: 13.0 months vs. 11.0 months, HR for death 0.77; 95% CI 0.61-0.98; p=0.04; PFS: 6.0 months vs. 4.0 months, HR for disease progression 0.57; 95% CI 0.44-0.73; p<0.0001)[6].

Around 7 to 34% of gastric cancer patients carry amplification or overexpression of HER2, which is an important biomarker and key driver of their tumorogenesis. HER2-positive status in gastric cancer was suggested to be associated with tumour invasion, high grade histology and poor prognosis. Trastuzumab is a monoclonal antibody that targets HER2. In TOGA study, a multi-centre, phase III randomised controlled trial, 594 patients with 3+ staining score on IHC or were FISH-positive (HER2: CEP 17 ratio ≥ 2) were randomised into chemotherapy (cisplatin/ carboplatin combined with fluorouracil) plus trastuzumab or chemotherapy alone[7]. The study revealed a significant improvement in median OS in trastuzumab plus chemotherapy compared with chemotherapy alone (13.8 months vs. 11.1 months, HR 0.74; 95% CI 0.60-0.91; p=0.0046). Median PFS was also significantly improved (median PFS: 6.7 vs 5.5 months, HR = 0.71; 95%CI: 0.59-0.85, p=0.0002). All grades of adverse events and serious adverse events (grade 3 or 4) were similar between the two groups. Since the publication of this promising result, combination of trastuzumab with platinum-based chemotherapy is the standard treatment for HER2-positive advanced gastric cancers.

Second-line chemotherapy

Most patients with metastatic gastric cancer are non-responders or eventually demonstrate disease progression after first-line chemotherapy. Several systematic reviews and meta-analyses have confirmed that second-line therapy resulted in significant survival

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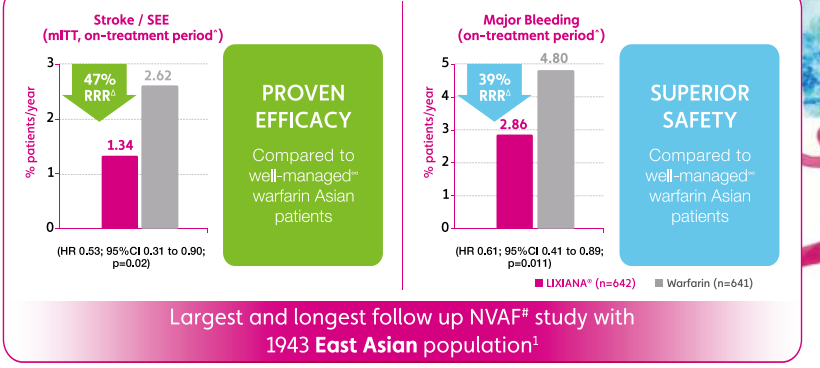

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benefit when compared with BSC alone in patients who failed first-line platinum-based chemotherapy[8-10]. A meta-analysis in 2013 involving 410 patients evaluated the benefit of second-line chemotherapy versus BSC. A significant reduction in the risk of death [HR = 0.64, 95% confidence interval (CI) 0.52-0.79, p< 0.0001] was observed with salvage chemotherapy[11].

Irinotecan and Taxanes

The chemotherapy agents commonly used in second-line setting include: irinotecan and taxanes (paclitaxel or docetaxel). A Korean phase III trial randomised 202 patients into two groups: salvage chemotherapy (single agent irinotecan or docetaxel) and best supportive care[12]. The study showed a longer median OS in the salvage chemotherapy group (5.3 months vs. 3.8 months, HR 0.657; 95% CI 0.485-0.891, P=0.007). There were no significant differences between docetaxel and irinotecan.

Ramucirumab

Ramucirumab is a fully human monoclonal antibody (IgG1) directed against vascular endothelial growth factor receptor 2 (VEGFR2). In the REGARD study, which involved 355 advanced gastric cancer patients who failed first-line treatment, both median OS (5.2 vs.3.8 months, HR 0.78, p=0.047) and PFS (2.1 vs. 1.3 months, HR 0.46, p<0.001) were longer in the group receiving ramucirumab compared with the best supportive care group[13]. The RAINBOW study, which randomised 665 patients to paclitaxel plus ramucirumab or paclitaxel alone, demonstrated a longer OS (9.6 vs. 7.4 months, HR 0.81, p=0.017) and PFS (4.4 vs. 2.9 months, HR 0.635, p<0.001) and improved objective tumour response (28% vs 16%, p<0.0001) in the combined paclitaxel and ramucirumab arm[14]. Fig. 2 showed a responding liver metastasis during second-line ramucirumab and paclitaxel treatment. Baseline and end-of-treatment results for global quality of life were similar in both groups. The results of these two studies have subsequently led to FDA and EMEA approval of ramucirumab as second-line treatment for advanced gastric cancer. The use of ramucirumab in combination with platinum-based therapy is now being studied in the first-line setting in a phase III RAINFALL study (NCT02314117) and an Asian phase II study (NCT02539225).

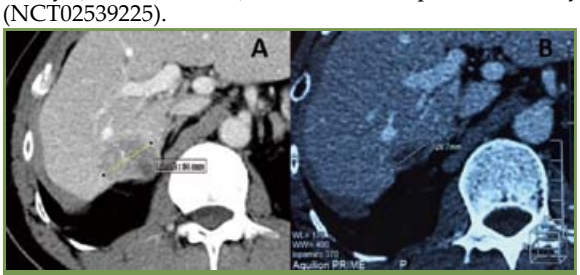

Fig. 2. Liver metastasis responding to second-line ramucirumab and paclitaxel. A) Liver metastasis at baseline; B) Same liver metastasis after 3 cycles.

Third-line treatment

With the development of new chemotherapies or targeted agents which are potentially more effective and less toxic, many patients can still maintain a good general condition after failing second-line therapies. A meta-analysis involving six RCTs showed third-line treatment could improve OS (HR 0.63; 95% CI 0.46-0.87, corresponding to an improvement in medial OS from 3.20 to 4.80 months) and PFS (HR 0.29; 95% CI 0.18-0.45) compared with BSC. However, the clinical benefits need to be balanced with more treatment-related toxicities[15].

Apatinib

Apatinib is an orally bioavailable, small-molecule tyrosine kinase inhibitor that highly selectively binds to and strongly inhibits VEGFR-2. In a phase III randomised controlled trial conducted in Mainland China , 267 participants with histologically confirmed advanced or metastatic adenocarcinoma of stomach who failed second-line chemotherapy were recruited and assigned to either apatinib (oral 850 mg daily) vs. placebo[16]. Apatinib showed significant clinical benefits compared with placebo in terms of OS (6.5 months vs. 4.7 months, HR 0.709, p=0.0156), PFS (2.6 months vs. 1.8 months, HR 0.444, p<0.001). The most common grade 3 to 4 non-haematologic adverse events were hand-foot syndrome, proteinuria, and hypertension. On the basis of the data from this phase III study, apatinib was approved in October 2014 by the China Food and Drug Administration for metastatic gastric or gastroesophageal junction adenocarcinoma after second-line chemotherapy.

Immune-checkpoint inhibitors

The use of immune checkpoint inhibitors has been approved for a number of cancers such as metastatic melanoma and renal cell carcinoma but they are still relatively new comers in gastric cancer.

The most clinically-relevant immune checkpoint inhibitors (CPIs) are monoclonal antibodies that target the programmed cell death-1/programmed cell death-ligand 1 (PD-1/PD-L1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) pathways. CTLA-4 and PD-1 are co-inhibitory receptors found on the cell surface of T cells. Upon binding to their corresponding ligands (CD80/86 and PD-L1/-L2, respectively) which are expressed on tumour cells, T cell activities become suppressed and the inflammatory responses against cancer cells are halted. The mechanism of CPIs is to bind to PD-1/PD-L1 and/or CTLA-4 either on T cells or cancer cells. This blockade would prevent immune suppression and can therefore unleash a renovated anti-tumour immune response.

In ATTRACTION-2 study, which was a double-blind, placebo-controlled phase 3 randomised controlled trial conducted in Japan, South Korea and Taiwan, nivolumab (anti-PD-1 monoclonal antibody) has shown its superior efficacy compared with placebo in advanced gastric cancer patients, irrespective of PD-1/PD-L1 expression, who have failed at least two lines of systemic treatment (OS: 5.32 months vs. 4.14 months, p<0.0001; 12-month OS: 26.6% vs. 10.9%)[17]. Nivolumab is also well-tolerated with acceptable safety profile. These encouraging results support the use of CPI as a treatment option in refractory gastric cancer. However, clinical benefits are marginal and there remains room for better selection of patients for this kind of treatment.

In another multicentre, open-label, phase 1b study (KEYNOTE-012), pembrolizumab, another anti-PD-1 monoclonal antibody, showed durable tumour

control and manageable safety profile for the heavily pre-treated, PD-L1 positive gastric cancer patients (OS 11.4 months, PFS 1.9 months, ORR 22.2%)[18]. Studies on pembrolizumab are now in progress, including KEYNOTE-062 comparing cisplatin and 5FU +/- pembrolizumab as first-line monotherapy and KEYNOTE-061 comparing pembrolizumab vs paclitaxel as second-line agent. Avelumab, a human IgG1 anti-PD-L1 antibody, has also been tested in phase III RCTs as first-line and third-line settings for gastric cancer (JAVELIN Gastric 100 and JAVELIN Gastric 300). The results are eagerly awaited and potentially practice-changing.

Conclusion

There has been significant progress in the management of advanced gastric cancer in the last decade. The rational combination of chemotherapy and targeted therapy against angiogenesis have improved the treatment options for many patients who were previously deemed refractory. Immune checkpoint inhibitors have shown early promise though more mature data are awaited before it can be widely, and wisely, adopted. In the future, researches in molecular subtyping, tumour microenvironment and immune landscape should help better understanding of this deadly cancer and enable development of more effective therapies.

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Symptoms have included hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritis, and urticaria. *Hypocalcemia and Mineral Metabolism*: Hypocalcemia may be exacerbated by the use of Prolia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia. Hypocalcemia following Prolia administration is a significant risk in patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis. Adequately supplement all patients with calcium and vitamin D. *Osteonecrosis of the Jaw (ONJ)*: ONJ has been reported in patients receiving Prolia. The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with Prolia in patients with concomitant risk factors. All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with Prolia. While on treatment, invasive dental procedures should be performed with caution and avoided in close proximity to Prolia treatment. *Atypical Subtrochanteric and Diaphyseal Femoral Fractures*: Atypical low-energy or low trauma fractures of the shaft have been reported in patients receiving Prolia. Patients should be advised to report new or unusual thigh, hip, or groin pain. *Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment*: Following discontinuation of Prolia treatment, fracture risk increases, including the risk of multiple vertebral fractures. If Prolia treatment is discontinued, consider transitioning to an alternative antiresorptive therapy. *Serious Infections*: Serious infections leading to hospitalization were reported in clinical trial. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis. *Dermatologic Adverse Reactions*: Dermatitis, eczema, and rashes. Most of these events were not specific to the injection site. Consider discontinuing Prolia if severe symptoms develop. Musculoskeletal Pain: Severe and occasionally incapacitating bone, joint, and/or muscle pain. Consider discontinuing use if severe symptoms develop. *Suppression of Bone Turnover*: In clinical trials treatment with Prolia resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. *Osteonecrosis of the external auditory canal*: Osteonecrosis of the external auditory canal has been reported with denosumab. Possible risk factors include steroid use and chemotherapy and/or local risk factors such as infection or trauma. **INTERACTIONS** In subjects with postmenopausal osteoporosis, Prolia (60 mg subcutaneous injection) did not affect the pharmacokinetics of midazolam, which is metabolized by cytochrome P450 3A4 (CYP3A4), indicating that it should not affect the pharmacokinetics of drugs metabolized by this enzyme in this population. **PREGNANCY AND LACTATION** *Pregnancy*: Pregnancy: Category X. *Breast-feeding*: It is not known whether Prolia is excreted into human milk. **PEDIATRIC, GERIATRIC AND RENAL IMPAIRMENT** *Pediatric*: Prolia is not recommended in pediatric patients. *Geriatric*: No overall differences in safety or efficacy were observed in clinical studies between elderly patients and younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. *Renal Impairment*: No dose adjustment is necessary in patients with renal impairment. **UNDESIRABLE EFFECTS** The most common adverse reactions reported with Prolia in patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. The most common adverse reactions reported with Prolia in men with osteoporosis are back pain, arthralgia, and nasopharyngitis. The most common (per patient incidence ≥ 10%) adverse reactions reported with Prolia in patients with bone loss receiving androgen deprivation therapy for prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer are arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials. The most common adverse reactions leading to discontinuation of Prolia in patients with postmenopausal osteoporosis are back pain and constipation. **OVERDOSE** There is no experience with overdosage with Prolia.
Abbreviated Prescribing Information Version: HKPROPI01
Please read the full prescribing information prior to administration and full prescribing information is available on request.
Prolia® is a registered trademark owned or licensed by Amgen Inc., its subsidiaries, or affiliates.

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4IC_567

Vectibix® (panitumumab)

PRIME

Adding Vectibix® to FOLFOX

≥30% TUMOR SHRINKAGE AT WEEK 8*[1]

59% for **Vectibix®** + FOLFOX

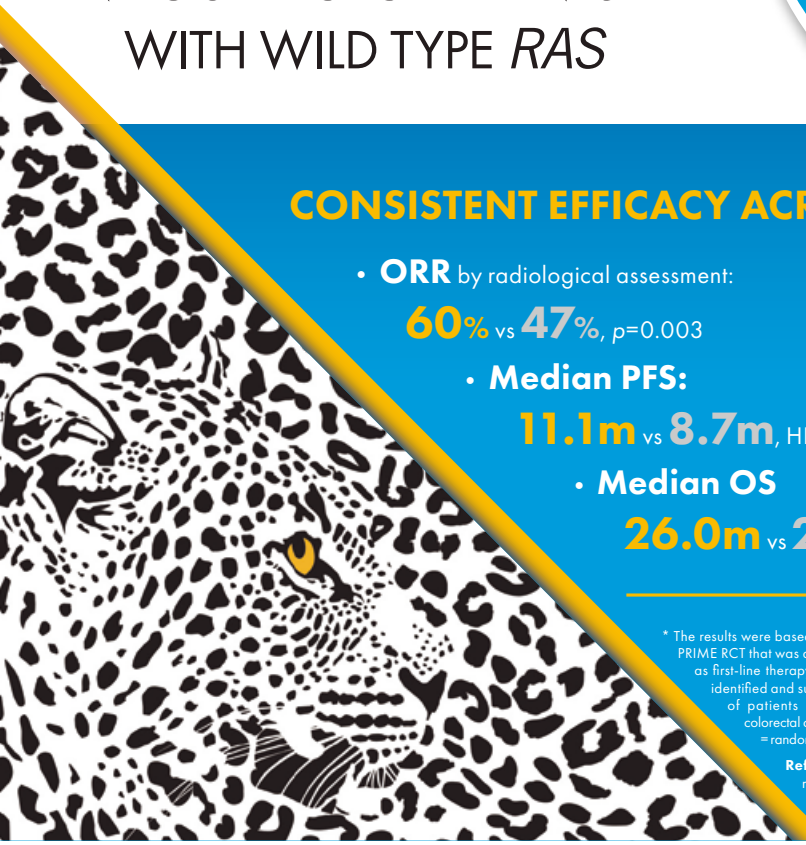
vs

38% for FOLFOX alone

Difference: 21.8%†, 95%CI: 12.7-30.9; p<0.001

Enhancing the chance for surgical resection of tumors

AGGRESSIVELY ACHIEVING **EARLY TUMOR SHRINKAGE** IN YOUR mCRC PATIENTS WITH WILD TYPE *RAS*



CONSISTENT EFFICACY ACROSS ENDPOINTS:[1]

- **ORR** by radiological assessment:
  60% vs **47%**, p=0.003
- **Median PFS:**
  11.1m vs **8.7m**, HR=0.74, 95%CI: 0.61-0.89, p=0.0015
- **Median OS**
  26.0m vs **20.2m**, HR=0.76, 95%CI: 0.63-0.92, p=0.0057

* The results were based on pre-defined prospective-retrospective extended *RAS* mutation analysis of phase III PRIME RCT that was designed to compare the efficacy and safety of Vectibix®-FOLFOX4 with FOLFOX4 alone as first-line therapy in 1,183 patients with mCRC. 505 patients without *RAS* mutation, i.e., WT *RAS* were identified and subject to OS/ PFS analyses. †59.4 % of patient receiving Vectibix® + FOLFOX, and 37.6% of patients receiving FOLFOX alone had ≥30% tumor shrinkage at week 8. mCRC = metastatic colorectal cancer, ORR = objective response rate, PFS = progression free survival, OS = overall survival, RCT = randomized clinical study, WT = wild-type

References: 1. Douillard JY, Siena S, Peeters M, *et al*. Impact of early tumour shrinkage and resection on outcomes in patients with wild-type *RAS* metastatic colorectal cancer. *Eur J Cancer* 2015;51:1231-1242.

Vectibix® (Panitumumab) Abbreviated Prescribing Information
Vectibix® Concentrate for Solution for Infusion 20 mg/mL

INDICATIONS: Vectibix is indicated for the treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC) as first-line in combination with FOLFOX or FOLFIRI, as second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan) and as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. **DOSAGE AND ADMINISTRATION:** The recommended dose of Vectibix is 6 mg/kg of bodyweight given once every two weeks. Prior to infusion, Vectibix should be diluted in sodium chloride 9 mg/mL (0.9%) solution for injection to a final concentration not to exceed 10 mg/mL. Modification of the dose of Vectibix may be necessary in cases of severe (≥ grade 3) dermatological reactions. There is no clinical data to support dose adjustments in the elderly. Vectibix must be administered as an intravenous (IV) infusion via an infusion pump, using a low protein binding 0.2 or 0.22 micrometer in-line filter, through a peripheral line or indwelling catheter. The recommended infusion time is approximately 60 minutes. If the first infusion is tolerated, then subsequent infusions may be administered over 30 to 60 minutes. Doses higher than 1000 mg should be infused over approximately 90 minutes. A reduction in the rate of infusion of Vectibix may be necessary in cases of infusion-related reactions. Vectibix must not administered as an intravenous push or bolus. **CONTRAINDICATIONS:** Vectibix is contraindicated in patients with a history of severe or life-threatening hypersensitivity reactions to the active substance or to any of the excipients, and in patients with interstitial pneumonitis or pulmonary fibrosis. The combination of Vectibix with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant RAS mCRC or for whom RAS mCRC status is unknown. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE:** *Dermatological reactions and soft tissue toxicity:* Dermatologic related reactions, a ph armacologic effect observed with epidermal growth factor receptor (EGFR) inhibitors, are experienced with nearly all patients (approximately 90%) treated with Vectibix. Severe (NCI-CTC grade 3) skin reactions were reported in 34% an d life-threatening (NCICTC grade 4) skin reactions in < 1% of patients who received Vectibix in combination with chemotherapy. *Pulmonary complications:* Cases of interstitial lung disease (ILD), both fatal and non-fatal, have been reported, mainly from the Japanese population. *Electrolyte disturbances:* Progressively decreasing serum magnesium levels leading to severe (grade 4) hypomagnesaemia have been observed in some patients. Other electrolyte disturbances, including hypokalaemia, have also been observed. *Infusion related reactions:* Across monotherapy and combination mCRC clinical studies, infusion-related reactions (occurring within 24 hours of an infusion) were reported in approximately 4% of Vectibix-treated patients, of which < 1% were severe (NCI-CTC grade 3 and grade 4). Hypersensitivity reactions occurring more than 24 hours after infusion have been reported including a fatal case of angioedema that occurred more than 24 hours after the infusion. *Acute renal failure:* Acute renal failure has been observed in patients who develop severe diarrhoea and dehydration. *Ocular toxicities:* Serious cases of keratitis and ulcerative keratitis have been rarely reported in the post-marketing setting. Vectibix should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration. *Patients with ECOG 2 performance status:* Assessment of benefit-risk is recommended prior to initiation of Vectibix in combination with chemotherapy for treatment of mCRC. A positive benefit-risk balance has not been documented in patients with ECOG 2 performance status. **INTERACTIONS:** The infusion line should be flushed with sodium chloride solution before and after Vectibix administration to avoid mixing with other medicinal products or Intravenous solutions. Vectibix should not be administered in combination with IFL chemotherapy or with bevacizumab-containing chemotherapy. **PREGNANCY, LACTATION AND FERTILITY:** *Pregnancy:* There are no adequate data from the use of Vectibix in pregnant women. *Breast-feeding:* It is unknown whether panitumumab is excreted in human breast milk. *Fertility:* Animal studies have shown reversible effects on the menstrual cycle and reduced female fertility in monkeys. Panitumumab may impact the ability of a woman to become pregnant. **UNDESIRABLE EFFECTS:** Very Commonly reported adverse reactions occurring in ≥ 20% of patients were gastrointestinal disorders [diarrhoea (50%), nausea (41%), vomiting (27%), constipation (23%) and abdominal pain (23%)]; general disorders [fatigue (37%), pyrexia (20%)]; metabolism and nutrition disorders [anorexia (27%)]; infections and infestations [paronychia (20%)]; and skin and subcutaneous disorders [rash (45%), dermatitis acneiform (39%), pruritus (35%), erythema (30%) and dry skin (22%)]. **OVERDOSE:** Doses up to 9 mg/kg have been tested in clinical trials. There have been reports of overdose at doses up to approximately twice the recommended therapeutic dose (12 mg/kg). Adverse events observed included skin toxicity, diarrhoea, dehydration and fatigue and were consistent with the safety profile at the recommended dose.

Abbreviated Prescribing Information Version: CDS24IPI08_EUSmPC042015API
Please read the full prescribing information prior to administration and full prescribing information is available on request.

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Hormonal Management of Advanced Carcinoma of the Breast

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Introduction

Breast cancer is the most common female cancer in Hong Kong. According to the Hong Kong Cancer Registry 2015, there were 3,900 new cases; the lifetime risk of having breast cancer was 1 in 16 females before 75 years old and the median age of having the disease was 56. There were 16.3% and 7.1% of patients presenting as stage III and IV disease respectively. Since about 60% of breast cancer patients had hormonal positive disease, hormonal therapy is one of the key treatments in breast cancer.

Choice of treatment

After decades of using tamoxifen alone, newer hormonal treatment and targeted therapy combination has emerged especially in the recent few years. Besides tamoxifen, newer choices include aromatase inhibitors (steroidal: anastrozole and letrozole; non steroidal: exemestane) selective oestrogen receptor downregulator (fulvestrant). Options of target therapy using with or without combination of hormonal therapy include mTOR inhibitors (everolimus), CDK4/6 inhibitor (palbociclib, ribociclib and abemaciclib) and PIK3CA inhibitors (taselisib).

The choice of treatment of hormonal positive advanced breast cancer (HR+ve ABC) depends on several factors: menopausal status, extend of disease, any visceral crisis due to cancer, hormonal therapy naïve or sensitive or resistant, last treatment regime and HER2 status.

Premenopausal patients

Since most of the hormonal therapy, except tamoxifen, are used in postmenopausal patients, the strategies we commonly use for premenopausal women are chemotherapy or tamoxifen or combined hormonal therapy. For the combined hormonal therapy, we would suggest ovarian suppression first, so that the patients can achieve menopausal status, followed by treatment as for postmenopausal women. Ovarian suppression can be achieved by using LHRH agonists subcutaneously or bilateral oophrectomy surgically or ovarian ablation by radiotherapy.

Postmenopausal patients

For postmenopausal hormonal receptor (HR) positive disease, it is clinically a spectrum rather than a discrete type of disease behaviour. It ranges from a rapidly progressive disease to a very indolent disease. For the rapidly progressive disease that threatens visceral organs (visceral crisis), we tend to use chemotherapy as the first line treatment owing to its fast onset of action and high response rate. For very indolent disease with no visceral metastases, such as limited bone metastasis only, hormonal therapy alone is good enough for disease control. Do note that hormonal therapy can give a good response despite a longer time to respond compared with chemotherapy.

In between the two extremes of disease behaviour, we can consider using hormone plus CDK4/6 inhibitors or mTOR inhibitors.

Sequencing of combining targeted therapy and hormonal therapy

Sequencing of treatment depends on the last line of treatment and hormonal sensitivity. If the patient has de novo metastatic breast cancer or the disease progresses after at least 12 months of last hormonal therapy, that would be classified as hormonal sensitive disease. Hormonal therapy alone can be the first line of treatment. Aromatase inhibitors (steroidal: anastrozole and letrozole; non steroidal: exemestane) perform similarly; the median time to progression (TPP) is around 12 months compared with tamoxifen, which is 6 months.[1]

The selective oestrogen receptor downregulator (fulvestrant) 500 mg subcutaneously shows superior progression free survival (PFS) than anastrozole; if there is no visceral metastasis, the PFS can be up to 22.3 months.[2,3]

Combining hormonal therapy with targeted therapy e.g. CDK 4/6 inhibitors could give a PFS around 25 months.[4] Second line treatment will depend on which first line therapy has been given. Treatment choices include hormonal therapy alone, hormonal therapy plus mTOR inhibitors (everolimus) or CDK 4/6 inhibitors. For aromatase inhibitors alone, the TTP is shorter than in the first line, which is around 3-4 months for exemestane.[5]

The use of mTOR inhibitors (everolimus) combining with exemestane can reverse the hormonal resistance of exemestane alone giving the median PFS of 7.8 months verses 3.2 months.[6]

Aromatase inhibitors or fulvestrant combined with CDK4/6 inhibitors in second line setting can give a 7-8 months PFS. [7]

The latest ASCO meeting presented a study showing PIK3CA inhibitor (Taselisib) plus estrogen receptor downregulator (fulvestrant) has 7.4 months PFS compared with fulvestrant, alone which is 5.4 months. [8]

Side effects

Apart from the side effect from the hormonal therapy alone, combination therapy can give rise to additional side effects. Common side effects of CDK 4/6 inhibitors include neutropenia, anaemia, diarrhoea etc; (Table 1). mTOR inhibitors can lead to stomatitis, rash, diarrhea, pneumonitis, etc. (Table 2)

Table 1: Adverse events with CDK4/6 inhibitors single-agent and combination therapy data form PALOMA3 Study.[9] Reproduced from Turner NC, Ro J, André F, et al. Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer. N Engl J Med. 2015;373(3):209-219. doi:10.1056/NEJMoa1505270.

	Palbociclib-Fulvestrant		
Event	Any Grade	Grade 3	Grade 4
Any adverse event	97.7%	58.6%	10.7%
neutopenia	78.8%	53.3%	8.7%
fatigue	38%	2%	0
nausea	29%	0	0
anaemia	26.1%	2.6%	0
diarrhea	19.1%	0	0
URI	19.4%	0	0
constipation	16.8%	0	0

Table 2 : Side effects of mTOR inhibitor Everolimus (EVE) Plus Exemestane (EXE)[10] Reproduced from Yardley DA, Noguchi S, Pritchard KI, et al. Everolimus Plus Exemestane in Postmenopausal Patients with HR+ Breast Cancer: BOLERO-2 Final Progression-Free Survival Analysis. Adv Ther. 2013;30(10):870-884. doi:10.1007/s12325-013-0060-1.

	Everolimus + exemestane		
Adverse event	All grade (%)	Grade 3 (%)	Grade 4 (%)
Stomatitis	59	8	0
Rash	39	1	0
Fatigue	37	4	<1
Diarrhea	34	2	<1
Nausea	31	<1	<1
Weight decreased	28	1	0
pneumonitis	16	3	0
hyperglycenmia	14	5	<1
Decreased appetite	31	1	0

Approximate cost per month in Hong Kong Dollars Tamoxifen: $140; Aromatase inhibitors: $2800; Faslodex : $10,000; CDK 4/6 inhibitors: 30,000-40,000; mTOR inhibitors: $35,000

Conclusion

The choice of treatment in advanced breast cancer depends on factors including the tumour biology and the disease pace/ behaviour. Furthermore, consideration of the efficacy, side effects and financial concern serve as key issues for the decision. New generation target therapies adding onto the hormonal therapy can prolong the disease free survival and overall survival in modern days. (Fig. 1)

Fig. 1 shows a summary of the treatment choices as reference.

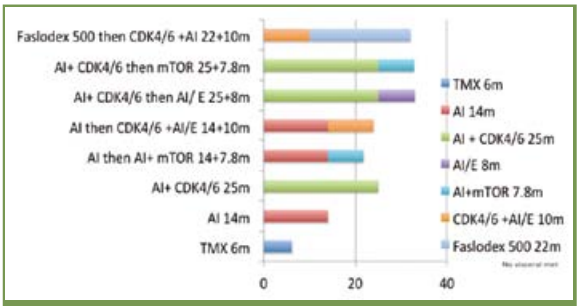

Fig.1. Extrapolation on different lines with different treatment combination (PFS) in months based on different studies of tamoxifen, aromatase inhibitors, selective oestrogen receptor downregulator, CDK 4/6 inhibitors and mTOR inhibitors; there were no head-to head trials for direct comparison.

AI: aromatase inhibitors; TMX: tamoxifen
CDK4/6: CDK 4/6 inhibitor
E: endocrine therapy (hormonal therapy)
mTOR: mTOR inhibitor

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START WITH ZYKADIA® NEW APPROVED DOSE:

450 mg Once Daily with Food

FOR THE TREATMENT OF ALK+ ADVANCED NSCLC[1]*

THEY HAVE PLANS. YOU HAVE *Zykadia®*.

*ZYKADIA® is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

Reference: 1. ZYKADIA® Hong Kong Prescribing Information.

Abbreviated Prescribing Information:
Important note: Before prescribing, consult full prescribing information. **Presentation:** Hard gelatin capsules containing 150 mg ceritinib; film-coated tablets containing 150 mg ceritinib. **Indications:** Zykadia is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). **Dosage and administration: Adults:** Recommended dose is 450 mg taken orally once daily with food at the same time each day. Maximum recommended dose is 450 mg taken orally once daily with food. • Temporary dose interruption and/or dose reduction of Zykadia therapy may be required based on individual safety and tolerability. • Zykadia should be discontinued in patients unable to tolerate 150 mg taken once daily with food. **Children (below the age of 18 years):** The safety and efficacy of Zykadia have not been established in pediatric patients. **Special populations:** • No dose adjustment necessary in patients with mild to moderate renal impairment. Use caution in patients with severe renal impairment. • No dose adjustment necessary in patients with mild hepatic impairment. • Not recommended in patients with moderate to severe hepatic impairment. • The limited data on the safety and efficacy of ceritinib in patients aged 65 years and older do not suggest that a dose adjustment is required in elderly patients. There are no available data on patients over 85 years of age. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients of Zykadia. **Warnings and precautions:** • **Hepatotoxicity:** Monitor with liver laboratory tests prior to the start of treatment every 2 weeks during the first three months of treatment and monthly thereafter. In patients who develop transaminase elevations, more frequent monitoring of liver transaminases and total bilirubin should be done as clinically indicated. • **Interstitial lung disease (ILD) / Pneumonitis:** Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes of ILD/pneumonitis, and permanently discontinue Zykadia in patients diagnosed with any-grade treatment-related ILD/pneumonitis. • **QT interval prolongation:** Avoid use of Zykadia in patients with congenital long QT syndrome. Periodic monitoring with electrocardiograms (ECGs) and periodic monitoring of electrolytes (e.g., potassium) is recommended in patients with pre-existing bradycardia (heart rate less than 60 beats per minute [bpm]), patients who have a history of or predisposition for QTc prolongation, patients who are taking anti-arrhythmics or other medicinal products that are known to prolong the QT interval and patients with relevant pre-existing cardiac disease and/or electrolyte disturbances. In case of vomiting, diarrhea, dehydration, or impaired renal function, correct electrolytes as clinically indicated. Permanently discontinue Zykadia in patients who develop QTc greater than 500 msec or greater than 60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. Withhold Zykadia in patients who develop QTc greater than 500 msec on at least 2 separate ECGs until recovery to baseline or a QTc less than 481 msec, then reinitiate Zykadia by reducing dose by 150 mg. • **Bradycardia:** Avoid use of Zykadia in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Monitor heart rate and blood pressure regularly. In cases of symptomatic bradycardia that is not life-threatening, withhold Zykadia until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, evaluate the use of concomitant medications, and adjust the dose of Zykadia if necessary. Permanently discontinue Zykadia for life-threatening bradycardia if no contributing concomitant medication is identified; however, if associated with concomitant medication known to cause bradycardia or hypotension, withhold Zykadia until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, and if concomitant medication can be adjusted or discontinued, reinitiate Zykadia by reducing dose by 150 mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring. • **Gastrointestinal adverse reactions:** No patients required dose reduction or discontinuation of Zykadia due to diarrhoea, nausea or vomiting. Monitor and manage patients using standards of care, including anti-diarrheals, anti-emetics, or fluid replacement, as clinically indicated. Dose interruption and dose reduction should be employed as necessary. If vomiting occurs during the course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose. • **Hyperglycemia:** Monitor fasting serum glucose prior to the start of Zykadia treatment and periodically thereafter as clinically indicated. Initiate or optimize anti-hyperglycemic medications as indicated. • **Elevations of lipase and/or amylase:** Monitor lipase and amylase prior to the start of Zykadia treatment and periodically thereafter as clinically indicated. **Pregnancy, lactation, females and males of reproductive potential: Pregnancy:** Should not be used during pregnancy unless the clinical condition of the woman requires treatment with ceritinib. **Lactation:** A decision should be made whether to discontinue breast-feeding or discontinue/abstain from Zykadia taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **Females of reproductive potential:** Females of reproductive potential to be advised to use a highly effective method of contraception while taking Zykadia and for up to 3 months after discontinuation. **Infertility:** The potential for Zykadia to cause infertility in male and female patients is unknown. **Adverse drug reactions: Very common (≥10%):** Liver laboratory test abnormalities, diarrhoea, fatigue, abdominal pain, nausea, decreased appetite, vomiting, weight decreased, constipation, blood creatinine increased, rash, anaemia, and oesophageal disorder. **Common (≥1 to <10%):** Electrocardiogram QT prolonged, hyperglycaemia, amylase increased, vision disorder, pericarditis, hypophosphataemia, lipase increased, bradycardia, abnormal liver function tests, pneumonitis, renal failure, hepatotoxicity, and renal impairment. **Uncommon (≥0.1 to <1%):** Pancreatitis. **Interactions: • Strong CYP3A inhibitors:** Avoid concurrent use of strong CYP3A inhibitors. If concomitant use of strong CYP3A inhibitors is unavoidable, including but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, and nefazodone, reduce the Zykadia dose by approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, resume the Zykadia dose that was taken prior to initiating the strong CYP3A inhibitor. • **P-gp inhibitors:** Exercise caution with concomitant use of P-gp inhibitors and carefully monitor adverse drug reactions. • **Strong CYP3A and P-gp inducers:** Avoid concomitant use of strong CYP3A inducers, including but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort (*Hypericum perforatum*). Exercise caution with concomitant use of P-gp inducers. • **Agents that affect gastric pH:** Caution is advised with concomitant use of proton pump inhibitors, as exposure of ceritinib may be reduced. • **CYP3A and CYP2C9 substrates:** Avoid co-administration of Zykadia with CYP3A substrates known to have narrow therapeutic indices (e.g., astemizole, cisapride, ciclosporin, ergotamine, fentanyl, pimozide, quinidine, tacrolimus, alfentanil and sirolimus) and CYP2C9 substrates known to have narrow therapeutic indices (e.g., phenytoin and warfarin). • **CYP2A6 and CYP2E1 substrates:** Exercise caution with concomitant use of CYP2A6 and CYP2E1 substrates and carefully monitor adverse drug reactions. • **Agents that are substrates of transporters:** Caution should be exercised with concomitant use of BCRP substrates (e.g. rosuvastatin, sulfasalazine) and P-gp substrates (digoxin, dabigatran, colchicine, pravastatin) and ADRs carefully monitored. • **Drug-food/drink interactions:** Zykadia should be taken with food. For patients who develop a concurrent medical condition and are unable to take Zykadia with food, Zykadia can be taken on an empty stomach as the alternate continued treatment regimen, in which no food should be eaten for at least two hours before and one hour after the dose. Patients should not alternate between fasted and fed dosing. Dose must be adjusted properly. Patients should be instructed to avoid grapefruit or grapefruit juice as they may inhibit CYP3A in the gut wall and increase the bioavailability of ceritinib. **Packs and prices:** 150 mg (50's, 3 x 50's), not all pack size are marketed. **Legal classification:** P1S1S3 **Reference:** EU APR 2018, including 0920s (ASCEND-8)

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Lifestyle But Not Food Alone to Prevent Cancer

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Introduction

It has been 5 years since the article "Myths about Food and Cancer: Hope, Hype or Hoax" was published in the September 2013 issue of The Hong Kong Medical Diary[1]. Unlike other areas in oncology where tremendous progress can be made within five years, many queries surrounding food and cancer remain unsolved. A search on Google on July 1, 2018 on the phrase" Food causing cancer" produces 449,000,000 links whereas a search on" anti-cancer food" produces 490,000,00 links. The overwhelming data and links on the Internet not only reflect the abundance of data, but more importantly they indicate the vast demand from the general public for knowledge on these subjects. The wide availability of user-provided content in online social media facilitates the aggregation of people pursuance around common interests, worldviews, and narratives. The World Wide Web (WWW) enables the rapid dissemination of unsubstantiated rumors and conspiracy theories that often elicit rapid, large, yet naive social responses[2] .

The fake health information and misleading ideas on cancer can be detrimental to patients' health. Anxious cancer patients and their relatives are particularly vulnerable to these scams, the latter making their already difficult lives even more miserable. Worse still, there are mix-ups in preclinical animal data obtained in experimental conditions with human data, and in potential carcinogenic food with food to be avoided in cancer patients. For example, cancer patients are often advised by well intentioned friends and relatives not to eat sugary food or milk product or even protein. It is true that sugary food and food high in fat and /or starch, like snacks, bakery foods and desserts should be limited only because they can lead to obesity[4] .

But if this health advice is given to cancer patients, who is often suffering from malnutrition, the consequence can be devastating. There is no strong evidence that sugary food and drinks carry a direct causation relationship with cancer nor dairy products are associated with any cancer risk. On the contrary, systematic review and meta-analysis suggest an inverse relation between the incidence of colorectal cancer and dairy intake[7] .

It is a common misconception that if a food item is associated with increased risk of cancer then the patient should avoid taking that food item even after cancer is developed. It is important to understand that causation factor is different from promoter factor. For example, obesity may have contributed to endometrial carcinoma but losing weight will not help to control the already developed malignancy.

British Research Council suggests certain lifestyle modification to prevent 4 out of 10 cancers[42]. A recent study[22] by David Whiteman from Australia showed that 16,700 (about 40 percent) of cancer deaths in Australia in the year 2013 are potentially preventable, including smoking (active/passive) which accounts for 23 percent, while dietary factors, obesity and infection (e.g. HCV and HPV) are each accountable for about 5 percent[22]. Similarly, another study by American Cancer Society estimated that diet with excessive red/processed meat and insufficient vegetables has contributed to 1.3% and 3% of cancer deaths respectively[33] . Despite only 5 percent of cancer can be prevented by modification of diet and no data suggests that a particular food can worsen the malignant disease, the belief that cancer patients (particularly among Chinese people) should abstrain from taking certain food (戒口) is so popular that almost any single food item can be named as the culprit.

Smoking

Smoking is obviously the most important carcinogenic factor and will not be discussed in detail in this article. According to a recent report[17], about 30% of human cancer can be attributed to smoking. Contrary to most public belief, electronic cigarette , although not entirely safe, was regarded by most reseachers to be able to reduce the incidence of cancer[18,19]. However, long term results are currently lacking and are eagerly awaited.

Obesity

Current data suggest that the increase of body weight (body fatness) is a much more important factor than previously thought. According to Vital Signs report from the Centers for Disease Control and Prevention (CDC)[20], obesity has been linked to 13 types of different cancers (Fig.1). Obesity can cause many metabolic and endocrine abnormalities such as the elevation of fasting insulin level and oestradiol[8] , and inflammatory mediators exerting proliferative effects[9]. These changes have been linked to carcinogensis. Sugary food alone is not a direct cause of cancer unless associated with obesity. The claim that cancer patients should not take food containing sugar is faulty. On the contrary sugar is a good source of energy, particularly for patients on treatment for cancer.

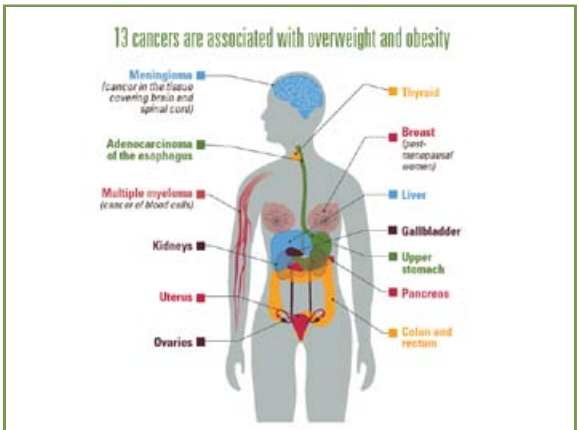


Fig. 1. Cancers associated with obesity Courtesy of the Center for Diseases Control and Prevention (CDC)

Red meat/processed meat

It is widely known that red meat and processed meat should be limited. Cooking meat at high temperature will produce heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAHs) which are potentially carcinogenic[10]. Haem iron intake has been associated with increase risk of colorectal carcinoma[11]. According to a recent study red/ processed meat contributed to 1.7% in man and 0.8% in woman of colorectal carcinoma[32]. On the other hand, there is no evidence that food rich in protein has increase risk or is harmful to patients who already have cancer. Food such as bird's nest, sea cucumber and fish maw are all considered safe.

Alcohol

Alcohol is well known as a carcinogen for orodigestive tract and liver. It is found to have increased colon cancer in man and breast cancer in woman. Mechanisms are diverse: including its toxic metabolite acetaldehyde and induction of oxidative stress through production of free radicals. It can also act as a solvent for other carcinogen and is associated with increased level of oestradiol. It causes about 4% of cancer-related death in the USA[32]. It is important to know that there is no safe amount (threshold limit) of alcohol that can be consumed[33].

Coffee and tea

Recently Readers' Digest[5] has listed out "30 Proven Foods to Help Prevent Cancer". These foods are in general healthy food and should be promoted. However excessive intake of beta carotene (rich in carrot) supplement have shown to have increased lung cancer[22] . So the common myth of drinking carrot juice to prevent cancer may produce contrary effects and should not be encouraged.

Coffee is also one of the listed food and it can prevent bowel cancer and liver cancer, supported by recent literature[15,16] . Interestingly, this is controversial with California court's ruling that coffee sold in California must have a sign warning consumer potential risk of cancer[3] (Fig. 2).

Fig. 2. Advertisement for coffee sold in California with the compulsory warning. http://tennesseestar.com/2018/04/02/

The concerned chemical in coffee is Acylamide, which also exists in other foods such as French fries, cracker, bread and cookies when heated to high temperature. Although Acylamide has been linked to increase cancer risk in animal studies[12] , there is no strong data to suggest it is carcinogenic in humans[13] . Moreover, many of the sources of Acylamide are present in everyday food intake and cannot be totally avoided. According to FDA, the current advice is to adopt a general healthy eating pattern rather than trying to lower the Acylamide intake[14] . It is always safer when cooking food to aim at "go for the gold" rather than over cook to dark.

Green tea, which is rich in anti-oxidant, has a clear image as a healthy food. However it has conflicting results in cancer prevention trials[35]. It is important to know that there were nine randomized trial in anti-oxidant supplement and all failed to provide evidence in cancer prevention[37] . Similarly, no data was found to support the use green tea in treating cancer patients.

Conversely recent data suggests that green tea may have a negative effect on Velcade[36], a commonly used chemotherapy for myeloma. We have to take caution that sometimes seemingly innocent supplements may create unexpected harm.

Superfood ?

In contrast to articles in many health magazine, there are actually no superfood that can prevent all cancer. There have been many claims in the Internet / TV/ radio promoting lemon, asparagusas, black garlic and broccoli. Unfortunately, there is no proof that they have any real benefit in preventing or treating cancer. In fact Ketchup, which is a rich source of lycopene and Vitamin A and C, may have similar health benefit as fresh tomato if one believes that the benefit of tomato is related to the presence of lycopene[58].

Herbs and spices

It is unarguable that there are a vast amount of substances in plants that can be used in different areas of medicine over thousands of years of human civilization. Some of these substances are found to be useful in medicine. Examples include the gout medicine, Colchicine, originally extracted from plants of the genus Colchicum and morphine isolated from poppy straw of the opium poppy etc.

There are many claims that some of these herbs and spices can cure cancer. One example is the Canadian ESSIAC tea, a herbal combination (Burdock root, sheep sorrel, slippery elm and Indian Rhubarb root) invented by a Ontario nurse Caisse in 1920 (ESSIAC is her name in reverse) for treating cancer. Subsequent trials failed to demonstrate any benefits[41]. FDA has issued a statement against its claim and trial in Ontario has not supported its efficacy. However compared to some other unproven alternative remedies which can be very expensive, Essiac isn't expensive: One month supply of Essiac tea costs around £6.00[39].

Another example is the "Selected Vegetable" or so called "Sun's soup" which was claimed by its developer to have cured his relative who was suffering from late stage lung cancer in 1980's. This vegetable combination was patented, and one randomized clinical trial (NCT00246727) of patients with stage IIIB or stage IV non-small cell lung cancer was conducted in the US as complementary or alternative medicine trial. The trial was started in Dec 2005 but result has not been reported or published[37].

Indeed, many of the chemotherapy agents are derived from plant products *(e.g. topotecan from Camptotheca, vinca alkaloids from Catharanthus, docetaxel and paclitaxel from Taxus bevifolia)* , but there is minimal efficacy when the original plant is used. Substances in plants may vary with climate, soil, storage, freshness and place of origin. The purity of the active ingredients cannot be judged from the plant appearance. In order to assess the effectiveness of the herbs, its active ingredients should be identified and purified. Dry extract of the plant is not the solution. In 2015 Youyou TU (屠呦呦) was awarded Nodel Prize in medicine due to her work in identification and purification of Artemisinin (青蒿素) a drug that has significantly reduced the mortality rates for patients suffering from Malaria.

Most herbs and dietary supplements use have not been studied together with chemotherapy drugs and their interactions remain unclear. When taken during chemotherapy, potentially it can cause profound drop in cell counts and hence it is advisable to stop taking these supplements during chemotherapy.

Many herbs exist in nature which may have anti-cancer properties, two common herbs include garlic and tumeric .

Garlic

While raw garlic has anti-microbe, anti-platelet activities and lowering cholesterol properties, its exact role in preventing cancer is not clear. A randomized trial in China using garlic extract supplement has reduced the incidence of stomach cancer in high risk population by more than 50%[46] . However another randomized trial of using garlic supplements in gastric precancerous lesion show no reduction of precancerous lesion and invasive disease[47]. A meta-analysis of 18 studies cannot confirm its role in cancer prevention[43].

Turmeric

Turmeric has been used for more than 3,000 years in cooking in different cultures. The bright yellow compound, Curcumin (薑黃素) , in turmeric has been widely studied in cancer research.

It demonstrates anti-inflammatory[49], immunomodulatory[50], anti-proliferative[51] and chemopreventive[52, 53] activities in lab studies. The proposed mechanisms on different stages of cancer development is as shown in Fig. 3.

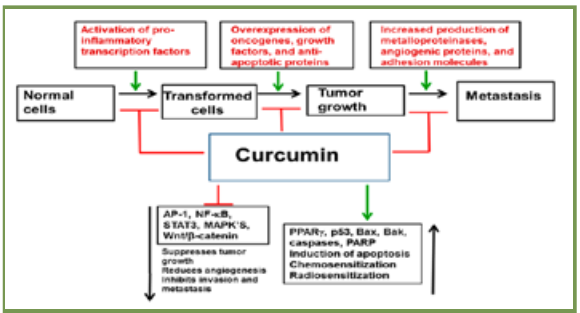


Fig. 3. The multifaceted role of curcumin in cancer prevention and treatment. Reproduced from Shanmugam MK et al. Molecules 2015, 20: 2728-2769

Biologically curcumin inhibits CYP1A4 and CYP3A4 but induces CYP2A6 enzymes[27,28] thereby altering the metabolism of some prescription drugs[44] . There are also ongoing human trials to study curcumin effect on human cancer patients. Recent study from Netherlands suggests the regular use of curcumin and tamoxifen can decrease the serum level of the latter[45] and therefore the use of it as an treatment outside clinical trial settings are not advised.

Organic food versus genetically modified food

Organic food has been promoted as an alternative to foods grown with conventional methods using chemical herbicides, pesticides, hormones or antibiotics. It also exclude genetically modified food sometimes known genetically modified organisms (GMOs). Organic food, often more expensive, is sometimes considered to be more nutritious than conventional food, although the evidence is not strong[21]. However, they are not necessarily free of lead or other heavy metals/pollutants if these chemicals already exist in the soil[28].

One of the main concern is the presence of the active chemical of weed killer "Roundup", Glyphosate, which is considered as a Category 2A (probably carcinogenic) by the International Agency of Research on Cancer (IARC) (Fig.4), same Category as red meat. This chemical has been widely used for more than 40 years and have been strictly regulated and they usually exist only in very low level in food and should not posed a significant risk. Review released in 2015 by the German Federal Institute for Risk Assessment (BfR) concluded that "glyphosate was unlikely to pose a carcinogenic risk to humans"[54].

Category		No.	EXAMPLES
1	Carcinogenic to humans *sufficient evidence, causal relationship established*	120	smoking , alcohol, UV and x-ray exposure, pollution, processed meats, EBV, HBV, HCV,HPV, Helicobacter pylori, chemotherapy
2A	Probably Carcinogenic to humans *Limited evidence in humans* *Sufficient evidence in animals*	82	high temperature frying, night shift work, glyphosate (roundup), working as barber/hair dresser, red meat, anabolic steroids, DDT
2B	Probably Carcinogenic to humans *Limited evidence in humans* *Insufficient evidence in animals*	302	Coffee, Talc-based body powder, pickled vegetables, aloe vera, gasoline exhaust, lead
3	Carcinogenicity not classifiable *Inadequate evidence in humans* *Inadequate evidence in animals*	501	Magnetic fields, Caffeine/tea, Selenium, hair coloring products, fluorescent lighting
4	Probably not Carcinogenic *Evidence suggests no carcinogenicity in humans/animals*	1	Caprolactam- a synthetic substance used in nylon production

Fig. 4. Classification of carcinogenic agents. International Agency for Research in Cancer (IACR),

High doses of some pesticides e.g. captafol, ethylene dibromide, glyphosate, malathion, diazinon and dichlorodiphenyltrichloroethane (DDT) can cause cancer in animals and are classified as Category II A. The levels found in foods are usually regulated to make sure they are in a very low dose level and therefore should not impose a high risk to human. Nevertheless, if someone is concerned about pesticide residues in fruit and vegetables, one should always wash them thoroughly under clean running water[56] which will effectively reduce surface contaminants, including pesticide residues. Soaking can also reduce pesticide residues in some studies, but it will also cause the losing of nutrients. Centre for Food Safety (CFS) no longer recommends soaking vegetables in view of the low level of pesticide residues detected and the fact that no food poisoning incidents related to pesticide residues have been reported in recent years[55].

A large study involving more than 600,000 women in the U.K. did not show any definite benefit from the regular consumption of organic food[56] . Conventional fruits and vegetables, fresh and thoroughly washed and consumed in adequate amount, helps to lower cancer risk.

Genetically Modified (GM) food, when approved to be sold in the market, is generally considered safe and there is no proof that it leads to increase cancer incidence in humans[24, 25]. However, many people are still concerned just because it is "not from the mother nature". In a recent survey[57] in England, more than one-third of the people participating in the survey believe GM food is carcinogenic. In order to safe-guard the public concern, it should be clearly labeled as recommended by Centre for Food Safety[65].

Physical activity

There are strong evidence that physical activity can reduce cancer risk of colon/rectal, postmenopausal breast and endometrium. Exercise will improve insulin sensitivity and reduce fasting insulin level[27]. Findings also show that exercise have immunomodulatory effects which are increasingly recognized in tumour surveillance. It can also decrease oxidative stress and enhance DNA repair mechanism. On the same note, physical inactivity can account for 1.3% of all cancer[33]. According to the latest Third Expert Report " *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*"[27] by the World Cancer Research Fund, not only the strenuous exercise can reduce the incidence of cancer. Exercise can reduce incidence of colorectal, endometrial and breast cancer developed after menopause. Simple exercise like walking have been shown to reduce breast cancer[26] (Fig. 5).

Fig. 5. Exercise can reduce incidences of these tumours.

To summarize, our diet, lifestyle, environment and most importantly the genetic make up all has its role to play in the development of malignancy but none of which is the sole cause. Abstinence from smoking and/or alcohol is probably most important modification that can be made to prevent cancer. Fighting against different infections causing cancer is being done (Vaccination of HPV and Hepatitis and treatment of Helicobacter pyloris). Food has been given a disproportional attention by the public. Resource have been drained to these areas. The importance of other lifestyle factors such as weight control and physical activity should be emphasized.

This article humbly serves to be an introduction to this big subject. There are far too much information and research related to food/ lifestyle and cancer. A very useful summary has been made by the World Cancer Research Fund International (Fig. 6). This is a comprehensive summary of all the strong evidence on diet, nutrition, physical activity and the prevention of cancer and should be a nice summary for ease of reference.

If the reader is eager to study more, there are a few sites, as shown below, providing unbiased information:

https://www.cancerresearchuk.org/about-cancer/causes-of-cancer/diet-and-cancer/food-controversies?
https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs
https://www.wcrf.org/sites/default/files/Summary-third-expert-report.pdf
https://www.fda.gov/forconsumers/protectyourself/healthfraud/default.htm

World Cancer Research Fund

American Institute for Cancer Research

CUP Continuous Update Project

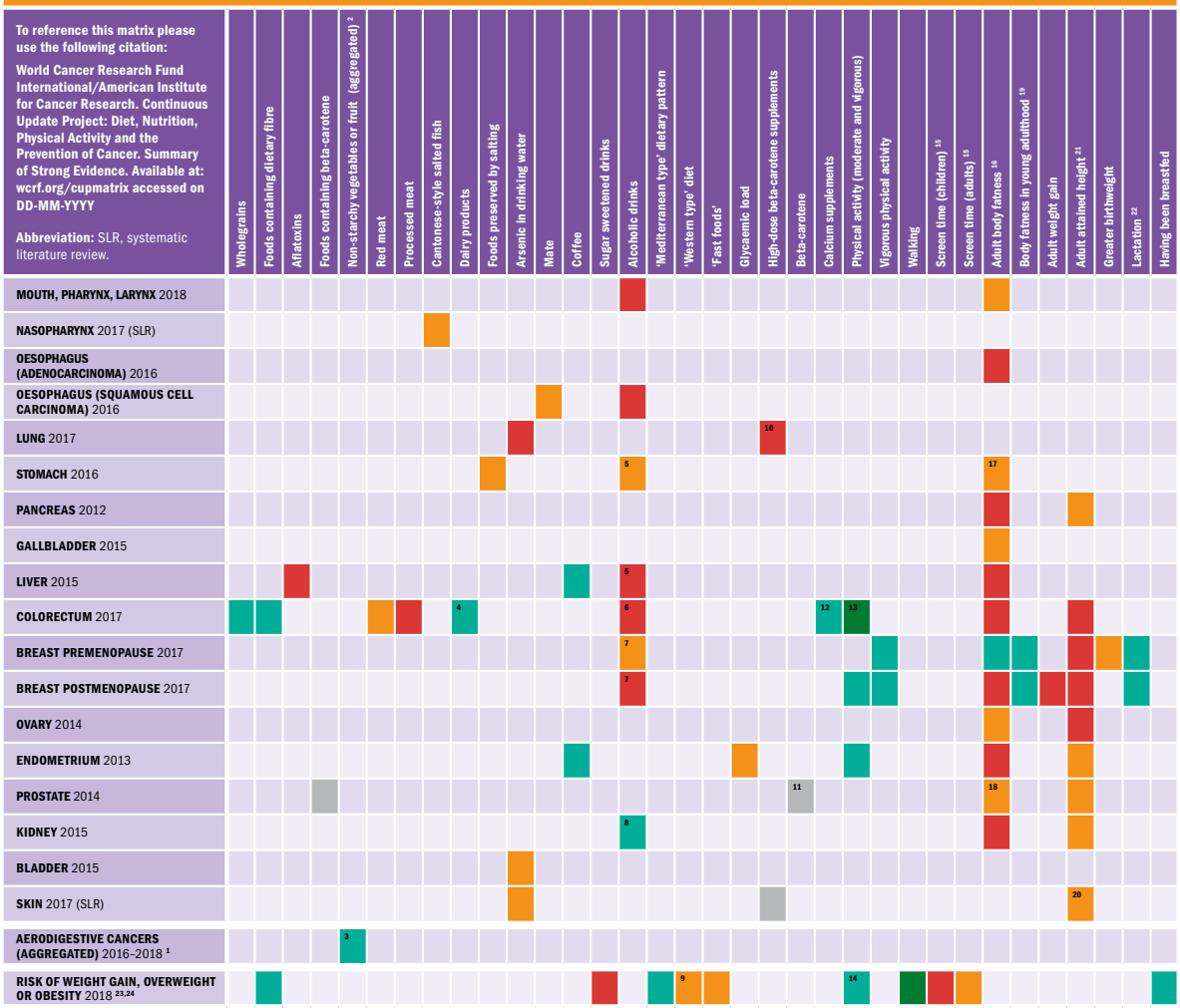
Analysing research on cancer prevention and survival

SUMMARY OF STRONG EVIDENCE ON DIET, NUTRITION, PHYSICAL ACTIVITY AND THE PREVENTION OF CANCER

To reference this matrix please use the following citation:

World Cancer Research Fund International/American Institute for Cancer Research. Continuous Update Project: Diet, Nutrition, Physical Activity and the Prevention of Cancer. Summary of Strong Evidence. Available at: wcrf.org/cupmatrix accessed on DD-MM-YYYY

Abbreviation: SLR, systematic literature review.



1 Includes mouth, pharynx and larynx, nasopharynx, oesophagus (squamous cell carcinoma and adenocarcinoma), lung, stomach and colorectal cancers.
2 Aggregated exposure which contains evidence for non-starchy vegetables, fruit and citrus fruit.
3 The Panel notes that while the evidence for links between individual cancers and non-starchy vegetables or fruits is limited, the pattern of association is consistent and in the same direction, and overall the evidence is more persuasive of a protective effect.
4 Includes evidence on total dairy, milk, cheese and dietary calcium intakes.
5 Stomach and liver: Based on intakes above approximately 45 grams of ethanol per day (about 3 drinks).
6 Based on intakes above approximately 30 grams of ethanol per day (about 2 drinks per day).
7 No threshold level of intake was identified.
8 Based on intakes up to 30 grams of ethanol per day (about 2 drinks per day). There is insufficient evidence for intake greater than 30 grams per day.
9 Such diets are characterised by high intakes of free sugars, meat and dietary fat; the overall conclusion includes all these factors.
10 Evidence is from studies of high-dose supplements in smokers.
11 Includes both foods naturally containing the constituent and foods which have the constituent added and includes studies using supplements.
12 Evidence derived from studies of supplements at dose >200 milligrams per day.
13 Colon cancer only.
14 Aerobic physical activity only.
15 Screen time is a marker of sedentary behaviour.
16 Body fatness is marked by body mass index (BMI) and where possible waist circumference and waist-hip ratio.
17 Stomach cardia cancer only.
18 Advanced prostate cancer only.
19 Young women aged about 18 to 30 years; body fatness is marked by BMI.
20 Malignant melanoma only.
21 Adult attained height is unlikely to directly influence the risk of cancer. It is a marker for genetic, environmental, hormonal and nutritional factors affecting growth during the period from preconception to completion of growth in length.
22 Evidence relates to effects on the mother who is breastfeeding and not to effects on the child who is being breastfed. Relates to overall breast cancer (unspecified).
23 The factors identified as increasing or decreasing risk of weight gain, overweight or obesity do so by promoting positive energy balance (increased risk) or appropriate energy balance (decreased risk), through a complex interplay of physiological, psychological and social influences.
24 Evidence comes mostly from studies of adults but, unless there is evidence to the contrary, also apply to children (aged 5 years and over).

dietandcancerreport.org May 2018

Fig. 6. This material has been reproduced with permission from the World Cancer Research Fund/American Institute for Cancer Research. Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report 2018. Available at dietandcancerreport.org

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THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG
香 港 醫 學 組 織 聯 會

Annual Scientific Meeting 2018

Medical Advances in Community Health

Date: 7 Oct 2018 (Sunday) Time: 9:30am - 5:00pm
Venue: Ballroom, 3/F, Sheraton Hong Kong Hotel & Towers, 20 Nathan Road, Tsim Sha Tsui, Kowloon

Opening Ceremony

Session I - Community Health
Chairpersons: Dr. Jane CHAN & Dr. Ludwig TSOI

- **The Role of Chinese Medical Association in the Belt & Road Initiative / The Changes Brought About by the 2-child Policy to the Medical System**
  CMA speaker
- **Ethical Issues in Community Healthcare**
  Dr. Derrick Kit-sing AU
  Director of the CUHK Centre for Bioethics, Medical Faculty, the Chinese University of Hong Kong

Session II - Hepatology & Cardiology
Chairpersons: Dr. Mario CHAK & Prof. Bernard CHEUNG

- **Hepatitis C in 2018**
  Prof. Ching-lung LAI
  Chair Professor, Department of Medicine, The University of Hong Kong, Queen Mary Hospital
- **Cholesterol Lowering**
  Prof. David Chung-wah SIU
  Department of Cardiology, HCO

Lunch Symposium - Brain Health
Chairperson: Dr. Samuel FUNG

- **Etiology Based Management of Epilepsy: How Genetics & Surgical Treatment Make a Difference?**
  Dr. Mario CHAK
  President, The Federation of Medical Societies of Hong Kong

Session III - Mental Health & Oncology
Chairpersons: Dr. Yin-kwok NG & Dr. Desmond NGUYEN

- **Depression**
  Prof. Siu-wa TANG
  Current Past and Founding President, Hong Kong Society of Biological Psychiatry
- **Colorectal Screening – Where Are We Heading?**
  Dr. William Chia-shing MENG
  Specialist in General Surgery

Session IVa - Respiratory Health
Chairpersons: Dr. Alson CHAN & Dr. Tony TO

- **One Airway Diseases Management: Allergic Rhinitis & Asthma**
  Prof. Henry P.H. PAU
  Specialist in ENT
- **Electronic Cigarette and New Tobacco Products To Ban or To Let Free?**
  Dr. Tai-hing LAM
  Chair Professor of Community Medicine and Sir Robert Kotewall Professor in Public Health, School of Public Health, The University of Hong Kong

Session IVb - Metabolic Disease
Chairpersons: Dr. Kai-ming CHAN & Dr. Victor YEUNG

- **Current Landscape of Obesity in Hong Kong**
  Dr. Michele Mae-ann YUEN
  Founding co-president, Hong Kong Obesity Society
- **Advances in Diabetic Nephropathy**
  Dr. Samuel Ka-shun FUNG
  Chief of Nephrology & Consultant Physician, Department of Medicine & Geriatrics, Princess Margaret Hospital

Session Va - Dermatology & Allergy
Chairpersons: Dr. Edwin YU & Ms. Tina YAP

- **Dermatology / Eczema**
  Dr. Kingsley Hau-ngai CHAN
  Specialist in Dermatology & Venereology
- **Diagnosis and Management of Allergic Diseases: A Practical Update**
  Dr. Alson Wai-ming CHAN
  Specialist in Paediatric Immunology & Infectious Diseases, Allergy Centre, Hong Kong Sanatorium & Hospital

Session Vb - Infection & Urology
Chairpersons: Dr. Thomas SO & Dr. Kwai-ming SIU

- **Benign Prostatic Hyperplasia**
  Dr. Victor YEUNG
  Specialist in Urology
- **Update in the Use of Antibiotics**
  Dr. Kai-ming CHAN
  Specialist in Infectious Diseases

Registration Fee

HK$100 Members of Member Societies of FMSHK
HK$400 Non-members

Registration

Application form can be found overleaf or downloaded from website http://www.fmshk.org
CME / CNE Accreditation is pending
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THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG
香 港 醫 學 組 織 聯 會

Annual Scientific Meeting 2018
"Medical Advances in Community Health"

7 October 2018 (Sunday) 9:30am - 5:00pm *(Registration at 9:00am)*
Ballroom, 3/F, Sheraton Hong Kong Hotel & Towers, 20 Nathan Road, Tsim Sha Tsui, Kowloon

REGISTRATION FORM

☐ Prof. ☐ Dr. ☐ Mr. ☐ Ms. ☐ Mrs.

Surname: _____ First name: _____

Tel no.: _____ *Email Address: _____

Occupation: _____ Organisation: _____

Member of: _____ (FMSHK Member Society)

※ *Please ☑ when appropriate*

1. **I would like to attend Annual Scientific Meeting 2018**

☐ **Morning Sessions**
- **Session I - Community Health**
  Time: 10:00am – 11:00am
- **Session II –Hepatology & Cardiology**
  Time: 11:20am – 12:20pm

☐ **Lunch Symposium –Brain Health (First 100 applicants)**
- *Time: 12:20pm – 1:20pm*
  ☐ *For Vegetarian Meal, please " ✓" in the box*

☐ **Afternoon Sessions**
- **Session III – Mental Health & Oncology**
  Time: 1:20pm – 2:20pm
- **Session IV(a) – Respiratory Health** ***(*parallel symposium)***
  Time: 2:40pm – 3:40pm
- **Session IV(b) – Metabolic Disease** ***(*parallel symposium)***
- *Time: 2:40pm – 3:40pm*
- **Session V(a) – Dermatology & Allergy** ***(*parallel symposium)***
  Time: 3:40pm – 4:40pm
- **Session V (b)– Infection & Urology** ***(*parallel symposium)***
  Time: 3:40pm – 4:40pm

2. Registration Fee: Member: $100 / Non-member: $400

Fee enclosed: ☐ $100 ☐ $400 Cheque No.: _____

3. Certificate of Attendance required (with CNE points awarded) ☐ Yes ☐ No

_____ _____
Signature Date

Remarks:
1. Confirmation will be sent by **EMAIL***
2. Please **send registration form with cheque** made payable to "**Federation of Medical Societies of Hong Kong**" to 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong on or before 26 September, 2018 (Wed).
3. No refund will be made if you have to cancel your registration afterwards
4. CME/CNE accreditation is pending

Tel: (852) 2527 8898 Fax: (852) 2865 0345 Homepage: www.fmshk.org E-mail: info@fmshk.org

Dermatology Quiz

Dr Lai-yin CHONG

MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)
Specialist in Dermatology & Venereology

Dr Lai-yin CHONG

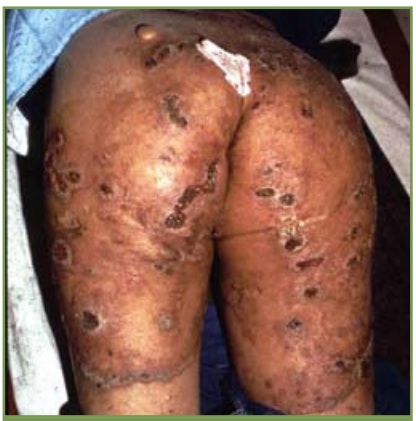

Fig.1: Extensive hyperkeratotic plaques over the buttocks and posterior thighs

A middle-aged Chinese male presented with a two-year history of non-itchy non-painful hyperkeratotic and warty plaques over his buttocks and posterior aspect of both thighs (Fig.1). The lesions gradually progressed and involved a wide area with well demarcated advancing edges. There were no lymphadenopathy and systemic symptoms. His past health was otherwise good.

Questions

1. What are your differential diagnoses?
2. How do you confirm the diagnosis?
3. What further investigations will you do after the establishment of diagnosis?
4. What is the mainstay of treatment?

(See P.44 for answers)

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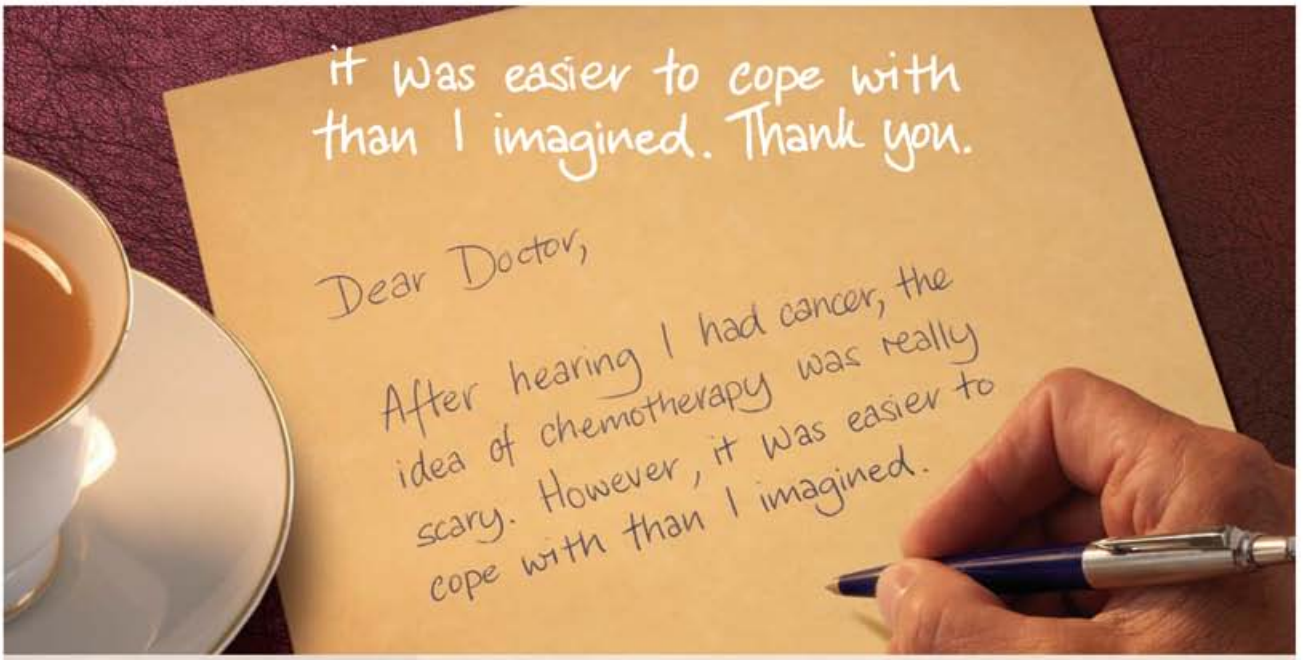
Queen Mary 2 Ship Visit

The Queen Mary 2 Ship Visit was successfully held on 30 Mar 2018. We were honored to have Exco Members, Foundation Directors, Presidents, Hon. Treasurers, Hon. Secretaries and Council Representatives of our Member Societies, and members of Federation to join us on board. All the guests had a delightful and lovely evening with an extensive ship tour and fine dining in the elegant setting of the Verandah restaurant. Our President, Dr. Mario CHAK marked the opening with a warm welcome speech. He updated our members Federation's latest activities and possible collaborations with the Chinese Medical Association as well as the medical professionals in the Greater Bay Area. All the joyfulness and enrichment of friendship were captured in the photos.



Presentation: Docetaxel concentrate and solvent for solution for infusion. **Indications and dosage:** Breast Cancer: In combination with doxorubicin and cyclophosphamide for adjuvant treatment of operable node-positive and node-negative breast cancer (docetaxel 75 mg/m² 1-hour after doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² every 3 weeks for 6 cycles); in combination with doxorubicin for treatment of locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy (docetaxel 75 mg/m² and doxorubicin 50 mg/m² every three weeks); monotherapy for the treatment of locally advanced or metastatic breast cancer after failure of cytotoxic therapy containing an anthracycline or an alkylating agent (docetaxel 100 mg/m² every three weeks); in combination with trastuzumab for treatment of metastatic breast cancer whose tumors overexpress HER2 and who previously have not received chemotherapy for metastatic disease (docetaxel 100 mg/m² every three weeks with trastuzumab administered weekly), in combination with capecitabine for the treatment of locally advanced/ metastatic breast cancer after failure of cytotoxic chemotherapy containing an anthracycline (docetaxel 75 mg/m² every three weeks combined with capecitabine at 1250 mg/m² twice daily (within 30 minutes after a meal) for 2 weeks followed by 1-week rest period); Non-small cell lung cancer, NSCLC: Treatment of locally advanced/ metastatic NSCLC after failure of prior platinum-based chemotherapy (docetaxel 75 mg/m² as a single agent); in combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic NSCLC and in patients who have not previously received chemotherapy for this condition (docetaxel 75 mg/m² immediately followed by cisplatin 75 mg/ m² over 30-60 minutes every three weeks); Prostate cancer: In combination with prednisone or prednisolone for treatment of hormone refractory metastatic prostate cancer (docetaxel 75mg/m² every three weeks and prednisone or prednisolone 5mg orally twice daily is administered continuously); Ovarian Cancer: Treatment of metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy (docetaxel 100mg/ m² as 1-hour infusion every three weeks); Head and Neck cancer: Monotherapy in treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck after failure of a previous chemotherapy regimen (docetaxel 100mg/m² as 1-hour infusion every three weeks); Induction treatment of locally advanced squamous cell carcinoma of the head and neck, followed by radiotherapy: docetaxel 75mg/m² as a 1 hour infusion, followed by cisplatin 75mg/m², as a 1 hour infusion (both on day 1only), followed by 5-fluorouracil 750mg/m² per day given as a continuous infusion for 5 days, repeated every 3 weeks for 4 cycles) followed by chemoradiotherapy: docetaxel 75mg/m² as a 1 hour infusion on day 1, followed by cisplatin 100mg/m², as a 30-minute to 3 hour infusion, followed by 5-fluorouracil 1000mg/m² per day given as a continuous infusion from day 1 to day 4, repeated every 3 weeks for 3 cycles), Gastric Adenocarcinoma: Treatment of metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease (docetaxel 75mg/m² as a 1 hour infusion, followed by cisplatin 75mg/m², as a 1 to 3 hour infusion (both on day 1 only), followed by 5-fluorouracil 750mg/m² per day given as a 24-hour continuous infusion for 5 days, starting at the end of the cisplatin infusion, repeated every 3 weeks), **Further Dosage Information:** Docetaxel is administered as a 1-hour infusion every three weeks, (Breast, non-small cell lung, ovarian & head and neck cancers) Premedication consisting of an oral corticosteroid, such as dexamethasone 16 mg per day (e.g. 8 mg BID) for 3 days starting 1 day prior to docetaxel administration, unless contraindicated, can be used. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities, (Prostate cancer) Given the concurrent use of prednisone or prednisolone the recommended premedication regimen is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion. For dosage adjustments during treatment, please refer to detailed prescribing information. **Contraindications:** Hypersensitivity to docetaxel or any excipients, patients with baseline neutrophil count of <1,500 cells/mm³, pregnancy and lactation, severe liver impairment. **Precautions:** Premedication consisting of an oral corticosteroid is needed. Frequent monitoring of complete blood counts (retreat with docetaxel if ANC ≥1,500 cells/mm³ before next cycle, and dose reduction recommended if severe neutropenia, i.e. <500 cells/mm³ for seven days or more). Patients treated with docetaxel in combination with cisplatin and 5-fluorouracil should receive prophylactic G-CSF to mitigate the risk of complicated neutropenia (febrile neutropenia, prolonged neutropenia or neutropenic infection) and should be closely monitored. Observe closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. Severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate therapy and should not be re-challenged. Monitor closely for severe fluid retention. If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated, and appropriately treated. For patients with elevated liver function test (LFTs), recommend dose is 75 mg/m² and LFTs should be measured at baseline and before each cycle. For patients with serum bilirubin levels >ULN and/or ALT and AST >3.5 times the ULN concurrent with serum alkaline phosphatase levels >6 times the ULN, docetaxel should not be used unless strictly indicated. The development of severe peripheral neurotoxicity requires a reduction of dose. When patients are candidates for treatment with docetaxel in combination with trastuzumab, they should undergo baseline cardiac assessment and further monitored during treatment (e.g., every three months). Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. In case cystoid macular oedema is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated. Contraceptive measures must be taken during and for at least three months after cessation of therapy. The concomitant use of docetaxel with strong CYP3A4 inhibitors should be avoided. **Additional precautions in adjuvant treatment of breast cancer:** G-CSF and dose reduction should be considered in complicated neutropenia. Evaluate and treat promptly on symptoms such as abdominal pain and tenderness, fever, diarrhea, with or without neutropenia. Monitor for symptoms of congestive heart failure during therapy and during the follow up period. **Interactions:** Metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by cytochrome P450-3A. Docetaxel may increase the clearance of carboplatin. CYP3A4 inhibitors. **Undesirable effects:** Neutropenia, anaemia, alopecia, nausea, vomiting, stomatitis, diarrhoea, asthenia, hypersensitivity reactions (flushing, rash with or without pruritis, chest tightness, back pain, dyspnoea, fever or chills etc.), Paresthesia, dysesthesia, pain, infusion site reactions, infections, thrombocytopenia, anorexia, peripheral sensory neuropathy, peripheral motor neuropathy, arrhythmia, hypertension, haemorrhage, nail disorders, myalgia, arthralgia, fluid retention, increase in blood bilirubin, alkaline phosphatase, AST, ALT. *For uncommon, rare and very rare undesirable effects, please refer to the full prescribing information.* Preparations: 20mg x 1 vial, 80mg x 1 vial. ***Full prescribing information is available upon request.*** API-HK-DOC-14.12

AXOTERE® (docetaxel)

Time Life Confidence

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Presentation: Cabazitaxel concentrate and solvent for solution for infusion. **Indications:** In combination with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer previously treated with a docetaxel containing regimen. **Dosage:** 25 mg/m² administered as a 1-hour intravenous infusion every 3 weeks in combination with oral prednisone or prednisolone 10 mg administered daily throughout treatment. The recommended premedication regimen should be given at least 30 minutes prior to each administration of cabazitaxel. Dose modifications should be made if patients experience prolonged Grade ≥5 neutropenia, febrile neutropenia or neutropenic infection, Grade ≥3 diarrhoea, or Grade ≥2 peripheral neuropathy. If patients continue to experience any of these reactions at 20 mg/m², further dose reduction to 15 mg/m² or discontinuation may be considered. **Contraindications:** Hypersensitivity to cabazitaxel or polysorbate 80 or excipients, or taxanes; neutrophil counts less than 1,500/mm3, severe hepatic impairment (bilirubin ≥ 3 x ULN), concomitant vaccination with yellow fever vaccine. **Precautions:** Premedication is recommended prior to the initiation of cabazitaxel infusion. Prophylactic G-CSF should be considered to reduce the risk or manage neutropenia complications, especially in patients with high risk clinical features (age >65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities). Bone marrow suppression manifested as neutropenia, anaemia, thrombocytopenia, or pancytopenia may occur. Caution advised in patients at risk of developing gastrointestinal complications: neutropenia, elderly, concomitant use with NSAIDs, anti-platelet therapy or anticoagulants, history of pelvic radiotherapy or gastrointestinal disease. Caution is recommended in patients with haemoglobin <10 g/dl and appropriate measures should be taken as clinically indicated. Treatment should be discontinued in case of any degradation of renal function to renal failure (CTCAE 4.0 Grade 3). Caution in patients with moderate and severe renal impairment, Elderly patients (≥65 years of age), Patients with haemoglobin <10 g/dl. Administration of live or live attenuated vaccines should be avoided. Haemoglobin and haematocrit should be checked before treatment with cabazitaxel and if patients exhibit signs or symptoms of anaemia or blood loss. If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated, and appropriately treated. **Interactions:** Strong CYP3A inhibitors and inducers. St. John's Wort. Organic Anion Transport Polypeptides (OATP1B1) substrates. Live or live attenuated vaccines. **Undesirable effects:** *Very common:* anaemia, leukopenia, neutropenia, febrile neutropenia, thrombocytopenia, diarrhoea, anorexia, dysgeusia, dyspnoea, cough, nausea, vomiting, constipation, abdominal pain, alopecia, back pain, arthralgia, haematuria, fatigue, pyrexia, asthenia. *For common, uncommon, rare and very rare undesirable effects, please refer to the full prescribing information.* **Preparation:** 60mg x 1 vial. **Legal Classification:** Part 1, First & Third Schedules Poison. ***Full prescribing information is available upon request.*** API-HK-CAB-18.01

mHRPC: Metastatic hormone refractory prostate cancer

JEVTANA® (cabazitaxel)

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SANOFI

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
						1
2	3	★ HKMA Tai Po Community Network - Current Paediatric Vaccine for Childhood Immunisation ★ HKMA Yau Tsim Mong Community Network - Dual Anti-Platelet Therapy – The Dawn of New Era ★ HKMA-HKS&H CME Programme 2018 -2019 ★ HKMA Kowloon West Community Network - Latest Evidence on Achieving Asthma Control at Primary Setting ★ FMSHK Certificate Course in Practical Obstetric Ultrasonography (5) ★ FMSHK Officers' Meeting ★ HKMA Council Meeting 4	★ HKMA Central, Western & Southern Community Network - Certificate Course on Psychiatry (Session 1) - Early Identification of Cognitive Impairment Made Easy With An Evidence-Based Brief Cognitive Screen for The Local Population ★ MPS Workshop - Building Resilience and Avoiding Burnout ★ FMSHK Certificate Course in Renal Medicine 2018 (1) 5	★ HKMA Kowloon East Community Network - Novel Combination of Basal Insulin and GLP1 ★ HKMA Hong Kong East Community Network - Update in the Management of Idiopathic Pulmonary Fibrosis ★ HKMA New Territories West Community Network - Advances in Hypertension Management ★ MPS Workshop - Achieving Safer and Reliable Practice ★ FMSHK Certificate Course in Respiratory Medicine 2018 (1) 6	7	8
9	10	★ HKMA Tai Po Community Network - Implications of EMPA-REG OUTCOME in Asian Patients with Type 2 Diabetes ★ FMSHK Certificate Course in Practical Obstetric Ultrasonography (6) 11	★ The Hong Kong Neurosurgical Society Monthly Academic Meeting –Updates on Neurofibromatosis type 1 ★ HKMA Central, Western & Southern Community Network - Certificate Course on Psychiatry (Session 2) - Management of Depression and Comorbidities ★ FMSHK Certificate Course in Renal Medicine 2018 (2) 12	★ FMSHK Certificate Course in Respiratory Medicine 2018 (2) 13	★ HKMA Kowloon City Community Network - Management on Diabetic Nephropathy 14	★ MPS Workshop - Mastering Adverse Outcomes 15
16	17	★ HKMA Kowloon West Community Network - Management of Lung Cancer: Update in EGFR Targeted Treatment ★ HKMA Tai Po Community Network - Management of Hypertension from Essential to Resistant 18	★ FMSHK Certificate Course in Renal Medicine 2018 (3) 19	★ HKMA Hong Kong East Community Network - Management of Lung Cancer: Update in EGFR Targeted Treatment ★ HKMA New Territories West Community Network - Novel Treatment in Diabesity ★ FMSHK Certificate Course in Respiratory Medicine 2018 (3) ★ FMSHK Executive Committee Meeting 20	★ HKMA Shatin Doctors Network - Community Elderly Nutritional Needs and Challenges ★ HKMA Yau Tsim Mong Community Network - Novel Combination of Basal Insulin and GLP1 21	22
23 30	24	25	★ HKMA Golf Tournament 2018 ★ FMSHK Certificate Course in Renal Medicine 2018 (4) 26	★ FMSHK Certificate Course in Respiratory Medicine 2018 (4) 27	28	29

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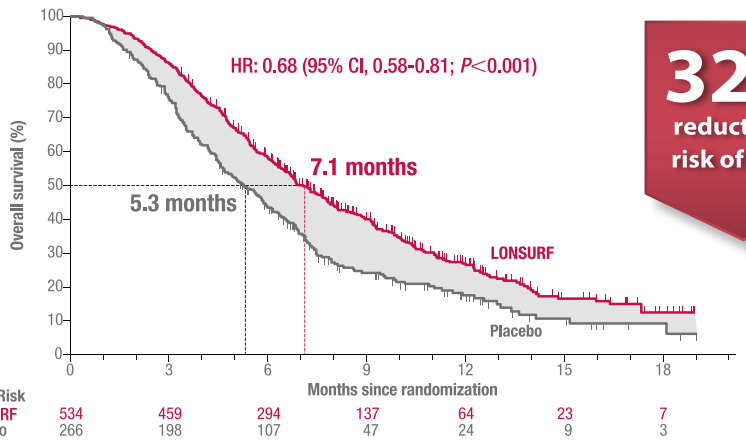

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HIGHLIGHTS OF PACKAGE INSERT
These highlights do not include all the information needed to use Lonsurf® safely and effectively. See full package insert for Lonsurf®.
Lonsurf® (trifluridine and tipiracil) film-coated tablets, for oral use

INDICATIONS AND USAGE
Lonsurf® is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

DOSAGE AND ADMINISTRATION
- Recommended dose: 35 mg/m²/dose orally twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle.
- Take Lonsurf® within 1 hour after completion of morning and evening meals.

DOSAGE FORMS AND STRENGTHS
Film-coated Tablets:
- 15 mg trifluridine/6.14 mg tipiracil (as 7.065 mg tipiracil hydrochloride)
- 20 mg trifluridine/8.19 mg tipiracil (as 9.420 mg tipiracil hydrochloride)

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
- Severe Myelosuppression: Obtain complete blood counts prior to and on Day 15 of each cycle. Reduce dose and/or hold Lonsurf® as clinically indicated.
- Embryo-Fetal Toxicity: Fetal harm can occur. Advise women of potential risk to a fetus.

ADVERSE REACTIONS
The most common adverse reactions (≥ 10%) are anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

USE IN SPECIFIC POPULATIONS
- Lactation: Do not breastfeed.
- Geriatric Use: Grade 3 or 4 neutropenia and thrombocytopenia and Grade 3 anemia occurred more commonly in patients 65 years old or older who received Lonsurf®.
- Hepatic Impairment: Do not initiate Lonsurf® in patients with baseline moderate or severe hepatic impairment.
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References:
1. LONSURF PI HK. DKSH Hong Kong Limited. 2. Mayer RJ, Van Cutsem E, Falcone A, *et al.*; for the RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015;372(20):1909-1919.

HK-LON-17-12-02

Date / Time	Function	Enquiry / Remarks
4 TUE 1:00 PM	**HKMA Tai Po Community Network - Current Paediatric Vaccine for Childhood Immunisation** Organiser: HKMA Tai Po Community Network; Chairman: TBC; Speaker: Dr. LEUNG Cheuk Wa, Wilfred; Venue: Chiuchow Garden Restaurant (潮江春), Shop 001-003, 1/F, Uptown Plaza, No. 9 Nam Wan Road, Tai Po	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Yau Tsim Mong Community Network - Dual Anti-Platelet Therapy – The Dawn of New Era** Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. CHAN Wai Keung, Ricky; Speaker: Dr. HUNG Yu Tak; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA-HKS&H CME Programme 2018 -2019** Organiser: Hong Kong Medical Association & Hong Kong Sanatorium & Hospital; Speaker: Dr. Chan Leung Kwai, Jason; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	HKMA CME Dept. Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Kowloon West Community Network - Latest Evidence on Achieving Asthma Control at Primary Setting** Organiser: HKMA Kowloon West Community Network; Chairman: Dr. LAM Ngam, Raymond; Speaker: Dr. LO Chi Wai; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chun, Mei Foo	Miss Antonia LEE Tel: 2527 8285 1 CME Point
7:00 PM	**FMSHK Certificate Course in Practical Obstetric Ultrasonography (5)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345
8:00 PM	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
9:00 PM	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association; Chairman: Dr. HO Chung Ping, MH, JP; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Christine WONG Tel: 2527 8285
5 WED 1:00 PM	**HKMA Central, Western & Southern Community Network - Certificate Course on Psychiatry (Session 1) - Early Identification of Cognitive Impairment Made Easy With An Evidence-Based Brief Cognitive Screen for The Local Population** Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. CHAN Hau Ngai, Kingsley; Speaker: Prof. Adrian WONG; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	Miss Antonia LEE Tel: 2527 8285 1 CME Point
6:30 PM	**MPS Workshop - Building Resilience and Avoiding Burnout** Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. Fung Shu Yan, Anthony; Venue: The Cityview, Kowloon	HKMA CME Dept. Tel: 2527 8285 3 CME Point
7:00 PM	**FMSHK Certificate Course in Renal Medicine 2018 (1)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345
6 THU 1:00 PM	**HKMA Kowloon East Community Network - Novel Combination of Basal Insulin and GLP1** Organiser: HKMA KLN East Community Network; Chairman: Dr. TING Ka Chu; Speaker: Dr. YEUNG Tok Fai, Vincent; Venue: Lei Garden Restaurant, Shop No. L5-8, apm, Kwun Tong, No. 418 Kwun Tong Road, Kowloon	Miss Antonia LEE Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Hong Kong East Community Network - Update in the Management of Idiopathic Pulmonary Fibrosis** Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. AU Chi Lap, Simon; Speaker: Dr. WONG King Ying; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA New Territories West Community Network - Advances in Hypertension Management** Organiser: HKMA New Territories West Community Network; Chairman: Dr. CHEUNG Kwok Wai, Alvin; Speaker: Dr. KO Yiu Kwan, Cyril; Venue: Pak Loh Chiu Chow Restaurant, Shop A316, 3/F, Yoho Mall II, 8 Long Yat Road, Yuen Long	Miss Antonia LEE Tel: 2527 8285 1 CME Point
6:30 PM	**MPS Workshop - Achieving Safer and Reliable Practice** Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. Cheng Ngai Shing, Justin; Venue: The Cityview, Kowloon	HKMA CME Dept. Tel: 2527 8285 3 CME Point
7:00 PM	**FMSHK Certificate Course in Respiratory Medicine 2018 (1)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345
11 TUE 1:00 PM	**HKMA Tai Po Community Network - Implications of EMPA-REG OUTCOME in Asian Patients with Type 2 Diabetes** Organiser: HKMA Tai Po Community Network; Chairman: TBC; Speaker: Dr. WU, Enoch; Venue: Chiuchow Garden Restaurant, Shop 001-003, 1/F, Uptown Plaza, No. 9 Nam Wan Road, Tai Po	Ms. Candice TONG Tel: 2527 8285 1 CME Point
7:00 PM	**FMSHK Certificate Course in Practical Obstetric Ultrasonography (6)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345
12 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –Updates on Neurofibromatosis type 1** Organiser: Hong Kong Neurosurgical Society; Chairman: Dr WONG Sui To; Speaker: Dr YEUNG Kam Tong; Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital	CME Accreditation College: 1.5 points College of Surgeons of Hong Kong Enquiry: Dr. WONG Sui To Tel: 2595 6456 Fax. No.: 2965 4061
1:00 PM	**HKMA Central, Western & Southern Community Network - Certificate Course on Psychiatry (Session 2) - Management of Depression and Comorbidities** Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. POON Man Kay; Speaker: Dr. MAK Wing Chit, Ivan; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	Miss Antonia LEE Tel: 2527 8285 1 CME Point

Date / Time	Function	Enquiry / Remarks
12 WED 7:00 PM	**FMSHK Certificate Course in Renal Medicine 2018 (2)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345
13 THU 7:00 PM	**FMSHK Certificate Course in Respiratory Medicine 2018 (2)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345
14 FRI 1:00 PM	**HKMA Kowloon City Community Network - Management on Diabetic Nephropathy** Organiser: HKMA Kowloon City Community Network; Chairman: Dr. CHIN Chu Wah; Speaker: Dr. CHAN Siu Kim; Venue: President's Room, Spotlight Recreation Club, 4/F., Screen World, Site 8, Whampoa Garden, Hunghom, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
15 SAT 2:30 PM	**MPS Workshop - Mastering Adverse Outcomes** Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. Cheng Ngai Shing, Justin; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	HKMA CME Dept. Tel: 2527 8285 3 CME Point
18 TUE 1:00 PM	**HKMA Kowloon West Community Network - Management of Lung Cancer: Update in EGFR Targeted Treatment** Organiser: HKMA Kowloon West Community Network; Chairman: Dr. TONG Kai Sing; Speaker: Dr. CHOI Kwok Keung, Calvin; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chun, Mei Foo	Miss Antonia LEE Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Tai Po Community Network - Management of Hypertension from Essential to Resistant** Organiser: HKMA Tai Po Community Network; Chairman: Dr. CHOW Chun Kwan, John; Speaker: Dr. KO Kwok Chun; Venue: Chiuchow Garden Restaurant, Shop 001-003, 1/F, Uptown Plaza, No. 9 Nam Wan Road, Tai Po	Ms. Candice TONG Tel: 2527 8285 1 CME Point
19 WED 7:00 PM	**FMSHK Certificate Course in Renal Medicine 2018 (3)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345
20 THU 1:00 PM	**HKMA Hong Kong East Community Network - Management of Lung Cancer: Update in EGFR Targeted Treatment** Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. WONG Chun Por; Speaker: Dr. YU Ka Tung, Stanley; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA New Territories West Community Network - Novel Treatment in Diabesity** Organiser: HKMA New Territories West Community Network; Chairman: Dr. CHEUNG Kwok Wai, Alvin; Speaker: Dr. TING Zhao Wei, Rose; Venue: Atrium Function Rooms, Lobby Floor, Hong Kong Gold Coast Hotel, 1 Castle Peak Road, Gold Coast, Hong Kong	Miss Antonia LEE Tel: 2527 8285 1 CME Point
7:00 PM	**FMSHK Certificate Course in Respiratory Medicine 2018 (3)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345
8:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
21 FRI 1:00 PM	**HKMA Shatin Doctors Network - Community Elderly Nutritional Needs and Challenges** Organiser: HKMA Shatin Doctors Network; Chairman: Dr. MAK Wing Kin; Speaker: Dr. CHAN Chun Chung, Ray; Venue: Diamond Room, 2/F, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Yau Tsim Mong Community Network - Novel Combination of Basal Insulin and GLP1** Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. LEUNG Wai Fung, Anders; Speaker: Dr. CHAN Wing Bun; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
26 WED 12:30 PM	**HKMA Golf Tournament 2018** Organiser: The Hong Kong Medical Association; Chairman: Dr. HOU Lee Tsun, Laurence; Venue: Eden Course, Hong Kong Golf Club, Fanling	Mr. Allen NG Tel: 2527 8285
7:00 PM	**FMSHK Certificate Course in Renal Medicine 2018 (4)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345
27 THU 7:00 PM	**FMSHK Certificate Course in Respiratory Medicine 2018 (4)** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345

Certificate Course for General Practitioners, Nurses and Health Care Providers who are interested in Cardiology

Course No. C321 **CME/CNE Course**

Certificate Course in

Cardiology 2018

Jointly organised by

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Objectives:

This course is designed for General Practitioners, Nurses and Health Care Providers who are interested in Cardiology. A series of lectures covering up-to-date cardiology knowledge and skill in day-to-day clinical practice.

Date	Topics	Speakers
15 Oct	Cardiovascular risk assessment and management (including update in management of hypertension and hypercholesterolemia)	Prof. CHEUNG Man Yung, Bernard Sun Chieh Yeh Heart Foundation Professor in Cardiovascular Therapeutics, Department of Medicine, University of Hong Kong, Queen Mary Hospital
22 Oct	Cardiac emergencies: acute pulmonary edema, acute pulmonary embolism, acute aortic disease and hypertensive crisis	Dr. FANG Jonathan Xinguo Resident, Cardiology and Internal Medicine, Queen Mary Hospital
29 Oct	Clinical approach to common cardiovascular symptoms and overview of cardiac investigations	Dr. KO Kwok Chun, Jason Specialist in Cardiology Private Practice
5 Nov	Management of heart failure	Dr. CHENG Yue Hong Resident, Division of Cardiology, Pok Oi Hospital
12 Nov	Management of acute coronary syndrome	Dr. LEE Kin Tong, Joe Specialist in Cardiology Private Practice
	Management of stable angina and chronic coronary artery disease	Dr. LEE Kar Fai, Victor Specialist in Cardiology Private Practice
19 Nov	Advances in management of valvular heart disease	Dr. CHEUNG Shing Him, Gary Associate Consultant and the Head of Structural Heart Intervention, Department of Medicine & Therapeutics, Prince of Wales Hospital
	Management of AF and role of LAAO	Dr. LUK Ngai Hong, Vincent Associate Consultant, Medical Department, Queen Elizabeth Hospital, Hong Kong

Date : 15, 22, 29 October and 5, 12, 19 November, 2018 (Every Monday)
Time : 7:00 p.m. – 8:30 p.m.
Venue : Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
Language Media : English (Supplemented with Cantonese)
Course Fee : HK$750 (6 sessions)
Certificate : Awarded to participants with a minimum attendance of 70%
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: info@fmshk.org

CME / CNE/ CPD Accreditation in application
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Answers to Dermatology Quiz

Answer:

1. The differential diagnoses include tuberculosis verrucosa cutis (TVC), lupus vulgaris, giant viral wart, mycobacteria marinum infection, chromomycosis, tertiary syphilis, leprosy, hypertrophic lichen planus and squamous cell carcinoma.

2. The essential investigation is a skin biopsy for histopathology. Acid-fast-bacillus (AFB) stain and tissue culture for mycobacterium tuberculosis, atypical mycobacteria and deep fungi should be ordered. If necessary, the specimen can also be sent for polymerase chain reaction (PCR) test for mycobacterium tuberculosis. In this patient, clinically TVC was the most likely diagnosis, which was supported by the histological finding of prominent epidermal changes such as hyperkeratosis, acanthosis and papillomatosis, plus tuberculous granulomas with caseous necrosis and positive AFB in the dermis. The histopathological diagnosis and clinical correlation are important because only a small percentage of cases would have positive smears or cultures in TVC.

   TVC infects patients through direct inoculation of the tubercle bacilli at the sites of trauma. The areas of predilection are therefore over the buttock, knee, elbow, hand and finger. In the old days, this condition was common in Hong Kong Chinese boys over their buttocks and knees. This was mainly due to their habit of playing and squatting in the streets with open-bottom trousers, together with a high prevalence of pulmonary tuberculosis and patients' spitting habit at that time.

3. TVC is a true cutaneous tuberculosis rather than tuberculid. Screening for extracutaneous tuberculosis, especially pulmonary tuberculosis, is important. Tuberculin test, interferon-gamma release assays, chest X-ray and morning urine for AFB should also be done.

4. Combination drugs therapy should be given to all true cutaneous tuberculosis such as lupus vulgaris, tuberculosis verrucosa cutis and scrofuloderma.

Dr Lai-yin CHONG
MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)
Specialist in Dermatology & Venereology

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KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) who are not eligible for cisplatin-containing chemotherapy.

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Selected Safety Information for KEYTRUDA (pembrolizumab)
Indications: • Melanoma –**KEYTRUDA** (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma. • Non-Small Cell Lung Cancer –**KEYTRUDA** is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD L1 expression [Tumor Proportion Score (TPS) ≥50%] as determined by a validated test, with no EGFR or ALK genomic tumor aberrations. –**KEYTRUDA** is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by a validated test with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on approved therapy for these aberrations prior to receiving **KEYTRUDA**. • Urothelial Carcinoma –**KEYTRUDA** is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy. –**KEYTRUDA** is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. **Dosage and administration:** Melanoma: 2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity. NSCLC: a) 200mg for NSCLC that has not been previously treated with chemotherapy or b) 2mg/kg for NSCLC that has been previously treated with chemotherapy. Should be administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. Select patients for treatment of metastatic NSCLC with **KEYTRUDA** based on the presence of positive PD-L1 expression. Urothelial Carcinoma: 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. **Contraindications:** • None **Precautions:** • Immune-Mediated Pneumonitis • Immune-Mediated Colitis • Immune-Mediated Hepatitis • Immune-Mediated Endocrinopathies (hypophysitis; thyroid disorders -hyperthyroidism, hypothyroidism and thyroiditis; Type 1 diabetes) • Immune-Mediated Nephritis and Renal Dysfunction • Severe skin reactions (SJS or TEN) • Other Immune-Mediated Adverse Reactions • Infusion-Related Reactions (including hypersensitivity and anaphylaxis) • Embryofetal Toxicity • For detailed precautions, please consult the full prescribing information **Adverse Events:** Most common adverse reactions (reported in ≥20% of patients) were fatigue, pruritus, diarrhea, decreased appetite, rash, dyspnea, constipation, and nausea. Additional adverse reactions reported in ≥20% of patients with cancers other than melanoma and NSCLC were pyrexia, cough, and musculoskeletal pain. • Immune-mediated pneumonitis • Immune-mediated colitis • Immune-mediated hepatitis • Immune-mediated endocrinopathies • Immune-mediated nephritis and renal dysfunction • Severe skin reactions (SJS or TEN) • Other immune-mediated adverse reactions • Infusion-related reactions • Selected adverse reactions occurring in ≥10% of Patients Receiving **KEYTRUDA** 2mg/kg or 10 mg/kg every 3 weeks include: For Melanoma- Ipilimumab-Naive Melanoma: fatigue, rash, vitiligo, arthralgia, back pain, cough, dyspnea, decreased appetite, headache, diarrhea, nausea and pruritus. Selected laboratory abnormalities (≥20%): Hyperglycemia; Hypertriglyceridemia; Hyponatremia; Increased AST; Hypercholesterolemia; Anemia; Lymphopenia; Increased hypoalbuminemia; increased ALT, increased alkaline phosphatase. For Ipilimumab-Refractory Melanoma: pyrexia, asthenia, pruritus, rash, constipation, diarrhea, abdominal pain, cough, and arthralgia, fatigue, nausea, decreased appetite and vomiting. Selected laboratory abnormalities (≥20%): Hyperglycemia; Hypoalbuminemia; Hyponatremia; Hypertriglyceridemia; Increased alkaline phosphatase Increased AST & ALT; Bicarbonate Decreased; Hypocalcemia; Anemia; Lymphopenia. • For NSCLC: decreased appetite; nausea, constipation, vomiting, dyspnea, cough, arthralgia, back pain, rash, pruritus, fatigue, diarrhea, asthenia and pyrexia. Selected laboratory abnormalities (≥20%): Hyponatremia; Alkaline phosphatase increased; Aspartate aminotransferase increased; Alanine aminotransferase increased; hyperglycemia; anemia; hypertriglyceridemia; lymphopenia; hypoalbuminemia and hypercholesterolemia. • For Urothelial Carcinoma: Anemia; Constipation; Diarrhea; Nausea; Abdominal pain; Elevated LFTs; Vomiting; Fatigue; Pyrexia; Weight decreased; Urinary tract infection; Decreased appetite; Hyponatremia; Musculoskeletal pain; Arthralgia; Blood creatinine increased; Hematuria; Cough; Dyspnea; Rash; Pruritis; Edema peripheral. Selected laboratory abnormalities (≥20%): Glucose increased; Hemoglobin decreased; Lymphocytes decreased; Albumin decreased; Sodium decreased; Alkaline phosphatase increased; Creatinine increased; Phosphate decreased; Aspartate aminotransferase increased; Potassium increased; Calcium decreased. • As with all therapeutic proteins, there is the potential for immunogenicity. • For detailed adverse events, please consult the full prescribing information.

Before prescribing, please consult the full prescribing information.

Reference: 1. KEYTRUDA Product Circular, MSD Hong Kong. 2.Bladder Cancer (2018), NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Version 4.2018, pp.38,78 22nd May, 2018, National Cancer Insititute Inc., USA

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