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Enquiry

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PROGRAM BOOK

Symposium 2024

State Key Laboratory of Liver Research (HKU)

RGC Theme-based Research Scheme Project on Translations to Enhance Liver Cancer Management

Date: 26 October 2024 (Saturday)
Time: 9:00 am to 4:30 pm
Venue: Concord Room, Renaissance Harbour View Hotel Hong Kong

Organized by

香港大學 肝病研究國家重點實驗室 State Key Laboratory of Liver Research The University of Hong Kong

UGC 大學教育資助委員會 University Grants Committee
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HEPATOCELLULAR CARCINOMA (HCC)

IMFINZI in combination with **IMJUDO** is indicated for the first-line treatment of adult patients with **unresectable hepatocellular carcinoma** (uHCC).[1,2]

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METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

IMFINZI in combination with **IMJUDO** and platinum-based chemotherapy for the treatment of adult patients with **metastatic non-small cell lung cancer (NSCLC)** with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.[1,2]

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BILIARY TRACT CANCER (BTC)

IMFINZI in combination with **gemcitabine and cisplatin** is indicated for the first-line treatment of adult patients with **locally advanced** or **metastatic biliary tract cancer** (BTC).[1]

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References: 1. IMFINZI Hong Kong Product Insert Feb.2024 2. IMJUDO Hong Kong Product Insert Dec. 2023

Imfinzi Abbreviated PI

Presentation: 500 mg/10mL and 120mg/2.4mL intravenous infusion. **Indications:** 1) Treatment of patients with unresectable Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. 2) In combination with etoposide and either carboplatin or cisplatin, as first- line treatment of adult patients with extensive-stage small cell lung cancer (ES- SCLC). 3) In combination with tremelimumab and platinum-based chemotherapy, for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. 4) In combination with gemcitabine and cisplatin, as treatment of adult patients with locally advanced or metastatic biliary tract cancer (BTC). 5) In combination with tremelimumab, for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC). **Dosage and administration:** Administer IMFINZI as an intravenous infusion over 60 minutes after dilution. **Stage III NSCLC:** 10mg/kg every 2 weeks or 1500mg every 4 weeks for patients weighing 30 kg and more until disease progression, unacceptable toxicity, or a maximum of 12 months. **ES-SCLC:** Patients weighing 30 kg and more: 1500mg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 1500mg every 4 weeks as a single agent until disease progression or unacceptable toxicity. Patients weighing less than 30kg: 20mg/kg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 20mg/kg every 4 weeks as a single agent until disease progression or unacceptable toxicity. **Metastatic NSCLC:** Patients weighing 30 kg and more: 1,500 mg every 3 weeks in combination with tremelimumab 75 mg and platinum-based chemotherapy for 4 cycles, and then administer IMFINZI 1,500 mg every 4 weeks as a single agent with histology-based pemetrexed maintenance therapy every 4 weeks, and a fifth dose of tremelimumab 75 mg in combination with IMFINZI dose 6 at week 16. Patients weighing less than 30kg: 20 mg/kg every 3 weeks in combination with tremelimumab 5 mg/kg and platinum-based chemotherapy, and then administer IMFINZI 20 mg/kg every 4 weeks as a single agent with histology-based pemetrexed therapy every 4 weeks, and a fifth dose of tremelimumab 1 mg/kg in combination with IMFINZI dose 6 at week. **BTC:** Patients weighing 30 kg and more: administer IMFINZI 1,500 mg every 3 weeks in combination with chemotherapy, and then 1,500 mg every 4 weeks as a single agent. Patients weighing less than 30kg: administer IMFINZI 20 mg/kg every 3 weeks in combination with chemotherapy, and then 20 mg/kg every 4 weeks as a single agent. **uHCC:** Patients weighing 30 kg and more: IMFINZI 1,500 mg in combination with tremelimumab 300 mg as a single dose at Cycle 1/Day 1, followed by IMFINZI as a single agent every 4 weeks. Patients weighing less than 30kg: IMFINZI 20 mg/kg in combination with tremelimumab 4 mg/kg as a single dose at Cycle 1/Day 1, followed by IMFINZI as a single agent every 4 weeks. **Contraindications:** None. **Precautions: Immune-mediated Adverse Reactions:** May be severe or fatal, can occur in any organ system or tissue, including immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, immune-mediated nephritis and renal dysfunction, and solid organ transplant rejection, and immune-mediated pancreatitis. Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. Withhold or permanently discontinue based on severity and type of reaction. **Infusion-Related Reactions:** Interrupt, slow the rate of infusion, or permanently discontinue IMFINZI based on the severity of the reaction. Complications of Allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. **Undesirable effects:** IMFINZI as a Single-Agent: Most common adverse reactions (≥20% of patients with unresectable, Stage III NSCLC) are cough, fatigue, pneumonitis/radiation pneumonitis, upper respiratory tract infections, dyspnea, and rash. IMFINZI in Combination with Platinum-Based Chemotherapy. Most common adverse reactions (≥20% of patients with extensive-stage SCLC) are nausea, fatigue/asthenia, and alopecia. IMFINZI in Combination with gemcitabine and cisplatin. Most common adverse reactions (≥20% of patients with BTC) are fatigue, nausea, constipation, decreased appetite, abdominal pain, rash, and pyrexia. IMFINZI in Combination with Tremelimumab: Most common adverse reactions (≥ 20%) of patients with uHCC are rash, diarrhea, fatigue, pruritis, musculoskeletal pain, and abdominal pain. IMFINZI in Combination with Tremelimumab and Platinum-Based Chemotherapy. Most common adverse reactions (≥ 20% of patients with metastatic NSCLC) were nausea, fatigue, musculoskeletal pain, decreased appetite, rash, and diarrhea. **Full local prescribing information is available upon request. API.HK.IMF.0224**

Imjudo Abbreviated PI

Presentation: 25 mg/1.25 mL and 300 mg/15 mL (20 mg/mL) intravenous infusion. **Indications:** IMJUDO is a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocking antibody indicated 1) in combination with durvalumab, for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC). 2) in combination with durvalumab and platinum-based chemotherapy for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. **Dosage and administration:** Administer IMJUDO as an intravenous infusion over 60 minutes after dilution. **uHCC:** Weight 30 kg and more: IMJUDO 300 mg as a single dose in combination with durvalumab 1,500 mg at Cycle 1/Day 1, followed by durvalumab as a single agent every 4 weeks. Weight less than 30 kg: IMJUDO 4 mg/kg as a single dose in combination with durvalumab 20 mg/kg at Cycle 1/Day 1, followed by durvalumab as a single agent every 4 weeks. **Metastatic NSCLC:** Weight 30 kg and more: 75 mg every 3 weeks in combination with durvalumab 1,500 mg and platinum-based chemotherapy for 4 cycles, and then administer durvalumab 1,500 mg every 4 weeks as a single agent with histology-based pemetrexed therapy every 4 weeks, and a fifth dose of IMJUDO 75 mg in combination with durvalumab dose 6 at week 16. Weight less than 30 kg: 1 mg/kg every 3 weeks in combination with durvalumab 20 mg/kg and platinum-based chemotherapy for 4 cycles, and then administer durvalumab 20 mg/kg every 4 weeks as a single agent with histology-based pemetrexed therapy every 4 weeks, and a fifth dose of IMJUDO 1 mg/kg in combination with durvalumab dose 6 at week 16. **Contraindications:** None. **Precautions: Immune-Mediated Adverse Reactions:** Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions and immune-mediated pancreatitis. Monitor for early identification and management. Evaluate liver enzymes, creatinine, adrenocorticotropic hormone level and thyroid function at baseline and before each dose. Withhold or permanently discontinue based on severity and type of reaction. **Infusion-Related Reactions:** Interrupt, slow the rate of infusion, or permanently discontinue treatment based on the severity of the reaction. **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. **Undesirable effects:** Most common adverse reactions (≥ 20%) of patients with uHCC are rash, diarrhea, fatigue, pruritus, musculoskeletal pain, and abdominal pain. Most common laboratory abnormalities (≥ 40%) of patients with uHCC are AST increased, ALT increased, hemoglobin decreased, sodium decreased, bilirubin increased, alkaline phosphatase increased, and lymphocytes decreased. Most common adverse reactions (≥ 20%) of patients with metastatic NSCLC were nausea, fatigue, musculoskeletal pain, decreased appetite, rash, and diarrhea. **Full local prescribing information is available upon request. API.HK.IMJ.1223**

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Welcome from the Director of SKLLR (HKU) and Project Coordinator of RGC TRS project

On behalf of the State Key Laboratory of Liver Research (SKLLR) of HKU and as the Project Coordinator of the Theme-based Research Scheme (TRS) grant, I would like to express my sincere gratitude and warmly welcome you to this Joint 13th Symposium of SKLLR and TRS.

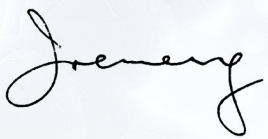
Established in June 2010, the SKLLR aims to reduce the incidence and mortality of hepatitis and liver diseases in Hong Kong, Mainland China and around the region through vigorous basic and translational research programs and meticulous clinical care.

For the TRS project (2023-2027) on 'Delineating and translating the mechanistic determinants to improve the clinical management of liver cancer' funded by HK Research Grants Council, the second TRS award we have obtained, the team aims to generate unique information for evidence-based translational application to improve the diagnosis and treatment outcome for patients with liver cancer.

To promote knowledge exchange with the scientific research and clinical community, we jointly hold an annual symposium on advances in liver research and liver diseases. This current Symposium features a very strong program, assembling the presentations of SKLLR and TRS research teams and internationally renowned experts to share their cutting-edge research and new basic and clinical developments on liver diseases. We are deeply honored and privileged to have Professor Mohammed ESLAM (Professor of Hepatology and Deputy Director, Storr Liver Centre, University of Sydney, Australia) and Professor Qiang GAO (Deputy Director and Professor, Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China) as our Keynote Speakers.

I wish you an inspirational and rewarding day with us.

Finally, I would like to express my sincere thanks to the organizing committee and speakers for their wonderful contributions, and the sponsors for their generous support. Their contributions have made this Symposium a success.



Irene Oi-Lin Ng

MBBS (HK), MD (HK), PhD (HK), FRCPath, FHKCPath, FHKAM (Pathology), FAASLD

Director, State Key Laboratory of Liver Research & Project Coordinator, TRS
The University of Hong Kong

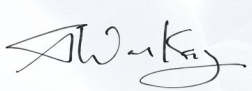
Welcome from the Chairpersons

On behalf of the Organizing Committee of Symposium 2024 of State Key Laboratory of Liver Research (SKLLR) and RGC Theme-based Research Scheme Project on Translations to Enhance Liver Cancer Management, we warmly welcome everyone to the 13th Symposium of SKLLR / TRS.

The Symposium features a comprehensive program ranging from basic research to clinical applications on the latest development of liver diseases. It brings together the research team members of SKLLR as along with other local and overseas experts to share cutting-edge research and new clinical developments in liver diseases. We are much honored to have Professor Qiang GAO from Fudan University, China, as our Keynote Speaker for the basic research session. He will present on "Multi-omics characterization of intrahepatic cholangiocarcinoma reveals new treatment opportunity", and "A pan-cancer single cell profiling of tumor neutrophils identifies antigen presentation potency". For the Keynote lectures in clinical sessions, we are equally honored to welcome Professor Mohammed ESLAM from the University of Sydney, Australia. He will deliver presentations on "Lean MAFLD", and "NAFLD, MAFLD or MASLD?"

It is the wish of the Organizing Committee that today's Symposium will continue to deliver significant discoveries and foster understanding and collaboration among researchers. We have succeeded in assembling an outstanding panel of speakers, and we hope you find the sessions both stimulating and fulfilling.

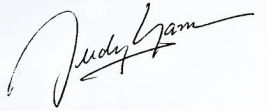
Last but not the least, we would like to express our heartfelt gratitude to all speakers and our generous sponsors: Platinum Sponsor (AstraZeneca Hong Kong Ltd.), Silver Sponsors (BioArrow Technology Ltd. and MedChemExpress), Bronze Sponsor (AbbVie Ltd.), and logo acknowledgement (Thermo Fisher Scientific Hong Kong). Their generous support has significantly contributed to the success of this Symposium.



Walter Wai-Kay SETO

MBBS(HK), MD(HK), MRCP (UK), FRCP (Edin, Glasg, Lond), FHKCP, FHKAM (Medicine)

Chairperson (Clinical)
Organizing Committee of
Symposium 2024 of SKLLR



Judy Wai-Ping YAM

BSc (Washington), MSc (HK), PhD (HK)
Chairperson (Basic)

Chairperson (Clinical)
Organizing Committee of
Symposium 2024 of SKLLR

Background and Mission

Liver disease due to hepatitis B virus (HBV) infection, end-stage liver disease (cirrhosis) and liver cancer remains one of the leading causes of morbidity and mortality in Hong Kong and in parts of the Mainland. Our mission is to enhance our understanding in the pathogenetic mechanisms of HBV, cirrhosis and liver cancer by engaging in cutting-edge basic laboratory research, and devise better diagnoses and new/better treatment modalities for HBV infection and liver cancer. The long-term objective is to reduce the incidence and mortality of hepatitis and liver diseases in Hong Kong, by offering our patients the best possible management and treatments. Through vigorous basic and translational research programs and meticulous clinical care, we are striving to establish a world-class State Key Laboratory of Liver Research of the highest standard in Hong Kong, Mainland and around the region for better prevention, more accurate diagnosis and more effective treatments for liver diseases.

Organizing Committee of Joint-SKLLR & TRS Symposium 2024

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The University of Hong Kong

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Dr Yu-Man TSUI
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Dr Eric Tin-Lok WONG
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Time	Session
09:00 - 09:05	**Opening Address: Professor Judy Wai-Ping Yam**
Session Chairpersons: Professor Dong-Yan JIN and Professor Xin-Yuan GUAN	
09:05 - 09:25	**Basic Young 1** **Ms Yiling CHEN** PhD Student, Department of Pathology, HKU Topic: The mevalonate pathway promotes liver cancer
09:25 - 09:45	**Basic Young 2** **Dr Vanilla Xin ZHANG** Postdoctoral Fellow, Department of Pathology, HKU Topic: Targeting the oncogenic m6A demethylase FTO suppresses tumorigenesis and potentiates immune response in hepatocellular carcinoma
09:45 - 10:05	**Basic Young 3** **Dr Yu-Man TSUI** Research Assistant Professor, Department of Pathology, HKU Topic: Sorted-cell sequencing on HCC specimens reveals a key player in CD24/CD13/EpCAM-triple positive, stemness-related HCC cells
10:05 - 10:45	**Basic Keynote 1** **Professor Qiang GAO, MD, PhD** Deputy Director and Professor, Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China Topic: A pan-cancer single cell profiling of tumor neutrophils identifies antigen presentation potency
10:45 - 11:10	**Tea Break**
Session Chairpersons: Professor Carmen Chak-Lui WONG and Professor Ken Hoi-Tang MA	
11:10 - 11:30	**Basic Presentation 1** **Professor Stephanie Kwai-Yee MA** Professor, School of Biomedical Sciences, HKU Topic: Discovery of potential therapies for CTNNB1 mutation-driven hepatocellular carcinoma using a genetically defined, syngeneic mouse organoid platform
11:30 - 11:50	**Basic Presentation 2** **Professor Clive Yik-Sham CHUNG** Assistant Professor, School of Biomedical Sciences, HKU Topic: Chemoproteomics-driven identification of new druggable hotspots in cancers and discovery of anticancer covalent ligands
11:50 - 12:10	**Basic Presentation 3** **Professor Judy Wai-Ping YAM** Professor, Department of Pathology, HKU Topic: Unraveling the uptake mechanisms of small extracellular vesicles and their significance in hepatocellular carcinoma

Time	Session
12:10 - 13:35	**Lunch**
Session Chairpersons: Dr James Yan-Yue FUNG and Professor Jack Chun-Ming WONG	
13:35 - 14:05	**Basic Keynote 2** **Professor Qiang GAO, MD, PhD** Deputy Director and Professor, Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China Topic: Multi-omics characterization of intrahepatic cholangiocarcinoma reveals new treatment opportunity
14:05 - 14:35	**Clinical Keynote 1** **Professor Mohammed ESLAM, MD, MSc, PhD** Professor of Hepatology and Deputy Director, Storr Liver Centre, University of Sydney, Sydney, Australia Topic: NAFLD, MAFLD or MASLD?
14:35 - 14:55	**Clinical Presentation 1** **Professor Walter Wai-Kay SETO** Clinical Professor, Department of Medicine, HKU Topic: The gut microbiome and liver disease: A genuine link?
14:55 - 15:20	**Tea Break**
Session Chairpersons: Professor Walter Wai-Kay SETO and Dr Regina Cheuk-Lam LO	
15:20 - 15:45	**Clinical Keynote 2** **Professor Mohammed ESLAM, MD, MSc, PhD** Professor of Hepatology and Deputy Director, Storr Liver Centre, University of Sydney, Sydney, Australia Topic: Lean MAFLD
15:45 - 16:05	**Clinical Presentation 2** **Professor Thomas Chung-Cheung YAU** Clinical Associate Professor, Department of Medicine, HKU Topic: Anti CTLA 4 in advanced hepatocellular carcinoma
16:05 - 16:25	**Clinical Presentation 3** **Professor Albert Chi-Yan CHAN** Clinical Professor, Department of Surgery, HKU Topic: Combining immunotherapy in surgical oncology: Current research and future perspectives
16:25 - 16:30	**Closing remarks: Professor Walter Wai-Kay Seto**

Keynote Lecture I

Professor Dong-Yan JIN
Professor
School of Biomedical Sciences, HKU

Professor Xin-Yuan GUAN
Chair Professor
Department of Clinical Oncology,
School of Clinical Medicine, HKU

Keynote Speaker

Professor Qiang GAO
Deputy Director and Professor,
Department of Liver Surgery and Transplantation,
Liver Cancer Institute, Zhongshan Hospital,
Fudan University,
Shanghai, China

A pan-cancer single cell profiling of tumor neutrophils identifies antigen presentation potency

Neutrophils, the most abundant and efficient defenders against pathogens, exert opposing functions across cancer types. However, given their short half-life, it remains challenging to explore how neutrophils adopt specific fates in cancer. Here, we generated and integrated single-cell neutrophil transcriptomes from 17 cancer types (225 samples from 143 patients). Neutrophils exhibited extraordinary complexity, with 10 distinct states including inflammation, angiogenesis, and antigen presentation. Notably, the antigen-presenting program was associated with favorable survival in most cancers and could be evoked by leucine metabolism and subsequent histone H3K27ac modification. These neutrophils could further invoke both (neo)antigen-specific and antigen-independent T cell responses. Neutrophil delivery or a leucine diet fine-tuned the immune balance to enhance anti-PD-1 therapy in various murine cancer models. In summary, these data not only indicate the neutrophil divergence across cancers but also suggest therapeutic opportunities such as antigen-presenting neutrophil delivery.

Keynote Lecture II

Dr James Yan-Yue FUNG
Consultant
Department of Medicine,
Queen Mary Hospital and
Honorary Clinical Associate Professor
Department of Medicine,
School of Clinical Medicine, HKU

Professor Jack Chun-Ming WONG
Professor
Department of Pathology,
School of Clinical Medicine, HKU

Keynote Speaker

Professor Qiang GAO
Deputy Director and Professor,
Department of Liver Surgery and Transplantation,
Liver Cancer Institute, Zhongshan Hospital,
Fudan University,
Shanghai, China

Multi-omics characterization of intrahepatic cholangiocarcinoma reveals new treatment opportunity

We performed proteogenomic characterization of intrahepatic cholangiocarcinoma (iCCA) using paired tumor and adjacent liver tissues from 262 patients. Integrated proteogenomic analyses prioritized genetic aberrations and revealed hallmarks of iCCA pathogenesis. Aflatoxin signature was associated with tumor initiation, proliferation, and immune suppression. Mutation-associated signaling profiles revealed that TP53 and KRAS co-mutations may contribute to iCCA metastasis via the integrin-FAK-SRC pathway. FGFR2 fusions activated the Rho GTPase pathway and could be a potential source of neoantigens. Proteomic profiling identified four patient subgroups (S1–S4) with subgroup-specific biomarkers. These proteomic subgroups had distinct features in prognosis, genetic alterations, microenvironment dysregulation, tumor microbiota composition, and potential therapeutics. SLC16A3 and HKDC1 were further identified as potential prognostic biomarkers associated with metabolic reprogramming of iCCA cells. This study provides a valuable resource for researchers and clinicians to further identify molecular pathogenesis and therapeutic opportunities in iCCA.

Dr James Yan-Yue FUNG
Consultant
Department of Medicine,
Queen Mary Hospital and
Honorary Clinical Associate Professor
Department of Medicine,
School of Clinical Medicine, HKU

Professor Jack Chun-Ming WONG
Professor
Department of Pathology,
School of Clinical Medicine, HKU

Keynote Speaker

Professor Mohammed ESLAM
Professor of Hepatology and Deputy Director,
Storr Liver Centre,
University of Sydney,
Sydney, Australia

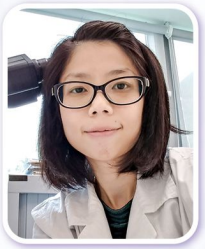
NAFLD, MAFLD or MASLD?

The year 2020 marked a watershed for Hepatology with the redefinition of fatty liver disease related to metabolic dysfunction. The term metabolic dysfunction-associated fatty liver disease (MAFLD) was introduced, and a new classification was created to better reflect the underlying causes of the disease. These criteria have been extensively validated with unequivocal evidence suggesting that it has superior utility for identifying adverse hepatic and extrahepatic outcomes, it deconvolutes disease heterogeneity by capturing homogenous groups of patients who fit into one of three well-characterised subgroups, and ultimately brings the disease back under the umbrella of the metabolic health spectrum. These changes are not only important for clinical research studies, but also for daily clinical practice. They are simple to use in clinical practice, even in resource-limited settings, which is crucial for widespread acceptance given how common this disorder is. More recently, an adapted version of the MAFLD term and diagnostic criteria, namely metabolic dysfunction-associated steatotic liver disease (MASLD) has been proposed. The changes

Clinical Keynote Lecture I

in the MASLD criteria compared to the validated MAFLD criteria include “liberalized” requirements for evidence of metabolic dysfunction to a single criterion instead of two for lean individuals. Additionally, some alterations in the used metabolic risk factor cut-offs, an aspect that was highlighted recently to have significant implications, particularly among the paediatric population was proposed. Both definitions also addressed the coexistence of the disease with other liver disease aetiologies differently. The SLD definition introduces a new term "MetALD" to describe patients with MASLD and excessive alcohol intake, with no other term for MASLD coexisting with any other cause. On the other hand, the MAFLD definition refrains from introducing a new term and instead includes the concept of dual etiologies, covering the coexistence of MAFLD with any other cause, including excessive alcohol intake. The talk will illustrate the similarities and differences between the various diagnostic criteria and the current evidence of their utility. I will also briefly touch on the future prospects and the way forward.

Professor Walter Wai-Kay SETO
Clinical Professor
Department of Medicine,
School of Clinical Medicine, HKU



Dr Regina Cheuk-Lam LO
Clinical Associate Professor
Department of Pathology,
School of Clinical Medicine, HKU

Keynote Speaker

Professor Mohammed ESLAM
Professor of Hepatology and Deputy Director,
Storr Liver Centre,
University of Sydney,
Sydney, Australia

Lean MAFLD

Excessive calorie consumption relative to expenditure, intake of unhealthy diets, and lack of physical activity are globally fuelling an increase in the prevalence of poor metabolic health, even in individuals of normal weight. Consequently, this trend entails increased risk of various metabolic disorders, including metabolic associated fatty liver disease (MAFLD), which affects up to a third of the global population.

MAFLD burden has grown in parallel with rising rates of type 2 diabetes and obesity and increases the risk of end-stage liver disease, hepatocellular carcinoma, death, and liver transplantation, and has extrahepatic consequences including cardiometabolic disease and cancers. Although classically is associated with obesity, there is accumulating evidence that not all overweight or obese develop fatty liver disease. On the other hand, a considerable proportion of patients with MAFLD are lean, indicating the importance of metabolic health in disease pathogenesis regardless of body mass index. A complex and dynamic interaction

Clinical Keynote Lecture II

between a multitude of factors, including genetic, epigenetic, dietary, and lifestyle factors, enterohepatic circulation, and gut microbiota is likely to shape individual metabolic health status.

The clinical profile, natural history and pathophysiology of lean patients with MAFLD is not well characterised. In this talk, I am going to provide the recent epidemiological data on this group of patients. The talk will illustrate the novel concept considering the overall metabolic health and metabolic adaptation as a framework to best explain the pathogenesis of MAFLD and its heterogeneity, both in lean and non-lean individuals. This framework provides a conceptual schema for interrogating the MAFLD phenotype in lean individuals that can translate to novel approaches for diagnosis and patient care. I will also touch briefly on the prospective aspects including the initiatives bringing together diverse stakeholders across the metabolic disease spectrum that are pivotal in our efforts to firstly understand and then to provide personalized, timely, equitable and affordable health interventions for lean patients with MAFLD.

Professor Dong-Yan JIN
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Professor Xin-Yuan GUAN
Chair Professor
Department of Clinical Oncology,
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Speakers

Ms Yiling CHEN
PhD Student,
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The mevalonate pathway promotes liver cancer

Ferroptosis is a novel form of regulated cell death triggered by iron-induced lipid peroxidation. The GPX4/glutathione and FSP1/Coenzyme Q10 systems are primary defense mechanisms against ferroptosis, neutralizing toxic lipid peroxides to prevent cell death. Our multi-omics screening has identified Mevalonate diphosphate decarboxylase (MVD), a crucial enzyme in the Mevalonate (MVA) pathway, as essential for hepatocellular carcinoma (HCC) survival and ferroptosis protection. MVD safeguards HCC from ferroptosis through two mechanisms: producing the antioxidant CoQ10 to eliminate oxidized lipids and facilitating the translation of the selenoprotein GPX4 by generating isopentenyl pyrophosphate (IPP), necessary for N6-isopentenyladenosine (i6A) modification of selenocysteine-tRNA. Selenoproteins are unique due to their selenium component, incorporated as selenocysteine, which is recoded by the stop codon UGA and delivered via selenocysteine-tRNA. The IPP-dependent i6A modification is crucial for the stability and function of selenocysteine-tRNA. Inhibition of MVD, either genetically or pharmacologically, disrupts CoQ10 synthesis and causes ribosome stalling during GPX4 translation. Furthermore, knocking out TRSP and TRIT1, encoding the selenocysteine-tRNA and the i6A modifying enzyme respectively, impairs selenoprotein translation and induces ferroptosis in HCC. Our study reveals that the MVA pathway supports liver cancer resistance to ferroptosis through CoQ10 production and selenoprotein translation, highlighting MVD as a valuable prognostic marker and therapeutic target in HCC.

Young Researcher Presentations

Dr Vanilla Xin ZHANG
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Targeting the oncogenic m6A demethylase FTO suppresses tumorigenesis and potentiates immune response in hepatocellular carcinoma

Objective: Fat Mass and Obesity-associated protein (FTO), an eraser of N6-methyadenosine (m6A), plays oncogenic roles in various cancers. However, its role in hepatocellular carcinoma (HCC) is unclear. Furthermore, small extracellular vesicles (sEVs, or exosomes) are critical mediators of tumorigenesis and metastasis, but the relationship between FTO-mediated m6A modification and sEVs in HCC is unknown.

Design: The functions and mechanisms of FTO and Glycoprotein Nonmetastatic Melanoma Protein B (GPNMB) in HCC progression were investigated in vitro and in vivo. Neutralizing antibody of syndecan-4 (SDC4) was used to assess the significance of sEV-GPNMB. FTO inhibitor CS2 was used to examine the effects on anti-PD1 and sorafenib treatment.

Results: FTO expression was up-regulated in patient HCC tumors. Functionally, FTO promoted HCC cell proliferation, migration, and invasion in vitro, and tumor growth and metastasis in vivo. FTO knockdown enhanced the activation and recruitment of tumor-infiltrating CD8+ T cells. Furthermore, we identified GPNMB to be a downstream target of FTO, which reduced the m6A abundance of GPNMB, hence stabilizing it from degradation by YTHDF2. Of note, GPNMB was packaged into sEVs derived from HCC cells and bound to the surface receptor SDC4 of CD8+ T cells, resulting in the inhibition of CD8+ T cell activation. A potential FTO inhibitor, CS2, suppresses the oncogenic functions of HCC cells and enhances the sensitivity of anti-PD1 and sorafenib treatment.

Conclusion: Targeting the FTO/m6A/GPNMB axis could significantly suppress tumor growth and metastasis, and enhance immune activation, highlighting the potential of targeting FTO signalling with effective inhibitors for HCC therapy.

Dr Yu-Man TSUI
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Sorted-cell sequencing on HCC specimens reveals a key player in CD24/CD13/EpCAM-triple positive, stemness-related HCC cells

Hepatocellular carcinoma (HCC) is a heterogeneous cancer with varying levels of liver cancer stem cells (LCSCs) in the tumors. We aimed to investigate the expression of different LCSC markers in human HCCs to identify their regulatory mechanisms in stemness-related HCC cells.

We performed a comprehensive, unbiased examination of LCSC markers on a total of 60 HCC resected specimens by flow cytometry. Significant heterogeneity was found in the expression of LCSC markers, CD24, CD13, and EpCAM. Concomitant expression of CD24, CD13 and EpCAM was detected in 32 HCC samples, and this was associated with advanced tumor stages. By fluorescence-activated cell-sorting (FACS), we sorted HCC cells for the three individual LCSC markers to perform subsequent transcriptomic analyses. There were diverse associated signaling pathways with only a low degree of overlapping among the different individual LCSC markers. Moreover, we identified EPS8L3 as a common gene associated with the three markers. Functionally, knockdown of EPS8L3 suppressed the expression of all the three LCSC markers in HCC cells. Multi-color immunofluorescence showed HCC cells with co-expression of the three LCSC markers and EPS8L3 in the clinical specimens. To search for the upstream regulation of EPS8L3, we found SP1 bound to EPS8L3 promoter to drive EPS8L3 expression. Lastly, using Akt inhibitor MK2206, we showed that Akt-signaling-driven SP1 drove the expression of these three LCSC markers.

Our findings provide insight into potential LCSC-targeting therapeutic strategies by offering a proof-of-concept support to suppress the upstream transcription regulatory machineries in a collective manner.

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Speakers

Professor Stephanie Kwai-Yee MA
Professor,
School of Biomedical Sciences, HKU

Discovery of potential therapies for CTNNB1 mutation-driven hepatocellular carcinoma using a genetically defined, syngeneic mouse organoid platform

Hepatocellular Carcinoma (HCC) is a disease with diverse cells and distinct molecular signatures, resulting in a complex and heterogeneous nature. The traditional 'one-size-fits-all' approach to treatment has been inefficient or ineffective for many individuals. A major challenge in analyzing human clinical samples is distinguishing driver from passenger mutations, leading to an incomplete understanding of the pathway dependency of specific driver mutations. To address this, we established a mouse organoid platform using HCC tissue with defined driver mutations (loss of TP53, Axin1, PTEN, Mcl1 overexpression or CTNNB1 activating mutations delivered via hydrodynamic tail vein injection, along with MYC and sleeping beauty transposase) to study the characteristics of driver-specific HCC and their response to therapy. We screened over 700 drugs and identified inhibitors targeting HMGCR and ERBB to be able to preferentially inhibit the growth and induce cell death of HCC carrying CTNNB1 mutations, one of the commonest alterations detected in human HCC cases. These reflections were observed both in vitro and in vivo and primary human HCC patient-derived organoids. Our study not only reports on the development and characterization of mouse HCC models and their corresponding organoids but also utilizes the platform to evaluate drug response heterogeneity. This scalable platform offers insights into the characteristics of cancer arising from specific driver mutations and has the potential to incorporate other functional aspects including microenvironmental interactions.

Professor Clive Yik-Sham CHUNG
Assistant Professor,
School of Biomedical Sciences, HKU

Chemoproteomics-driven identification of new druggable hotspots in cancers and discovery of anticancer covalent ligands

Chemoproteomics is an advanced proteomics technology using chemical probes to study functions and activities of proteins. As many functional proteins are associated with disease development and progression, the applications of chemoproteomics have been extended to drug target identification and covalent drug development for EGFR, BTK and KRAS G12C covalent inhibitors. In this talk, I will first discuss the unique features of our chemoproteomic probe, NAIA, which can significantly advance the chemoproteomics platform by expanding the pool of targetable hotspots, even on proteins which were once considered as undruggable. Then, I will showcase how anticancer covalent ligands targeting these new hotspots can be developed from chemoproteomics-coupled screening experiments. Through covalent binding with Rac1 Cys178, CL1 disrupts Rac1-GEF interactions, thus inhibiting Rac1 activity in hepatocellular carcinoma (HCC) cells. This leads to downregulation of pRb, cyclin D1 and E2F1, and hence G1-phase cell cycle arrest in the HCC cells. The versatile chemoproteomics platform also enables the discovery of CL26 to target AGPAT4, which is a functional regulator of cancer cell plasticity in HCC. The covalent binding of CL26 onto Cys228 of AGPAT4 induces steric hindrance on substrate binding to the active site, thus resulting in strong inhibitory effects on AGPAT4. This allows CL26 to demonstrate promising anticancer effects through overcoming sorafenib-resistance in HCC cells and patient-derived tumor xenograft models. All these results should highlight the powerful application of our chemoproteomics platform in liver cancer research and drug development.

Basic Research Presentations

Professor Judy Wai-Ping YAM
Professor,
Department of Pathology,
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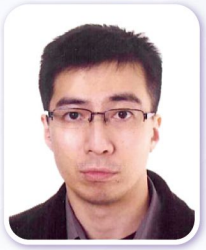
Unraveling the uptake mechanisms of small extracellular vesicles and their significance in hepatocellular carcinoma

Small extracellular vesicles (sEVs) play a critical role in intercellular communication by facilitating the transfer of bioactive molecules between different cell types. These membrane-bound particles are secreted by various cells and have the ability to modulate cellular phenotype and signaling pathways upon uptake by recipient cells. In our recent research, we focused on elucidating the intricate interplay between sEVs and hepatocellular carcinoma (HCC). Our study unraveled the mechanisms through which sEVs contribute to the progression of HCC, particularly in promoting tumor growth, angiogenesis, and metastasis, which are crucial processes in cancer development. The entry pathway of sEV is of vital importance in determining the effect of EVs in the recipient cells. However, how sEV enters HCC cells remains obscure. This study aims to elucidate the mechanistic basis underlying the internalization of sEV by HCC cells. We identified macropinocytosis as the primary uptake mechanism of sEVs by HCC cells. Macropinocytosis refers to the process by which cells engulf extracellular fluid and particles. Mechanistically, we delineate how a high level of NHE7, a sodium-hydrogen exchanger, regulates intracellular and endosomal pH, leading to the maturation of macropinosomes. Inducible inhibition of NHE7 in established tumors delays tumor development and suppresses metastasis. Clinically, NHE7 is upregulated and associated with poor prognosis of HCC. Here, we provide evidence that macropinocytosis controls the internalization of sEV and their effect on the recipient cells. In addition, this study provides insights into the blockade of sEV uptake as a therapeutic strategy for HCC.



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Professor Jack Chun-Ming WONG
Professor
Department of Pathology,
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Speakers

Professor Walter Wai-Kay SETO
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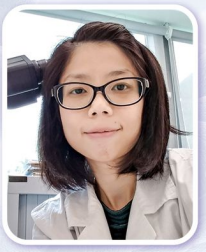
The gut microbiome and liver disease: A genuine link?

The gut microbiome has been linked to many aspects of human health, including the liver. This talk will review the latest findings on the gut-liver axis, including the role of the microbiome in liver metabolism, inflammation, and in various chronic liver diseases, including viral hepatitis, metabolic associated fatty liver disease, liver cirrhosis and liver cancer. We will also discuss emerging strategies for manipulating the gut microbiome to promote liver health, such as probiotics, and fecal microbiota transplantation. The presentation aims to provide a comprehensive overview of this burgeoning field, emphasizing the importance of understanding the gut microbiome's impact on liver health and disease management.

Clinical Research Presentations



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Anti CTLA 4 in advanced hepatocellular carcinoma

The systemic treatment of unresectable hepatocellular carcinoma (uHCC) has undergone an evolution in recent few years. The immune checkpoints Programmed cell death protein 1 pathway (PD-1), programmed death ligand 1 (PDL-1)) and the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathway are heavily implicated in tumour immune escape. The blockade of these two pathways by immune checkpoint inhibitors has considerably improved the outcomes in uHCC patients. In March 2020, the combination nivolumab and ipilimumab(N+I) was approved by the US FDA for treatment of uHCC patients who received prior sorafenib. This was based on the results of the phase I/II CheckMate- 040 cohort 4 trial, which showed a good overall response rate and encouraging overall survival (OS) with a manageable safety profile. Furthermore, in the first line setting, the Phase 3 HIMALAYA study, which investigated the use of durvalumab (D) with tremelimumab(T) in uHCC demonstrated that a single priming dose of T plus regular interval D significantly improved OS vs sorafenib. This combination was also approved by the US FDA as the first line treatment of uHCC patients in 2022. More recently, in Phase III trial Checkmate 9DW trial, the trial results showed promising response rate and long-term OS in using the N+I combination as the first line treatment of uHCC patients.

Named Lecture by AstraZeneca

Professor Albert Chi-Yan CHAN
Clinical Professor,
Department of Surgery,
School of Clinical Medicine, HKU

Combining immunotherapy in surgical oncology: Current research and future perspectives

TBC

Memo

HEPATOCELLULAR CARCINOMA (HCC)

IMFINZI in combination with **IMJUDO** is indicated for the first-line treatment of adult patients with **unresectable hepatocellular carcinoma** (uHCC).[1,2]

IMFINZI® 英飛凡® (durvalumab)

IMJUDO® (tremelimumab) Concentrate for Solution for Infusion

METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

IMFINZI in combination with **IMJUDO** and platinum-based chemotherapy for the treatment of adult patients with **metastatic non-small cell lung cancer (NSCLC)** with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.[1,2]

IMFINZI® 英飛凡® (durvalumab)

IMJUDO® (tremelimumab) Concentrate for Solution for Infusion

BILIARY TRACT CANCER (BTC)

IMFINZI in combination with **gemcitabine and cisplatin** is indicated for the first-line treatment of adult patients with **locally advanced** or **metastatic biliary tract cancer** (BTC).[1]

IMFINZI® 英飛凡® (durvalumab)

References: 1. IMFINZI Hong Kong Product Insert Feb.2024 2. IMJUDO Hong Kong Product Insert Dec. 2023

Imfinzi Abbreviated PI

Presentation: 500 mg/10mL and 120mg/2.4mL intravenous infusion. **Indications:** 1) Treatment of patients with unresectable Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. 2) in combination with etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). 3)in combination with tremelimumab and platinum-based chemotherapy, for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. 4) in combination with gemcitabine and cisplatin, as treatment of adult patients with locally advanced or metastatic biliary tract cancer (BTC). 5) in combination with tremelimumab, for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC). **Dosage and administration:** Administer IMFINZI as an intravenous infusion over 60 minutes after dilution. **Stage III NSCLC:** 10mg/kg every 2 weeks or 1500mg every 4 weeks for patients weighing 30 kg and more until disease progression, unacceptable toxicity, or a maximum of 12 months. **ES-SCLC:** Patients weighing 30 kg and more: 1500mg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 1500mg every 4 weeks as a single agent until disease progression or unacceptable toxicity. Patients weighing less than 30kg: 20mg/kg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 20mg/kg every 4 weeks as a single agent until disease progression or unacceptable toxicity. **Metastatic NSCLC:** Patients weighing 30 kg and more: 1,500 mg every 3 weeks in combination with tremelimumab 75 mg and platinum-based chemotherapy for 4 cycles, and then administer IMFINZI 1,500 mg every 4 weeks as a single agent with histology-based pemetrexed maintenance therapy every 4 weeks, and a fifth dose of tremelimumab 75 mg in combination with IMFINZI dose 6 at week 16. Patients weighing less than 30kg: 20 mg/kg every 3 weeks in combination with tremelimumab 1 mg/kg and platinum-based chemotherapy, and then administer IMFINZI 20 mg/kg every 4 weeks as a single agent with histology-based pemetrexed therapy every 4 weeks, and a fifth dose of tremelimumab 1 mg/kg in combination with IMFINZI dose 6 at week. **BTC:** Patients weighing 30 kg and more: administer IMFINZI 1,500 mg every 3 weeks in combination with chemotherapy, and then 1,500 mg every 4 weeks as a single agent. Patients weighing less than 30kg: administer IMFINZI 20 mg/kg every 3 weeks in combination with chemotherapy, and then 20 mg/kg every 4 weeks as a single agent. **uHCC:** Patients weighing 30 kg and more: IMFINZI 1,500 mg in combination with tremelimumab 300 mg as a single dose at Cycle 1/Day 1, followed by IMFINZI as a single agent every 4 weeks. Patients weighing less than 30kg: IMFINZI 20 mg/kg in combination with tremelimumab 4 mg/kg as a single dose at Cycle 1/Day 1, followed by IMFINZI as a single agent every 4 weeks. **Contraindications:** None. **Precautions: Immune-mediated Adverse Reactions:** May be severe or fatal, can occur in any organ system or tissue, including immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, immune-mediated nephritis and renal dysfunction, and solid organ transplant rejection, and immune-mediated pancreatitis. Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. Withhold or permanently discontinue based on severity and type of reaction. **Infusion-Related Reactions:** Interrupt, slow the rate of infusion, or permanently discontinue IMFINZI based on the severity of the reaction. Complications of Allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. **Undesirable effects:** IMFINZI as a Single Agent: Most common adverse reactions (≥20% of patients with unresectable, Stage III NSCLC) are cough, fatigue, pneumonitis/radiation pneumonitis, upper respiratory tract infections, dyspnea, and rash. IMFINZI in Combination with Platinum-Based Chemotherapy. Most common adverse reactions (≥20% of patients with extensive-stage SCLC) are nausea, fatigue/asthenia, and alopecia. IMFINZI in Combination with gemcitabine and cisplatin. Most common adverse reactions (≥20% of patients with BTC) are fatigue, nausea, constipation, decreased appetite, abdominal pain, rash, and pyrexia. IMFINZI in Combination with Tremelimumab: Most common adverse reactions (≥ 20%) of patients with uHCC are rash, diarrhea, fatigue, pruritis, musculoskeletal pain, and abdominal pain. IMFINZI in Combination with Tremelimumab and Platinum-Based Chemotherapy. Most common adverse reactions (≥ 20% of patients with metastatic NSCLC) were nausea, fatigue, musculoskeletal pain, decreased appetite, rash, and diarrhea. **Full local prescribing information is available upon request. API.HK.IMF.0224**

Imjudo Abbreviated PI

Presentation: 25 mg/1.25 mL and 300 mg/15 mL (20 mg/mL) intravenous infusion. **Indications:** IMJUDO is a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocking antibody indicated 1) in combination with durvalumab, for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC). 2) in combination with durvalumab and platinum-based chemotherapy for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. **Dosage and administration:** Administer IMJUDO as an intravenous infusion over 60 minutes after dilution. **uHCC:** Weight 30 kg and more: IMJUDO 300 mg as a single dose in combination with durvalumab 1,500 mg at Cycle 1/Day 1, followed by durvalumab as a single agent every 4 weeks. Weight less than 30 kg: IMJUDO 4 mg/kg as a single dose in combination with durvalumab 20 mg/kg at Cycle 1/Day 1, followed by durvalumab as a single agent every 4 weeks. **Metastatic NSCLC:** Weight 30 kg and more: 75 mg every 3 weeks in combination with durvalumab 1,500 mg and platinum-based chemotherapy for 4 cycles, and then administer durvalumab 1,500 mg every 4 weeks as a single agent with histology-based pemetrexed therapy every 4 weeks, and a fifth dose of IMJUDO 75 mg in combination with durvalumab dose 6 at week 16. Weight less than 30 kg: 1 mg/kg every 3 weeks in combination with durvalumab 20 mg/kg and platinum-based chemotherapy for 4 cycles, and then administer durvalumab 20 mg/kg every 4 weeks as a single agent with histology-based pemetrexed therapy every 4 weeks, and a fifth dose of IMJUDO 1 mg/kg in combination with durvalumab dose 6 at week 16. **Contraindications:** None. **Precautions: Immune-Mediated Adverse Reactions:** Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions and immune-mediated pancreatitis. Monitor for early identification and management. Evaluate liver enzymes, creatinine, adrenocorticotropic hormone level and thyroid function at baseline and before each dose. Withhold or permanently discontinue based on severity and type of reaction. **Infusion-Related Reactions:** Interrupt, slow the rate of infusion, or permanently discontinue treatment based on the severity of the reaction. **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. **Undesirable effects:** Most common adverse reactions (≥ 20%) of patients with uHCC are rash, diarrhea, fatigue, pruritus, musculoskeletal pain, and abdominal pain. Most common laboratory abnormalities (≥ 40%) of patients with uHCC are AST increased, ALT increased, hemoglobin decreased, sodium decreased, bilirubin increased, alkaline phosphatase increased, and lymphocytes decreased. Most common adverse reactions (≥ 20%) of patients with metastatic NSCLC were nausea, fatigue, musculoskeletal pain, decreased appetite, rash, and diarrhea. **Full local prescribing information is available upon request. API.HK.IMJ.1223**

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