



ISSP



# Molecular landscape of Peritoneal Metastases: Biomarkers and Therapeutic Targets

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Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura



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# Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

#### STATE LAW:

The California legislature has passed <u>Assembly Bill (AB) 1195</u>, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed <u>AB 241</u>, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

#### The following CLC & IB components will be addressed in this presentation:

• Cover world-wide treatment options





## PARADIGM

#### TO TREAT CANCER, ONE NEEDS TO KILL CANCER CELLS





#### Figure 38.3

Effects of various treatments on the cancer cell burden in a hypothetical cancer patient.



Chemotherapy

Oncologist

#### Single Cell Atlas of Gastric Cancer



#### Kumar\*, Ramnarayanan\*, Sundar\* et al, Can Dis 2022

#### scRNA-seq reveals rare cell populations





Kumar\*, Ramnarayanan\*, Sundar\* et al, Can Dis 2022

## **Checkpoint Blockade**



National University Cancer Institute Singapore

Sundar et al, Frontiers in Oncol 2020

#### 16:30 - 18:15 Presidential Symposium II

CHAIRS : KARIN JORDAN, FLORIAN LORDICK 6.P - Paris Auditorium

#### Major pathologic response in 95% of patients; 67% pCR



Chalabi, ESMO AM 2022

## **PARADIGM SHIFT**

#### TO TREAT CANCER, ONE NEEDS TO KILL CANCER CELLS

#### TO TREAT CANCER, ONE CAN ASSIST THE BODY IN ELIMINATING IT





Singapore

## **Metastatic Gastric Cancer Treatment Biomarker Strategy: 2021**



## **Metastatic Gastric Cancer Biomarker and Treatment Strategy: 2025**



For educational purpose only, we do not recommend off-label use of any medication

Speaker's personal opinion

# State of Precision Oncology for Peritoneal Metastases

## Seminal studies in Gastric Cancer Peritoneal Metastases





Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

Cityof Hope



## TEAD1 inhibition in GCPM





#### **Genomic Drivers**



Tanaka et al, Nat Can 2021

## Inhibition of Oncogene Drivers in PM



Tanaka et al, Nat Can 2021

## PIGR



Johansen et al, Mucosal Immunol 2011





#### Development of a GCPM specific Prognostic Signature





Wang et al, Nat Med 2021

## **Colorectal Peritoneal Mets**



PM recapitulate primary phenotype and composition and low CNV

Mutation analysis: less APC, p53 similar, KRAS more in CRC PM

# CMS4 poorest survival

#### Lenos et al, Nat Com 2022

## **Different CMS4 Subtypes of CRC PM**









Dellinger et al, JCO PO 2022 City of Hope

National University Cancer Institute Singapore



National University Cancer Institute Singapore

#### TNF-α via NFκβ upregulated in responders

Metabolic pathways downregulated

Dellinger et al, JCO PO 2022



Singapore

Change in PD-L1 expression and stromal PD-1 of CD8 + TILS in responders

Dellinger et al, JCO PO 2022

## **Paracrine Factors**



## **Targeting Paracrine Factors in Malignant Ascites**



Hendrikson et al, Cell Rep Med 2022

## **Peritoneal Microenvironment**



## Immune Cell Mediated Immunosuppressive Niche



#### TME of GCPM has two major subtypes: T-cell exclusive and T-cell exhausted

Immune checkpoint TIM-3, its ligand galectin-9 and VISTA were highly expressed in the T-cell exhausted (mesenchymal) subtype, as well as TGF-β1, suggesting an immune suppressive micro-environment

## **Adoptive cellular therapy**



#### www.mskcc.org



Table 2

Clinical trials with CAR-T cell therapy in peritoneal carcinomatosis of gastric origin (source: ClinicalTrials.gov (accessed on 25 October 2021)).

Identifier	Trial Phase	Target Antigen	Gastric Cancer Condition	CAR-T Infusion Route	Start- Completion Date	Study Status	Country
NCT03563326	Ι	EpCAM	Peritoneal metastasis	Intraperitoneal	Aug 2018-Dec 2022	Recruiting	China
<u>NCT03682744</u>	Ι	CEA	Peritoneal metastases or malignant ascites	Intraperitoneal	Sep 2018-Mar 2021	Active, recruitment closed	United States

Open in a separate window

Qian et al, J Clin Med 2021

#### **Biological hallmarks of GCPM**

11 hallmarks across 4 categories:

- Tumor-related factors
- Peritoneal microenvironment
- Paracrine factors
- Bio-mechanical forces



# Raising the bar in Peritoneal Precision Oncology

- Molecular characterization of PM has been challenging previously, but is now becoming easier with increased access to tissue and ascites
- Characterization of the peritoneal tumors, surrounding microenvironment and malignant ascites continue to yield therapeutic targets and prognostic biomarkers
- This will guide novel therapeutic targets and strategies including a combination of locoregional surgery and systemic therapy







## Thank you

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