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Introduction to Immunotherapy for Gastrointestinal Cancers

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Disclosures

- Consulting Fees: Astra-Zeneca, MSD, Eisai, BMS
- Fees for Non CE Services: Bayer, Astra-Zeneca, Eisai, Roche, MSD
- Contracted Research: MSD, Bayer, Eisai, Ipsen, SIRTEX

Outline (20 minutes)

- Introduction
- Overview of role of immunotherapy in different tumour types
  - Gastroesophageal cancer
  - Hepatobiliary cancer
  - Colorectal cancer
- Conclusions

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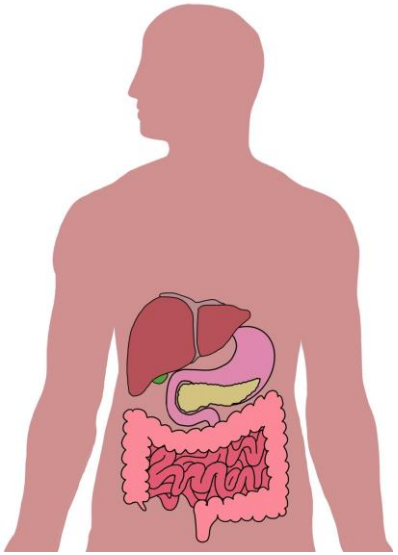
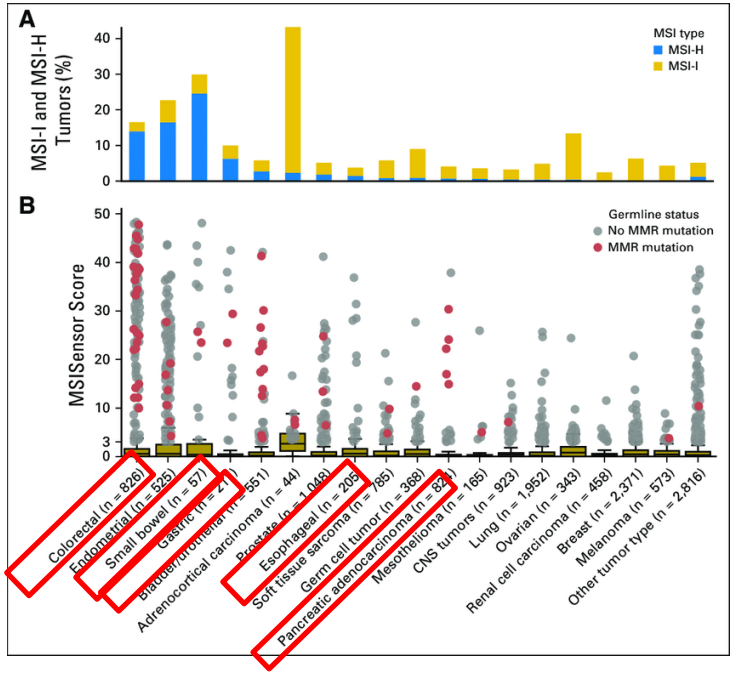
Introduction

GI Cancers – a heterogeneous collection

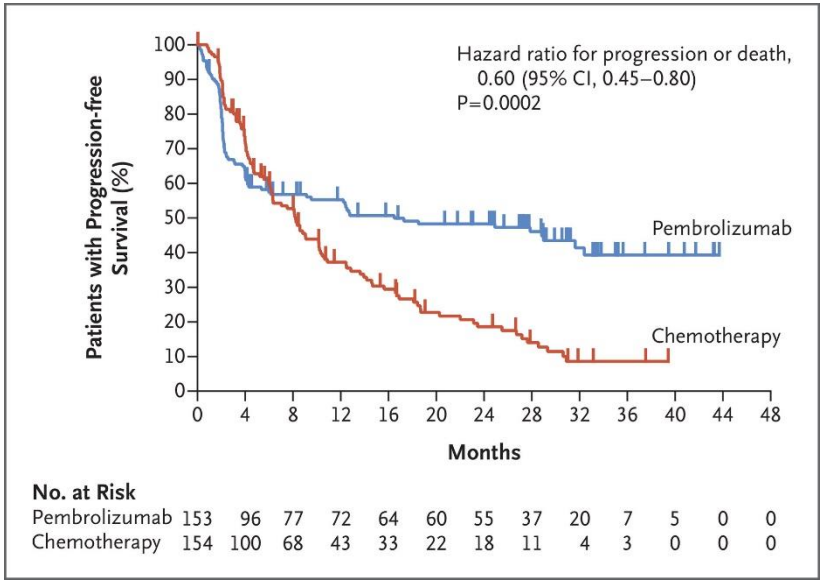


- Colorectal cancers
- Non-colorectal cancers
  - Gastro-esophageal cancers
  - Pancreatic cancers
  - Hepatobiliary cancers
  - Small bowel tumors
  - Neuroendocrine tumors

MSI-H/d-MMR: tissue agnostic therapy



Latham A et al. J Clin Oncol. 2019; 37: 286-295.



Andre T et al. NEJM. 2020; 383:2207-2218

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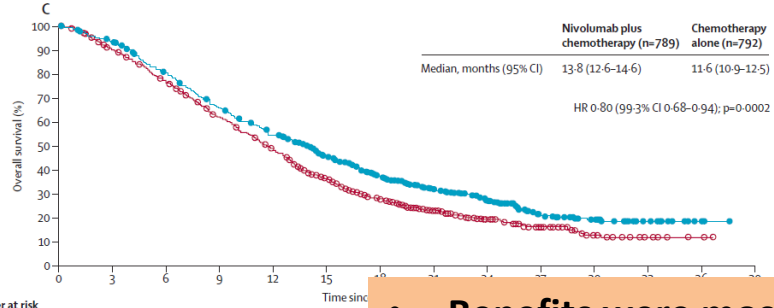
Gastroesophageal cancer

Anti-PD1 + Chemotherapy as 1st line (GE adenocarcinoma)

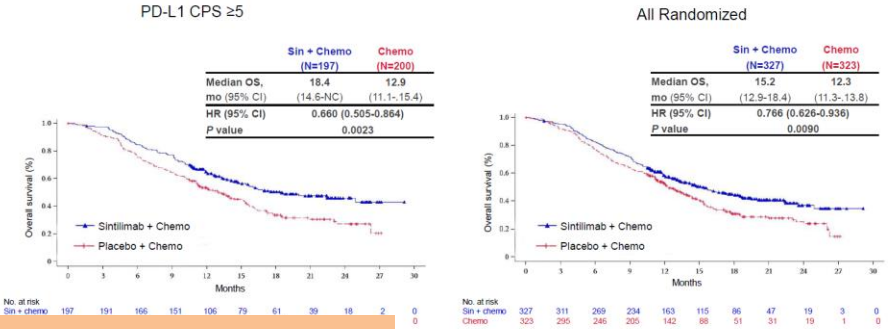
First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial

Yelena Y Janjigian, Kohei Shitara*, Markus Moehler, Marcelo Garrido, Pamela Salman, Lin Shen, Lucjan Wyrwicz, Kensei Yamaguchi, Tomasz Skoczylas, Arinilda Campos Bragagnoli, Tianshu Liu, Michael Schenker, Patricio Yanez, Mustapha Tehfe, Ruben Kowalyszyn, Michalis V Karamouzis, Ricardo Bruges, Thomas Zander, Roberto Pazo-Cid, Erika Hitre, Kynan Feeney, James M Cleary, Valerie Poulart, Dana Cullen, Ming Lei, Hong Xiao, Kaoru Kondo, Mingshun Li, Jaffer A Ajani*



Sintilimab plus chemotherapy (chemo) versus chemo as the first-line treatment for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma (ORIENT-16)

Overall survival



- **Benefits were mostly observed in PDL1 CPS ≥5**
- **? Similar benefits in PDL1 CPS ≥1-<5**

s chemo in PD-L1 CPS≥5 and all randomized patients.

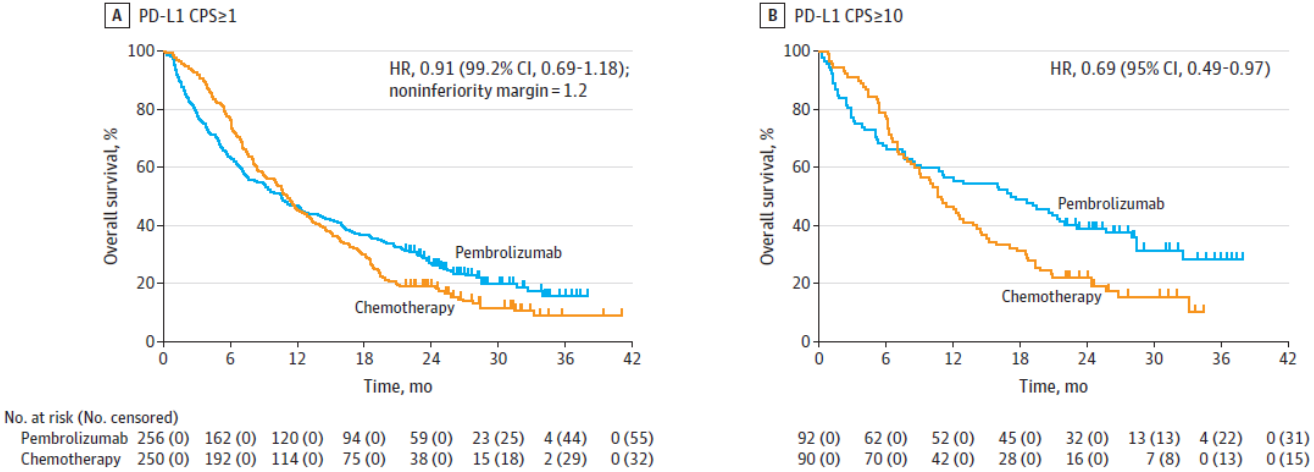
Janjigian Y et al. Lancet 2021. 398: 27-40.

Xu J et al. Ann Onco. 2021; 32 (suppl_5): S1283-1346.

Monotherapy anti-PD1 (GE adenocarcinoma)

KN062: Pembro + chemo vs. Placebo + chemo vs. Pembro alone

Figure 2. Kaplan-Meier Estimates of Overall Survival According to Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS)



No. at risk (No. censored)

Pembrolizumab	256 (0)	162 (0)	120 (0)	94 (0)	59 (0)	23 (25)	4 (44)	0 (55)
Chemotherapy	250 (0)	192 (0)	114 (0)	75 (0)	38 (0)	15 (18)	2 (29)	0 (32)

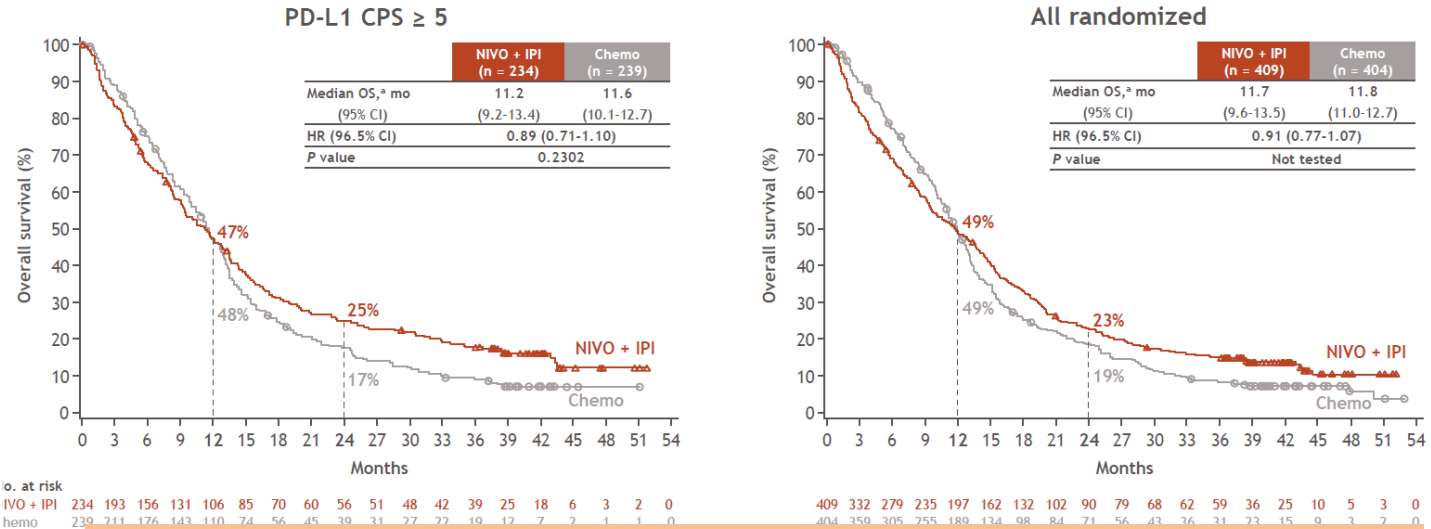
	92 (0)	62 (0)	52 (0)	45 (0)	32 (0)	13 (13)	4 (22)	0 (31)
	90 (0)	70 (0)	42 (0)	28 (0)	16 (0)	7 (8)	0 (13)	0 (15)

- **Initial inferior survival with pembrolizumab**
- **Anti-PD1 + chemotherapy also works in this group of patient.**

Shitara K et al. JAMA Oncol. 2020; 6: 1571-1580

Anti-CTLA4 + anti-PD1 in GE adenocarcinoma

Overall survival: NIVO + IPI vs chemo



- **Nivolumab + Ipilimumab does not improve mOS than chemotherapy.**
- **? Due to toxicity in the N+I arm (G3-4 hepatitis: 12%; G3-4 GI: 6%)**

Janjigian Y et al. ESMO 2021; LBA 7

HER2-overpressing GE adenocarcinoma

Keynote 811

	Pembrolizumab + Trastuzumab + Chemotherapy n=133	Placebo + Trastuzumab + Chemotherapy n=131
ORR, % (95% CI)[2]	74.4 (66.2-81.6)	51.9 (43.0-60.7)
ORR difference[a]	22.7 (11.2-33.7) *P*=0.00006[b]	
Disease control rate, % (95% CI)	96.2 (91.4-98.8)	89.3 (82.7-94.0)
Best response, n (%)		
Complete response[2]	15 (11)	4 (3)
Partial response[2]	84 (63)	64 (49)
Stable disease	29 (22)	49 (37)
Progressive disease	5 (4)	7 (5)
Not evaluable	0	2 (2)
Not assessed	0	5 (4)
Duration of response[c]	**n=99**	**n=68**
Median[d] DOR,		.4+)
≥6-month dura		
≥9-month dura		

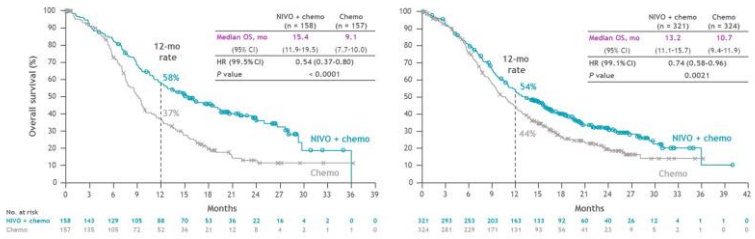
- **Accelerated approval by FDA for HER2 overexpression GEC**
- **Await full set of data on PFS and OS**

Janjigian Y et al. J Clin Oncol. 39, no. 15_suppl (May 20, 2021) 4013-4013.

Anti-PD1 + Chemo as 1st line in ESCC

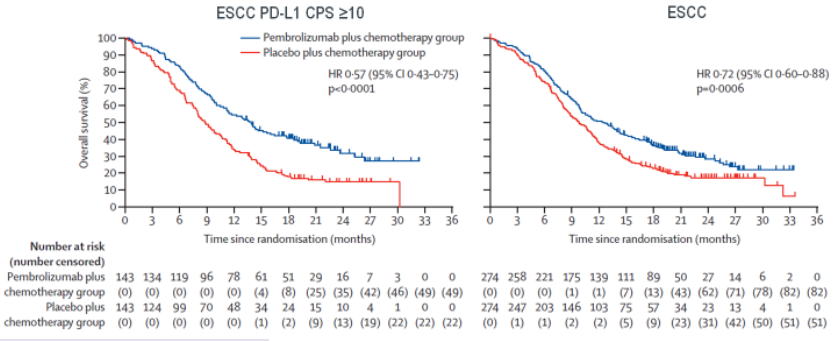
Nivolumab + Chemo

Overall survival: NIVO + chemo vs chemo

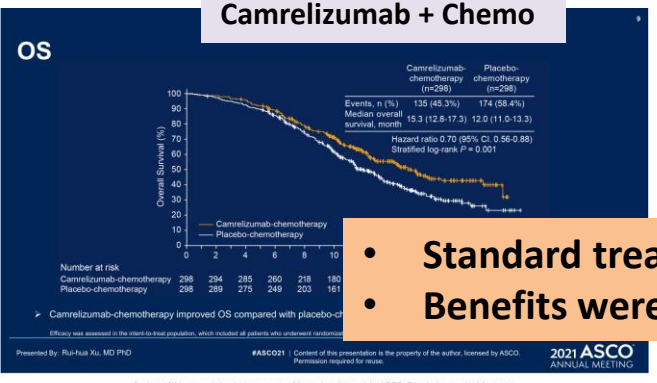


- Superior OS with NIVO + chemo vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 46% reduction in the risk of death and a 6.3-month improvement in median OS
  - All randomized: 26% reduction in the risk of death and a 2.5-month improvement in median OS

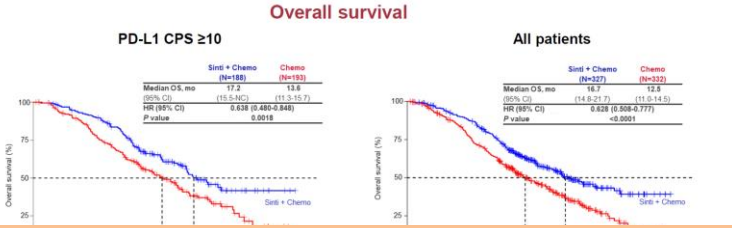
Pembrolizumab + Chemo



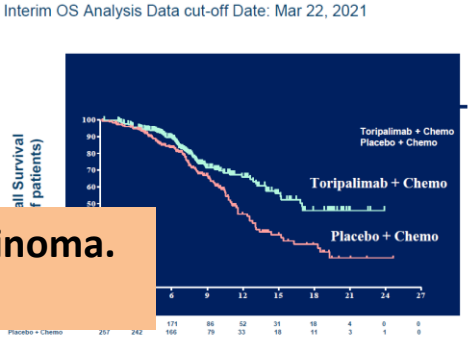
Camrelizumab + Chemo



Sintilimab + Chemo



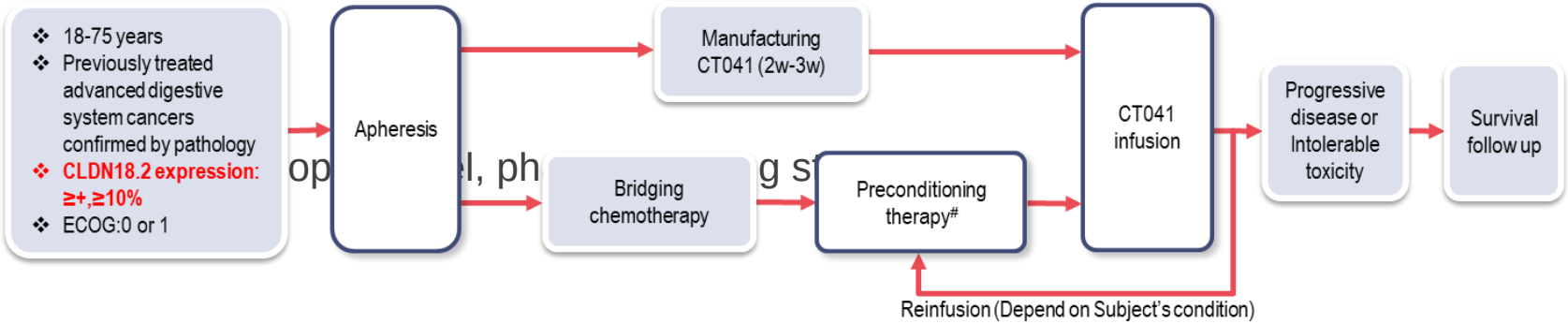
Toripalimab + Chemo



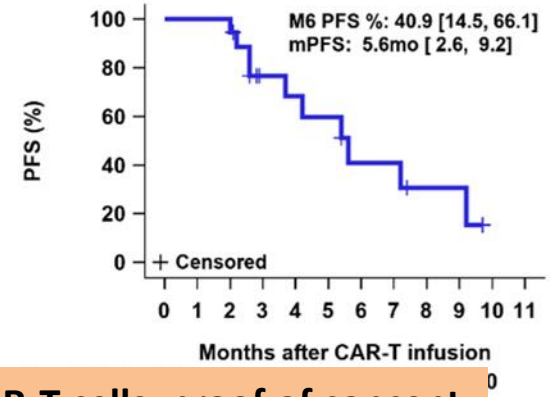
- **Standard treatment for esophageal squamous cell carcinoma.**
- **Benefits were also observed in all/lower PDL1 cut-off.**

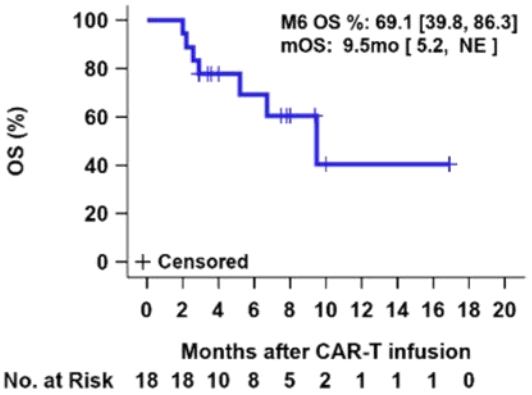
CAR-T cells against Claudin 18.2

- op l, ph g s



≥2 lines GC patients at 2.5 × 10^8 cells (N=18)	
Best Overall Response	
CR	0
PR	11 (61.1%)
SD	4 (22.2%)
PD	3 (16.7%)
ORR [95% CI]	11 (61.1%) [35.75, 82.70]
DCR [95% CI]	15 (83.3%) [58.58, 96.42]
mPFS*	5.6m [2.6, 9.2]
mOS*	9.5m [5.2, NE]
mDOR	6.4m [2.7, NE]





CAR-T cells: proof of concept

Qi C et al. ESMO 2021

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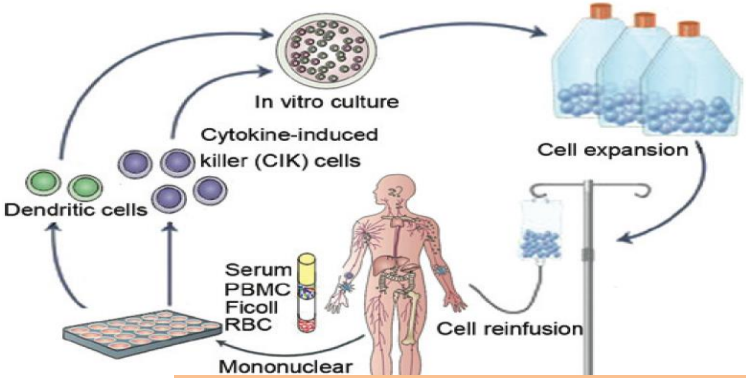
Hepatobiliary cancers

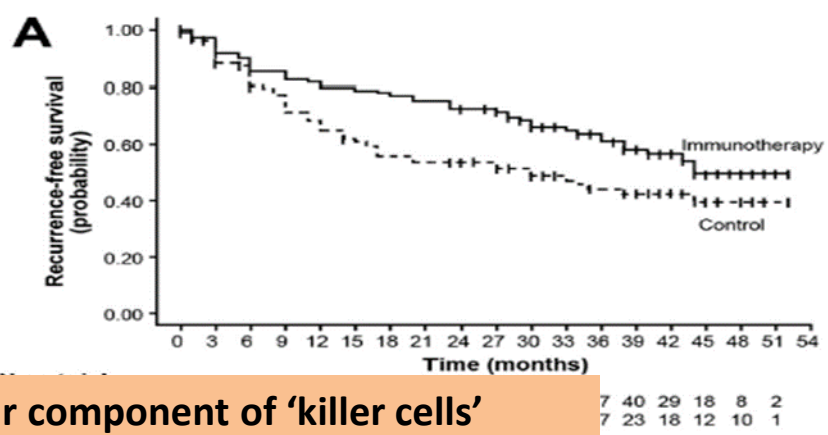
HCC – initial ‘immunotherapy’

Gastroenterology 2015;148:1383–1391

Adjuvant Immunotherapy With Autologous Cytokine-Induced Killer Cells for Hepatocellular Carcinoma

Joon Hyeok Lee,[1,*] **Jeong-Hoon Lee**,[2,*] Young-Suk Lim,[3] Jong Eun Yeon,[4] Tae-Jin Song,[5] Su Jong Yu,[2] Geum-Youn Gwak,[1] Kang Mo Kim,[3] Yoon Jun Kim,[2] Jae Won Lee,[6] and Jung-Hwan Yoon[2]





- **Generalized use limited by unclear component of ‘killer cells’**
- **Proof-of-concept: immune mediated clearance is effective in HCC**

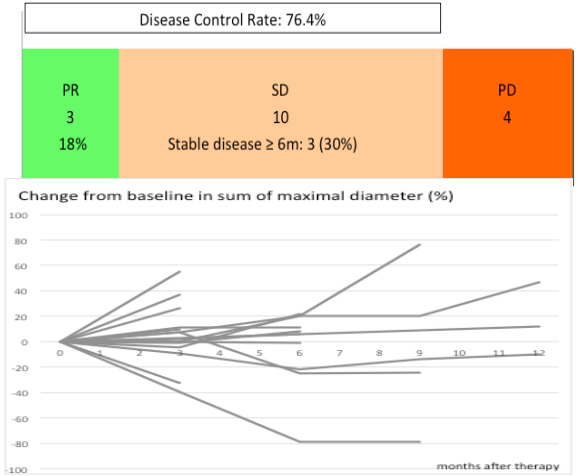
Lee JH et al. Gastroenterology. 2015; 148: 1383-91.

Monotherapy of anti-CTLA4 or anti-PD1 in HCC

A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C☆

Bruno Sangro[1,2,*], Carlos Gomez-Martin[3], Manuel de la Mata[4,2,5], Mercedes Iñarrairaegui[1,2], Elena Garralda[3], Pilar Barrera[4,2], Jose Ignacio Riezu-Boj[6], Esther Larrea[6], Carlos Alfaro[7], Pablo Sarobe[6], Juan José Lasarte[6], Jose L. Pérez-Gracia[7], Ignacio Melero[6,7,†], Jesús Prieto[1,2,6,†]

[1]*Liver Unit and HPB Oncology, Clinica Universidad de Navarra, Pamplona, Spain;* [2]*Centro de Investigacion Biomedica en Red de Enfermedades Hepaticas y Digestivas (CIBERehd), Spain;* [3]*Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain;* [4]*Hepatology, Hospital Universitario Reina Sofia, Córdoba, Spain;* [5]*Instituto Maimónides de Investigación Biomédica de Córdoba, Córdoba, Spain;* [6]*Center for Applied Medical Research (CIMA), Pamplona, Spain;* [7]*Medical Oncology, Clinica Universidad de Navarra, Pamplona, Spain*



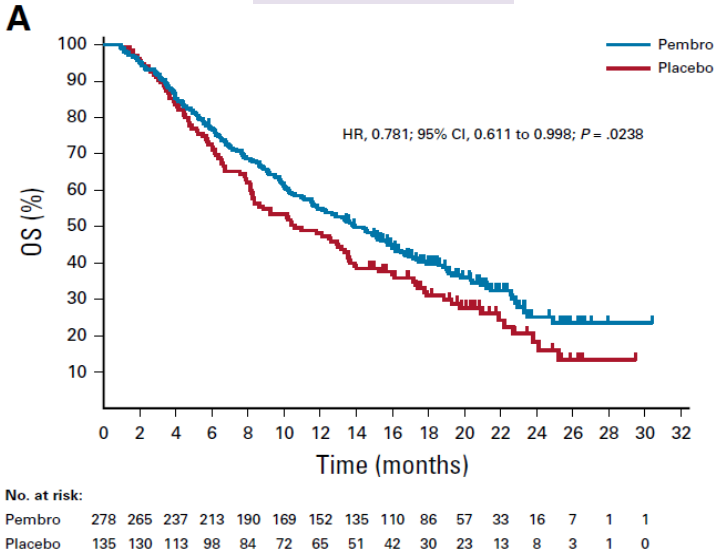
Sangro B et al. J Hepatology. 2013; 59: 81-8

	Checkmate 040	Keynote 224
Drug	**Nivolumab**	**Pembrolizumab**
Response rate (RECIST 1.1)	20% (dose-expansion) 15% (dose-escalation)	17%
CR rate	1%	1%
Median PFS	4 months	4.9 months
Median OS	15.6 months (sorafenib-treated)	12.9 months (Sorafenib-treated)
Serious immune related toxicity	4%	3%
US FDA Approval for HCC	22 Sept 2017 (accelerated approval) for HCC previously treated with sorafenib	9 Nov 2018 (accelerated approval) for HCC previously treated with sorafenib

El-Khoueiry AB et al. Lancet 2017
Zhu AX et al. Lancet Oncology 2018

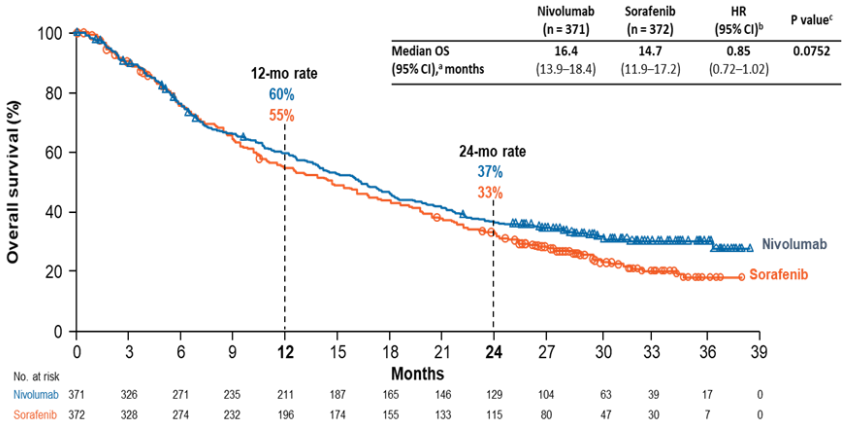
HCC: Disappointment of monotherapy Anti-PD1 in Phase III clinical trial

Keynote 240



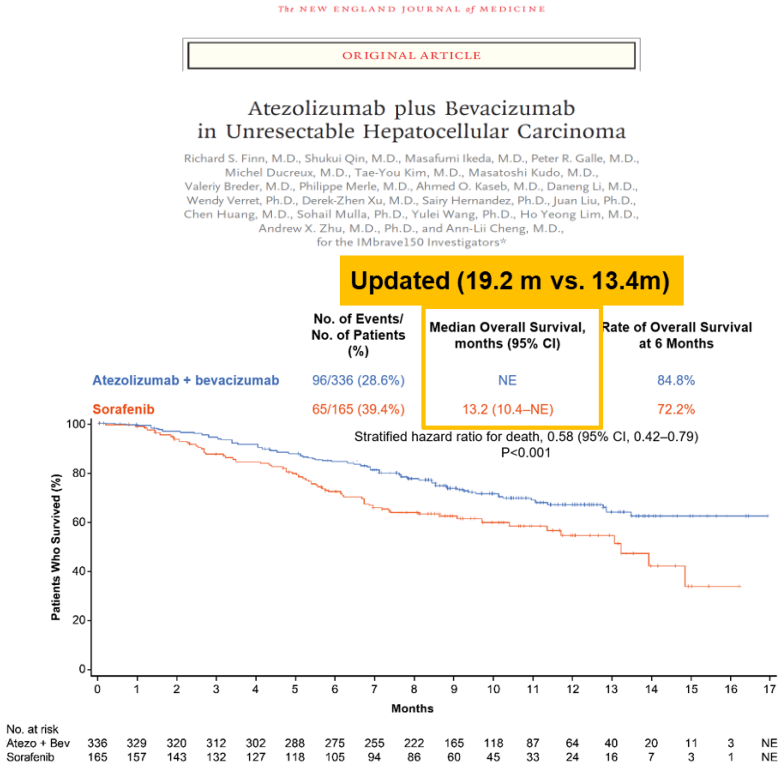
Finn R et al. J Clin Oncol 2020; 38: 193-20.

Checkmate 459



Sangro B et al. ESMO World GI. 2020 LBA3.

Immuno-combination in HCC as 1st line treatment



Finn R et al. NEJM. 2020. 382: 2894-1905.

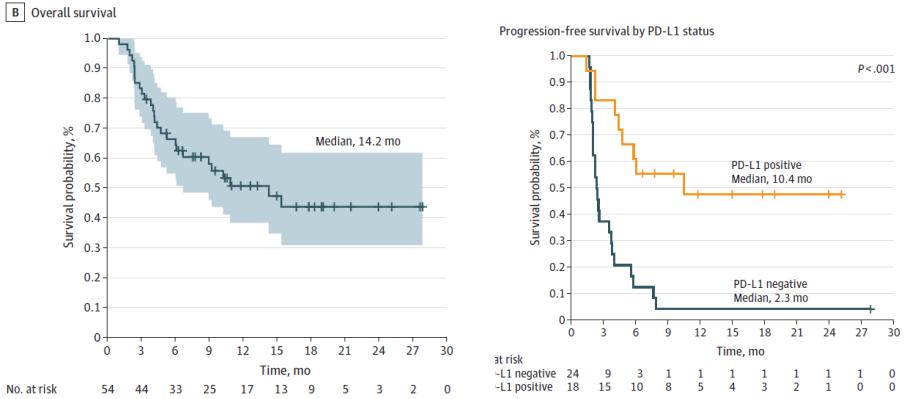
Clinical trial	Treatment arm	Status
HIMALAYA	STRIDE Durvalumab Sorafenib	To be presented
COSMIC-312	Atezolizumab + Cabozantinib Cabozantinib Sorafenib	To be presented in ESMO Asia week
LEAP002	Pembrolizumab + Lenvatinib Lenvatinib	Completed accrual
CM9DW	Ipilimumab + Nivolumab Sorafenib	Completed accrual
NCT03764293	Camrelizumab + Apatinib Sorafenib	Completed accrual

Biliary tract cancer: Monotherapy anti-PD1

JAMA Oncology | Original Investigation

A Phase 2 Multi-institutional Study of Nivolumab for Patients With Advanced Refractory Biliary Tract Cancer

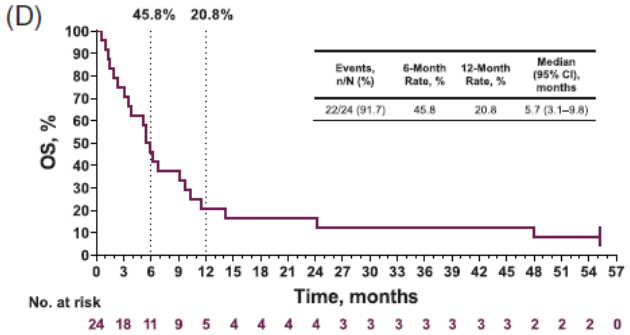
Richard D. Kim, MD; Vincent Chung, MD; Olatunji B. Alese, MD; Bassell F. El-Rayes, MD; Daneng Li, MD; Taymeyah E. Al-Toubah, BS; Michael J. Schell, PhD; Jun-Min Zhou, BS; Amit Mahipal, MD; Baek Hui Kim, MD; Dae Won Kim, MD



Kim R et al. JAMA Oncol. 2020; 6: 888-894.

Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: Results from the KEYNOTE-158 and KEYNOTE-028 studies

Sarina A. Piha-Paul[1] | Do-Youn Oh[2] | Makoto Ueno[3] | David Malka[4] | Hyun Cheol Chung[5] | Adnan Nagrial[6] | Robin K. Kelley[7] | Willeke Ros[8] | Antoine Italiano[9] | Kazuhiko Nakagawa[10] | Hope S. Rugo[11] | Filippo de Braud[12] | Andrea Iolanda Varga[13] | Aaron Hansen[14] | Hui Wang[15] | Suba Krishnan[16] | Kevin G. Norwood[16] | Toshihiko Doi[17]



Piha-Paul SA et al. Int J Cancer. 2020; 147: 2190-2198.

Biliary tract cancer: Anti-PD1/PDL1 + chemo

ORIGINAL ARTICLE

Anti-PD-1 therapy combined with chemotherapy in patients with advanced biliary tract cancer

Danyang Sun[1] · Junxun Ma[1] · Jinliang Wang[1] · Chun Han[1] · Yuanyu Qian[1] · Guangying Chen[1] · Xiaoyan Li[1] · Juan Zhang[1] · Pengfei Cui[1] · Wushuang Du[1] · Zhaozhen Wu[1] · Shixue Chen[1] · Xuan Zheng[1] · Zhichao Yue[1] · Jia Song[2] · Chan Gao[2] · Xiaochen Zhao[2] · Shangli Cai[2] · Yi Hu[1]

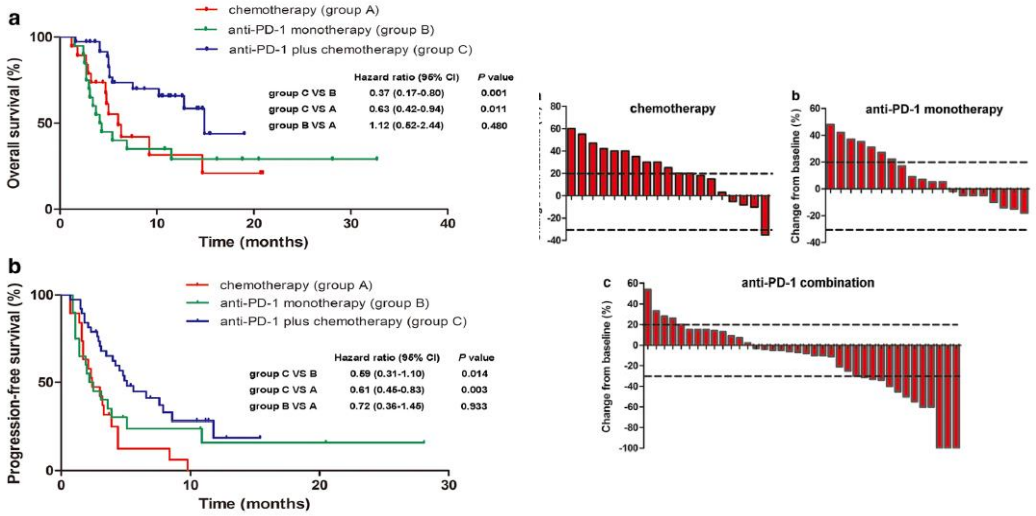


Fig. 2 Kaplan–Meier estimates of overall survival (**a**) and progression-free survival (**b**)

Sun D et al. Cancer Immuno 2019; 68: 1527-1535

Phase III clinical trials

TOPAZ1: Durvalumab/Placebo + Gem-cisplatin

KN966: Pembrolizumab/Placebo + Gem-cisplatin

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Colorectal cancers

Immune checkpoint inhibitors in CRC

MSI-H/d-MMR

Name of trial	Phase of trial	Drug and dose	Objective response rate in dMMR	Disease control rate >12weeks in dMMR	FDA approval date
KEYNOTE 028 Le *et al.*[28]	Phase II	Pembrolizumab 10 mg/kg every 14 days	40%	90%	May 2017
CheckMate 142 Overman *et al.*[29]	Phase II	Nivolumab 3 mg/kg every 14 days	31.1%	69%	August 2017
CheckMate 142 (further analysis of subgroup) André *et al.*[30]	Phase II	Nivolumab 3 mg/kg +Ipilumumab 1 mg/kg every 21 days	55%	80%	July 2018

dMMR, DNA mismatch repair deficient; FDA, United States Food and Drug Administration; mCRC, metastatic colorectal cancer; pMMR, proficient mismatch repair proficient.

MSS/MSI-L/pMMR

Name of study	Clinical phase	Line of therapy	Clinicaltrials.gov Identifier
Nivolumab and Relatlimab in patients with MSS advanced CRC	Phase II	Second Line	NCT03642067
Modulation of the tumor microenvironment using either vascular disruption agents or STAT 3 inhibition in order to synergize with PD1 Inhibition in MSS refractory CRC	Phase II	Second Line	NCT03647839
Nivolumab plus Ipilimumab and Temozolomide in MSS, MGMT silenced CRC	Phase II	Second Line	NCT03832621
Study of Durvalumab and Tremelimumab after radiation for MSS metastatic CRC progressing on chemotherapy	Phase II	Second Line	NCT03007407
Pembrolizumab, Capecitabine and Bevacizumab in treating patients with MSS CRC that is locally advanced, metastatic or cannot be removed by surgery	Phase II	Second Line	NCT03396926
Safety and efficacy of Vicriviroc (MK-7690) in combination with Pembrolizumab (MK-3475) in participants with advanced/metastatic MSS CRC	Phase II	Second Line	NCT03631407
Nivoluman and Ipilimumab and radiation therapy in MSS and MSI-H CRC and pancreatic Ca	Phase II	Second Line	NCT03104439
Avelumab combined with cetuximab and irinotecan for treatment refractory metastatic CRC MSS cancer	Phase II	Third Line	NCT03608046
Nivolumab and metformin in patients with treatment refractory MSS CRC	Phase II	Second Line	NCT03800602

CRC, colorectal cancer; MGMT, O^6-methylguanineDNA methyltransferase; MMR-p, proficient mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; PD1, programmed cell death 1; STAT, signal transducer and activator of transcription.

Conclusions

- Immune checkpoint inhibitors play an increasingly important role in the treatment of GI cancers, as monotherapy or combination with conventional treatment/targeted therapy.

- Current status (late 2021)
  - GE adenocarcinoma: Chemotherapy + anti-PD1 is the standard; cut-off of PDL1 to be defined
  - ESCC: Chemotherapy + anti-PD1; PDL1 less important
  - HCC: Atezolizumab + Bevacizumab; more new regimens are expected 2022
  - BTC: Anti-PD1/PDL1 + chemo expected to be standard; await phase III data
  - CRC: Anti-PD1 +/- anti-CTLA4 in MSI-H/d-MMR subtype

Thank you!

Email:chanlam_Stephen@cuhk.edu.hk @StephenLChan1