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Treatment of GI Cancers with checkpoint inhibitors and immunotherapy: are we on the edge of a new era?

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Any off-label data shown are used to support the educational message of the presentation and not intended to endorse use of any drug in any way

Disclosures

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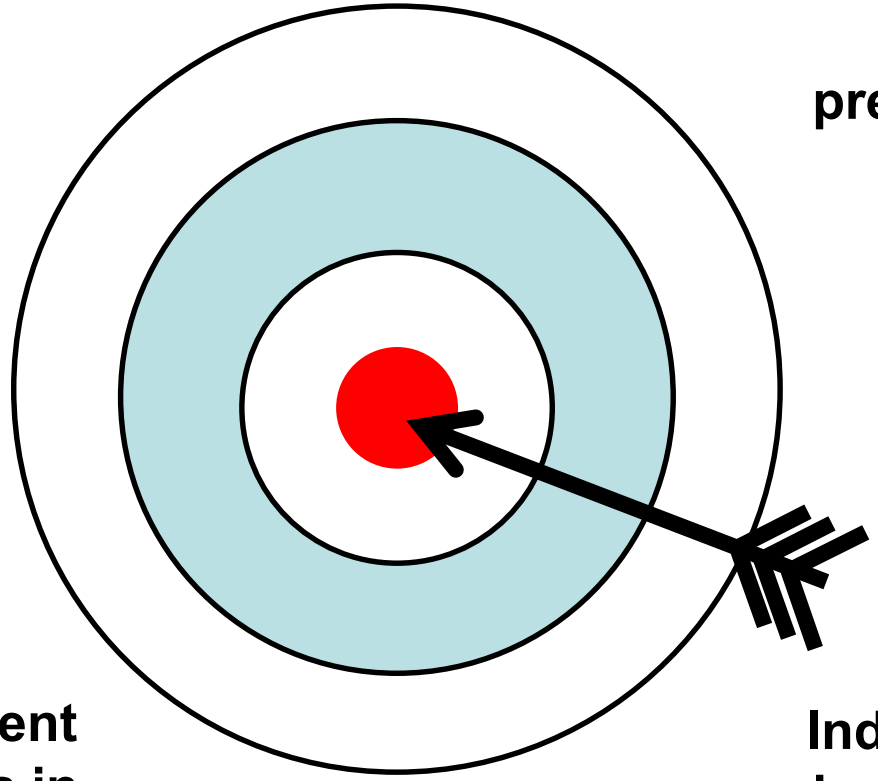
Receipt of honoraria or consultation fees:	Bayer, BMS, Celgene, Lilly, Merck, Merck KgA, Novartis, Servier

How to progress in GI cancer treatment

Better define subgroups with different prognostic and different treatments

Find predictive markers for precision medecine



Combine different targeted agents in accordance with the molecular profile of the patients tumor

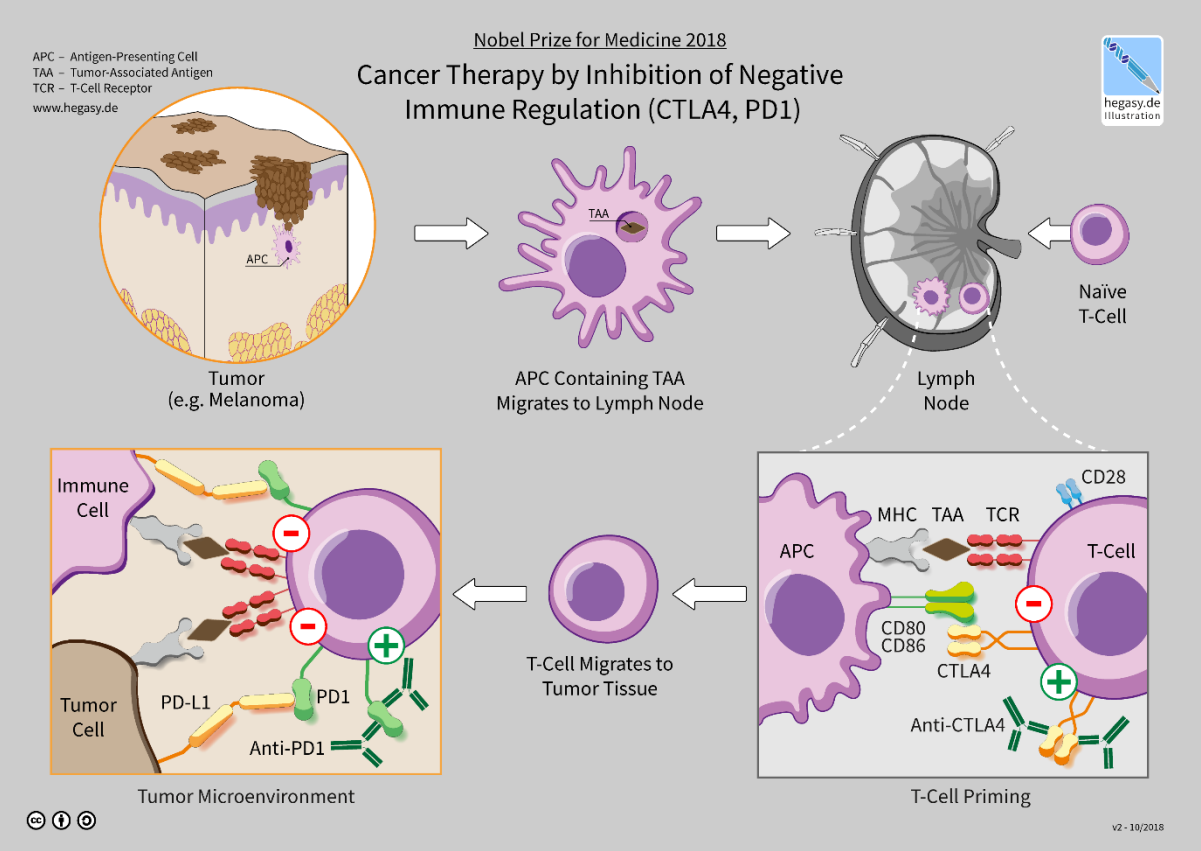
Induce an efficient immune response from the host against the tumor

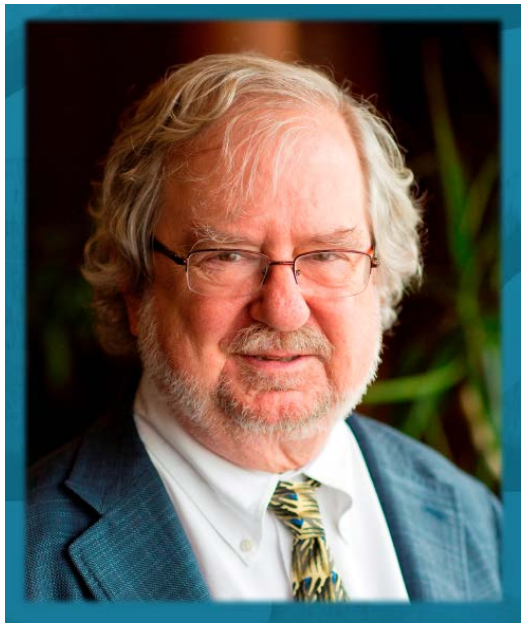
Gastro-Intestinal Cancers:
objectives and outline

- Objectives:
  - Understand the current and potential future role of checkpoint inhibitors in GI cancers, including discussions about patient selection
  - Understand new challenging topics and directions in IO and GI cancer

- Focus:
  - Gastroesophageal cancer
  - Colorectal cancer: MSI-H
  - Hepatocellular carcinoma

James Allison





Doctor Honoris Causa, University Leuven, 2017
Noble Prize 2018

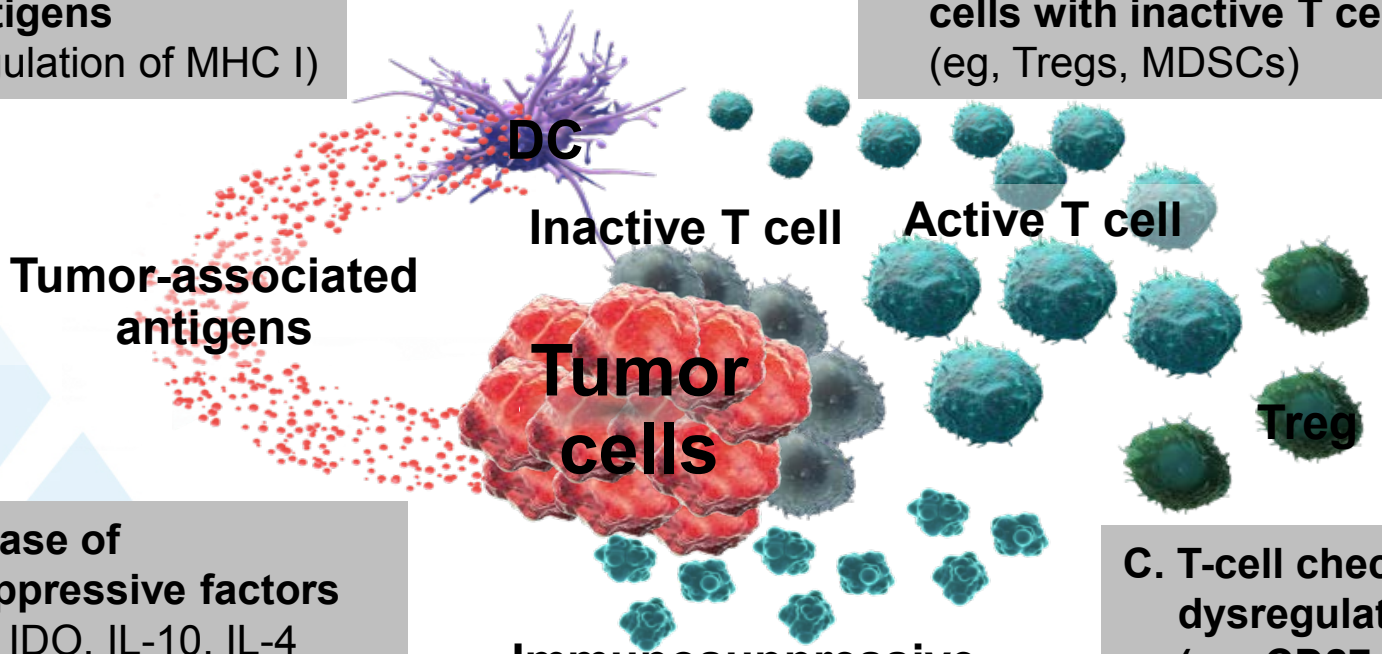
He plays the harmonica for a blues band of immunologists and oncologists called the Checkpoints.
He also plays with a local band called the Checkmates

Source Wikepedia

Tumors Use Complex, Overlapping Mechanisms to Evade and Suppress the Immune System

A. Ineffective presentation of tumor antigens (eg, downregulation of MHC I)

B. Recruitment of immunosuppressive cells with inactive T cells (eg, Tregs, MDSCs)



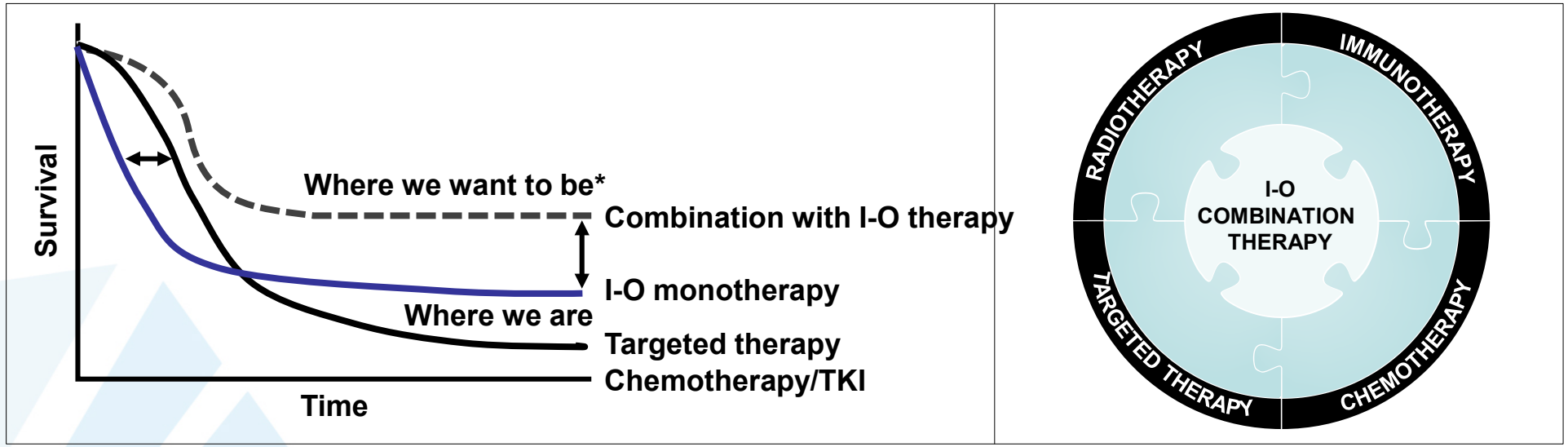
D. Tumor release of immunosuppressive factors (eg, TGF-β, IDO, IL-10, IL-4 from CSCs[2])

C. T-cell checkpoint dysregulation (eg, CD27, CD137, CTLA-4, LAG-3, OX-40, PD-1, TIM-3)[2]

CD, cluster of differentiation; CSC, cancer stem cells; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IDO, indoleamine 2,3-dioxygenase; LAG-3; lymphocyte activation gene-3; IL, interleukin; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; PD-1, programmed death-1; TGF-β, transforming growth factor beta; TIM-3, T cell immunoglobulin and mucin domain-3; Treg, regulatory T cell.

1. Vesely MD et al. *Ann Rev Immunol*. 2011;29:235-271. 2. Todaro M et al. *Cell Stem Cell*. 2007;1(4):389-402. 3. Clinicaltrials.gov.

I-O Therapies as a Critical Backbone for Cancer Treatment



I-O combination therapies have demonstrated durable benefit across a number of tumor types[1,2]

- **Nivolumab + ipilimumab demonstrated benefit over SOC in NSCLC, melanoma, and RCC[3-5]**
- **Pembrolizumab + chemotherapy, atezolizumab + chemotherapy demonstrated benefit over SOC in NSCLC[6-8]**

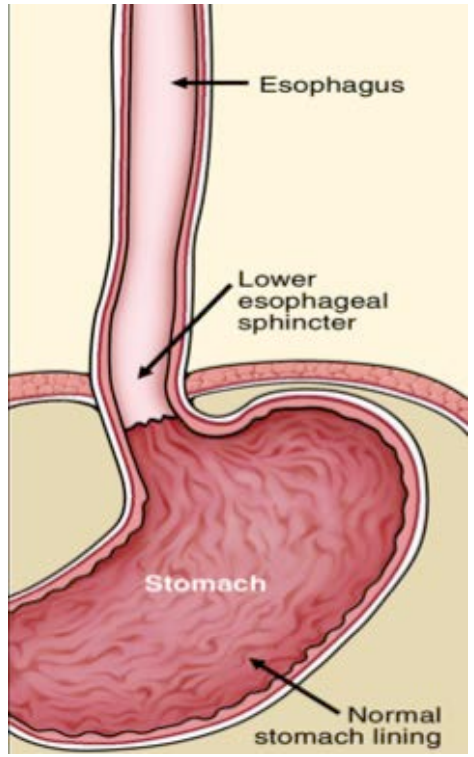
Many ongoing efforts are investigating I-O therapies as the backbone for novel combinations

*Hypothetical chart illustrating a scientific concept that is beyond data available so far. This chart is not intended to predict what may actually be observed in clinical studies.

1. Voena C, Chiarle R. *Discov Med.* 2016;21(114):125-133. 2. Sharma P, Allison JP. *Cell.* 2015;161(2):205-214. 3. Bristol-Myers Squibb [press release]. February 5, 2018. 4. Larkin J et al. *N Engl J Med* 2015;373(13):1270-1271. 5. Motzer RJ et al. Oral presentation at SITC 2017. O38. 6. Merck & Co. [press release]. January 18, 2018. 7. F.eck et al. Oral Presentation at ESMO IO 2017. LBA1. 8. Roche [press release]. March 20, 2018.

‘New’ targets in gastric cancer

- Cytotoxics: modest impact: median survival of doublets/triplets usually <12 months
- New Targets
  - Her2: trastuzumab*
  - Angiogenesis: ramucirumab*
  - EGFR
  - mTOR
  - cMET
  - PD**/PDL
  - CTLA4
  - FGF
  - Claudine
  - Stemcell: STAT3
  - MMP9
  - PARP
  - …..

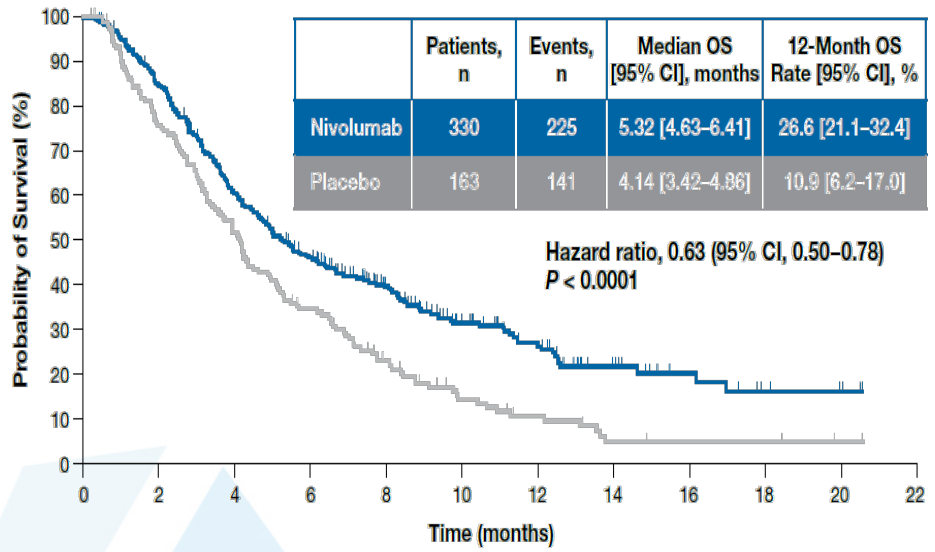


*Approved agents in EU and most other regions
**Approved USA, Japan, Switzerland

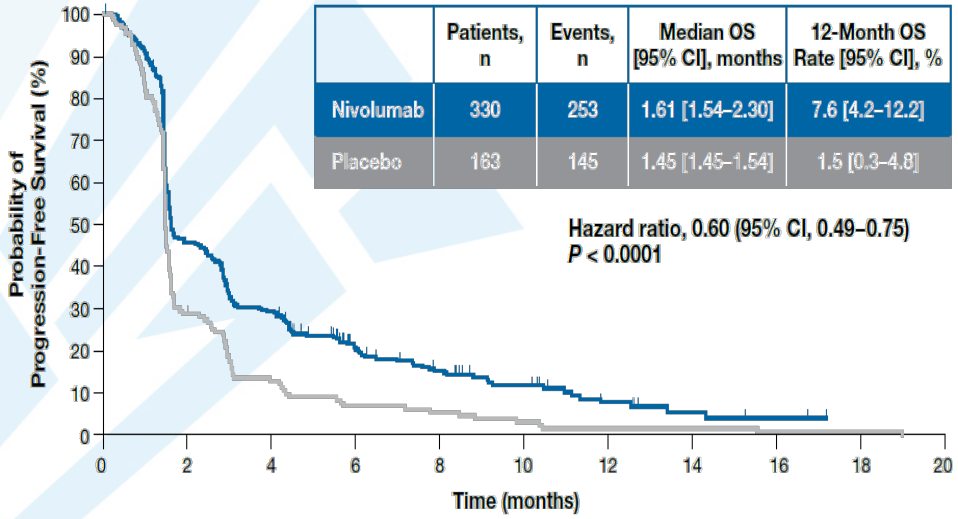
Challenges of IO in gastric and oesophageal cancer

- **Role of PD(L) antibodies in gastric and oesophageal adenocarcinoma:**
  - **Nivolumab and pembrolizumab are active in pretreated patients**
  - **Combination with chemotherapy?**
  - **Early lines?**
  - **Maintenance treatment?**
  - **Adjuvant or neo-adjuvant therapy?**
  - **Increasing activity: combination of IO approaches**
  - **Understanding mechanism of action**
    - **Pseudoprogression**
    - **…..**
  - **Selection: biomarkers: PDL-IHC, MSI-H, EBV, TML,…..**

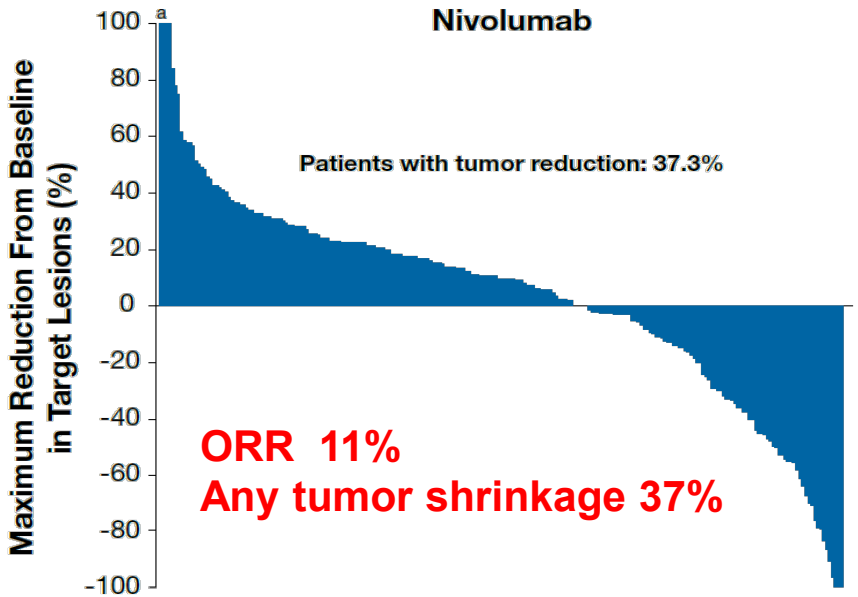
Phase 3 ATTRACTION-2: Nivolumab for GC after standard treatment



	Patients, n	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], %
Nivolumab	330	225	5.32 [4.63–6.41]	26.6 [21.1–32.4]
Placebo	163	141	4.14 [3.42–4.86]	10.9 [6.2–17.0]



	Patients, n	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], %
Nivolumab	330	253	1.61 [1.54–2.30]	7.6 [4.2–12.2]
Placebo	163	145	1.45 [1.45–1.54]	1.5 [0.3–4.8]

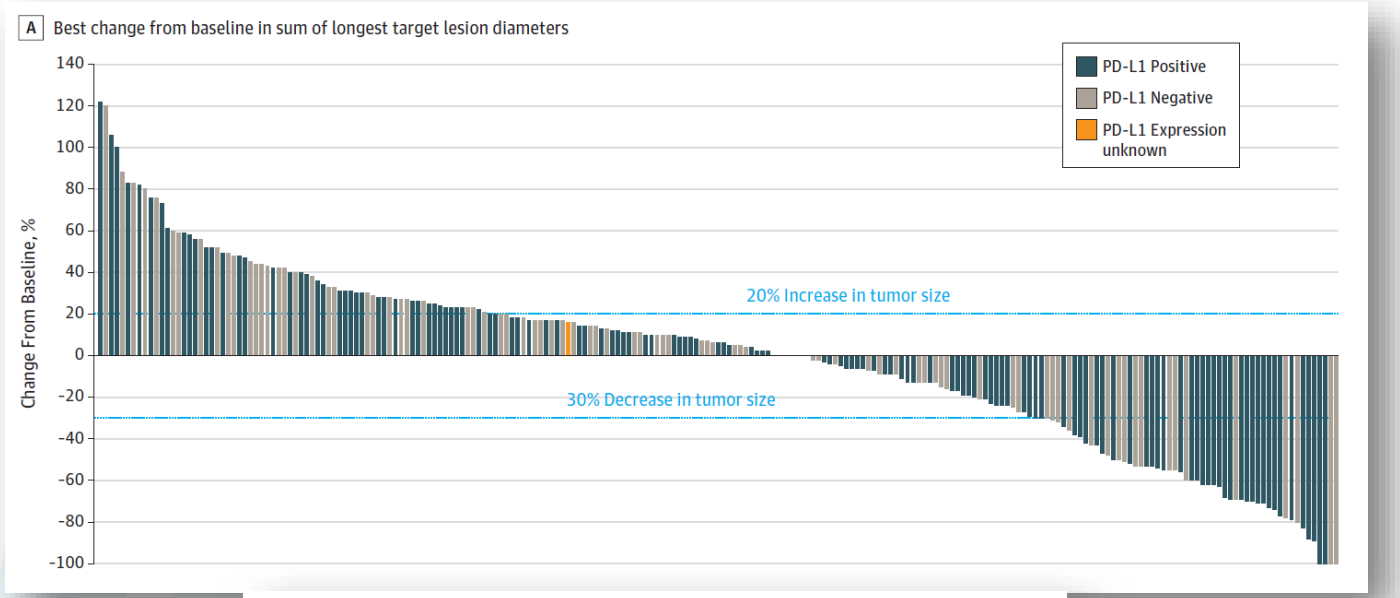


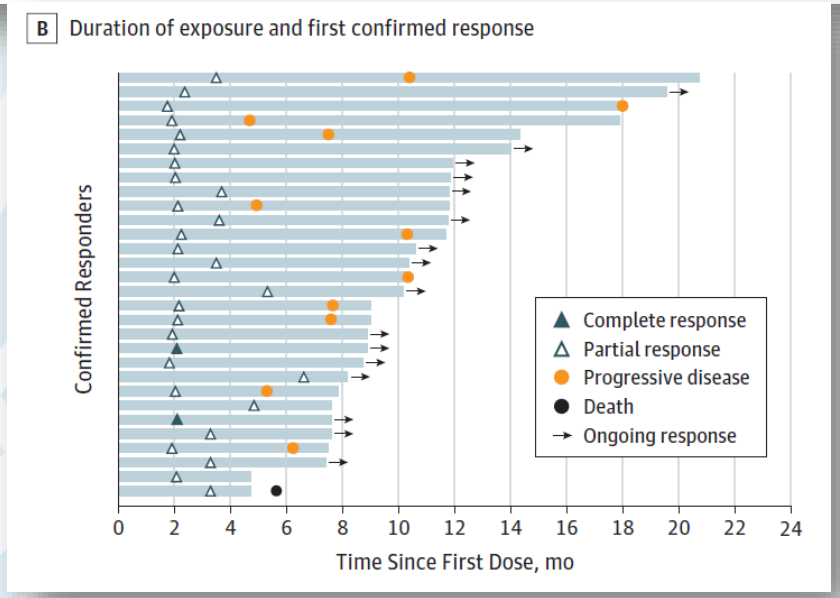
Significant OS benefit in Asian pts
(MST+1.2ms, 1y OS 26.6%, HR 0.63)

Well tolerated in pretreated GC pts
(d/c by AE 7% same with placebo)

Kang Y-K et al. Lancet. 2017;390:2461-2471.

KEYNOTE-059:
Pembrolizumab in refractory gastric cancer – cohort 1



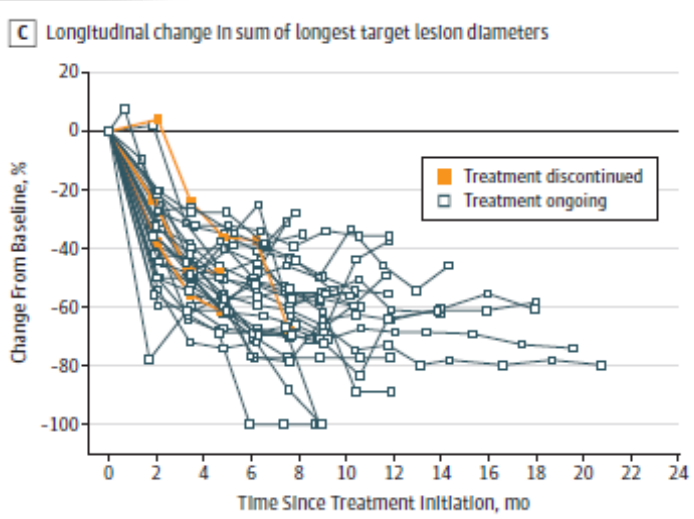


Keynote-059 (n=259)

Objective response rate 11.6%

MSI-high (n=7): 57.1%
Non-MSI-high (n=167): 9.0%
PDL pos (n=148): 15.5%
PDL neg (n=109): 6.4%

Median duration of response 8.4 mos



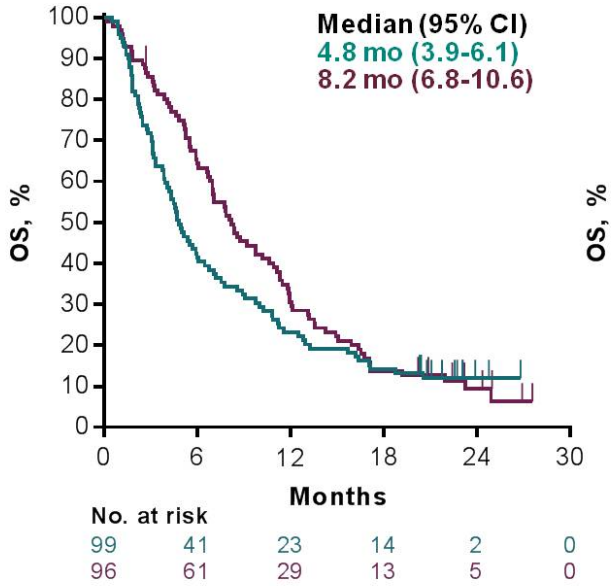
Fuchs C, et al. JAMA Oncol 2018

Keynote 061: 2nd line gastric cancer: pembrolizumab vs paclitaxel: survival in CPS ≥1

Overall Survival by PD-L1 CPS

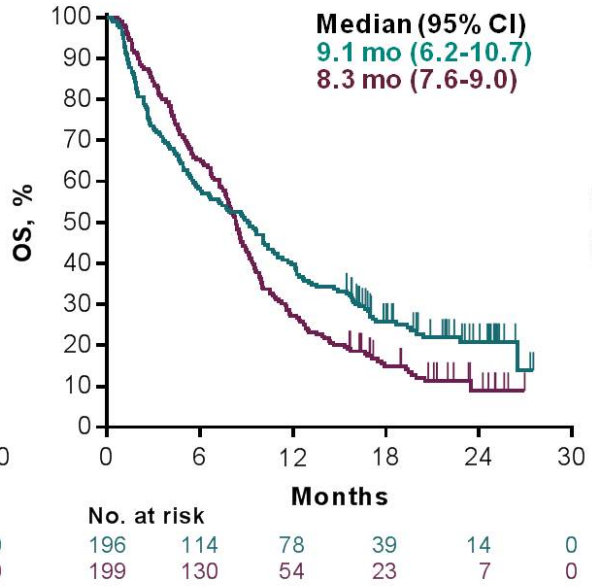
CPS <1

	Events/ Pts	HR (95% CI)
Pembrolizumab	87/99	1.20 (0.89-1.63)
Paclitaxel	86/96	



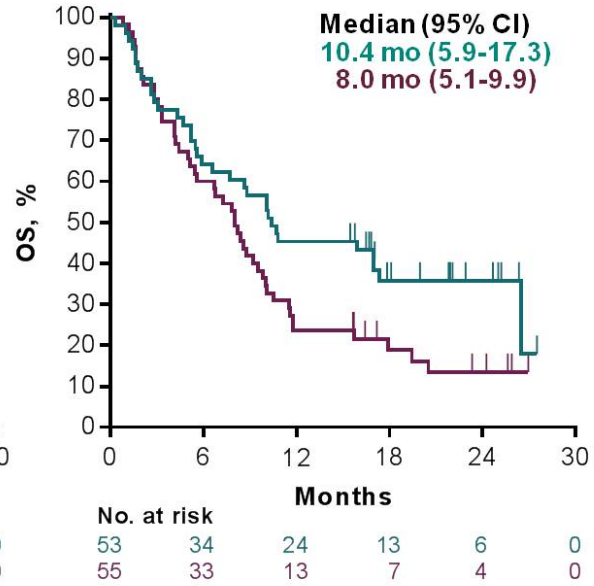
CPS ≥1[a]

	Events/ Pts	HR (95% CI)
Pembrolizumab	151/196	0.82 (0.66-1.03)
Paclitaxel	175/199	



CPS ≥10

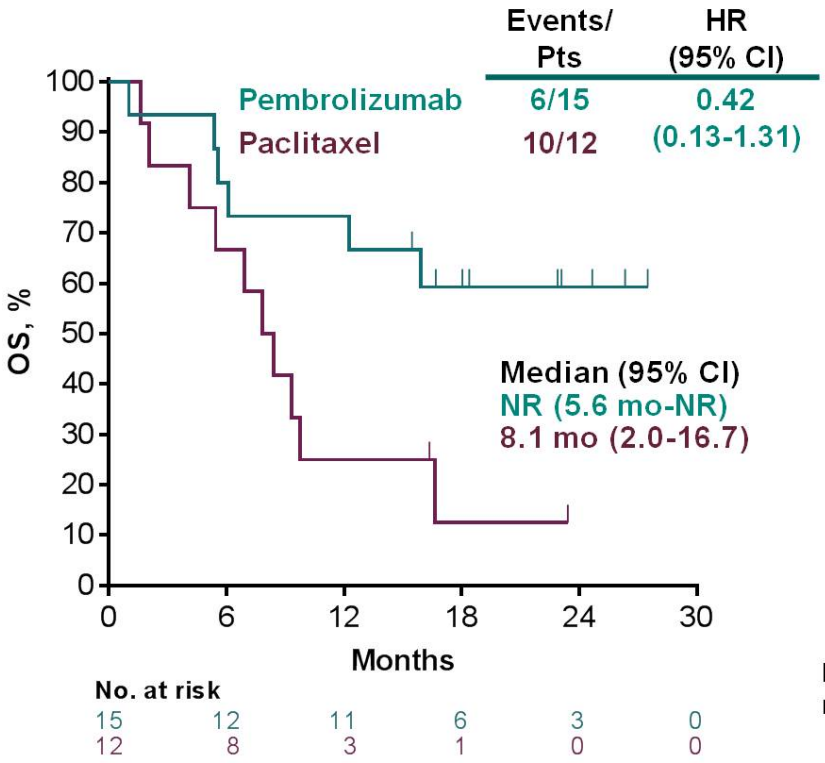
	Events/ Pts	HR (95% CI)
Pembrolizumab	34/53	0.64 (0.41-1.02)
Paclitaxel	46/55	

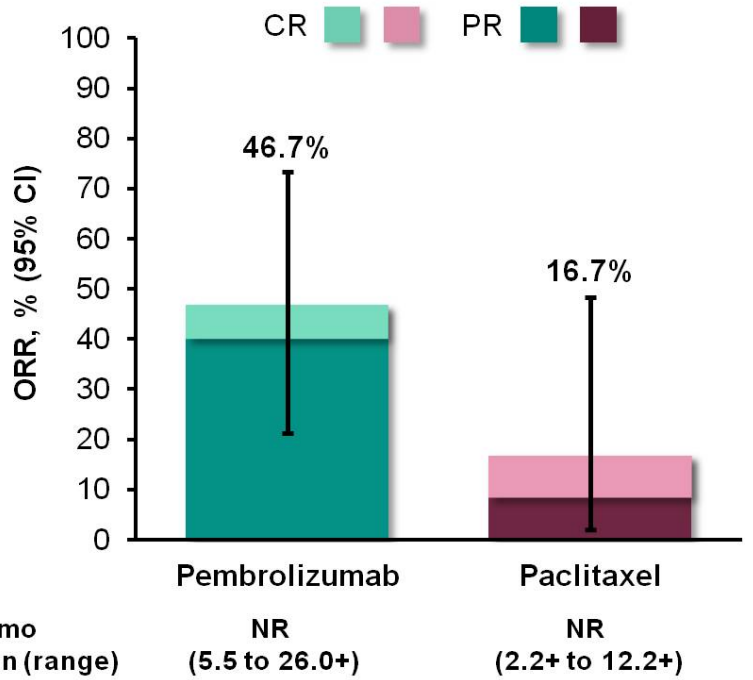


[a]Primary end point. Data cutoff date: Oct 26, 2017.

Keynote 061: 2nd line gastric cancer: pembrolizumab vs paclitaxel in MSI-H tumors

OS, ORR, and DOR for MSI-H Tumors[a]





[a]Post-hoc subgroup analysis. Data cutoff date: Oct 26, 2017.

Molecular characterization of clinical responses to pembrolizumab in metastatic gastric cancer

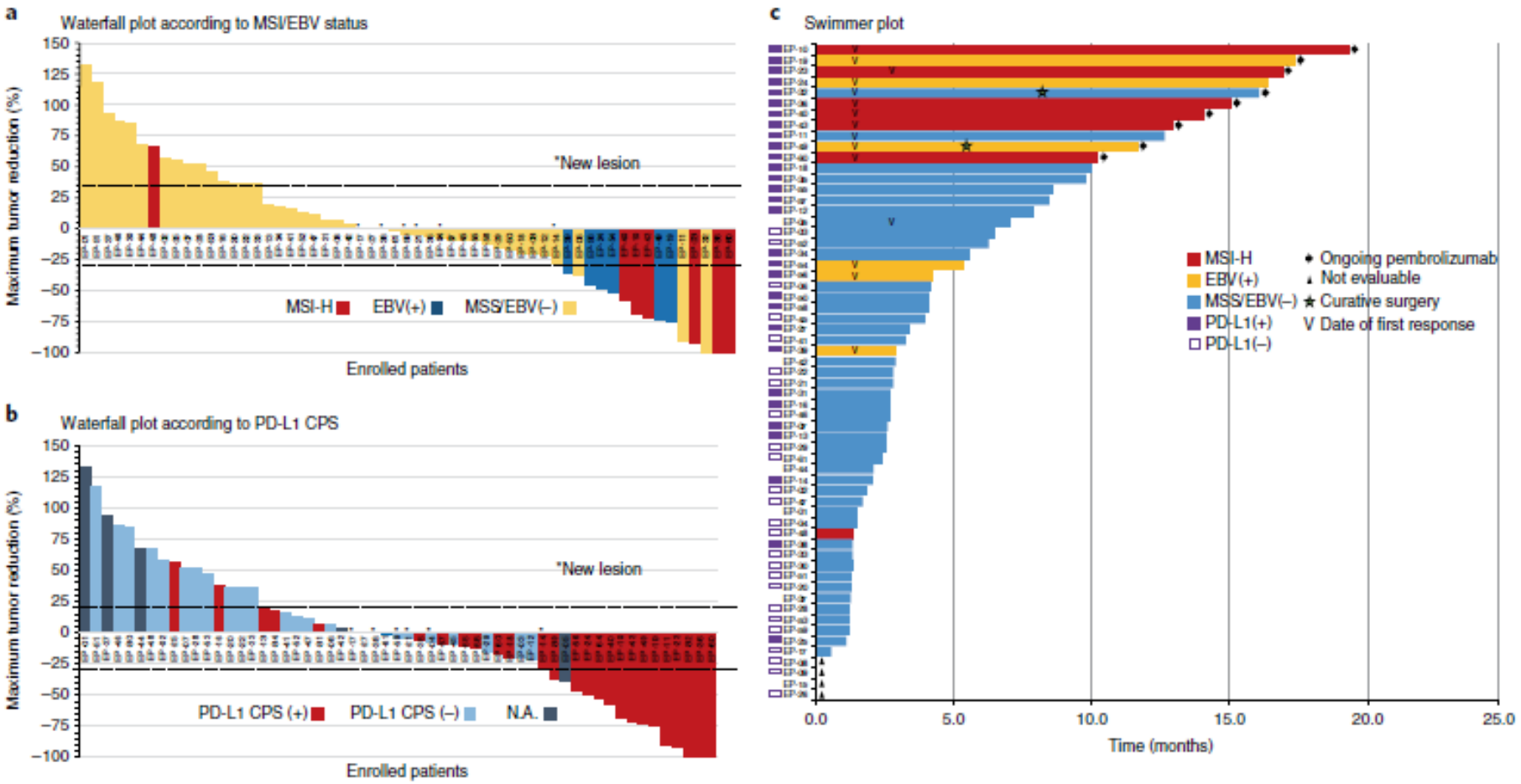
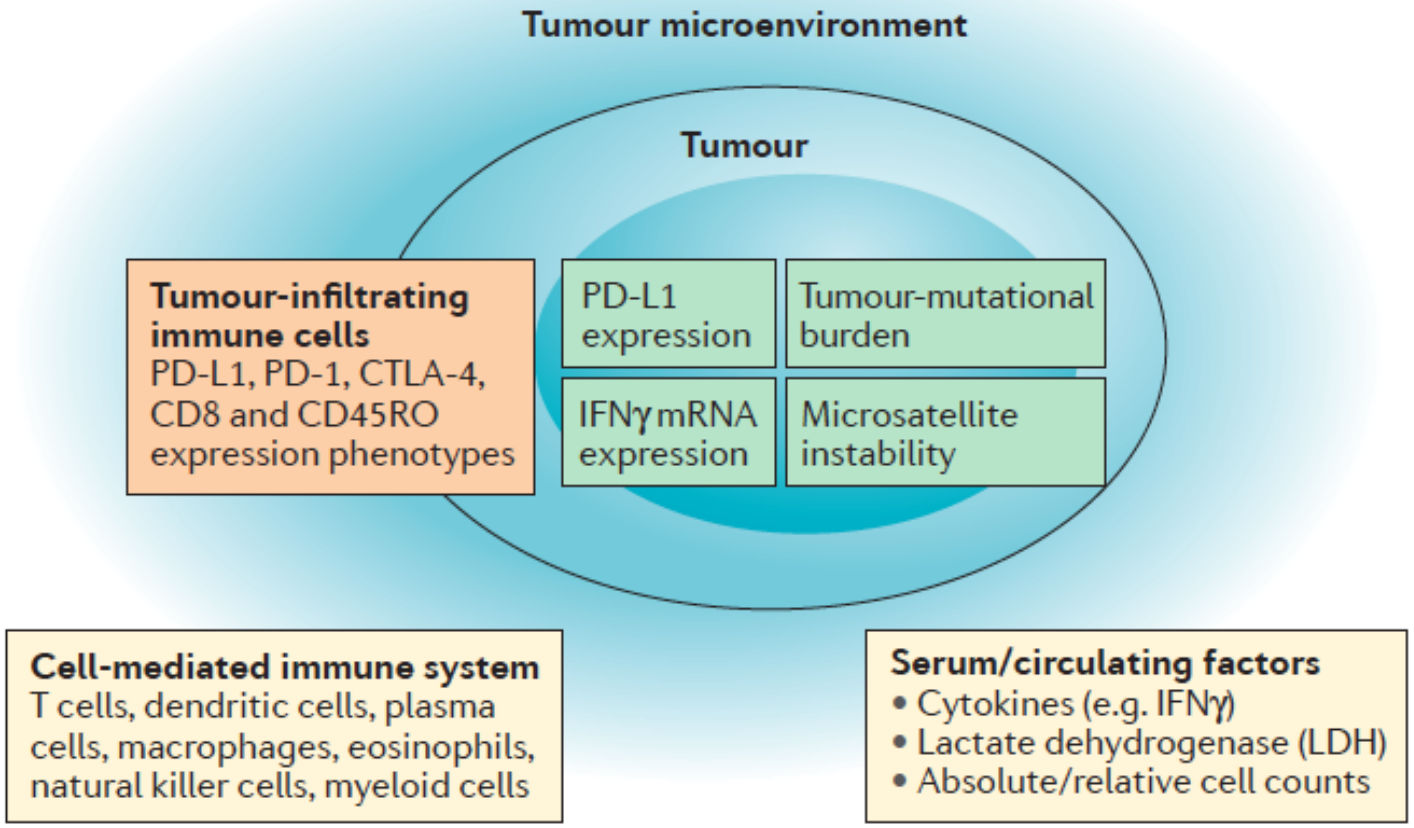


Fig. 1 | Response to pembrolizumab in patients with gastric cancer. a, Waterfall plot of response to pembrolizumab according to MSI status and EBV. EP represents each patient's identification number. *Y* axis represents percentage of maximum tumor reduction assessed according to RECIST 1.1 criteria. Lower dotted line represents tumor reduction of 30% per RECIST, which defines partial response (PR). **b**, Waterfall plot according to PD-L1 CPS. *Y* axis represents percentage of maximum tumor reduction assessed according to RECIST 1.1 criteria. **c**, Swimmer plot. Each lane represents a single patient's data. *X* axis represents the duration of pembrolizumab therapy for each patient. Patient identity number is provided in Table 2. NA, not available.

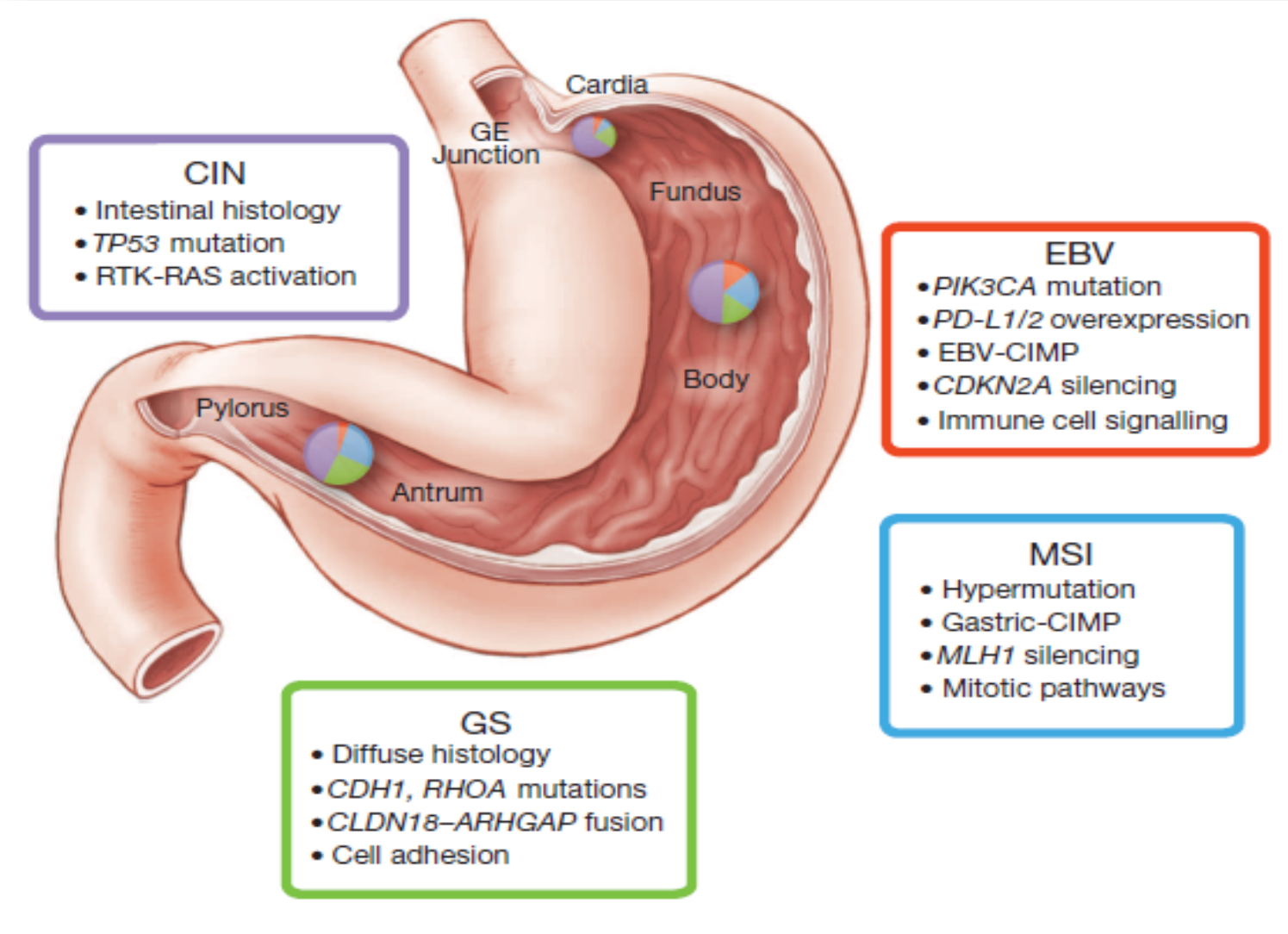
Kim S et al, Nature Medicine 2018

Checkpoint inhibition: biomarkers



Nishino et al. Nat Rev Clin Oncol 2017

Comprehensive Molecular Characterization



The Cancer Genome Atlas Research Network, *Nature* 2014; 11th September, 513: 202-209

Checkmate-032: nivolumab or nivolumab + ipilimumab in gastric cancer

Table 2. ORR, DCR, and DOR per Investigator Assessment and BICR

Variable	NIVO3 (n = 59)		NIVO1 + IPI3 (n = 49)		NIVO3 + IPI1 (n = 52)	
	Investigator	BICR	Investigator	BICR	Investigator	BICR
ORR, No. (%; 95% CI)	7 (12; 5 to 23)	4 (7; 2 to 17)	12 (24; 13 to 39)	10 (20; 10 to 34)	4 (8; 2 to 19)	2 (4; 1 to 13)
Complete response	1 (2)	0	1 (2)	1 (2)	0	1 (2)
Partial response	6 (10)	4 (7)	11 (22)	9 (18)	4 (8)	1 (2)
Stable disease	12 (20)	18 (31)	8 (16)	13 (27)	15 (29)	17 (33)
Progressive disease	34 (58)	26 (44)	23 (47)	18 (37)	24 (46)	25 (48)
Unable to determine	6 (10)	11 (19)	6 (12)	8 (16)	9 (17)	8 (15)
DCR, No. (%)*	19 (32)	22 (37)	20 (41)	23 (47)	19 (37)	19 (37)
Median TTR, months (range)	1.6 (1.2 to 4.0)	1.4 (1.2 to 2.1)	2.7 (1.2 to 14.5)	2.6 (1.1 to 4.2)	2.6 (1.3 to 2.8)	2.0 (1.2 to 2.7)
Median DOR, months (95% CI)	7.1 (3.0 to 13.2)	14.1 (2.8 to 14.1)	7.9 (2.8 to NE)	NR (2.7 to NE)	NR (2.5 to NE)	NR (NE to NE)

Abbreviations: BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NE, not estimable; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; NR, not reached; ORR, objective response rate; TTR, time to response.
*Patients with a best objective response of complete response, partial response, or stable disease.

Janjigian Y et al, J Clin Onc 2018

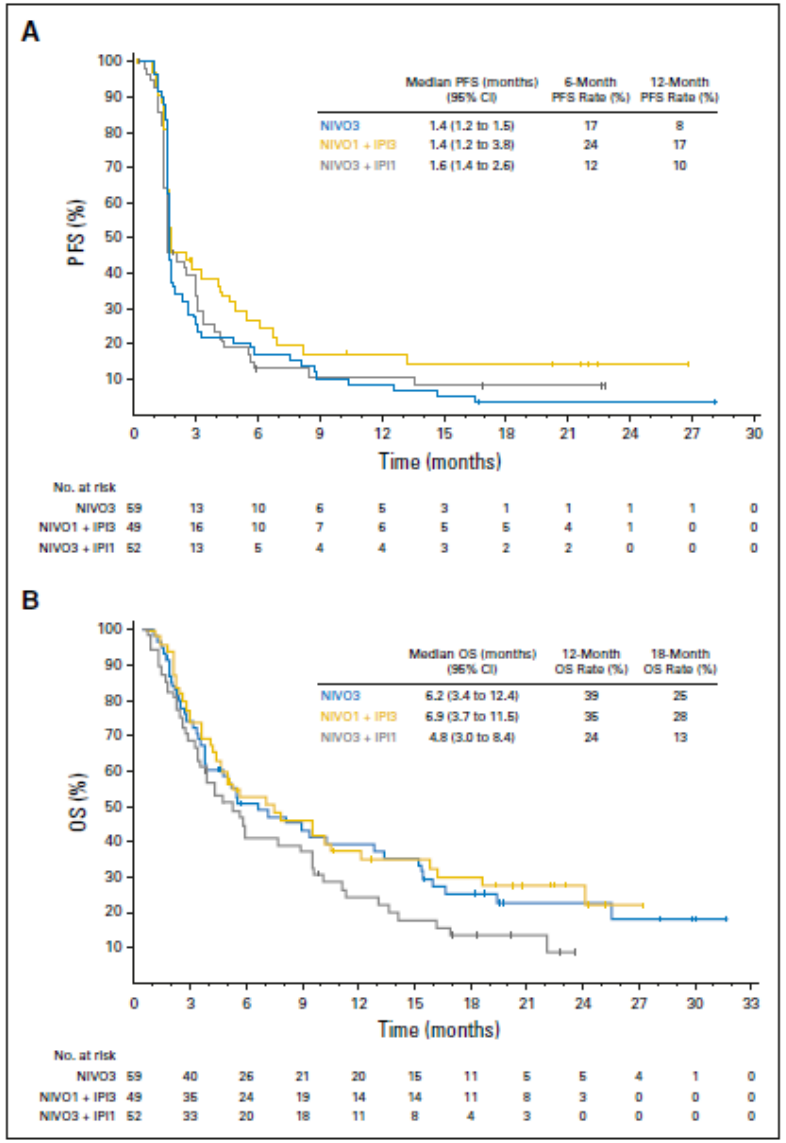
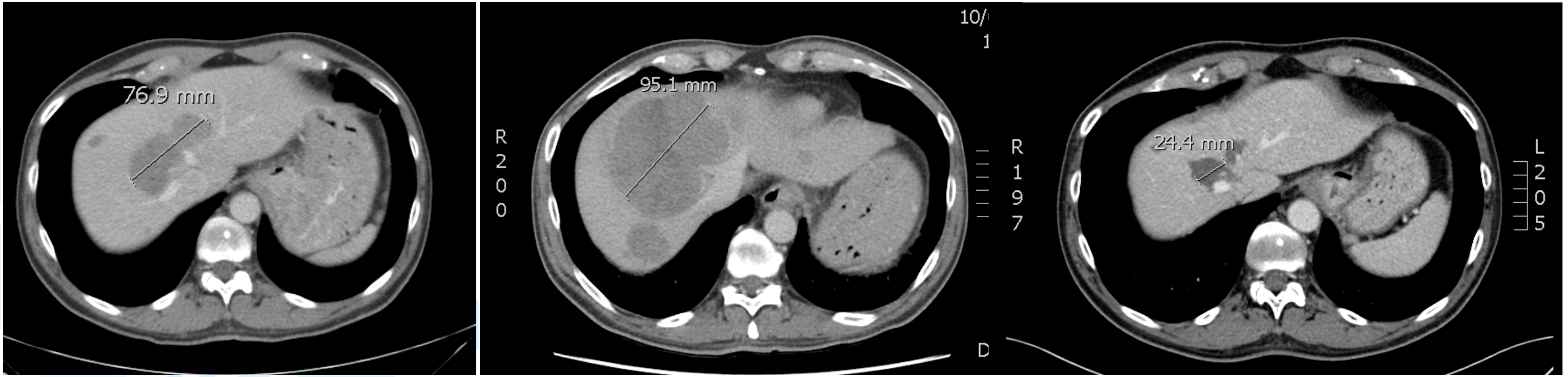


Fig 2. Kaplan-Meier curves of (A) investigator-assessed progression-free survival (PFS) and (B) overall survival (OS) in all enrolled patients by treatment group: nivolumab 3 mg/kg (NIVO3), nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (NIVO1 + IPI3), and NIVO3 plus ipilimumab 1 mg/kg (NIVO3 + IPI1). Hash marks indicate censored observations.

Metastatic GE junction adenocarcinoma: combination of IO agents

Treatment with Nivolumab + MM9-AB

3/2017 | 5/2017 | 8/2018



Understanding pseudoprogression

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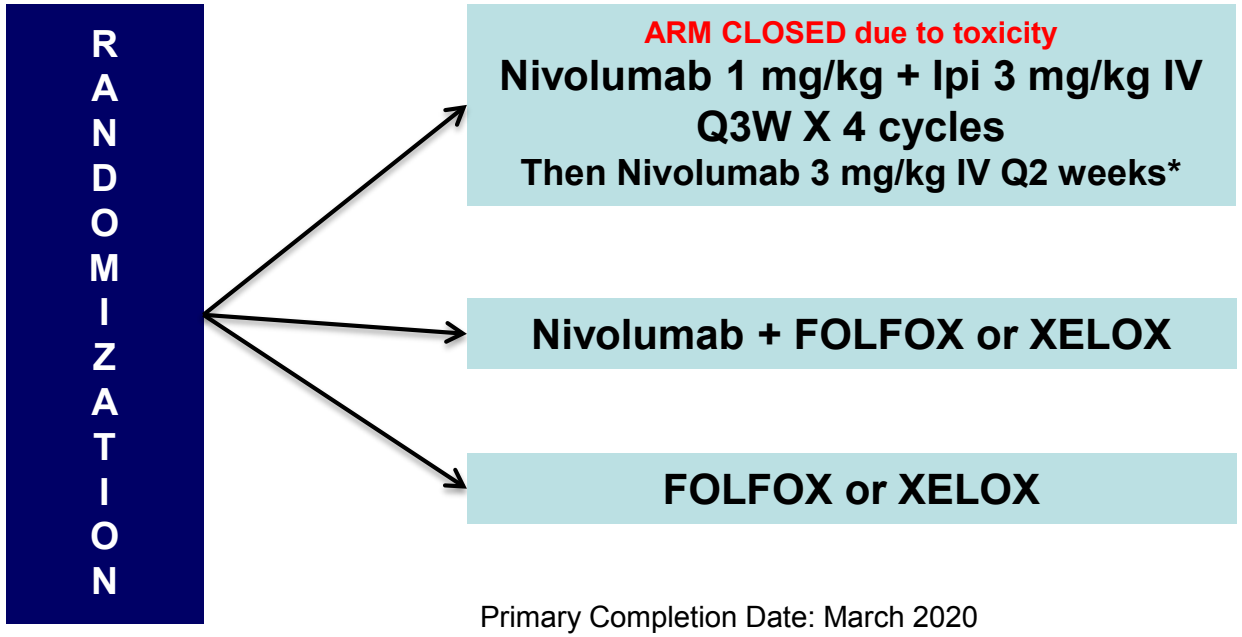
CheckMate-649

Untreated Advanced/Metastaic Gastric/GEJ Cancer
Nivo + Ipi or Nivo + FOLFOX vs FOLFOX – open label, randomized phase 3 study

N=1649

Enrolling all-comers

- Unresectable advanced or recurrent gastric cancer (including GEJ)
- No adjuvant/neoadjuvant ≤6 mos prior
- ECOG PS 0-1
- Must provide tissue sample



Primary Endpoints:
- Nivo+chemo OS/PFS/ORR all-comers
- Nivo-Ipi OS PD-L1+

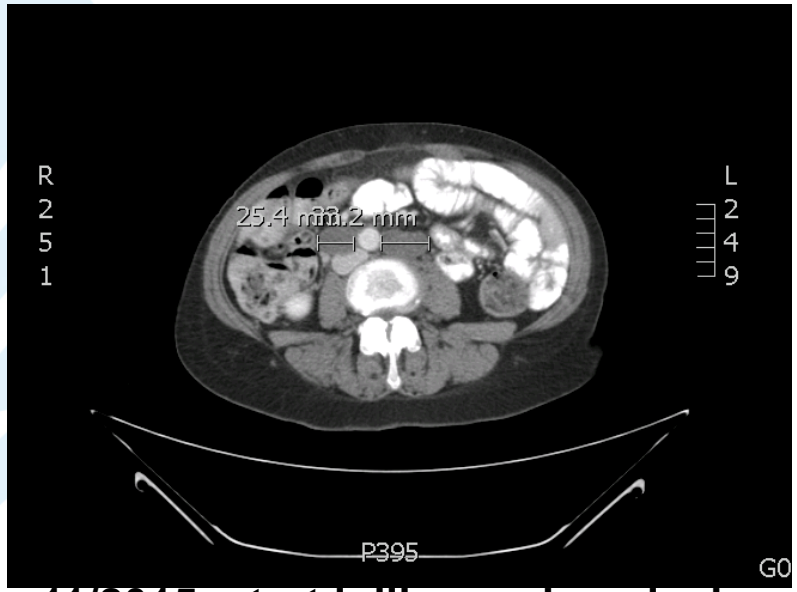
Secondary Endpoints:
- Nivo-Ipi OS in all-comers
- Nivo-Ipi or Nivo/Chemo PFS in PD-L1+
- QoL (TTSD)

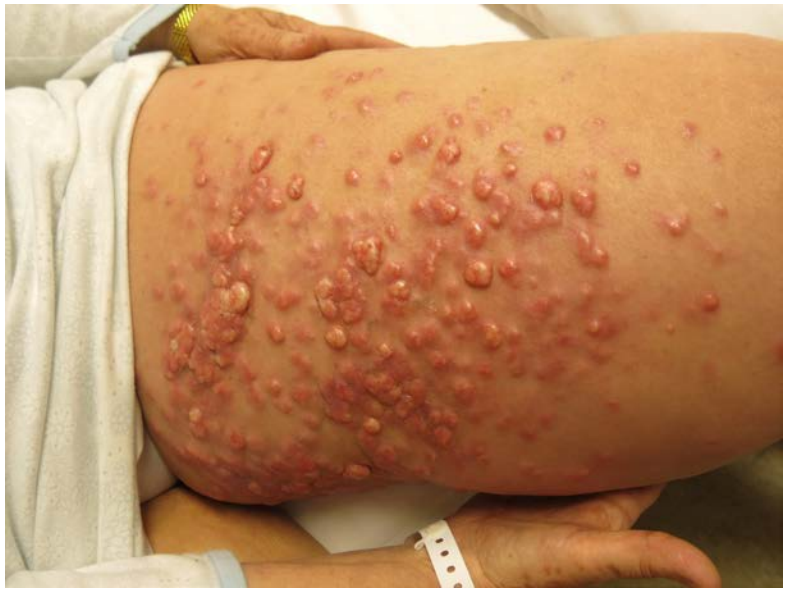
Primary Completion Date: March 2020
Opened 10/16
190 study sites

NCT0287216

COLON CANCER
Female, 66y

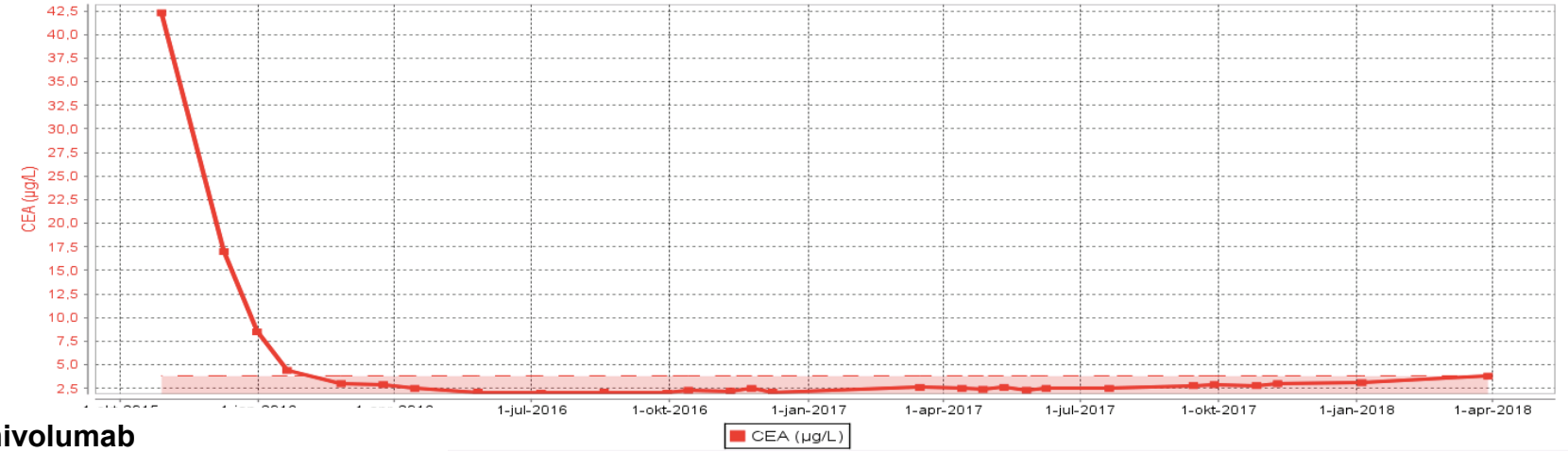
- Lynch syndrome, germline MSH2 mutation
- 2008: endometrium carcinoma – R/ surgery
- 7/2013: sigmoidadenocarcinoma pT4N2M1 (MSI-H, RAS mt)
  - Resection of the primary tumor
  - 9/2013 – 12/2013: mFolfiri-bevacizumab
  - 1/2015: Progressive Disease (PD): restart mFolfiri-bevacizumab
  - 7/2015: PD with cutaneous metastases, retroperitoneal and inguinal lymph nodes
  - 9/2015: PD, mFolfox-bevacizumab
  - 11/2015: PD





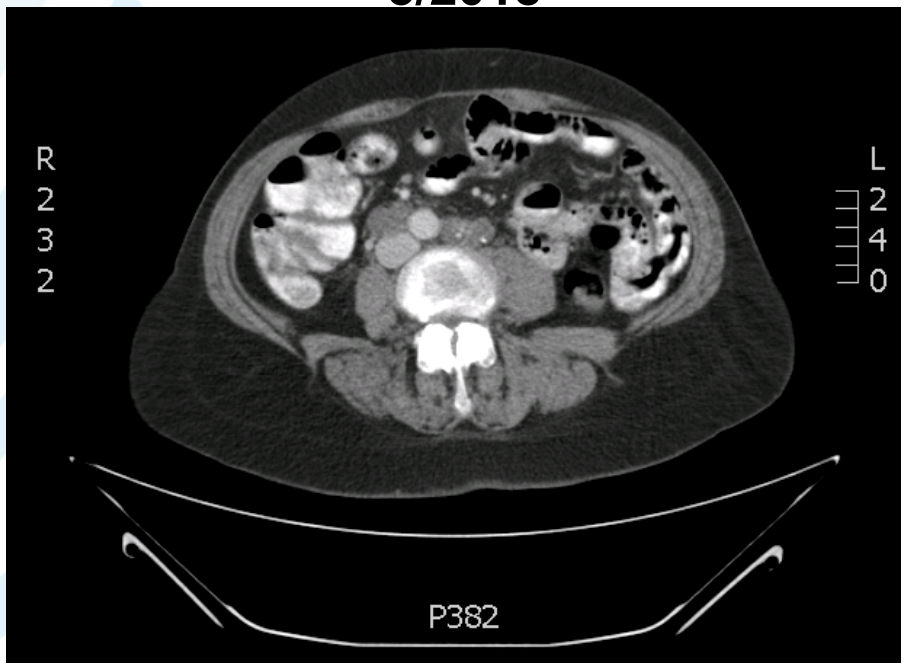
11/2015: start ipilimumab + nivolumab

COLON CANCER
Female, 66y

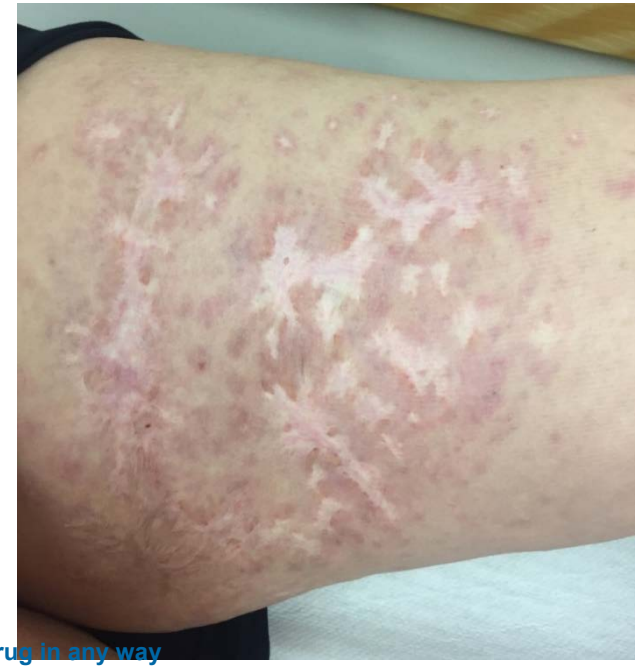


11/2015: start ipilimumab + nivolumab

3/2018



6/2018



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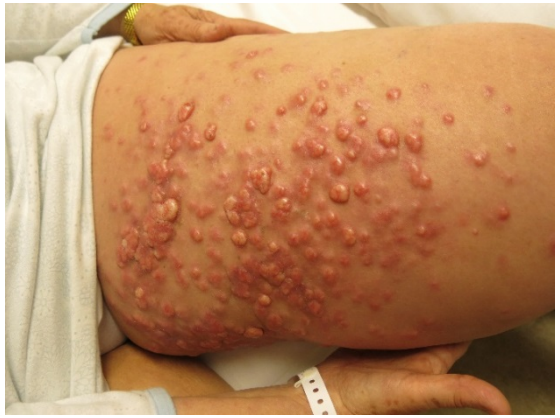
COLON CANCER
Female, 66y

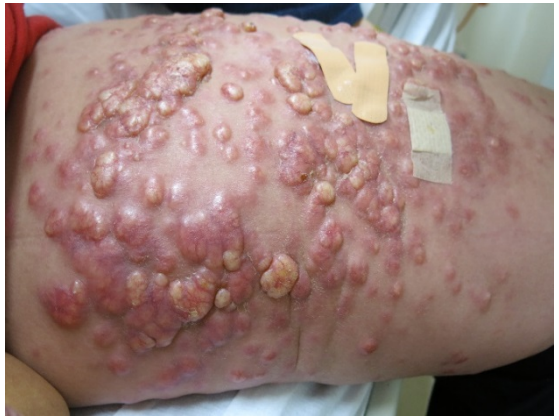
11/2015: start ipilimumab + nivolumab

Pseudoprogression

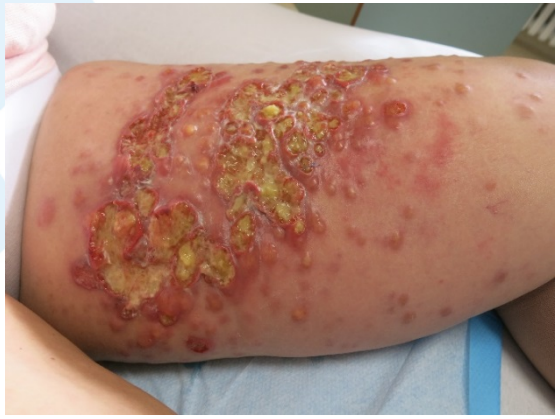
10/2015



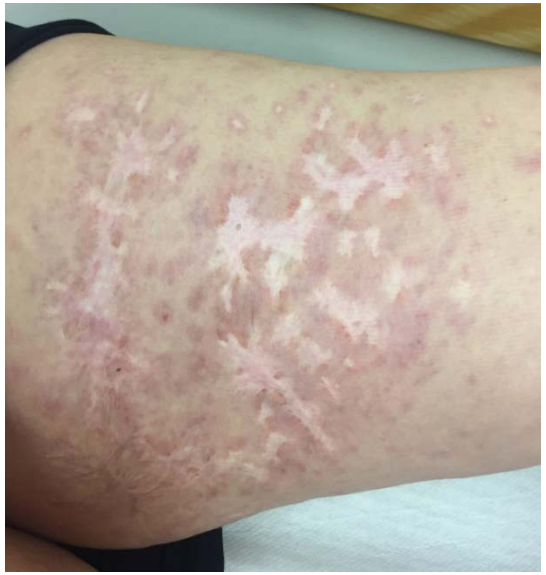
11/2015



02/2016



12/2018

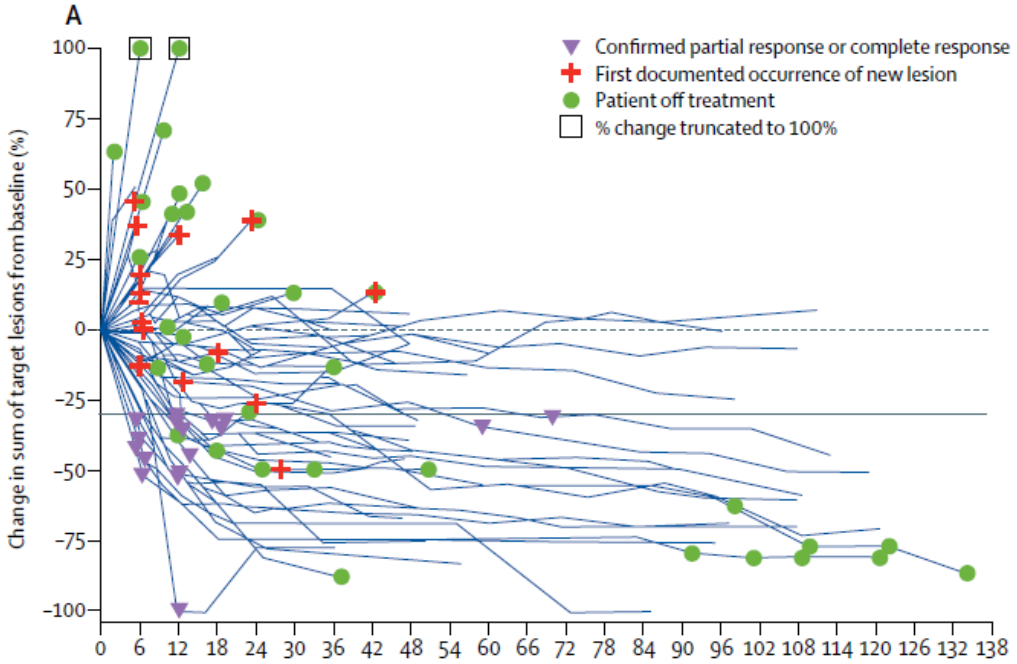


Nivolumab in MSI-H mCRC

	dMMR/MSI-H per local assessment (n=74)		dMMR/MSI-H per central assessment (n=53)	
	Investigator	Blinded independent central review	Investigator	Blinded independent central review
Objective response	23 (31·1%, 20·8–42·9)	24 (32%, 22–44)	19 (36%, 23–50)	19 (36%, 23–50)
Best overall response				
Complete response	0	2 (3%)	0	1 (2%)
Partial response	23 (31%)	22 (30%)	19 (36%)	18 (34%)
Stable disease	28 (38%)	25 (34%)	20 (37%)	19 (36%)
Progressive disease	19 (26%)	21 (28%)	11 (21%)	12 (23%)
Not determined	4 (5%)	4 (5%)	3 (6%)	3 (6%)
Disease control for ≥12 weeks	51 (69%, 57–79)	47 (64%, 52–74)	39 (74%, 60–85)	37 (70%, 56–82)

Data are n (%, 95% CI) or n (%). dMMR/MSI-H=DNA mismatch repair deficient/microsatellite instability-high.

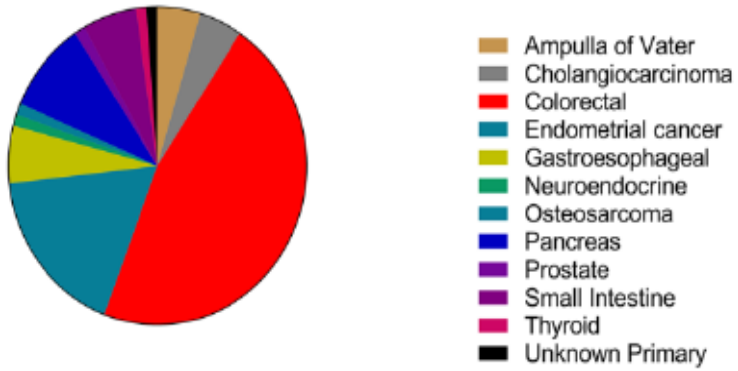
Table 2: Objective response, best overall response, and disease control per investigator and masked independent central review assessments



Overman M et al, Lancet Oncol 2017

Response to Pembrolizumab in MSI-High / deficient MMR tumors

Type of response	Patients (n = 86)
Complete response	18 (21%)
Partial response	28 (33%)
Stable disease	20 (23%)
Progressive disease	12 (14%)
Not evaluable	8 (9%)
Objective response rate 95% CI	53% 42% to 64%
Disease control rate 95% CI	77% 66% to 85%
Median progression-free survival time 95% CI	NR 14.8 months to NR
2-year progression-free survival rate 95% CI	53% 42% to 68%
Median overall survival time 95% CI	NR NR to NR
2-year overall survival rate 95% CI	64% 53% to 78%



- **11 patients achieved a CR and were taken off therapy after 2 years of treatment.**
- **No evidence of cancer PD has been observed in those patients with a median time off therapy of 8.3 months.**

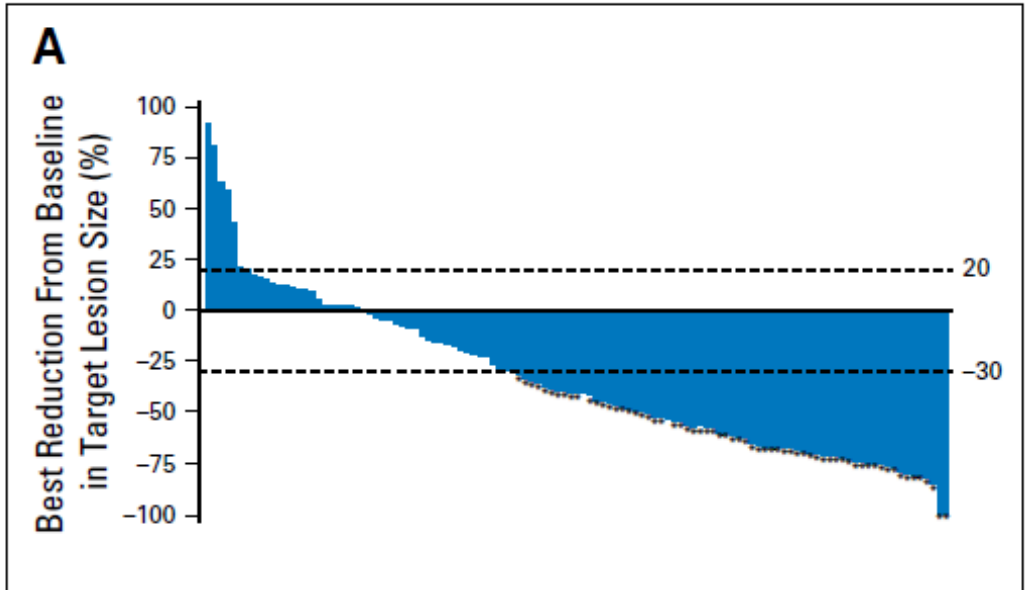
Le DT et al, Science 2017

Durable Responses with nivolumab + ipilimumab in MSI-H mCRC

Table 2. ORR, Best Overall Response, and DCR per Investigator Assessment (N = 119)

Response	No. (%)	95% CI
ORR	65 (55)	45.2 to 63.8
Best overall response		
Complete response	4 (3)	
Partial response	61 (51)	
Stable disease	37 (31)	
Progressive disease	14 (12)	
Not determined	3 (3)	
Disease control for ≥ 12 weeks	95 (80)	71.5 to 86.6

Abbreviations: DCR, disease control rate; ORR, objective response rate.



Overman M et al, J Clin Onc 2018

CheckMate 142 in first line MSI-H mCRC

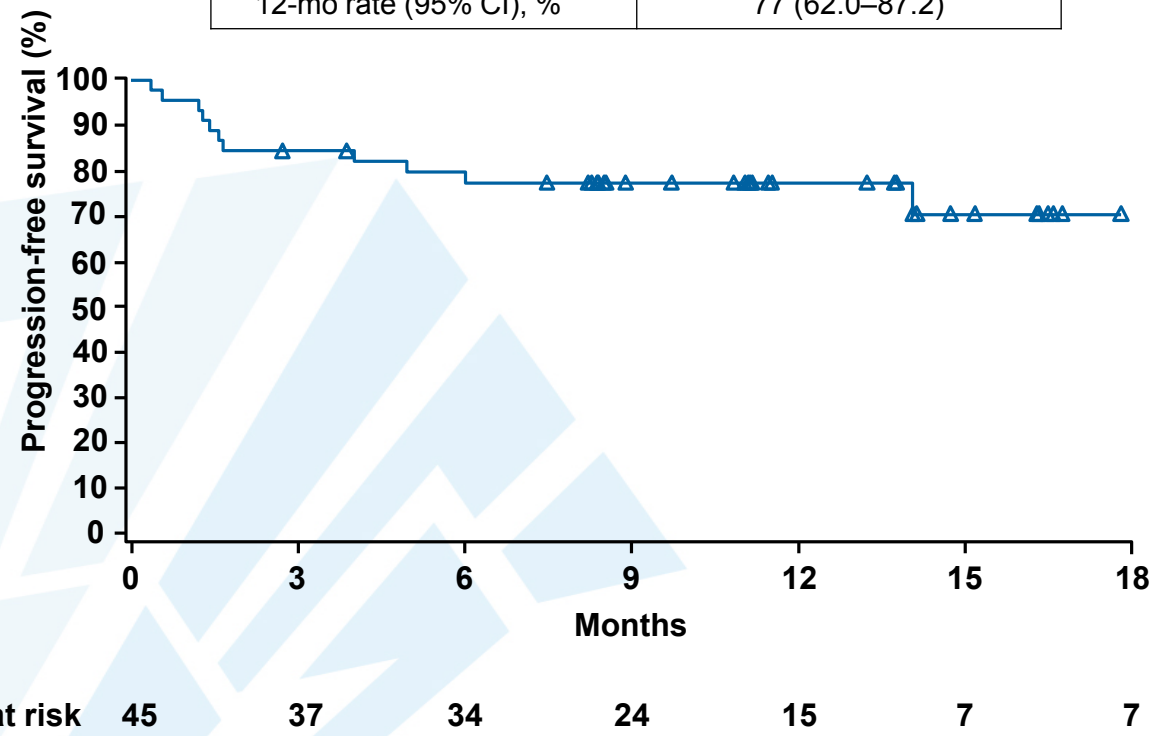
Investigator-assessed	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
ORR[a], n (%) [95% CI]	27 (**60**) [44.3–74.3]
Best overall response, n (%)* CR PR SD PD Not determined	 3 (**7**) 24 (53) 11 (24) 6 (13) 1 (2)
DCR[b], n (%) [95% CI]	38 (**84**) [70.5–93.5]

- **Responses were observed regardless of tumor PD-L1 expression, *BRAF* or *KRAS* mutation status, or diagnosis of Lynch syndrome**
  - **The ORR and DCR in patients with a *BRAF* mutation (n = 17) were 71% and 88%, respectively**

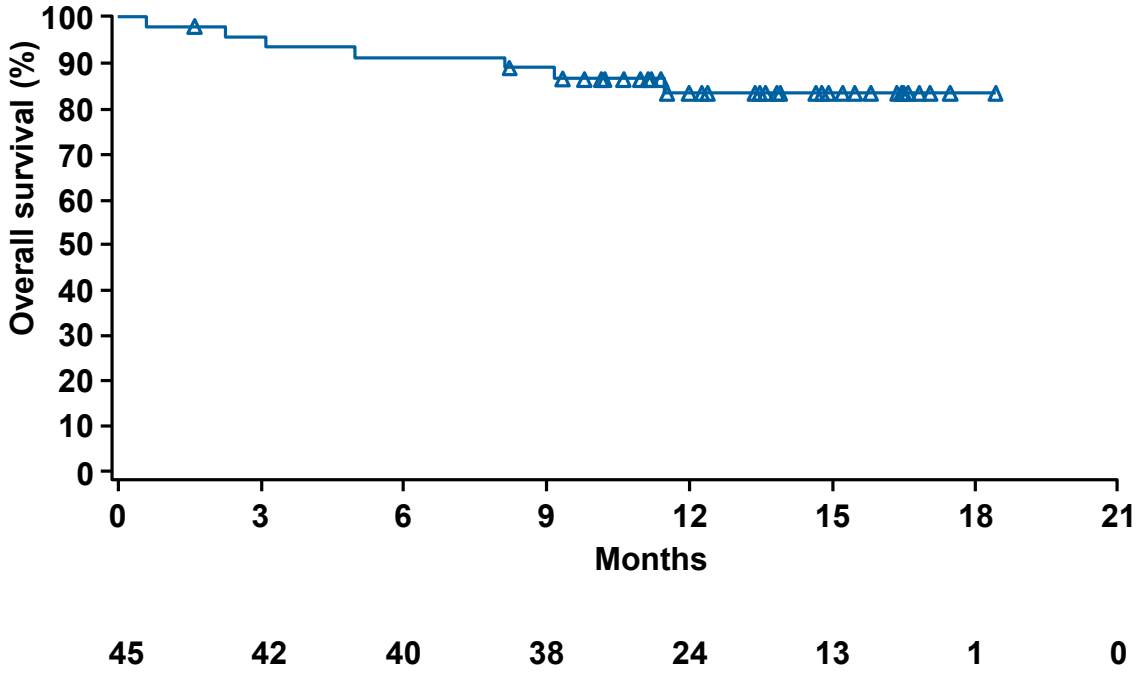
Lenz H, Van Cutsem E et al, Ann Oncol, ESMO Munich 2018

CheckMate 142 in first line MSI-H mCRC

PFS[a]	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
Median PFS, months (95% CI)	NR (14.1–NE)
9-mo rate (95% CI), %	77 (62.0–87.2)
12-mo rate (95% CI), %	77 (62.0–87.2)



OS[a]	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
Median OS, months (95% CI)	NR (NE)
9-mo rate (95% CI), %	89 (74.9–95.1)
12-mo rate (95% CI), %	83 (67.6–91.7)

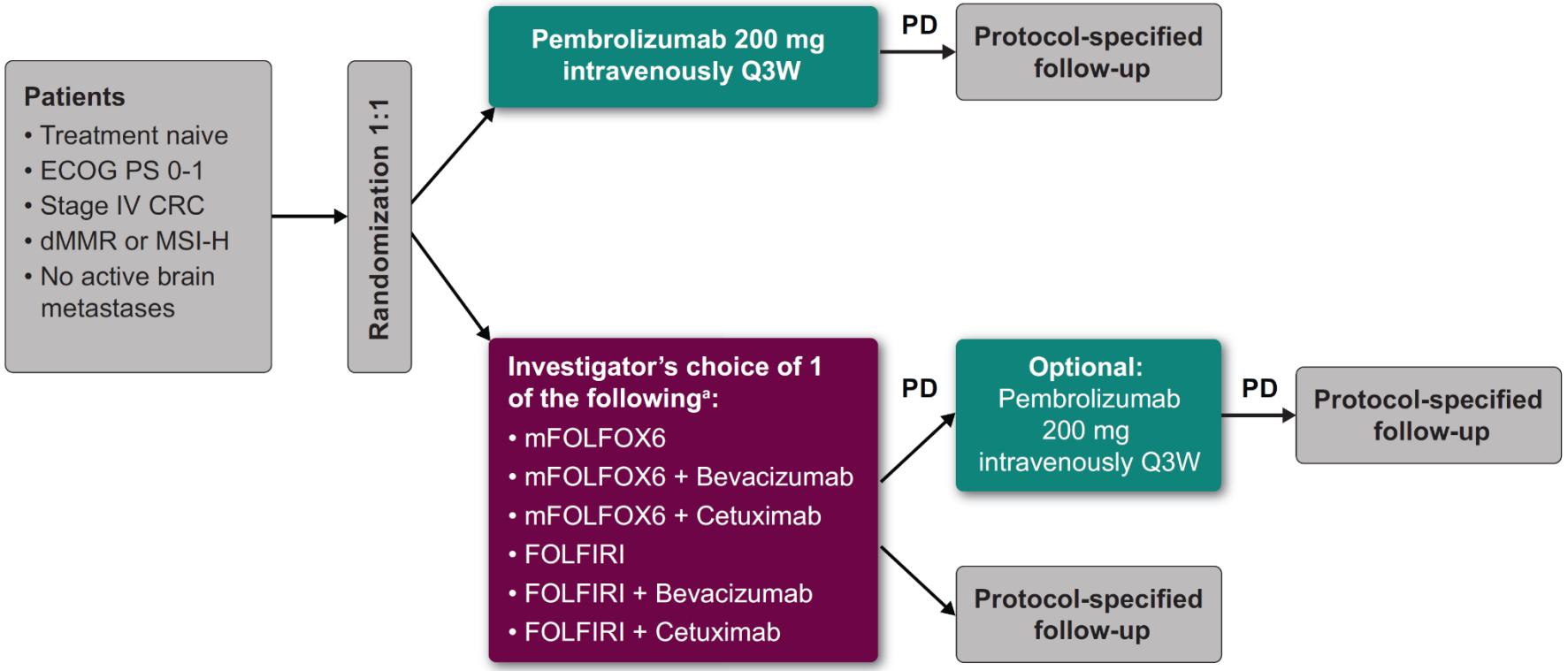


[a]Per investigator assessment.
mo = month; NE = not estimable; NR = not reached

Lenz H, Van Cutsem E et al, Ann Oncol, ESMO Munich 2018

First-Line Trial for Mismatch Repair–Deficient or Microsatellite Instability–High Metastatic Colorectal Carcinoma

KEYNOTE-177 is a 2-arm, randomized, open-label, multisite, phase 3 trial



NCT02563002

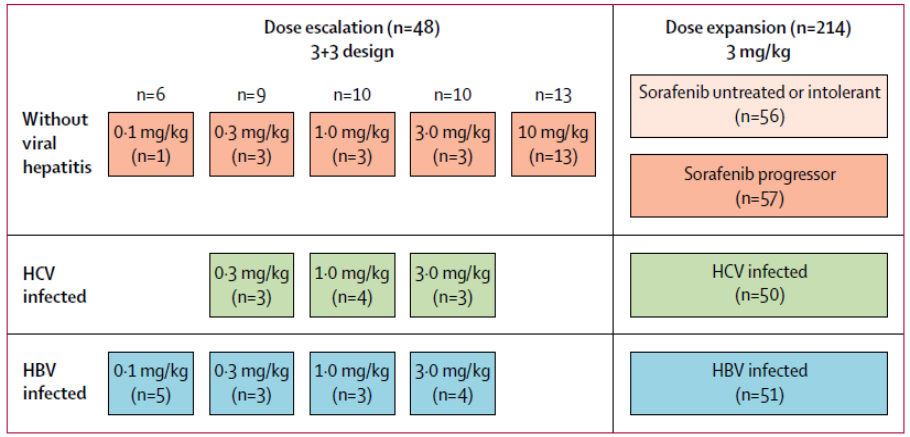
Diaz L et al, ASCO GI 2018

Conclusions in mCRC

- Nivolumab and pembrolizumab provided durable responses in MSI-H CRC patients who received ≥1 prior therapy
- Nivolumab with or without ipilimumab provided also durable responses in MSI-H CRC patients who received ≥1 prior therapy and in first line treatment
- Ongoing studies in first line and in stage III MSI-H colon cancer
- Activity of IO agents in MSS cancer:
  - ✓No activity of atezoluzimab + cobimetinib
  - ✓No activity of atezoluzimab + bevacizumab +5FU/LV in maintenance of first line mCRC
  - ✓New approaches:….

CHECKMATE-040

Nivolumab in 2nd line HCC



Recommended dose for expansion:
3 mg/kg

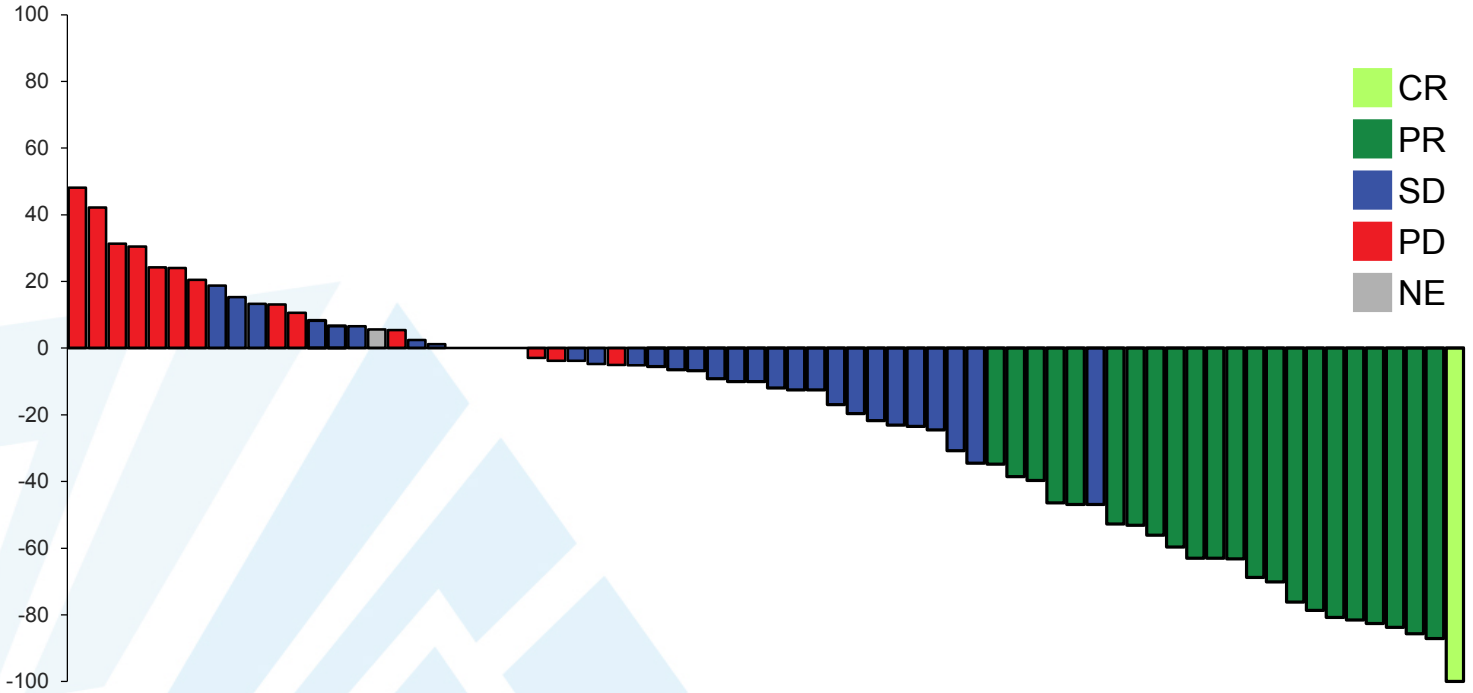
	Uninfected untreated/ intolerant (n=56)	Uninfected progressor (n=57)	HCV infected (n=50)	HBV infected (n=51)	All patients (n=214)
Objective response*	13 (23%; 13 to 36)	12 (21%; 11 to 34)	10 (20%; 10 to 34)	7 (14%; 6 to 26)	42 (20%; 15 to 26)
Complete response	0	2 (4%)	0	1 (2%)	3 (1%)
Partial response	13 (23%)	10 (18%)	10 (20%)	6 (12%)	39 (18%)
Stable disease	29 (52%)	23 (40%)	23 (46%)	21 (41%)	96 (45%)
Progressive disease	13 (23%)	18 (32%)	14 (28%)	23 (45%)	68 (32%)
Not evaluable	1 (2%)	4 (7%)	3 (6%)	0	8 (4%)
Duration of response*					
KM median	8·4 (8·3 to NE)	NR	9·9 (4·5 to 9·9)	NR	9·9 (8·3 to NE)
Ongoing, n/N (%)	8/13 (62%)	7/12 (58%)	8/10 (80%)	5/7 (71%)	28/42 (67%)
Disease control*	42 (75%; 62 to 86)	35 (61%; 48 to 74)	33 (66%; 51 to 79)	28 (55%; 40 to 69)	138 (64%; 58 to 71)
Disease control with stable disease for ≥6 months	22 (39%; 27 to 53)	22 (39%; 26 to 52)	17 (34; 21 to 49)	18 (35%; 22 to 50)	79 (37%; 30 to 44)
Overall survival					
6 months	89% (77 to 95)	75% (62 to 85)	85% (72 to 93)	84% (71 to 92)	83% (78 to 88)
9 months	82% (68 to 90)	63% (49 to 74)	81% (66 to 90)	70% (55 to 81)	74% (67 to 79)
KM median	NR	13·2 (8·6 to NE)	NR	NR	NR
Progression-free survival*					
KM median	5·4 (3·9 to 8·5)	4·0 (2·6 to 6·7)	4·0 (2·6 to 5·7)	4·0 (1·3 to 4·1)	4·0 (2·9 to 5·4)

Unless otherwise indicated, data are n (%; 95% CI); n (%); months (95% CI); or % (95% CI). HCV=hepatitis C virus. HBV=hepatitis B virus. KM=Kaplan-Meier estimate. NR=not reached. NE=not estimable. RECIST=Response Evaluation Criteria In Solid Tumors. *Determined by investigator assessment using RECIST version 1.1.

Table 4: Nivolumab efficacy in the dose-expansion phase

El-Khoueiry A et al. Lancet 2017; 389: 2492–502

Phase 1b in HCC: atezolizumab plus bevacizumab



CR, complete response; NE, not evaluable or missing; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameter.
[a] Data from 4 patients (6%) not evaluable or missing. [b] One patient without region information. [c] Baseline AFP data from 5 patients missing. [d] EHS/MVI baseline data missing from 1 patient.
Data cutoff: 26 July 2018.

ORR	
Overall, n (%)[a]	**23/73 (32)**
CR	1/73 (1)
PR	22/73 (30)
SD	33/73 (45)
PD	13/73 (18)
By region, n/n (%)[b]	
Asia excluding Japan	12/41 (29)
Japan/USA	10/31 (32)
By aetiology, n/n (%)	
HBV	11/36 (31)
HCV	10/23 (43)
Non-viral	2/14 (14)
By baseline AFP, n/n (%)[c]	
< 400 ng/mL	12/41 (29)
≥ 400 ng/mL	11/27 (41)
By EHS/MVI, n/n (%)[d]	
EHS and/or MVI	18/64 (28)
MVI negative	13/32 (41)
EHS negative	9/22 (41)
Neither EHS nor MVI	5/8 (63)

Pishvaian et al, Ann Onc, ESMO Munich 2018

Ongoing ImmunoOncology Key Studies in HCC

Study Name	Design / 1ry endpoint	Primary Completion Date
CHECKMATE-459 (Phase III)	Nivolumab vs. sorafenib (1st line HCC) 1ry endpoint: OS	1ry completion: Oct 16, 2018
IMbrave150 (Phase III)	Atezolizumab + bevacizumab vs. sorafenib (1st line HCC) 1ry endpoint: OS/ORR	1ry completion: May, 2021
HIMALAYA (Phase III)	Durvalumab ± tremelimumab vs. sorafenib (1st line HCC) 1ry endpoint: OS	1ry completion: March, 2020
BGB-A317 (Phase III, with safety run-in)	BGB-A317 (PD-1 Ab) vs. sorafenib (1st line HCC) 1ry endpoint: OS (+ PK/PD info)	1ry completion: January, 2022

Reference: Clinicaltrials.gov

Conclusions in HCC

- Nivolumab and pembrolizumab demonstrated promising clinical efficacy and manageable safety in patients with advanced HCC, previously treated with sorafenib
  - Clinical efficacy was durable
  - Safety profile was generally comparable to that established in other indications with few immune-mediated hepatic events and no viral flares
- Phase 3 studies in first and second line treatment of HCC are ongoing to evaluate the role of checkpoint inhibitors
- Early small studies suggest the feasibility and potential high activity of combinations of checkpoint inhibitors and angiogenesis inhibitors (e.g. pembrolizumab with lenvatinib and atezolizumab with bevacizumab)

Major immunotherapeutic approaches

Many novel approaches over and above the NOBEL checkpoint inhibitors:

Adoptive transfer: transfer of cells into patients

Anti-cancer vaccines

Checkpoint blockade

Microen-vironment

CAR T-cell therapy antigen targets in clinical trials

CAR T cells have been engineered to target many different antigens to treat various cancers

Hematologic malignancies[1]

Antigen	Cancer
BCMA	MM
CD123	AML, leukemia, lymphoma
CD138	MM
CD16V	DLBCL, MCL, PMBCL, FL
CD19	CLL, NHL, ALL, DLBCL, PMBCL, MCL, DLBCL transf. FL, lymphoma, FL, PLL, DMBCL, leukemia, SLL, BAL, HL, MLBCL, MM
CD19/CD20	DLBCL
CD19/CD22	Leukemia, lymphoma
CD20	ALL, CLL, PLL, DLBCL, FL, MCL, leukemia, Lymphoma, SLL, MZL, NHL
CD22	FL, ALL, NHL, DLBCL, MCL, leukemia, lymphoma
CD30	NHL, HL, lymphoma, CD30+ cancer
CD33	AML
CD38[2]	B cell malignancies
CD70	CD70+ cancer
CD123[2]	B cell malignancies
Ig k	CLL, NHL, MM
IL-1RAP	CLL
Lewis Y	MM, AML, MDS
NKG2D ligand	AML, MDS, MM
ROR1	CLL, SLL, MCL, ALL

Solid malignancies[1]

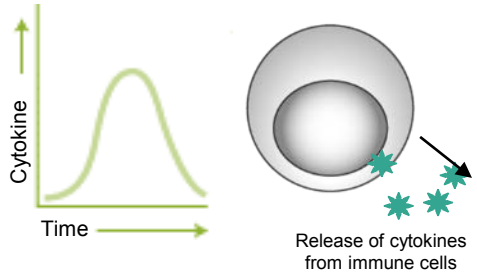
Antigen	Cancer
CAIX	Renal cell carcinoma
CEA	Liver metastases, liver, adenocarcinoma, gastric, colorectal, breast
C-MET	Breast
EGFR	EGFR+ solid tumors, GBM, glioma
EGFRvIII	Glioma, GBM, glioblastoma
EpCam	Liver, stomach, breast
EphA2	Malignant glioma
ErbB2/Her2	HER2+ malignancy, sarcoma, GBM, head and neck, breast, glioblastoma,
FAP	Metastatic mesothelioma
FR-a	Ovarian
GD2	Neuroblastoma, sarcomas
GPC3	Hepatocellular carcinoma, LSCC, GPC3+ solid tumor
IL-13Ra2	Malignant glioma, brain and CNS
L1-CAM	Neuroblastoma
Mesothelin	MPM, MPDAC, malignant pleural disease, pancreatic, breast, mesothelin+ tumors
MUC1	Hepatocellular carcinoma, NSCLC, TNBC, PC, malignant glioma, CC, GC
MUC16ecto	Ovarian
PD-L1	GBM
PSCA	Pancreatic
PSMA	Prostate
ROR1	NSCLC, breast cancer (TNBC)
VEGFR-2	various

Expanded abbreviations in notes section.

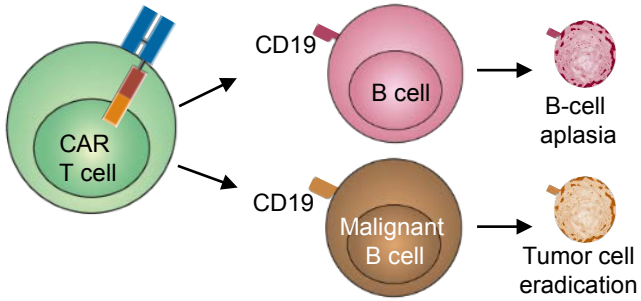
1. Hartmann et al. EMBO Mol Med 2017;9:1183–97. 2. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT03125577. Accessed April 2018.

CAR T cells: selected adverse events

Reported/potential toxicities following the use of CAR T cells[1]



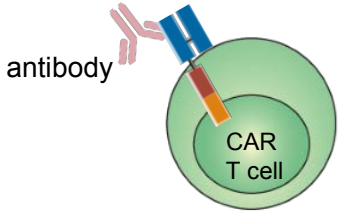
To date, the most prevalent adverse effect following infusion of CAR T cells is the onset of immune activation, known as CRS[1] (5.6–90% in clinical trials)[2]



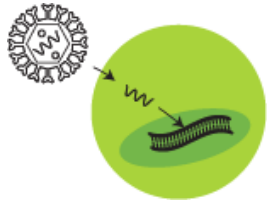
The severity of reported events for 'on-target, off-tumor' toxicity has ranged from manageable lineage depletion (B-cell aplasia) to severe toxicity (death), depending on the target[1]

The development of neurologic toxicities, including confusion, delirium, expressive aphasia, obtundation, myoclonus, and seizure, has been reported in patients who received CD19-specific CAR T cells[1] (12–48% in clinical trials)[2]

Several dermatologic complications have also been described, including secondary cutaneous malignancies[3]



Both cellular and humoral rejection of CAR T cells have been demonstrated due to the immunogenicity of foreign protein. Host reaction can manifest as anaphylaxis or allergy[1]



The risk of insertional oncogenesis following gene transfer into T cells is seemingly low; however, investigators must remain vigilant and adhere to strict monitoring[1]

CAR, chimeric antigen receptor; CD, cluster of differentiation; CRS, cytokine-release syndrome.

1. Bonifant et al. Mol Ther Oncolytics 2016;3:16011. 2. Kerre. Belgian J Hematol 2017;8:94–101. 3. Rubin et al. J Am Acad Dermatol 2016;75:1054–7.

Principles of irAE management: cooperation between all players

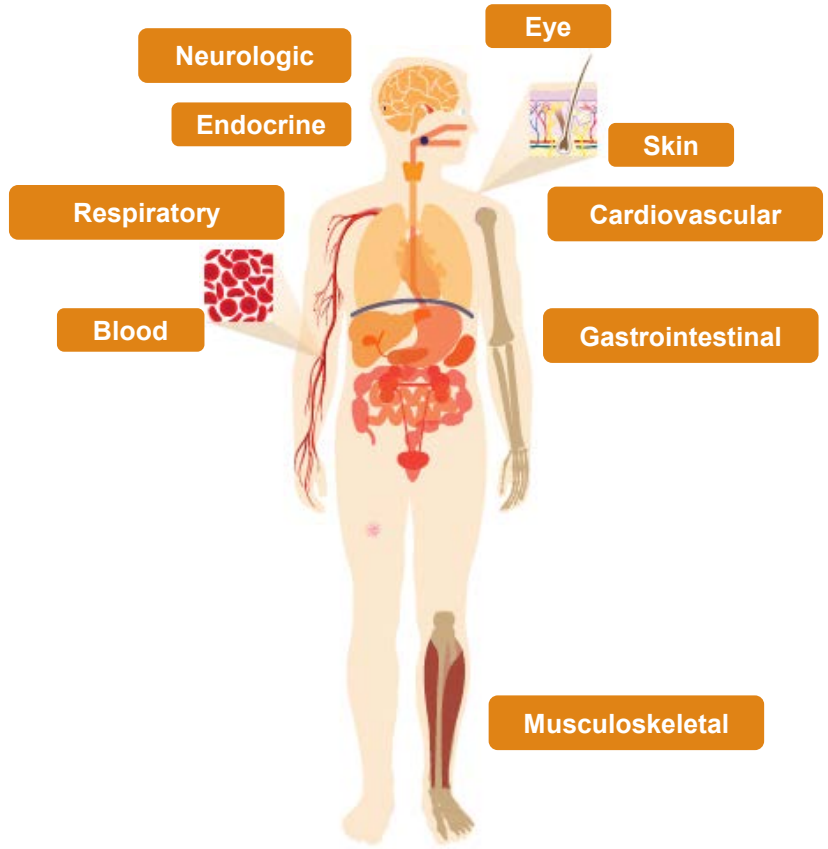
The type, onset and severity of immunotherapy-related adverse events varies. Healthcare providers are advised to remain vigilant for any symptoms at all times and refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Communication between patients, healthcare providers and oncologists is vital to successful irAE management[1,2]

Oncologist	Patient	Healthcare provider e.g. GP
Know the immune-toxicity spectrum	Be informed about possible toxicities	Be informed about possible toxicities and their onset

All individuals, patients in particular, should be aware that the onset of toxicities is usually within 3 months of starting treatment[2]

Nearly all organ systems can be affected[1,3]

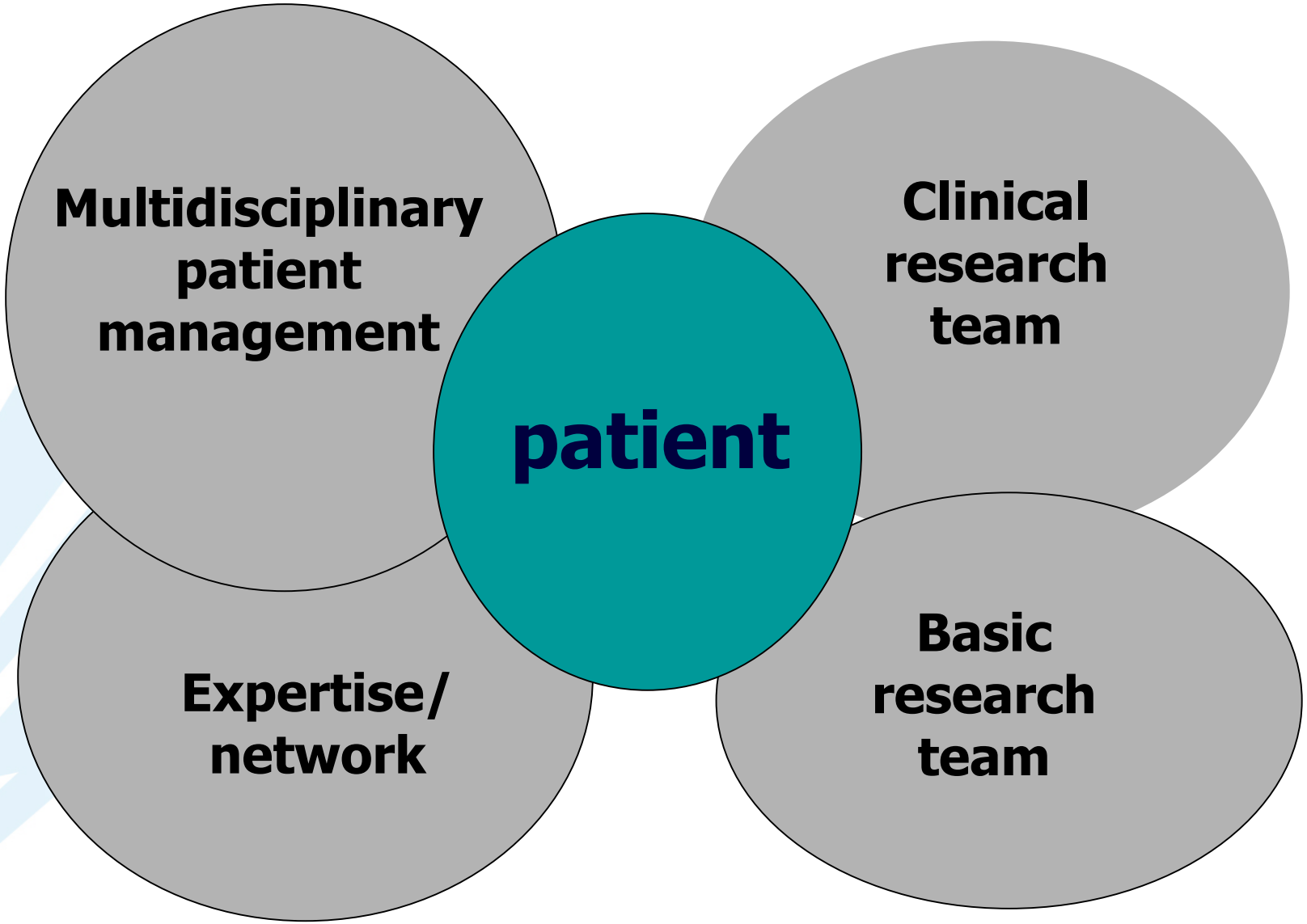


Most irAEs are mild in intensity but ~10% of patients develop grade 3–4 irAEs

GP, general practitioner; irAE, immune-related adverse event.

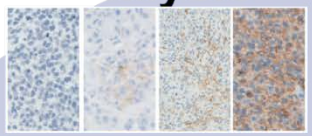
1. Champiat et al. Ann Oncol 2016;27:559–74. 2. Haanen et al. Ann Oncol. 2017;28:iv119–iv142. 3. Postow et al. NEJM 2018;378:1586–8.

Collaboration for optimal patient management

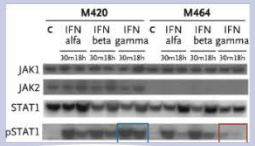


NEW CHALLENGES IO approach of CA patients

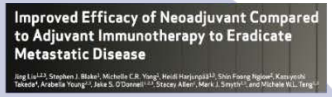
Biomarker Analysis



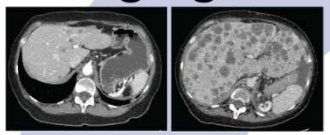
Understanding Resistance



Neoadjuvant treatment

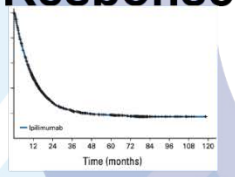


Imaging Patterns



Immunotoxicity management

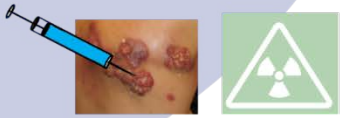
Duration of Response



Clinical Trial Organisation

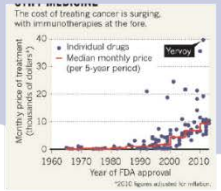
Education

Local Therapy



Epigenetics

Financial Toxicity



Microbiome

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