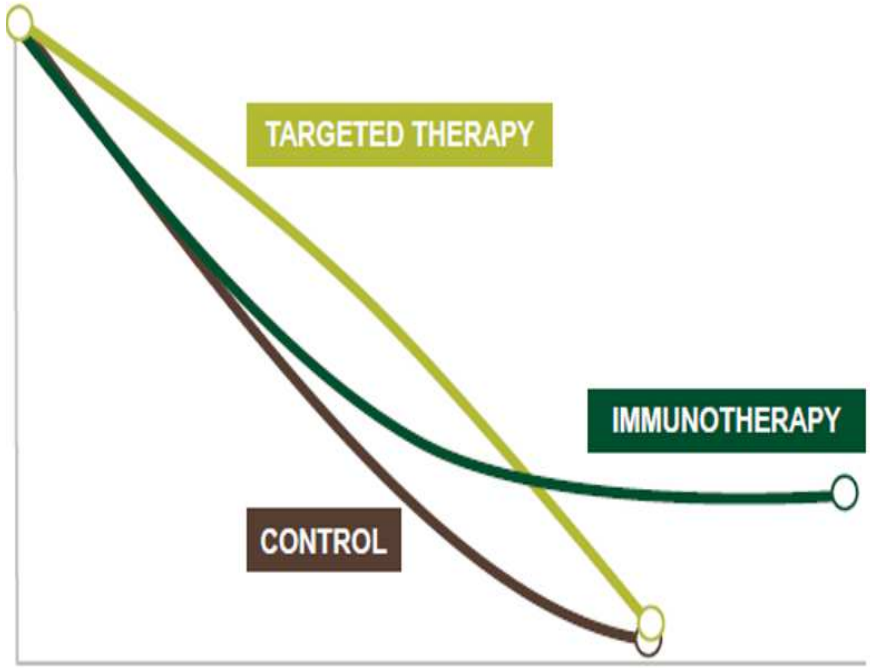
Immunotherapy in gastrointestinal cancer

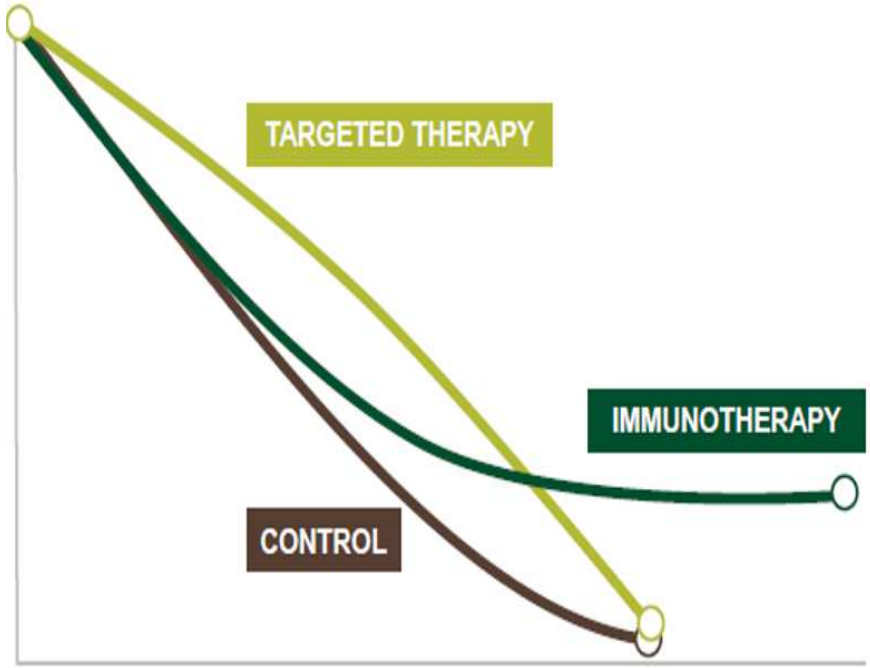
Checkpoint inhibitors under evaluation



Markus Moehler
University Medical Center Mainz, Germany

Immunotherapy in gastrointestinal cancer
will improve patient outcome

Checkpoint inhibitors under evaluation
Summary of recent data from ASCO and ASCO



Short overview

Colon Cancer

Gastric Cancer

HCC

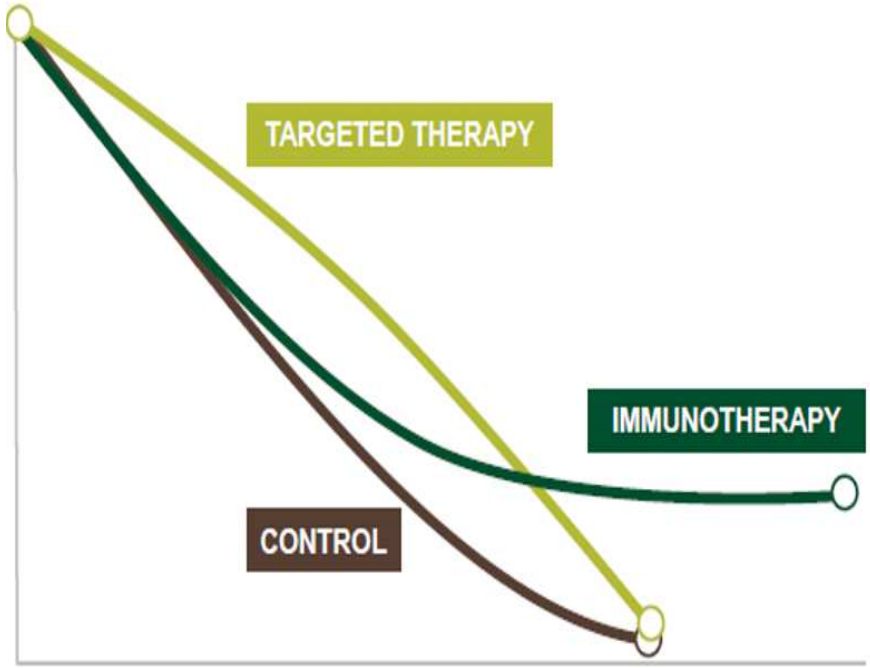
Future Perspectives

Immunotherapy in gastrointestinal cancer

will improve patient outcome

Checkpoint inhibitors under evaluation

Summary of recent data from ASCO and ASCO

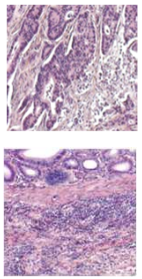


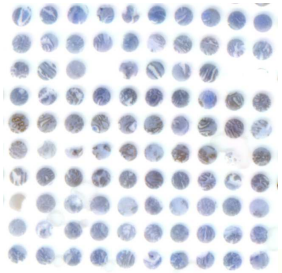
3 recent approvals by FDA and Japan

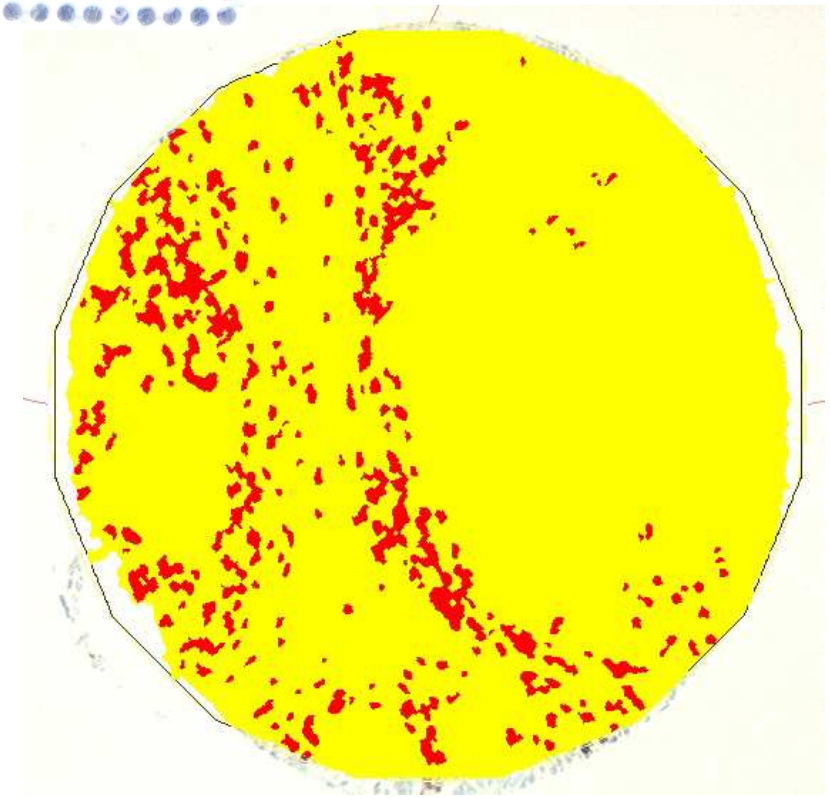
Distribution of immune cells in Colon Cancer tumors

center versus invasion margin

Tissue MicroArrays (TMA) : 415 colorectal cancer patients







Galon J et al. ***Science*** 313(5795):1960-4, 2006

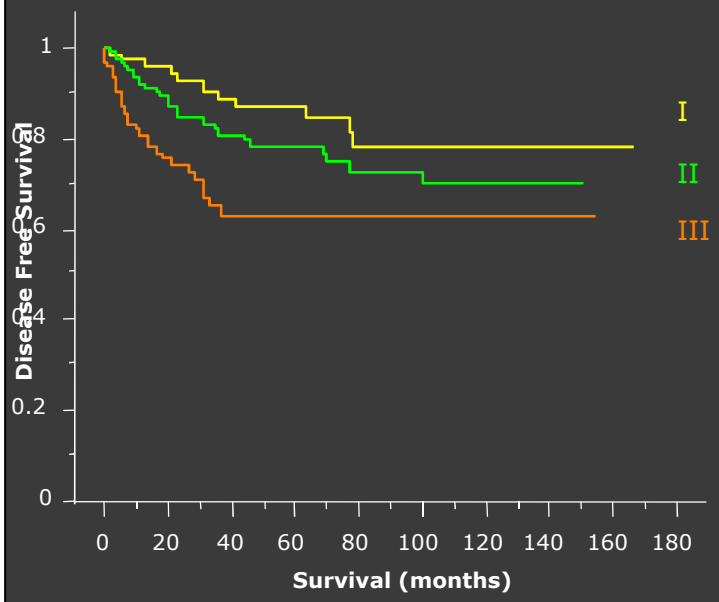
Distribution of immune cells in Colon Cancer tumors

center versus invasion margin

Tumor Histopathologic Findings

UICC-TNM Colorectal Cancer

Current prognosis classification

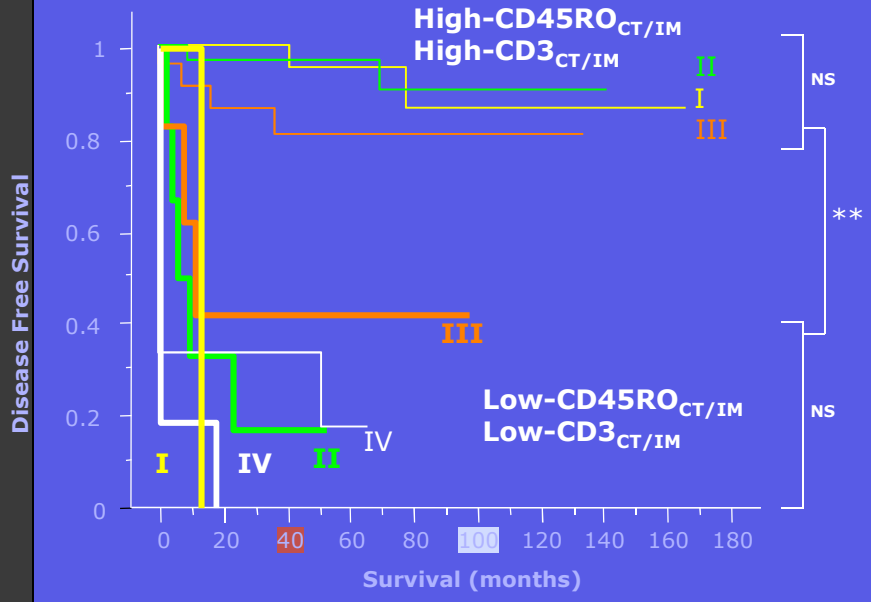


Immune cells analysis

$CD3_{CT}/CD3_{IM}$ evaluation

plus

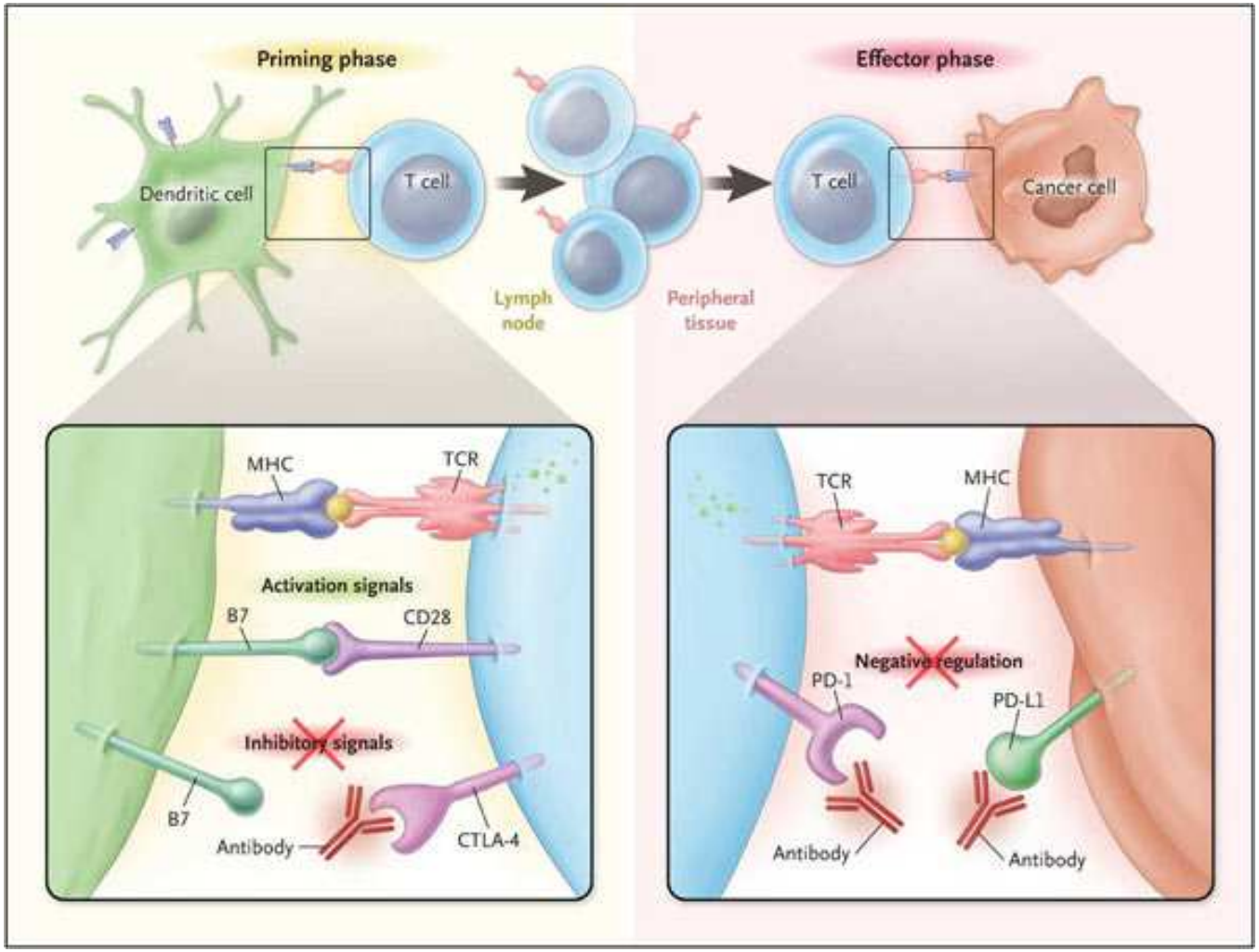
$CD45RO_{CT}/CD45RO_{IM}$ evaluation



Adaptive immune reaction in tumor predicts clinical outcome

Galon J et al. ***Science*** 313(5795):1960-4, 2006

Tumor-mediated immune evasion



Check-Point-Inhibitors

Ipilimumab
Tremelimumab

Nivolumab, Atezolizumab
Pembrolizumab, Avelumab

New England Journal of Medicine ©2012

Immunotherapy in Colon Cancer

PD-1 Blockade in Tumors with Mismatch Repair Deficiency

Dung Le, Jennifer Uram, Hao Wang, Bjarne Bartlett, Holly Kemberling, Aleksandra Eyring, Andrew Skora, Brandon Luber, Nilofer Azad, Daniel Laheru, Barbara Biedrzycki, Ross Donehower, Atif Zaheer, George Fisher, Todd Crocenzi, Steven Duffy, James Lee, Richard Goldberg, Albert de la Chapelle, Minori Koshiji, Feriyl Bhaijee, Thomas Huebner, Ralph Hruban, Laura Wood, Nathan Cuka, Drew Pardoll, Nickolas Papadopoulas, Kenneth Kinzler, Shibin Zhou, Toby Cornish, Janis Taube, James Eshleman, Robert Anders, Bert Vogelstein and Luis Diaz Jr.

The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
Providence Cancer Center, Portland, OR
Stanford University School of Medicine, Stanford, CA
Bons Secours Cancer Institute, Richmond, VA
University of Pittsburgh, Pittsburgh, PA

N Engl J Med 2015;372:2509-20

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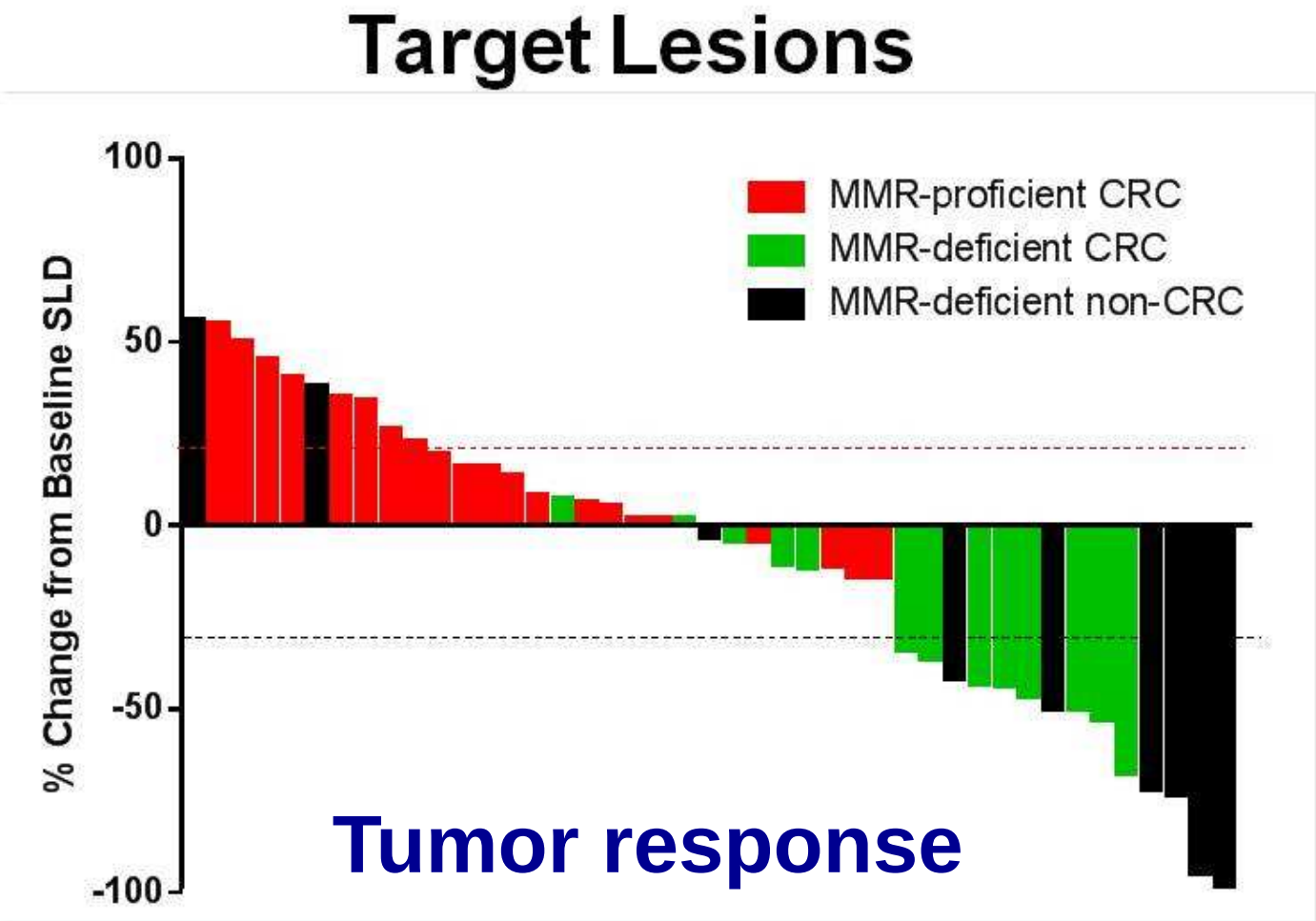
PRESENTED AT: ASCO Annual '15 Meeting

Presented By Dung Le at 2015 ASCO Annual Meeting

Immunotherapy in Colon Cancer



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Presented By Dung Le at 2015 ASCO Annual Meeting

Immunotherapy in Colon Cancer

	MMR-deficient CRC	MMR-proficient CRC	MMR-deficient non-CRC
N	13	25	10
Objective Response Rate	62%	0%	60%
Disease Control Rate	92%	16%	70%

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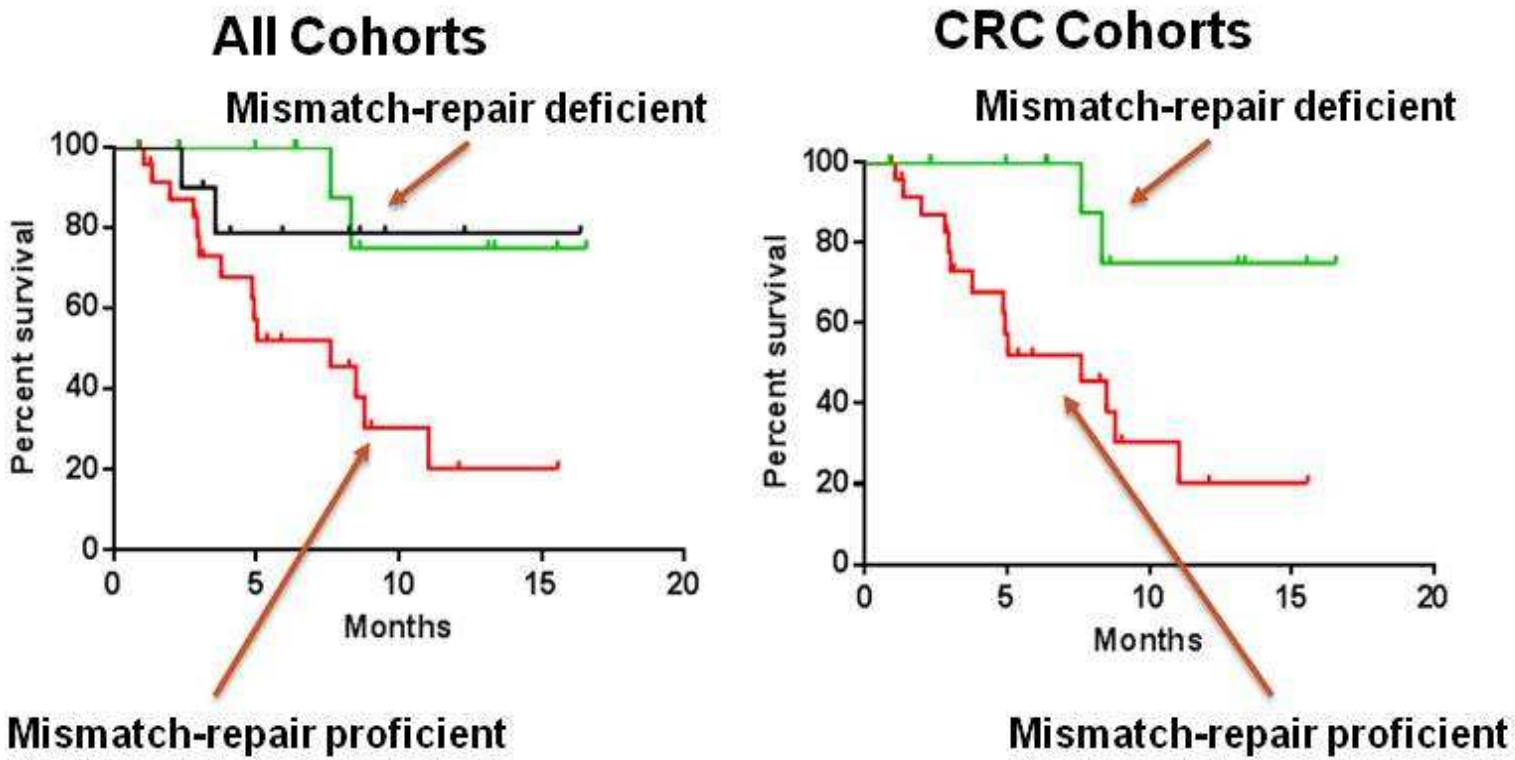
Presented By Dung Le at 2015 ASCO Annual Meeting

Immunotherapy in Colon Cancer

Pembrolizumab is highly effective in metastatic MSI Colon Cancer



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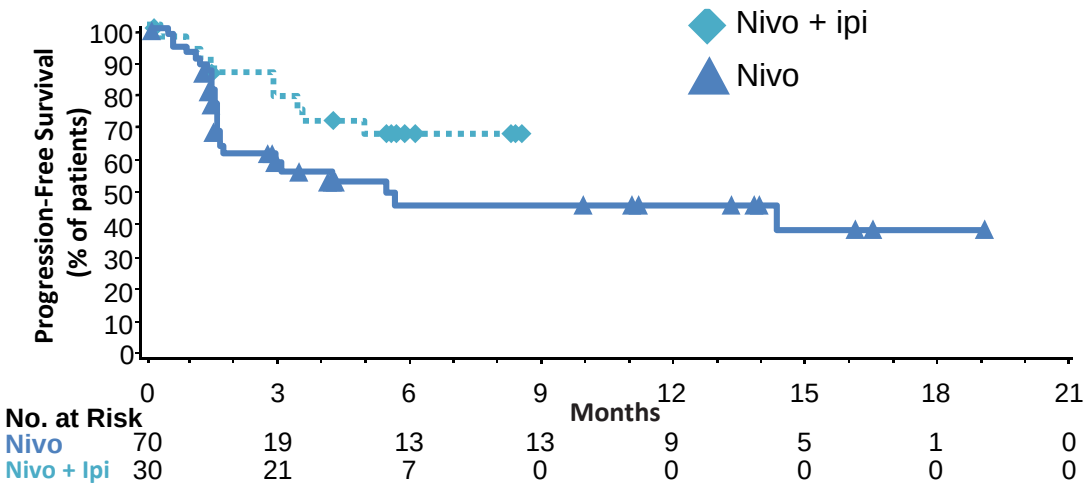
PRESENTED AT: ASCO Annual '15 Meeting

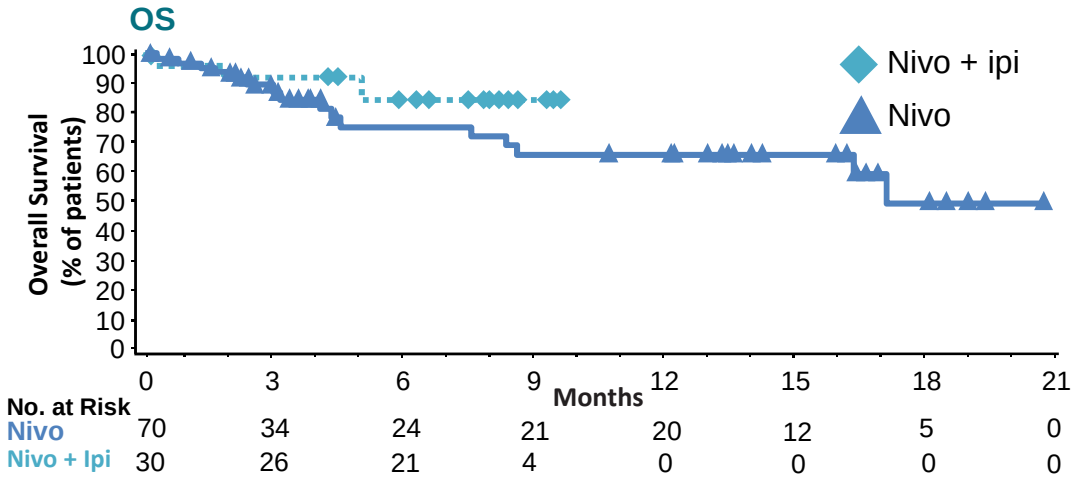
Presented By Dung Le at 2015 ASCO Annual Meeting

Immunotherapy in Colon Cancer

Nivolumab +/- Ipilimumab is highly effective in metastatic MSI Colon Cancer



	N3 (n=70)	N3 + I1 (n=30)
PFS rate, % (95% CI)		
6 mo	45.9 (29.8, 60.7)	66.6 (45.5, 81.1)
9 mo	45.9 (29.8, 60.7)	NE
12 mo	45.9 (29.8, 60.7)	NE
mPFS, mo (95% CI)	5.3 (1.5, NE)	NE (3.4, NE)

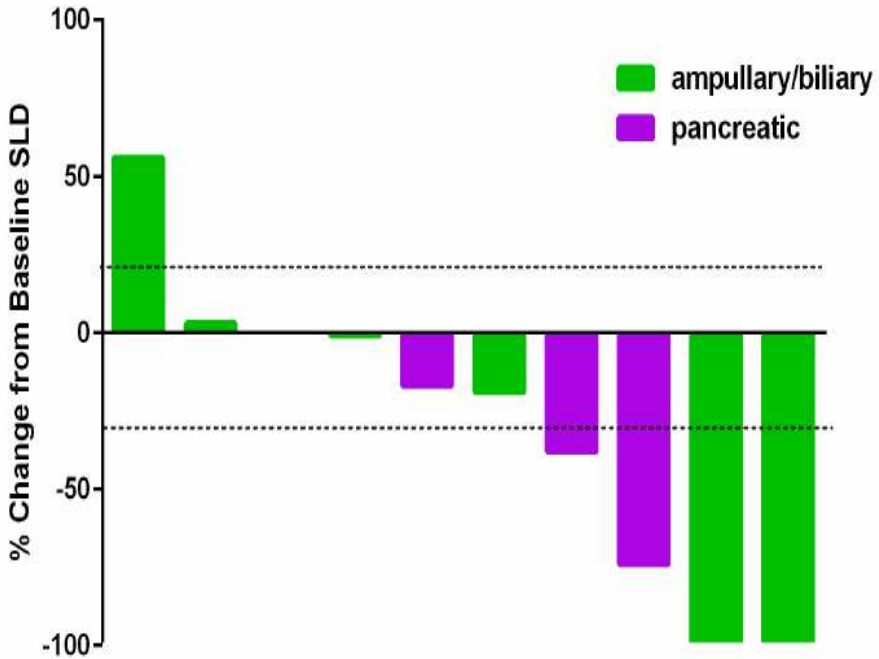


	N3 (n=70)	N3 + I1 (n=30)
OS rate, % (95% CI)		
6 mo	75.0 (58.5, 85.7)	85.1 (65.0, 94.2)
9 mo	65.6 (48.0, 78.6)	85.1 (65.0, 94.2)
12 mo	65.6 (48.0, 78.6)	NE
mOS, mo (95% CI)	17.1 (8.6, NE)	NE (NE, NE)

Overman M et al. Oral presentation at ASCO 2016. 3501.

Immunotherapy in Hepatobiliary Cancer

Pembrolizumab is highly effective in metastatic MSI Pancreatic and Biliary Tract Cancer



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Pembrolizumab for MSI-H Tumors

FDA Approves Merck's KEYTRUDA® (pembrolizumab) for Adult and Pediatric Patients with Unresectable or Metastatic, Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient Cancer

May 23, 2017

KEYTRUDA Now Approved for Patients with MSI-H or Mismatch Repair Deficient Solid Tumors That Have Progressed Following Prior Treatment and Who Have No Satisfactory Alternative Treatment Options, Which Includes MSI-H or Mismatch Repair Deficient Colorectal Cancer That Has Progressed Following Treatment with a Fluoropyrimidine, Oxaliplatin, and Irinotecan

KENILWORTH, N.J.--(BUSINESS WIRE)-- Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) has approved a new indication for KEYTRUDA® (pembrolizumab), the company's anti-PD-1 therapy. KEYTRUDA is now indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair

- deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
- colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Pembrolizumab for MSI-H Tumors

Activation and priming of T cells
- mAb against PD-1, PD-L1, CTLA-4
- IL-2
- IL-12
- Agonists for CD137, OX40, CD27

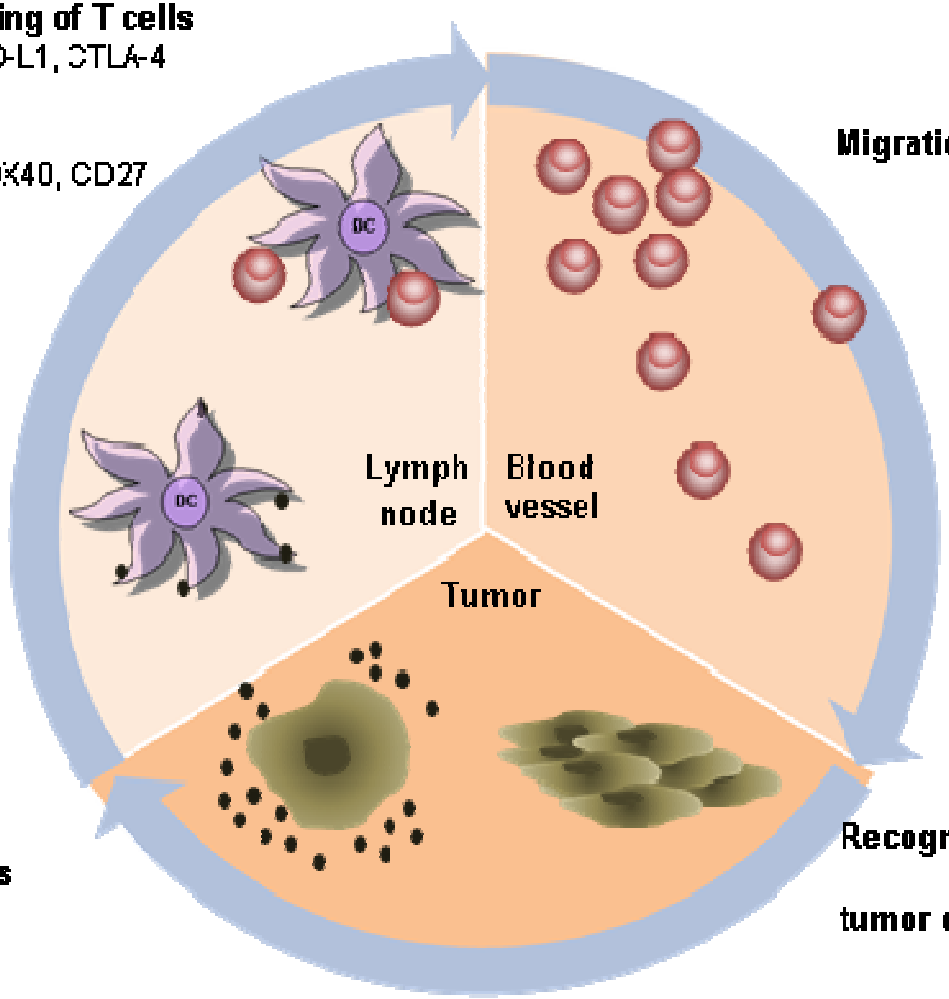
Presentation of tumor associated antigens

- Vaccines
- IFN-α
- GM-CSF

MSI-H

Release of tumor associated antigens

- Chemotherapy
- Radiotherapy



Migration of activated T cells

Immigration of T cells into the tumor

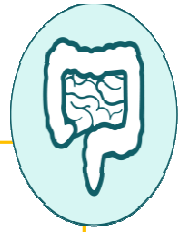
Recognition and killing of tumor cells

Moehler Eur J Cancer 2016

Biomarkers for Immunotherapy

New Cancer Genome Atlas (TCGA)

Colorectal cancer subtypes[1]



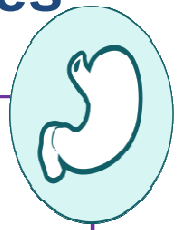
MSI Immune (CMS1; 14%)
- MSI, CIMP high, hypermethylation
- *BRAF* mutations
- Immune infiltration/activation
- Worse survival after relapse

Canonical (CMS2; 37%)
- SCNA high
- WNT and MYC activation

Metabolic (CMS3; 13%)
- Mixed MSI status, SCNA low, CIMP low
- *KRAS* mutations
- Metabolic deregulation

Mesenchymal (CMS4; 23%)
- SCNA high
- Stromal infiltration, TGF-β activation, angiogenesis
- Worse relapse-free and overall survival

Gastric cancer subtypes[2]



Chromosomal Instability (~50%)
- Intestinal histology
- *TP53* mutation
- RTK-RAS activation

Epstein-Barr Virus (~9%)
- *PIK3CA* mutation
- PD-L1/2 overexpression
- EBV-CIMP
- *CDKN2A* silencing
- Immune cell signaling

Genomically Stable (~20%)
- Diffuse histology
- *CDH1, RHOA* mutations
- CLDN18-ARHGAP fusion
- Cells adhesion

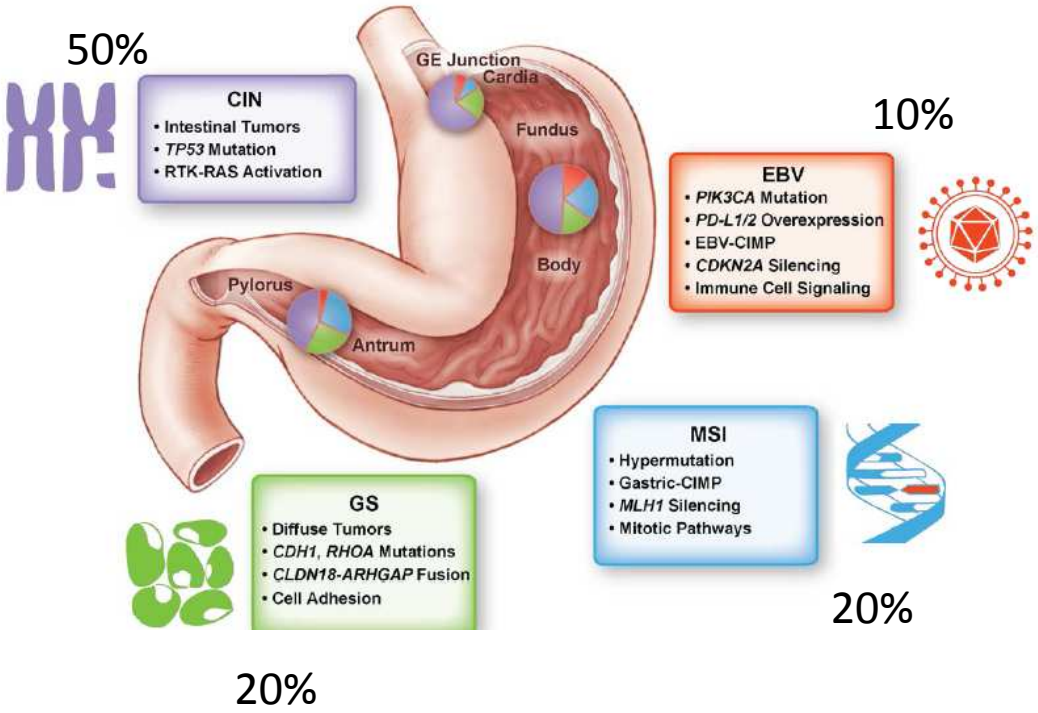
MSI (~22%)
- Hypermutation
- Gastric-CIMP
- *MLH1* silencing
- Mitotic pathways

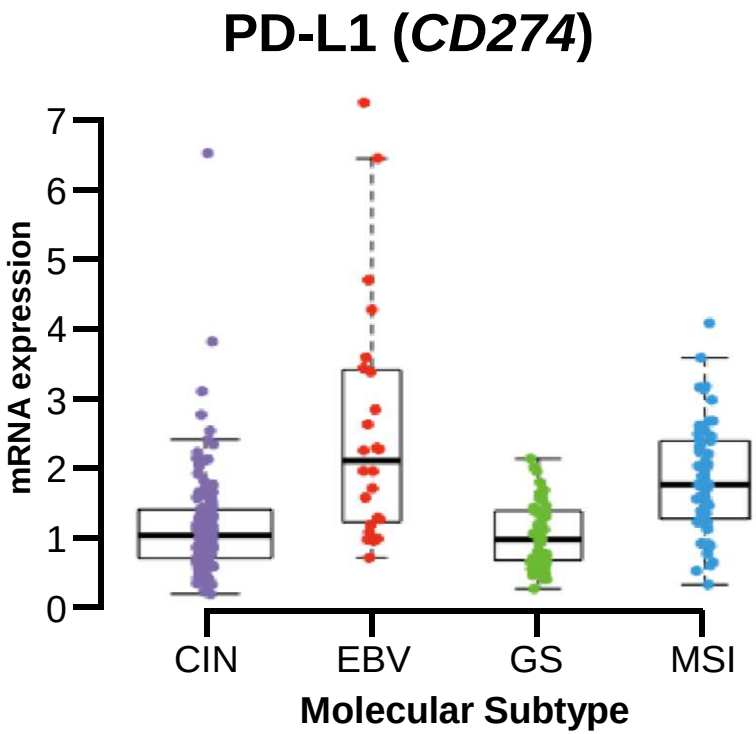
BRAF, B-Raf proto-oncogene; CIMP, CpG island methylator phenotype; CMS, consensus molecular subtypes; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; MSI, microsatellite instability; MYC, avian myelocytomatosis vial oncogene homolog; SCNA, somatic copy number alterations; TGF-β, transforming growth factor beta; WNT, wingless-related integration site.

1. Guinney J et al. *Nat Med.* 2015;21(11):1350-1356. 2. TCGARN. *Nature.* 2014;513(7515):202-209.

Biomarkers for Immunotherapy

Genetic subtypes, MSI, PD-L1

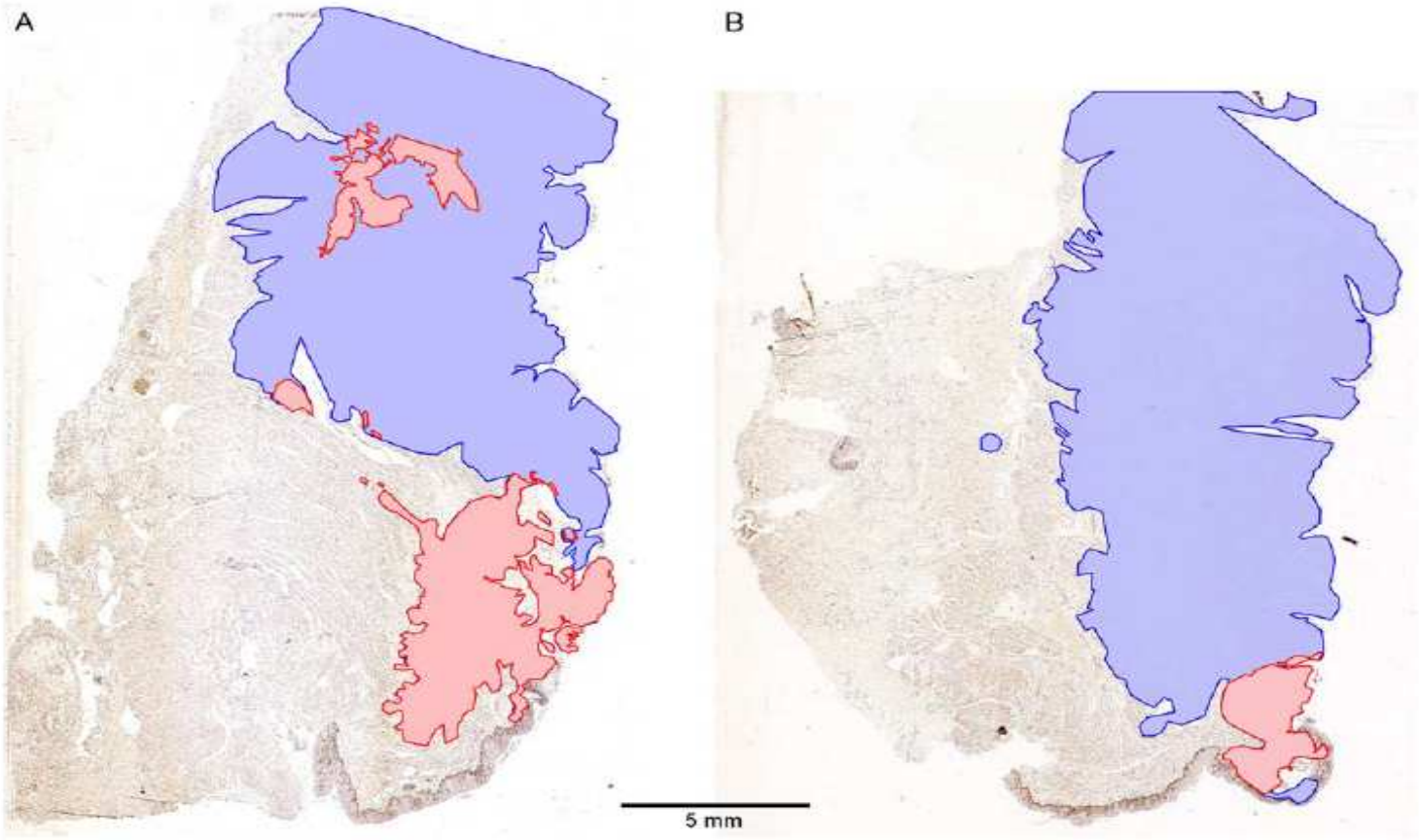




The Cancer Genome Atlas Research Network Nature 2014.

Biomarkers for Immunotherapy

Genetic subtypes, MSI, PD-L1



MSI in 37 studies: 0-44 % in Gastric Cancer

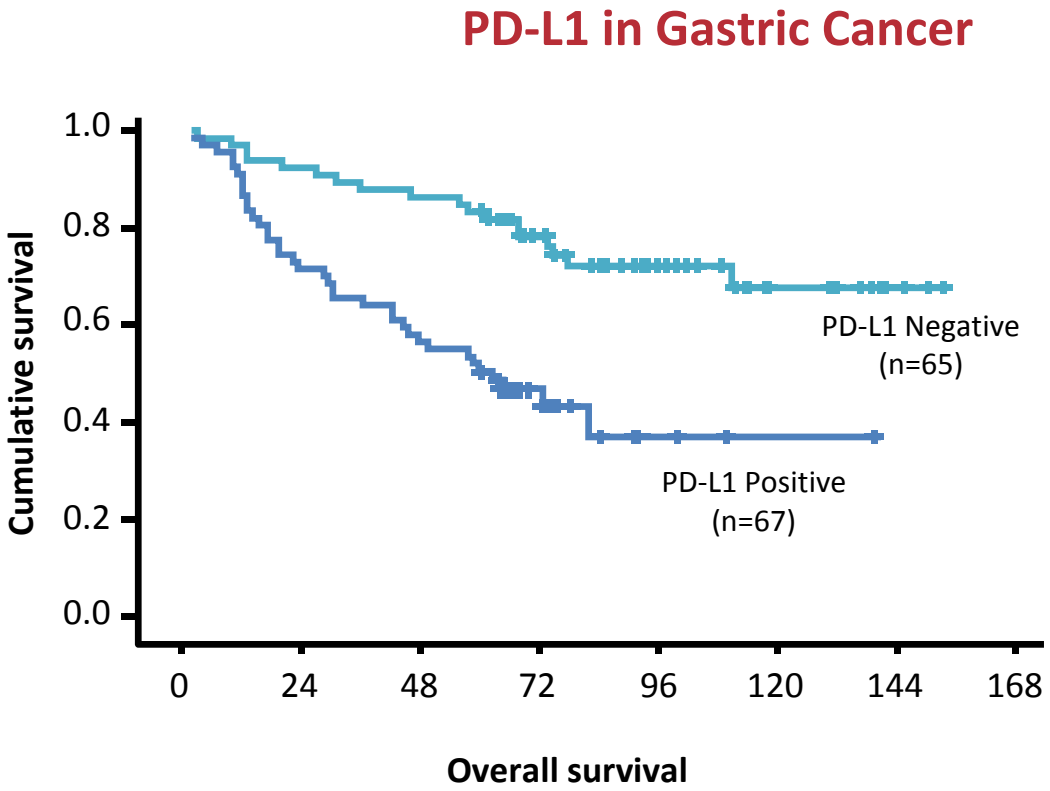
~5-11 % in white population

Quality-controlled diagnosis is important !

Mathiak, M. et al. Appl Immunohistochem Mol Morphol 2015

Biomarkers for Immunotherapy

Genetic subtypes, MSI, PD-L1

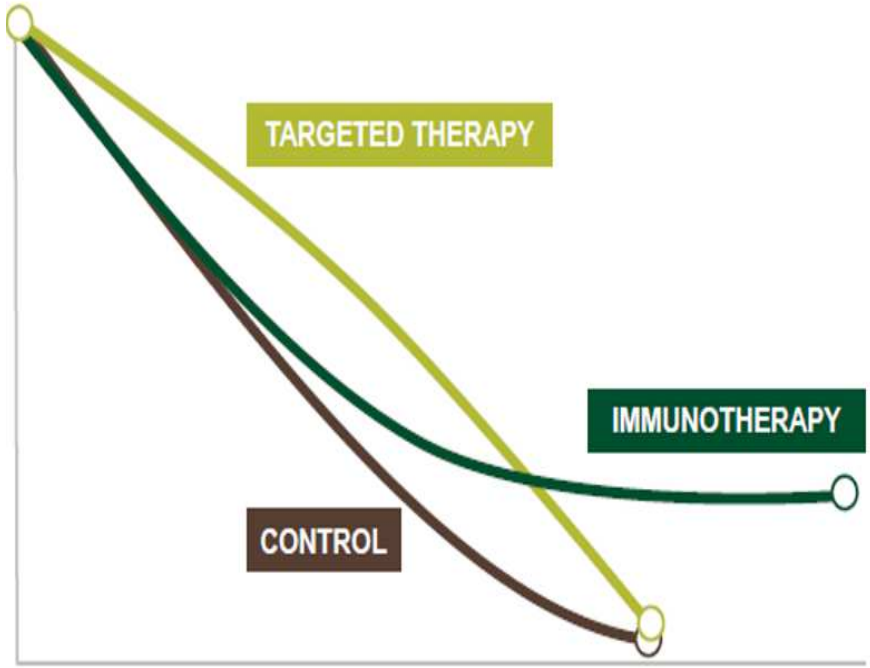


5Zhang L et al. *Int J Clin Exp Pathol*. 2015;8:11084–91.

Immunotherapy in gastrointestinal cancer

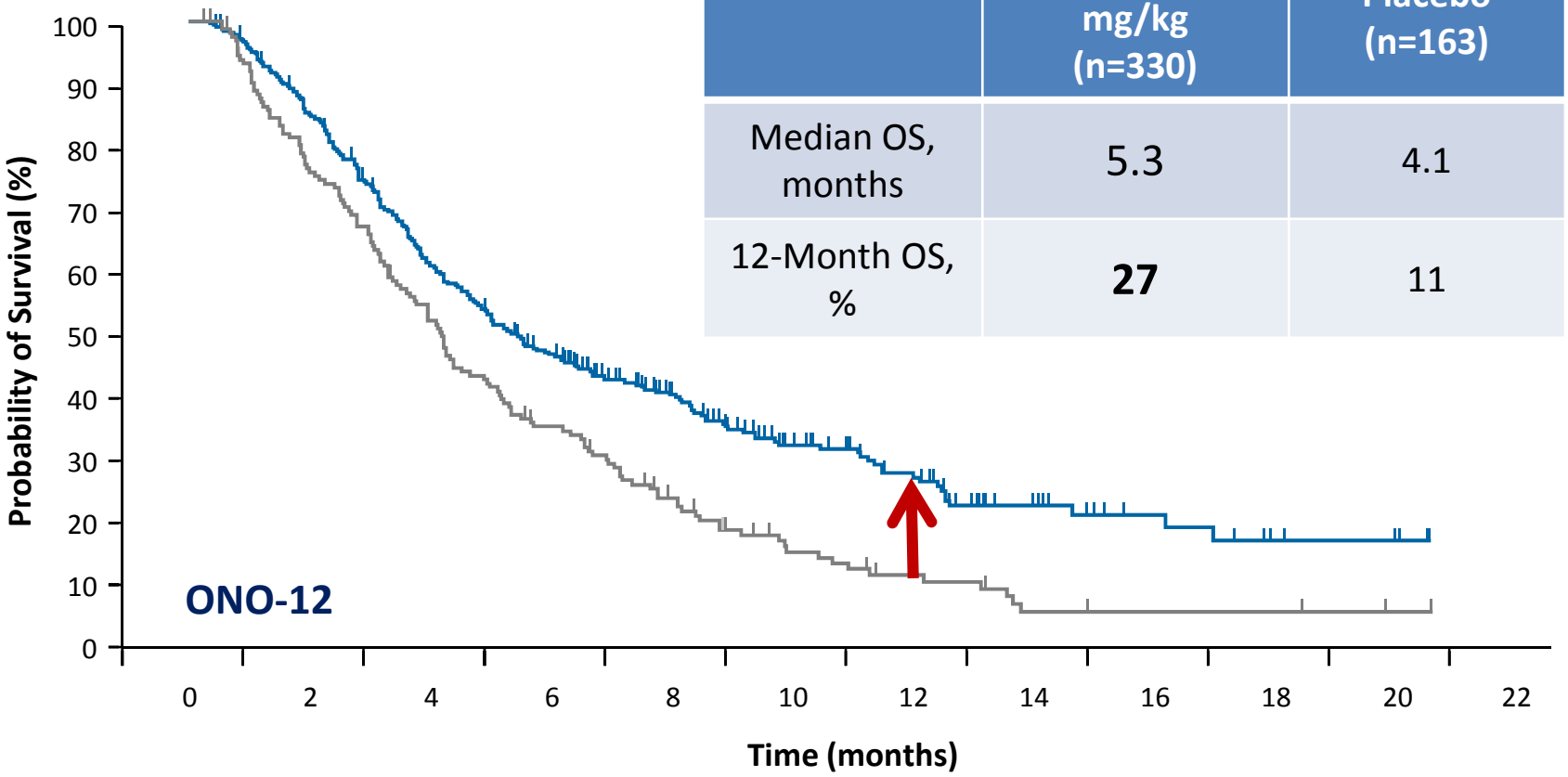
will improve patient outcome

Gastric Cancer



3L+ Nivolumab Phase in advanced GC

ATTRACTION-02/ONO-12 (Asia)



	Nivolumab 3 mg/kg (n=330)	Placebo (n=163)
Median OS, months	5.3	4.1
12-Month OS, %	**27**	11

Kang YK et al. Oral presentation at ASCO GI 2017. Abstract 2 (poster); NCT02267343.

3L+ Nivolumab Phase in advanced GC

ATTRACTION-02/ONO-12 (Asia)

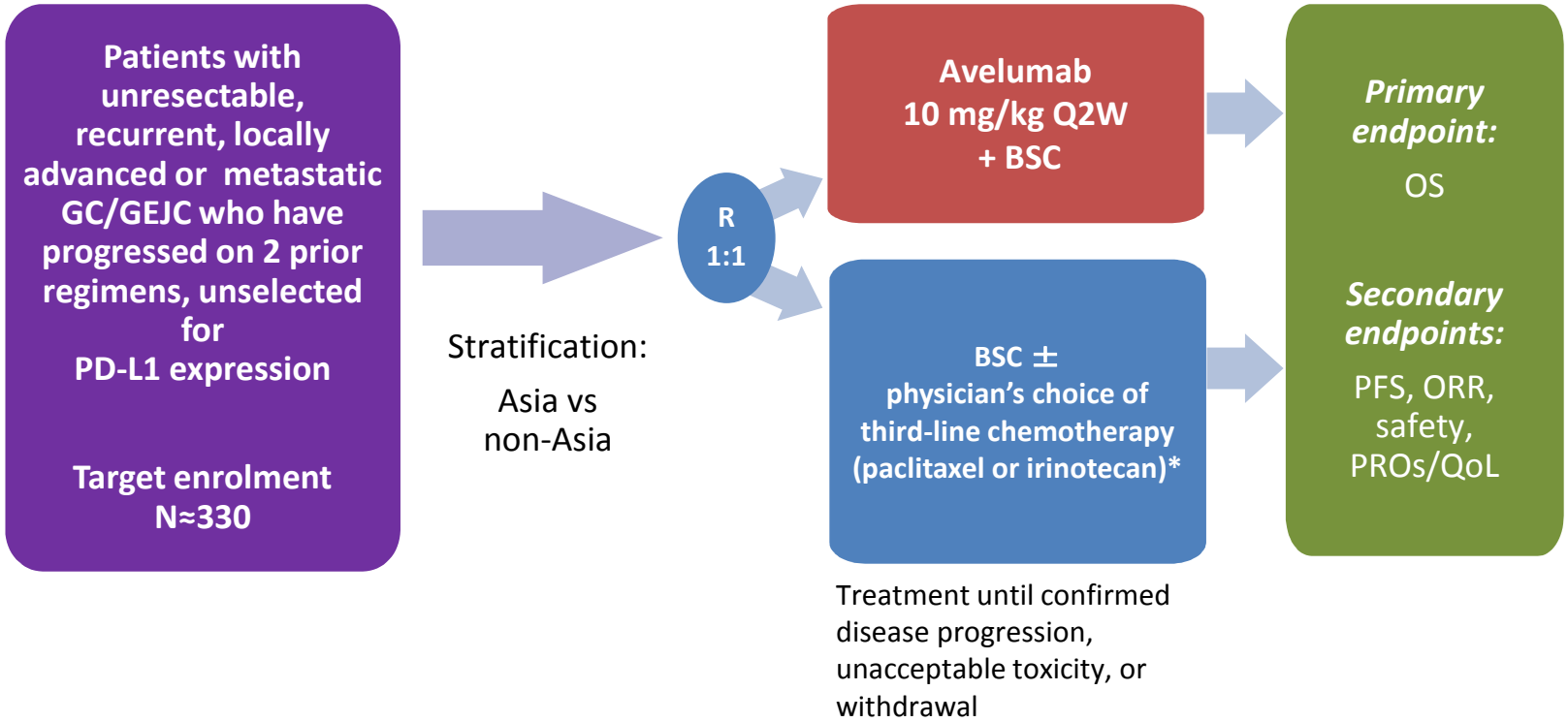
Bristol-Myers Reports Approval Of Nivolumab For Recurrent Gastric Cancer In Japan

September 22, 2017, 05:12:00 AM EDT

Bristol-Myers Squibb Company announced the Japanese Ministry of Health, Labor and Welfare has approved Opdivo (nivolumab) for the treatment of unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy. Opdivo has now been approved for six indications in Japan.

3L Avelumab in advanced GC/GEJC

JAVELIN Gastric 300: **global** Phase III trial[1,2]



JAVELIN Gastric 300

1. NCT02625623. Available at: www.clinicaltrials.gov (accessed September 2017);
2. Bang et al. ASCO 2016. Abstract TPS4135 (Poster).

Immuno-oncology important within *continuum of care* *….development from 3L to 1L*

Line of therapy	(Neo) adjuvant	First-line		Maintenance	Second-line
Regimens	Platinum + fluoropyrimidine doublet Or triplet (FLOT) ± RT[1,2]	**HER2-positive:** Trastuzumab + cisplatin + capecitabine / 5-FU[1,2]	**HER2-negative:** Platinum + 5-FU doublet or triplet based on patient PS[1,2]	Treatment for 6–8 cycles or until disease progression *Rechallenge with first-line treatment dependent on treatment interval[3]*	Irinotecan, docetaxel or paclitaxel[1,2] Ramucirumab ± paclitaxel[2] *Duration dependent on tolerability/QoL*

Potential role for checkpoint inhibitors as monotherapy or in combination with: Chemotherapy, targeted agents, other immunotherapies

1. Waddell T et al., Ann Oncol 2013; 2. NCCN Clinical Practice Guidelines in Oncology. Gastric Cancer. VI.2016; 3. Hershman et al. J Clin Oncol. 2014.

1L Pembrolizumab in GC

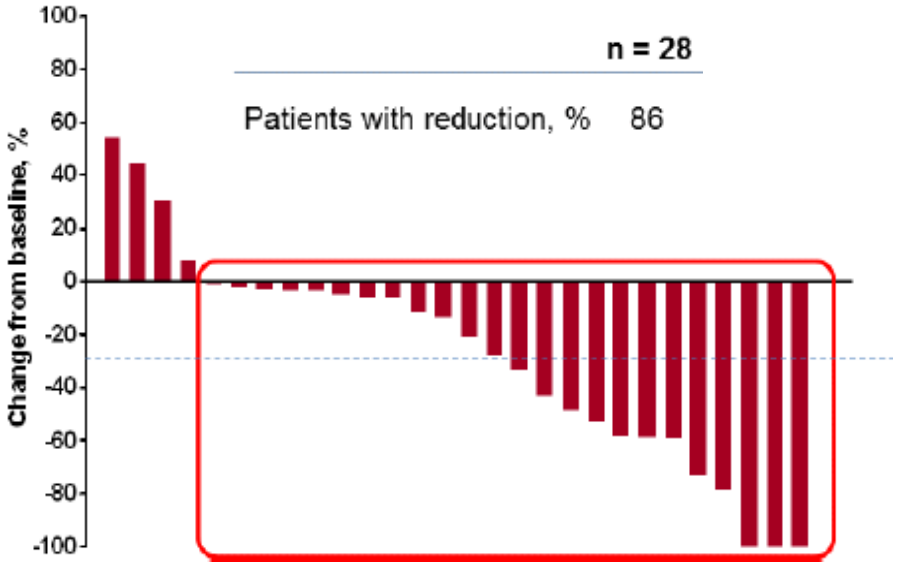
KEYNOTE-059 Cohort 3, PD-L1+

Just to give Checkpoint-Inhibitor alone is not enough

Responses

Response	All patients (N = 31)	
	%	95% CI
ORR (CR+PR)	26	12-45
CR	3	<1-17
PR	23	10-41
SD	29	14-48
PD	39	22-58
DCR[a]	36	19-55

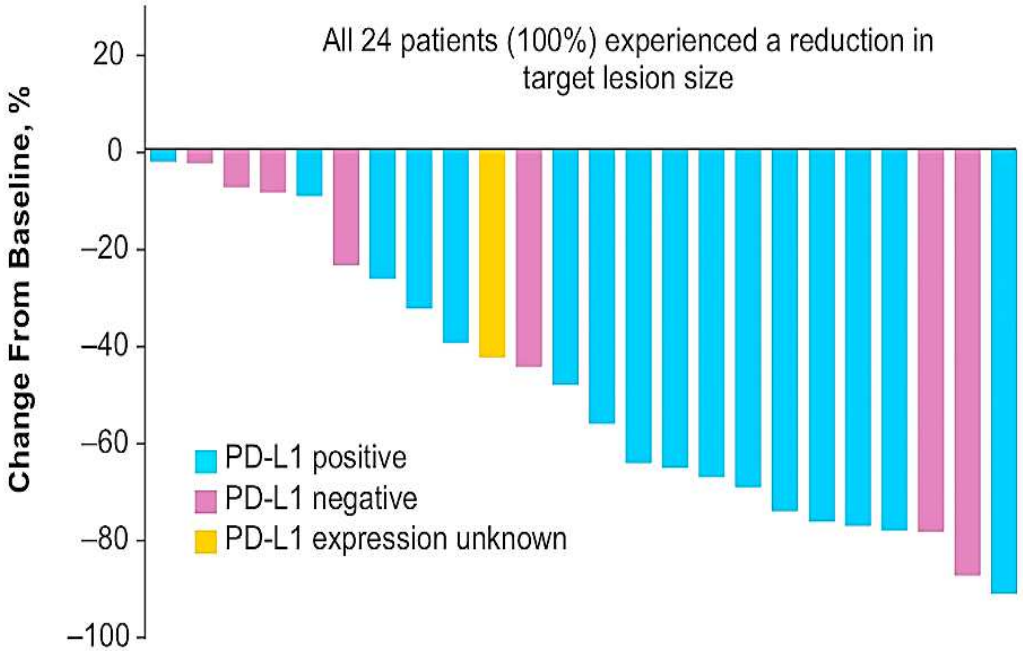
Reduction in tumour size



Catenacci et al. LBA-009. Ann Oncol 2017;28 (suppl 3):mdx302.008.

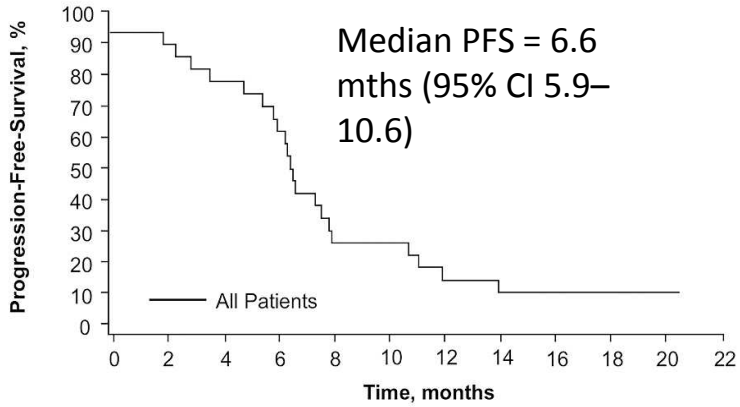
1L Pembrolizumab + Cisplatin + 5-FU for GC

KEYNOTE-059 Cohort 2

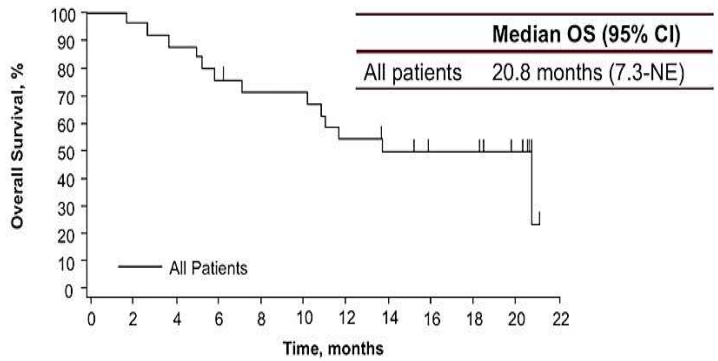


Maximum % change from baseline in tumour size*

Progression-free survival



Overall survival



Bang Y-J et al. ASCO 2017. Abstract 4012. (Poster).

Immunotherapy as Maintenance ?

Current paradigm

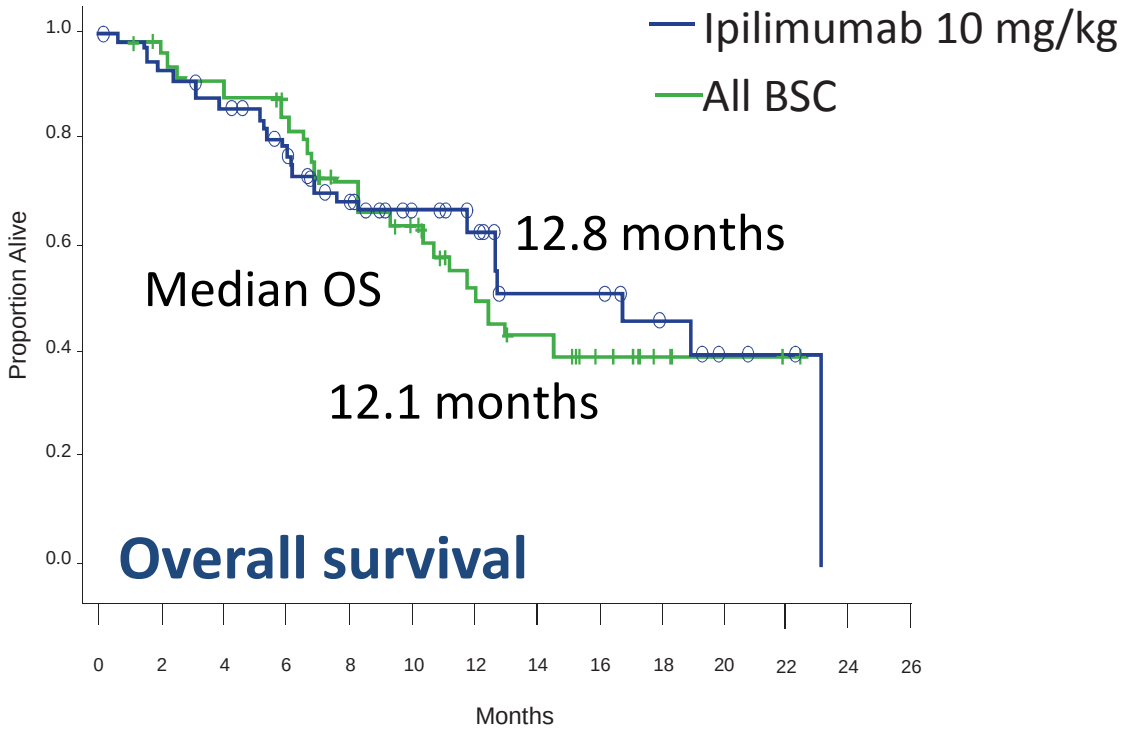
Paradigm established for Colon Cancer, but not yet in Gastric Cancer

1. Arnold D et al. ASCO 2014. Abstract 3503; 2. Hegewisch-Becker S et al. Lancet Oncol 2015;16:1355–69; 3. Simkens LH et al. Lancet 2015;16:e582–3.

Immunotherapy as Maintenance ?

Sequential Ipilimumab versus BSC after 1.line chemotherapy in patients with metastatic gastric cancer

World-wide randomized Ph II study to reduce toxicity, improve QOL and OS

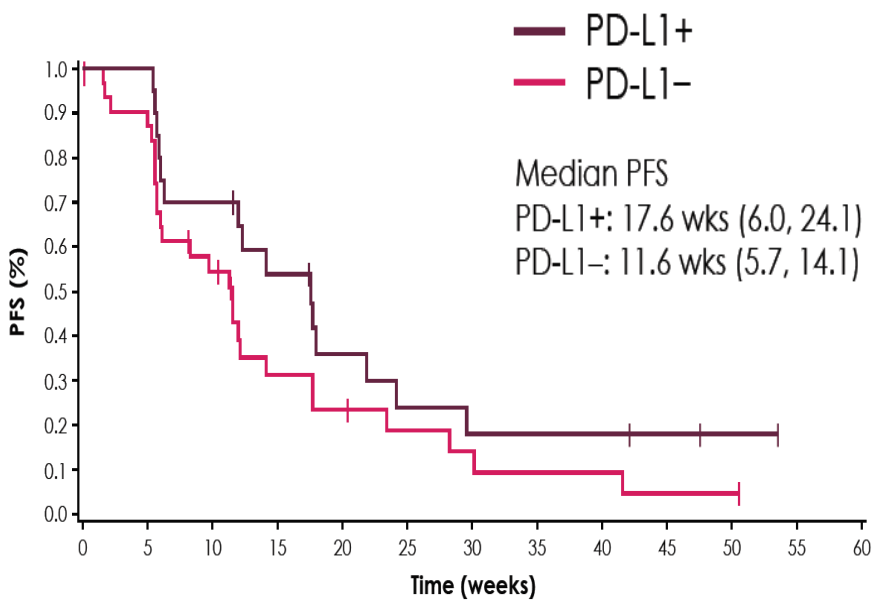


Moehler et al., ASCO 2016
Clin Cancer Res 2017 in press

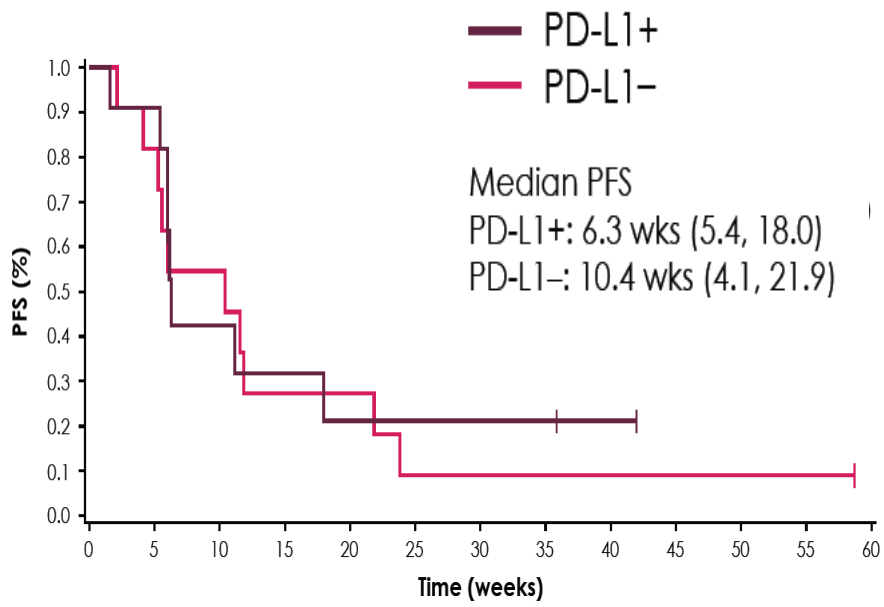
Immunotherapy as Maintenance ?

Avelumab in metastatic GC

JAVELIN Solid Tumor cohort



Maintenance subgroup



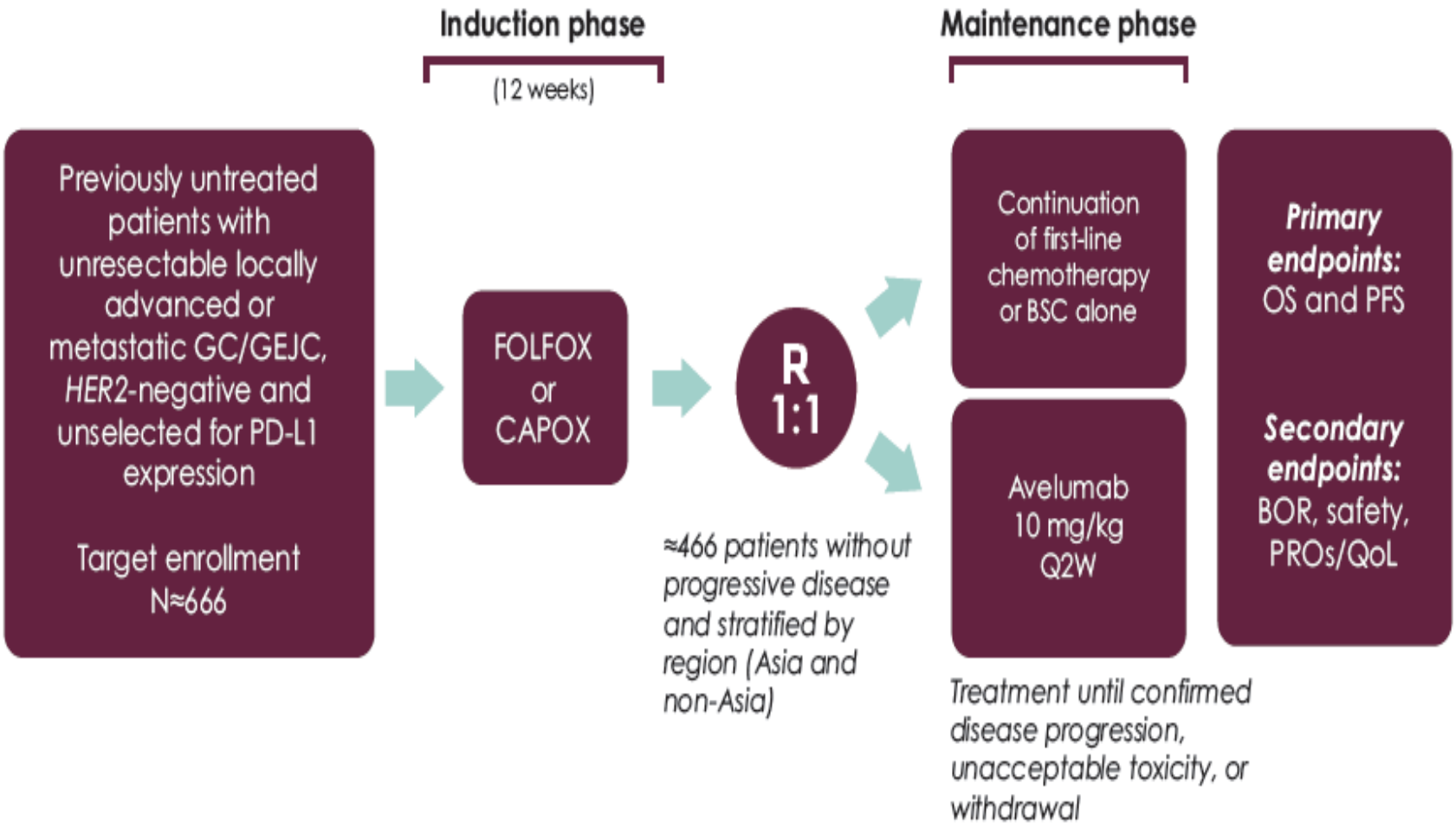
Second-line subgroup

*Based on a ≥1% threshold for tumour cell staining.
Chung H et al. ASCO 2016. Abstract 4009 (Poster).

Agent has not yet received EMA approval for treatment of indication listed

Immunotherapy as Maintenance ?

Avelumab first-line maintenance global phase III:

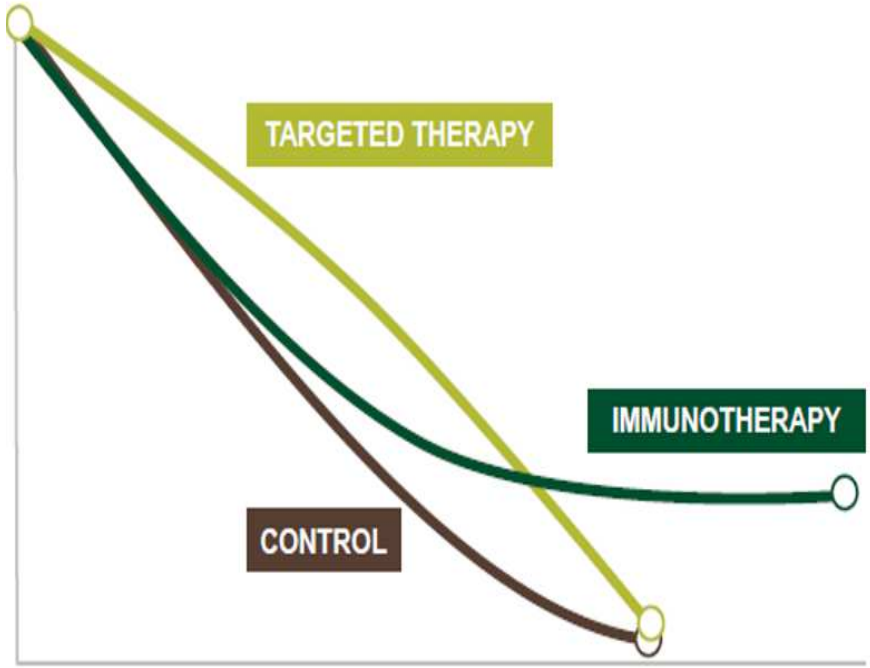


Taieb et al., Poster presentation at ESMO GI 2016. Abstract No. P-281

Immunotherapy in gastrointestinal cancer

will improve patient outcome

HCC



Checkmate 040: Nivolumab in advanced HCC

Bristol-Myers Squibb's Opdivo® (Nivolumab) Receives **FDA Approval for Treatment of Hepatocellular Carcinoma Patients** Previously Treated with Sorafenib

September 22, 2017, 06:10:00 PM EDT

Opdivo is the first and only Immuno-Oncology agent to receive this FDA approval; this **accelerated** approval is based on tumor response rate and durability of response in these patients

The CheckMate -040 pivotal study evaluated Opdivo in patients with and without active Hepatitis B or C infection, and across PD-L1 expression levels [1,2]

- HCC is the most common type of liver cancer and incidence rates are increasing[3,]

Checkmate 040: Nivolumab in advanced HCC

- **Disease control rates (BICR) were 54% in sorafenib-naive patients and 55% in all sorafenib-experienced patients**
- **Long-term survival across sorafenib-naive and - experienced cohorts**

Patients, n (%)	Sorafenib Naive ESC + EXP (n=80)		Sorafenib Experienced ESC (n=37)		Sorafenib Experienced EXP (n=145)	
	BICR	INV	BICR	INV	BICR	INV
Objective response using RECIST v1.1	**16 (20)**	**18 (23)**	**7 (19)**	**6 (16)**	**21 (14)**	**28 (19)**
Complete response	1 (1)	1 (1)	1 (3)	3 (8)	2 (1)	4 (3)
Partial response	15 (19)	17 (21)	6 (16)	3 (8)	19 (13)	24 (17)
Stable disease*	27 (34)	32 (40)	13 (35)	15 (41)	60 (41)	65 (45)
Progressive disease	32 (40)	26 (33)	13 (35)	12 (32)	56 (39)	47 (32)
Not evaluable	5 (6)	4 (5)	4 (11)	4 (11)	8 (6)	5 (3)
Objective response using mRECIST	**19 (24)**	**NA**	**8 (22)**	**NA**	**27 (19)**	**NA**
TTR, median (range), mos	2.7 (1.3–5.5)		1.4 (1.3–6.9)		2.8 (1.2–7.0)	
DOR, median (range), mos	**17.15 (4.2–17.1+)**		19.35 (2.8–38.2+)		16.59 (3.2–16.8+)	
Overall survival, median (95% CI), mos		**28.6 (16.6–NE)**		**15.0 (5.0–28.1)**		**28.6 (16.6–NE)**
12 months		73 (61.3–81.3)		58 (40.2–72.2)		60 (51.4–67.5)
18 months		57 (44.3–67.1)		46 (29.5–61.7)		44 (35.3–51.9)

Crocenzi TS et al. Poster presentation at ASCO 2017. Abstract 4013.

Checkmate 040: Nivolumab in advanced HCC

Responses independend by PD-L1 Status

Sorafenib Naive ESC + EXP

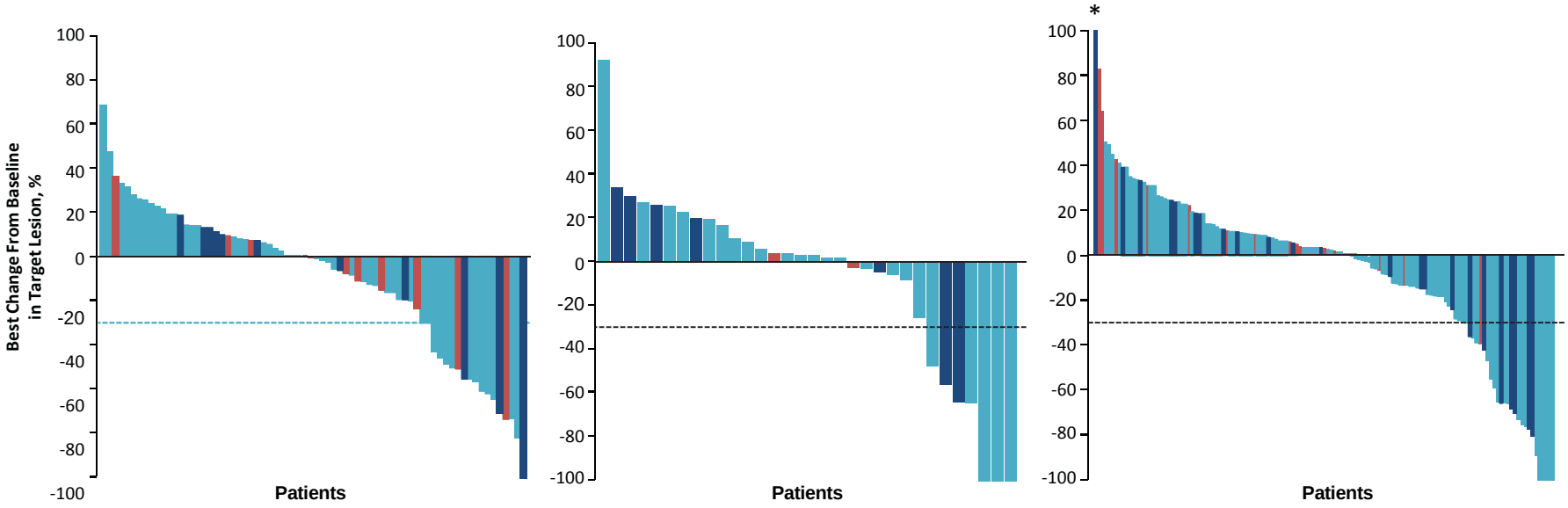
	PD-L1⁺	PD-L1⁻	UTD
ORR, n/N (%)	3/11 (27)	11/56 (20)	2/13 (15)

Sorafenib Experienced ESC

	PD-L1⁺	PD-L1⁻	UTD
ORR, n/N (%)	2/9 (22)	5/26 (19)	0/2 (0)

Sorafenib Experienced EXP

	PD-L1⁺	PD-L1⁻	UTD
ORR, n/N (%)	7/25 (28)	13/102 (13)	1/18 (6)



Responses occurred across baseline tumor-cell PD-L1 expression status

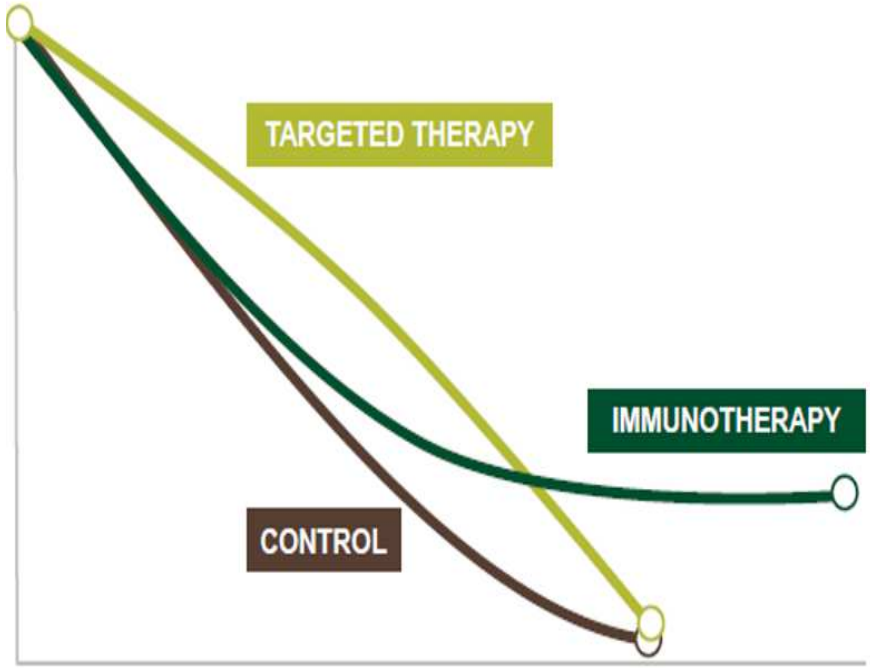
Tumor response assessed by BICR using RECIST v1.1; plots include patients who were evaluable for tumor response and had at least one post-baseline target lesion assessment (sorafenib naive, n = 72; sorafenib experienced (ESC), n = 32; and sorafenib experienced (EXP), n = 135). PD-L1⁺, ≥ 1% tumor cells expressing PD-L1; PD-L1⁻, < 1% tumor cells expressing PD-L1; UTD, unable to determine PD-L1 expression. * Percent change truncated to 100%.

BICR, blinded independent central review; ESC, dose escalation; EXP, dose expansion; PD-L1, programmed death ligand 1; UTD, unable to determine.

Crocenzi TS et al. Poster presentation at ASCO 2017. Abstract 4013.

Immunotherapy in gastrointestinal cancer
will improve patient outcome

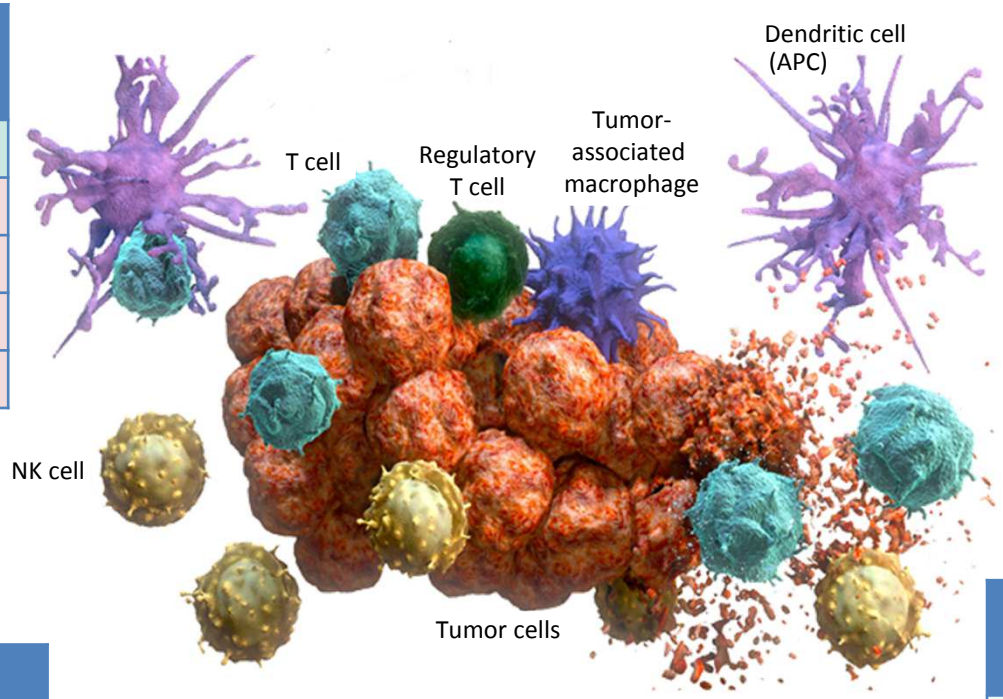
Future Perspectives



How to heat up “cold” tumors ?
Combination is key

Potential Immuno-oncology Targets

Effector T cell mechanisms	
Activating	**Inhibitory**
CD137	CTLA-4
GITR	PD-1
OX40	LAG-3
CD27	…



Non-effector immune cell mechanisms	
Inhibitory	
CD73	OX40
CSF1R	CCR4
CTLA-4	TGFR
GITR	IDO

NK cell mechanisms	
Activating	**Inhibitory**
SLAMF7	KIR
CD137	…

Tumor cell targeted pathways	
BCR-ABL	HER2
BET	Mesothelin
CXCR4	Glypican-3
Fucosyl-GM1	CD30

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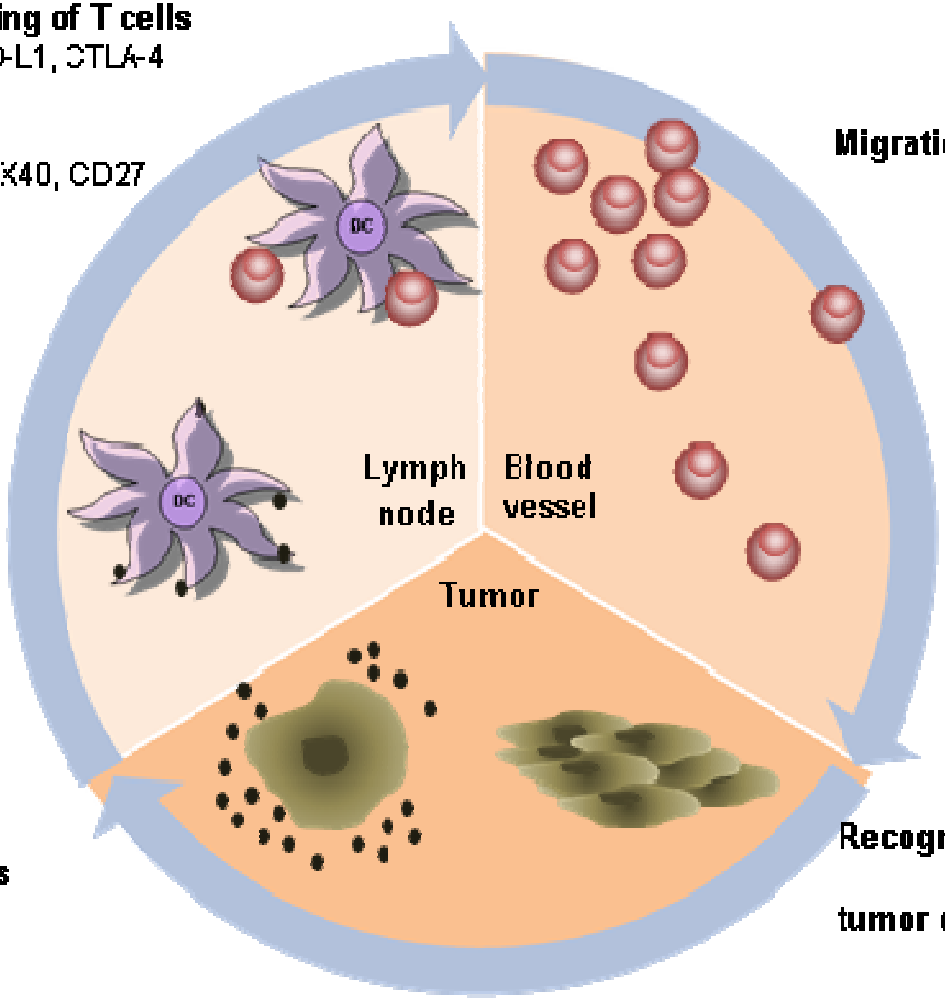
HCC

Activation and priming of T cells
- mAb against PD-1, PD-L1, CTLA-4
- IL-2
- IL-12
- Agonists for CD137, OX40, CD27

Presentation of tumor associated antigens

- Vaccines
- IFN-α
- GM-CSF



Migration of activated T cells

Immigration of T cells into the tumor

Recognition and killing of tumor cells

Release of tumor associated antigens

- Chemotherapy
- Radiotherapy

Moehler Eur J Cancer 2016

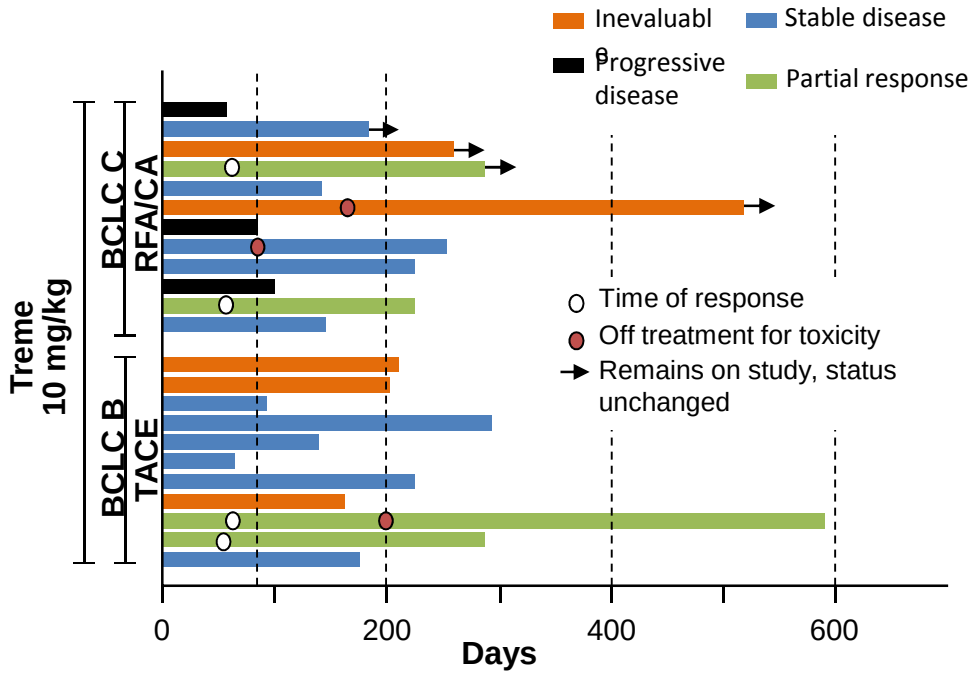
How to heat up “cold” tumors ?

Combination is key

HCC

Tremelimumab with Chemoembolization or Ablation in Advanced HCC

	Treme + RFA/CA (n=12)	Treme + TACE (n=11)
Median OS, mos (95% CI)	10 (5-16)	14 (8-UD)
12-mos survival, % (95% CI)	**47** (18-72)	81 (42-95)



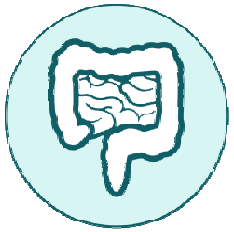
Tremelimumab + TACE had a longer survival

But durable response was observed in both TACE and ablation combinations

Duffy AG et al. *J Hepatol*. 2017;66(3):545-551.

How to heat up “cold” tumors ?

Combination is key

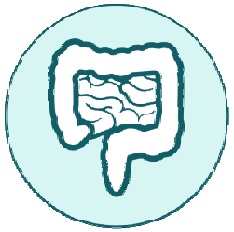


CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGFβ activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

Guinney et al., Nature Med 2015

How to heat up “cold” tumors ?

Combination is key



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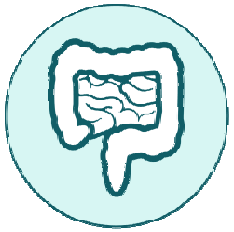
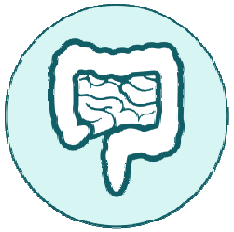


Immune Subgroup	Molecular Subgroups	Escape Mechanisms	Immuno-Therapeutic Goals	Potential Approach
Immunogenic	CRC hypermutated	Immune checkpoints: PD-1 axis, LAG-3, CTLA-4	Boost intratumor CTLs	Checkpoint blockade
Inflammatory	CRC mesenchymal	• Hypoxia • TGF-β • PD-1 axis	• Dampen inflammation and suppression • Establish normoxia • Boost intratumor suppressed CTLs	• Anti-angiogenic • Anti-TGFβ • Checkpoint blockade
Immune-neglected	CRC canonical and metabolic	Low class I MHC expression	• Attract CTLs in tumors • Bypass class I MHC presentation	• CAR T cells • Bispecific antibodies

Becht E et al. *Curr Opin Immunol*. 2016;39:7-13.

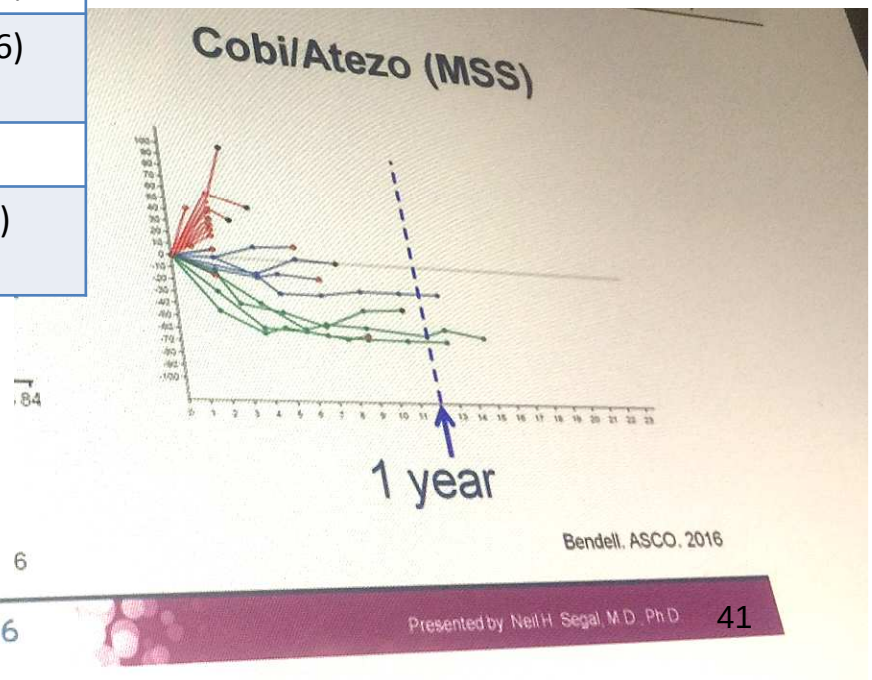
How to heat up “cold” tumors ?
Combination is key



	KRAS^{mt} CRC Cohort (n=20)	All CRC Patients (n=23)
ORR,* % (95% CI)	20 (5.7, 43.7)	17 (5.0, 38.8)
PR,* %	20	17
SD,* %	20	22
PD,* %	50	52
NE,* %	10	9
mPFS (95% CI)	2.3 mo (1.8, 9.5)	2.3 mo (1.8, 9.5)
6 mo PFS, % (95% CI)	**39** (0.16, 0.61)	35% (0.14, 0.56)
mOS, % (95% CI)	NE (6.5, NE)	NE (6.5, NE)
6 mo OS, % (95% CI)	***77*** (0.57, 0.97)	72 (0.52, 0.93)

- 4 patients had PRs
- 3/4 responders were pMMR
- Tumor volume reduction not associated with PD-L1

Atezolizumab with Cobimetinib (c-met) Phase Ib: MSS mCRC



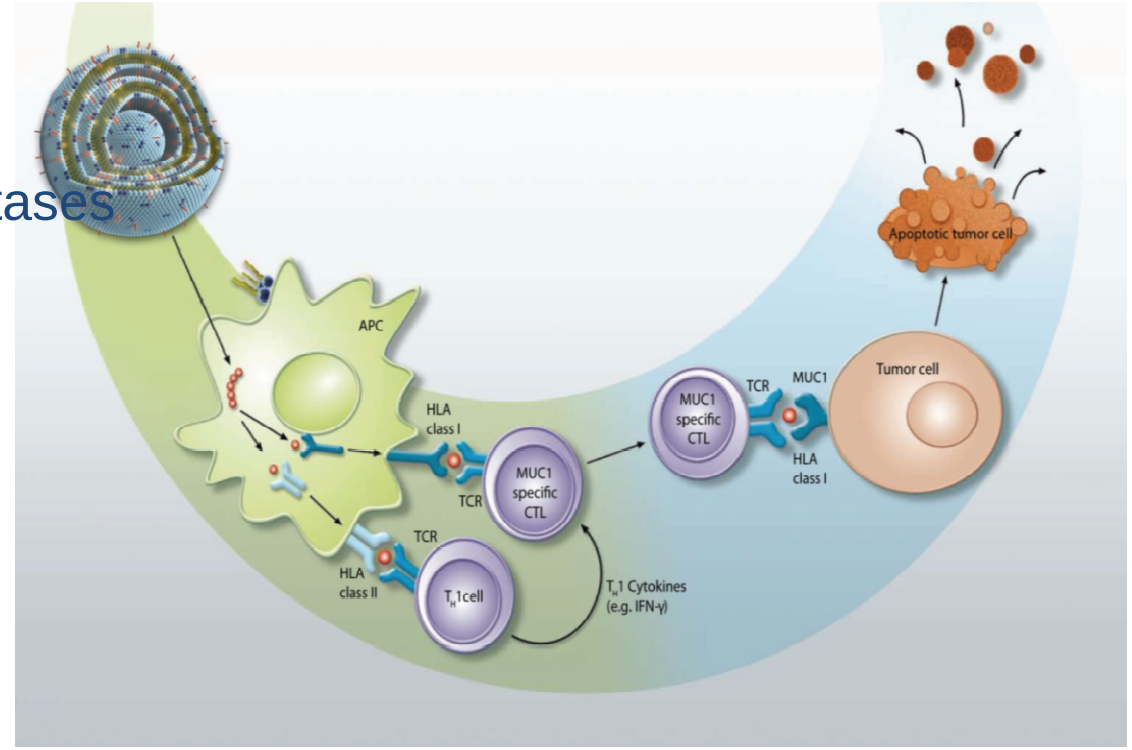
Confirmed response per RECIST v1.1.
Bendell J et al. Oral presentation at ASCO 2016. 3502.

How to heat up “cold” tumors ?
Combination is key

Multi-national randomized, double-blind, placebo-controlled vaccination phase II trial

Tecemotide, an active MUC1 cancer vaccine

120 **colorectal cancer** patients
following R0/R1 resection
of Colon Cancer hepatic metastases

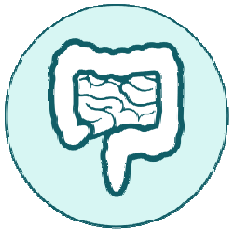


Schimanski, Moehler et al. BMC Cancer. 2012

Federal Ministry
of Education
and Research

How to heat up “cold” tumors ?

Combination is key



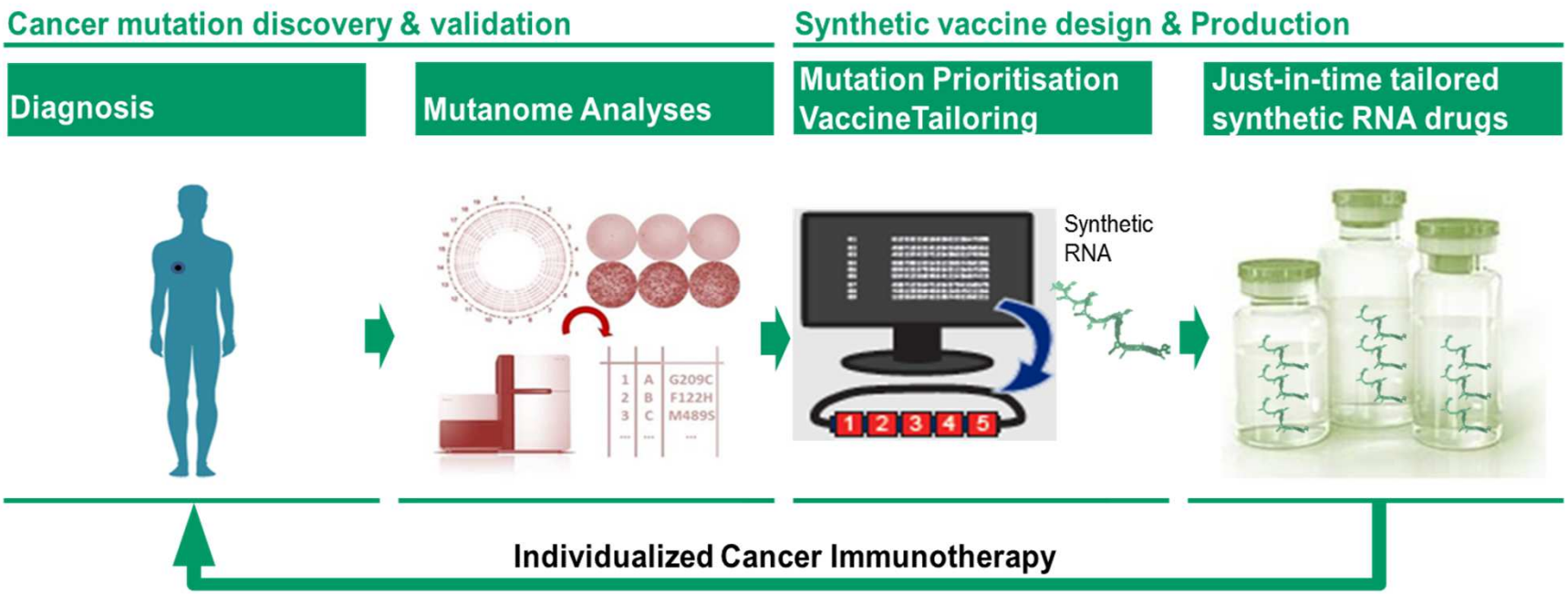
LETTER

doi:10.1038/nature14426

Mutant MHC class II epitopes drive therapeutic immune responses to cancer

Sebastian Kreiter[1], Mathias Vormehr[2*], Niels van de Roemer[2*], Mustafa Diken[1], Martin Löwer[1], Jan Diekmann[1,3], Sebastian Boegel[1], Barbara Schrörs[1], Fulvia Vascotto[1], John C. Castle[1], Arbel D. Tadmor[1], Stephen P. Schoenberger[4], Christoph Huber[2], Özlem Türeci[1]§ & Ugur Sahin[1,2,3]§

Individualized Mutanome as Vaccine



Kreiter et al, Nature 520, 692–696 (30 April 2015)

Sahin *et al. Nature* 1–5 (2017) doi:10.1038/nature23003

Immuno-Oncology
Our vision

Checkpoint-Inhibitors in HCC,GI + MSI Tumors
improve responses and prolong survival
New chemo-immuno-therapy combinations
can potentially cure localized or metastatic disease
Combinations of different immunogenic agents
foster precision medicine with biomarkers
Vaccines and oncolytic viruses
re-activate and reorgnize the immune system

Please participate in national
or international trials,
such as EORTC !!