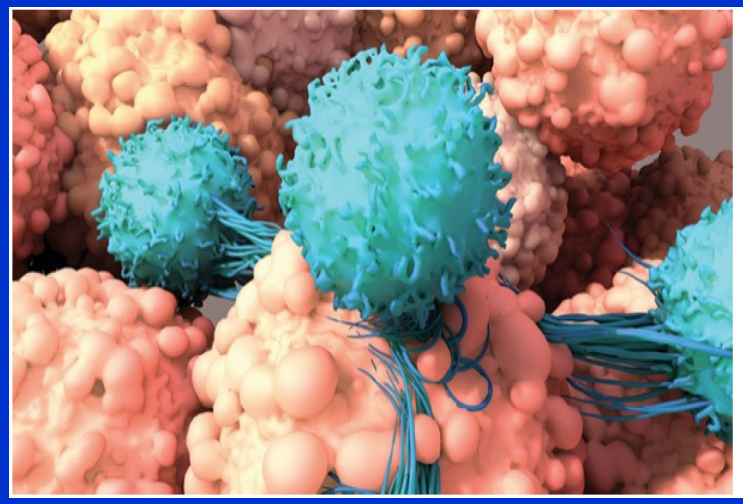
Revolution in the way we treat GI cancer
Immunotherapy
IAGH Tir 1403



Reza malekzadeh M.D AGAF
Distinguished Professor of Medicine
DDRI/TUMS

Exploration of Innovative Therapeutic Strategies for Cancer

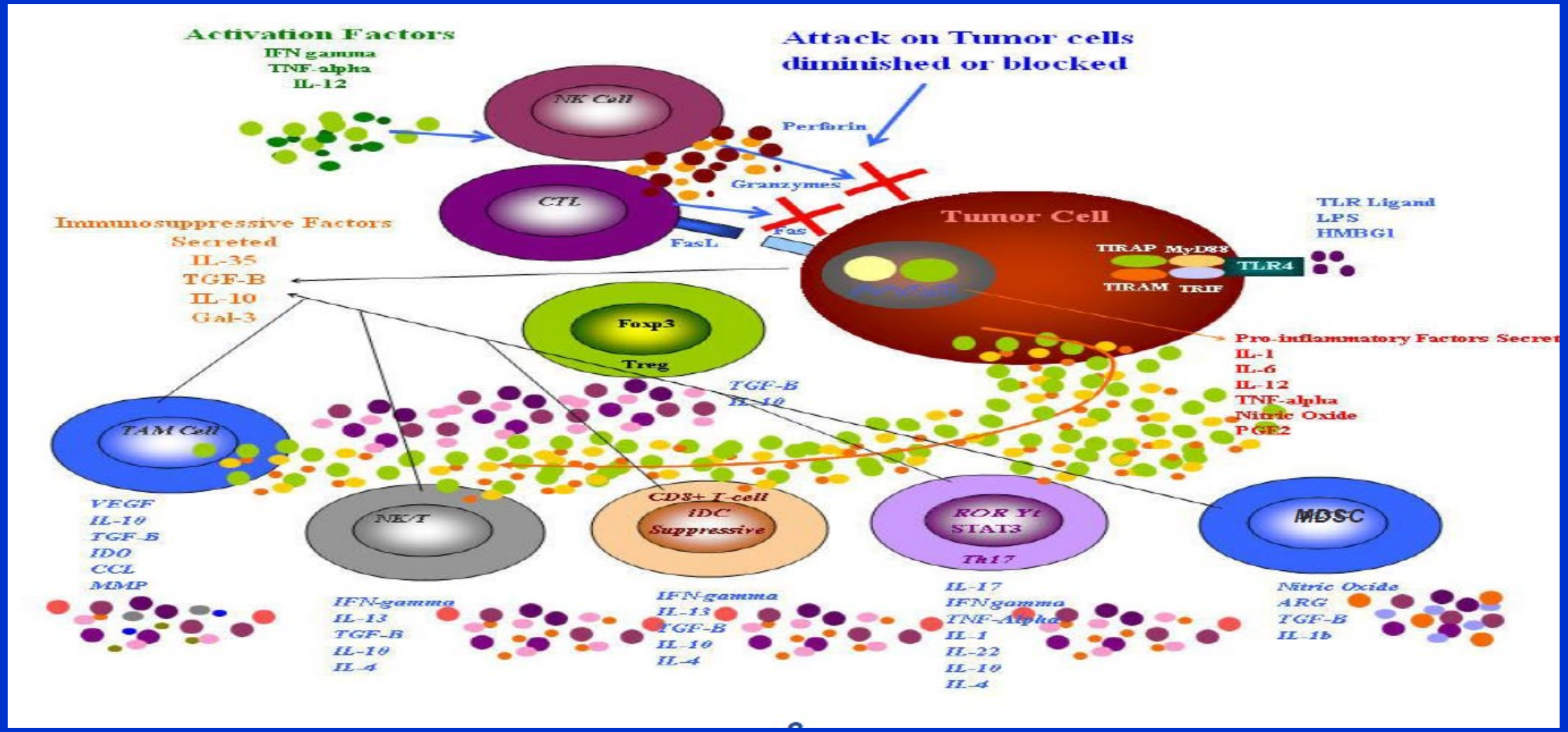
- The rise of drug resistance in cancer cells presents a formidable challenge in modern oncology, necessitating the exploration of innovative therapeutic strategies.

- The intricate molecular insights into drug resistance, including genetic mutations, efflux pumps, altered signaling pathways, and micro environmental influences, are the main players.

Promising future cancer therapeutics

- Targeted therapies,
- Combination treatments,
- Immunotherapies.
- Precision medicine approaches.

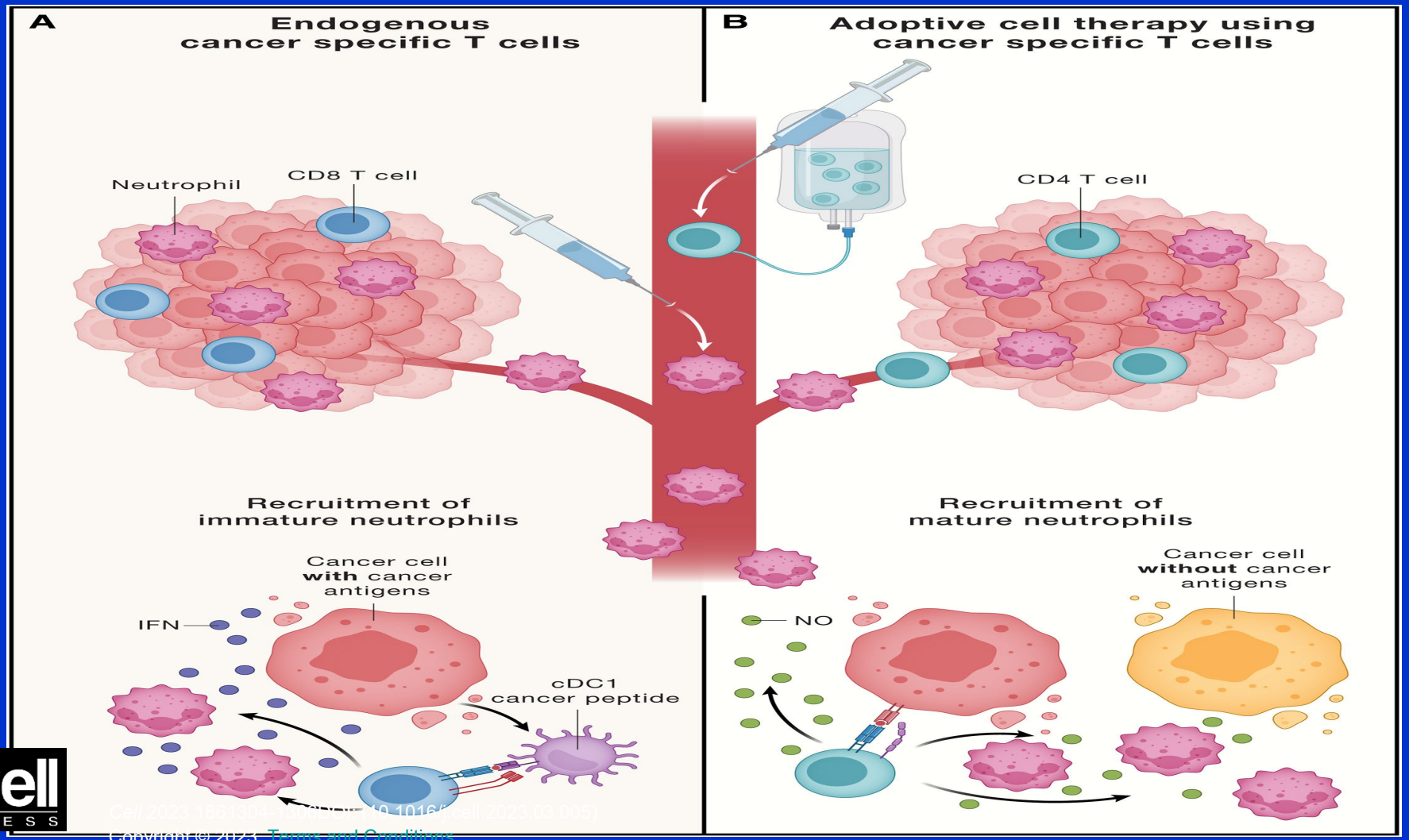
Mechanism of Tumor induced Immunotolerance



The presence of the immune-active or -silent environment is related to five mechanisms

- Tissue-specific destruction.
- Autoimmunity
- Tumor rejection
- Pathogen clearance
- Allograft rejection
- Requiring the coordinated involvement of three major players, i.e. T-cell response, self- non-self-recognition and innate immunity

T-cells and neutrophils working together to attack cancers



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Cell 2023 - 861304-1808DC-ch10.1016/j.cell.2023.03.005)
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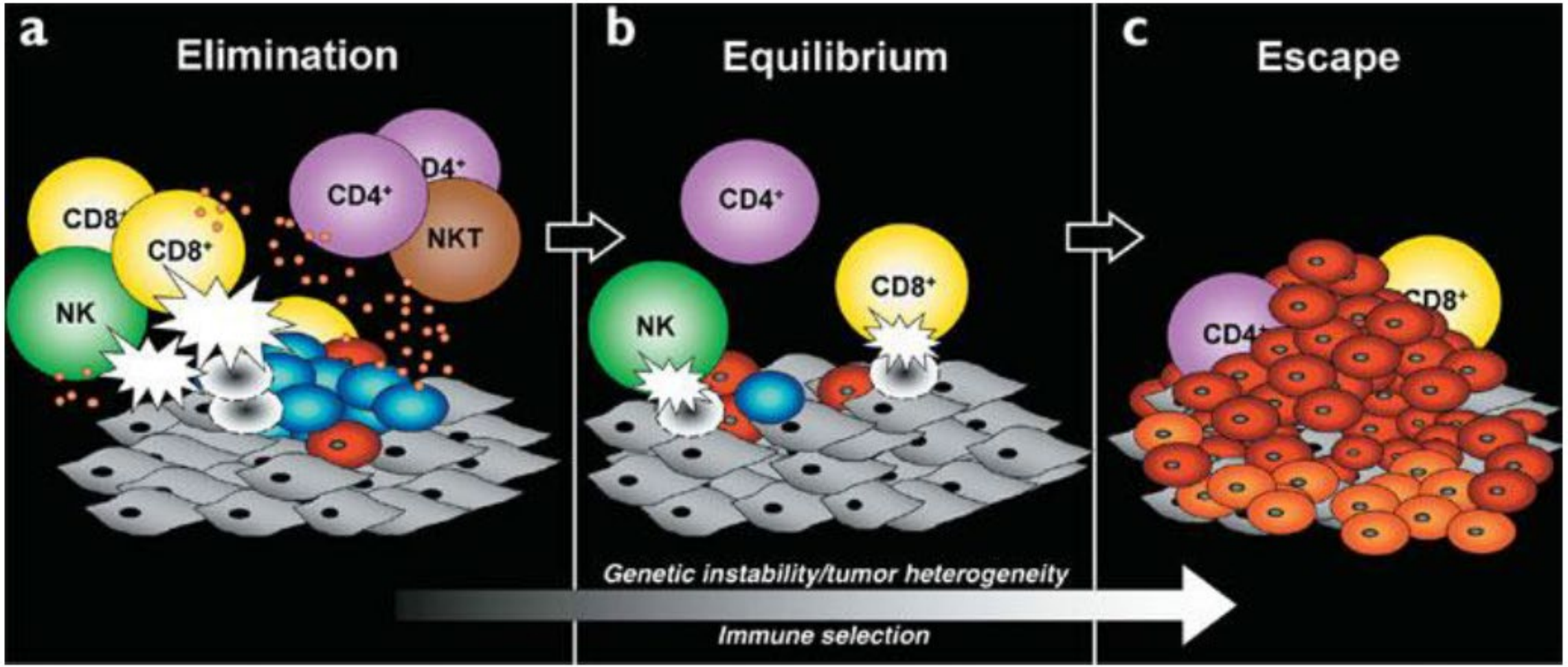
Cancer is the Consequence of Failed Natural Immune response



Types of Cancer Immunotherapy

- Cancer Vaccines – educate T cells to better recognize and kill the pre-existing tumor
- Adoptive Immunotherapy – activate and increase T cell numbers to better kill tumor
- Immunomodulation – use drugs or antibodies to either:
  - increase immune stimulation
  - overcome immune inhibition

Cancer Vaccine Design

Vaccine Requirements

- Contain a desired antigen(s)
- Possess an adjuvant capable of stimulating/generating an immune response

Cancer mRNA vaccine: A new Paradigm in Cancer therapy

- A personalised cancer vaccine that uses the same messenger-RNA technology as Covid jabs.
- It is designed to prime the immune system to seek and destroy cancerous cells.
- This could lead to revolutionary new ways to fight skin, bowel and other types of cancer.
- That's an important finding and I think it has the potential to be a new paradigm in the treatment of cancer patients."

T Cell Therapy

- CARs – chimeric antigen receptors
- TCRs – T cell receptors
- TILs – Tumor infiltrating lymphocytes
- MILs – Marrow infiltrating lymphocytes
- Allogeneic BMT

Immunotherapy by Antibody

- Immunomodulation – use drugs or antibodies to either:
  - increase immune stimulation
  - overcome immune inhibition

Immunotherapy

- Immunotherapy represents one of the most important advancements in the cancer therapy Field.
- Cancer immunotherapy is now established as a powerful way to treat cancer.
- Inhibitors of immune checkpoints CTLA4, PD-1 and PD-L1 dramatically improved therapeutic results.

Evolving landscape of immunotherapeutic

- Immune checkpoint inhibitors
- Adoptive cell therapies

Immune checkpoint blockade (ICB) is in the midst of an explosive expansion

- The therapeutic strategy of neoadjuvant (pre-surgical) immune checkpoint blockade (ICB) is in the midst of an explosive expansion since the initial reports 5 years ago.

- This treatment approach uses the primary tumor in situ as an immunologic driver of systemic anti-tumor immunity in patients with operable cancers to "mop up" any distant micro-metastatic tumor foci that could ultimately become the source of post-surgical relapse.

Immune checkpoint inhibitors

- Are new generation cancer immunotherapies, which activate the immune system against cancer by preventing the interactions of molecules such as PD-L1 and PD-1.
- This will achieve with monoclonal antibodies drugs that will prevent the work of molecules that inactivate the immune system.
- PD-L1 blockade will produce an antitumor immune response of course healthy cells may also be partially affected by this increased immune response

Diferential expression of ICR in Cancer type

- Significant diferential expression was observed for each ICR molecule in many cancer types.
- A 7-molecules profle was found to specifcally discriminate melanoma patients from controls.
- Two diferent 6-molecules profles discriminate pancreatic cancer patients and Testicular Germ Cell Tumors from matched controls.
- Highly signifcant survival improvement was found to be related to the expression levels of all nine ICRs in a wide spectrum of malignancies.
- .

Biomarker-driven strategies for predicting and monitoring treatment responses

- Microsatellite instability (MSI) is caused by defective DNA mismatch repair (dMMR) genes and is characterized by a decrease or increase in repeated nucleotide sequences, which can lead to evasion of apoptosis, development of malignant mutations, and tumorigenesis

- Protein expression of MLH1, MSH2, MSH6, and PMS2 was detecte)d by immunohistochemistry (IHC)

Defective DNA mismatch repair (dMMR) Genes

- Microsatellite instability (MSI) is caused by defective DNA mismatch repair (dMMR) genes and is characterized by a decrease or increase in repeated nucleotide sequences, which can lead to evasion of apoptosis, development of malignant mutations, and tumorigenesis

- MSI is a marker of dMMR.

Biomarkers for Immunotherapy

- dMMR and MSI-H have been demonstrated as effective predictors of immunotherapy response
- Both biomarkers have been approved by US FDA as biomarkers for the treatment of solid tumors with immune checkpoint inhibitors targeting programmed death 1 (PD-1), regardless of tumor origin .

Germline pathogenic mutations in the DNA Mismatch repair gene

- Germline pathogenic mutations in the DNA mismatch repair genes are also the hallmarks of **Lynch syndrome**, an autosomal dominant disorder associated with a genetic predisposition for developing a wide spectrum of cancers.
-

dMMR and MSI-H have been found in GI and Non GUI Solid tumors

- Colorectal,
- Small intestinal,
- Stomach
- Esophagus
- Non GI Tumors :uterine, ovarian,, urothelial, central nervous system, and adrenal gland tumors

MSI Status determination in Solid Tumors

- MSI status can be determined by immunohistochemistry (IHC), polymerase chain reaction (PCR), and next-generation sequencing (NGS).
- Generally, the PCR and NGS methods divide tumors into high frequency MSI (MSI-H), low-frequency MSI (MSI-L), or microsatellite stable (MSS) tumors

MMR/MSI H status has been screened in a variety of tumors

- 15% of colon tumors
- 15–31% of uterine tumors
- 16% of hepatocellular carcinoma in non-alcoholic and non-virally infected livers,
- 9.2% patients with gastric cancer
- 0% to 22% pancreatic ductal adenocarcinoma

Prognostic value of these dMMR/MSI-H Biomarkers

- Varies between tumor types.
- dMMR/MSI-H has been associated with poor prognosis in individuals with colorectal cancer that was insensitive to 5-fluorouracil (FU)-based adjuvant chemotherapy
- while dMMR/MSI-H were associated with good prognosis in gastric cancer .

PD-L1 Protein

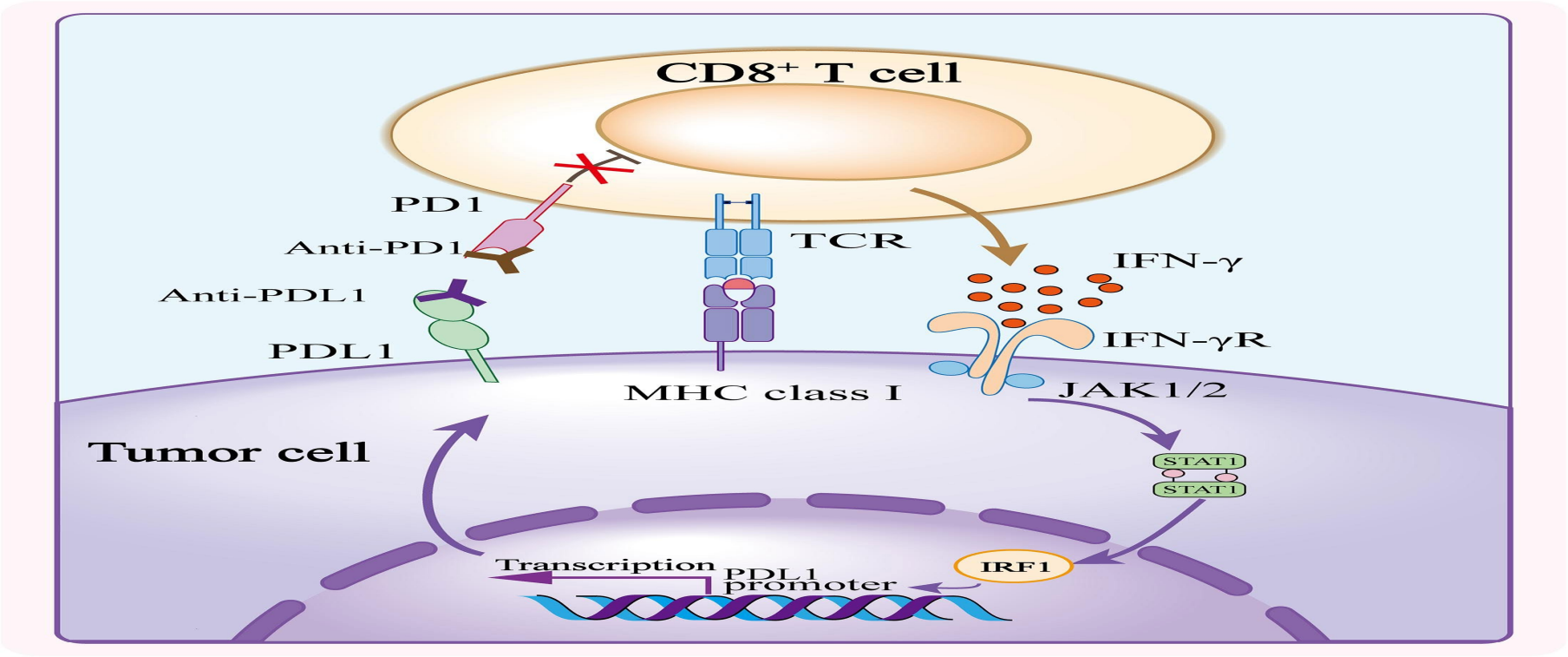
- Programmed death-ligand 1 (PD-L1) is a cell membrane protein found on the surface of cancer cells, immune system cells in the tumor microenvironment and various healthy tissues, and plays an important role in suppressing the immune system.

- It is a 40kDa type 1 transmembrane protein that has been speculated to play a major role in suppressing the adaptive arm of immune systems during particular events such as pregnancy, tissue allografts, autoimmune disease and other disease states such as hepatitis.

Programmed death ligand 1 (PD-L1) is expressed on tumor and inflammatory cell membranes and plays a role in regulating immune response

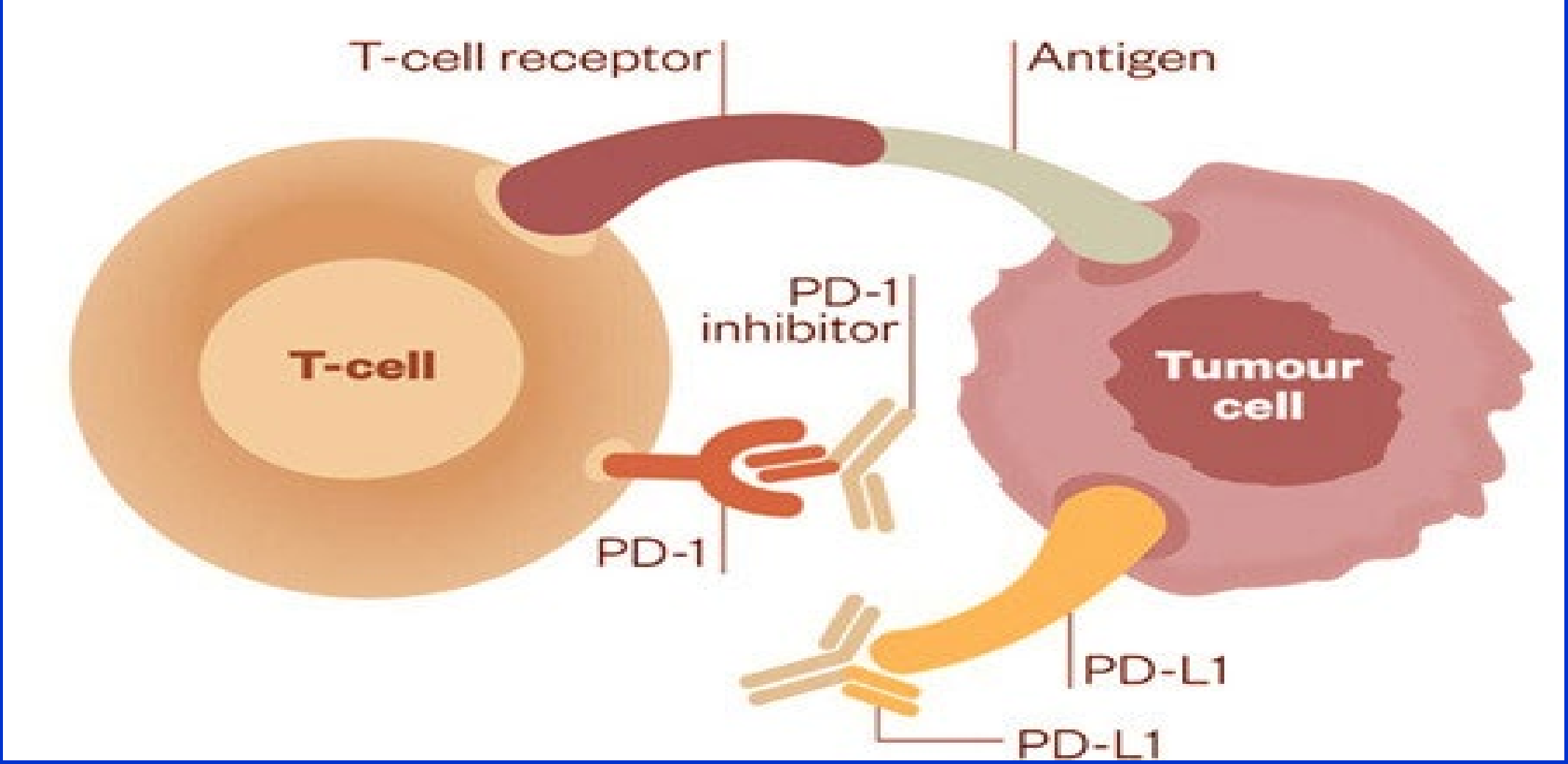
- PD-L1can turn your T cells off so they can't attack the cancer cells actually a T-cell brake
- If high amounts of PD-L1 are found on cancer cells, immunotherapy medicines called "immune checkpoint inhibitors" may be used.
- These medicines prevent the PD-L1 protein from putting the brakes on T cells. This frees your T cells to fight cancer.

PD-L1 Receptor on Tumor cell



PD-L1 binds to its receptor, PD-1, found on activated T cells, B cells, and myeloid cells, to modulate activation or inhibition.

PD-L1 protein action on Immune response



Mechanism of Action PD-L1

- Normally the adaptive immune system reacts to antigens that are associated with immune system activation by exogenous or endogenous danger signals.
- The binding of PD-L1 to the inhibitory checkpoint molecule PD-1 transmits an inhibitory signal based on interaction with phosphatases (SHP-1 or SHP-2) via Immunoreceptor Tyrosine-Based Switch Motif (ITSM).
- This reduces the proliferation of antigen-specific T-cells in lymph nodes, while simultaneously reducing apoptosis in regulatory T cells further mediated by a lower regulation of the gene Bcl-2.

Immunotherapy a ‘game-changer’ for CRC

Superiority of immunotherapy over chemotherapy

- Phase II trial results have shown the superiority of immunotherapy pembrolizumab over chemotherapy when given before surgery in patients with stage two or stage three MMR deficient/MSI-High bowel cancer.

- The results were presented by researchers at University College London (UCL) and UCLH at the American Society of Clinical Oncology (ASCO) Annual Meeting 2024 and Published in NEJM.

Neoadjuvant Immunotherapy before surgery better than chemotherapy in in Locally Advanced MRDCRC

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 6, 2024 VOL. 390 NO. 21

Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair–Deficient Colon Cancer

Myriam Chalabi, M.D., Ph.D., Yara L. Verschoor, M.D., Pedro Batista Tan, M.Sc., Sara Balduzzi, Ph.D., Anja U. Van Lent, M.D., Ph.D., Cecile Grootscholten, M.D., Ph.D., Simone Dokter, M.Sc., Nikè V. Büller, M.D., Ph.D., Brechtje A. Grotenhuis, M.D., Ph.D., Koert Kuhlmann, M.D., Ph.D., Jacobus W. Burger, M.D., Ph.D., Inge L. Huibregtse, M.D., Ph.D., Tjeerd S. Aukema, M.D., Ph.D., Eduard R. Hendriks, M.D., Steven J. Oosterling, M.D., Ph.D., Petur Snaebjornsson, M.D., Ph.D., Emile E. Voest, M.D., Ph.D., Lodewyk F. Wessels, Ph.D., Regina G. Beets-Tan, M.D., Ph.D., Monique E. Van Leerdam, M.D., Ph.D., Ton N. Schumacher, Ph.D., José G. van den Berg, M.D., Ph.D., Geerard L. Beets, M.D., Ph.D., and John B. Haanen, M.D., Ph.D.

ABSTRACT

BACKGROUND

Mismatch repair–deficient (dMMR) tumors can be found in 10 to 15% of patients with nonmetastatic colon cancer. In these patients, the efficacy of chemotherapy is limited. The use of neoadjuvant immunotherapy has shown promising results, but data from studies of this approach are limited.

METHODS

We conducted a phase 2 study in which patients with nonmetastatic, locally advanced, previously untreated dMMR colon cancer were treated with neoadjuvant nivolumab plus ipilimumab. The two primary end points were safety, defined by timely surgery (i.e., ≤2-week delay of planned surgery owing to treatment-related toxic events), and 3-year disease-free survival. Secondary end points included pathological response and results of genomic analyses.

RESULTS

Of 115 enrolled patients, 113 (98%; 97.5% confidence interval [CI], 93 to 100) underwent timely surgery; 2 patients had surgery delayed by more than 2 weeks. Grade 3 or 4 immune-related adverse events occurred in 5 patients (4%), and none of the patients discontinued treatment because of adverse events. Among the 111

The authors' affiliations are listed in the Appendix. Dr. Chalabi can be contacted at m.chalabi@nki.nl or at the Department of Gastrointestinal Oncology, Netherlands Cancer Institute, Plesmanlaan 121, 1066CX, Amsterdam, the Netherlands.

N Engl J Med 2024;390:1949-58.
DOI: 10.1056/NEJMoa2400634

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CME

100%Immunotherapy group were cancer free compare to only 5% in chemotherapy group

- Around 15% of CRC patients with have MMR deficient/MSI-High bowel cancer, which represents around 1800 and 1500 CRC cases per year in the Iran.
- All of the patients in the trial were cancer-free after treatment and are still cancer-free many months later.
- When standard care chemotherapy is given to patients with this genetic profile, less than 5% have no signs of cancer after surgery.

Immunotherapy prior to surgery could well become a ‘game-changer

- Immunotherapy prior to surgery could well become a ‘game-changer’ for these patients with this type of cancer.
- Not only is the outcome better, but it saves patients from having more conventional chemotherapy, which often has more side-effects.
- In the future, immunotherapy may even replace the need for surgery. However, more trials are needed to confirm these exciting early results.”

Immunotherapy the first-line treatment of metastatic colorectal cancer (CRC),

2024 American Society of Clinical Oncology Gastrointestinal Cancers Symposium.

First-line treatment of metastatic colorectal cancer (CRC)

- The immunotherapy combination nivolumab plus ipilimumab rivals chemotherapy as well as pembrolizumab monotherapy in the first-line treatment of metastatic colorectal cancer (CRC), new data indicated.

PFC 72% in Immunotherapy compared with 14% in chemotherapy

- CHECKMATE-8HW trial revealed that first-line nivolumab plus ipilimumab led to a significant improvement in progression-free survival (PFS) compared with chemotherapy among patients with metastatic CRC.
- At 2 years, progression-free survival (PFS) was **72%** among patients with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) randomized to the immunotherapy combination compared with just **14%** among those randomized to chemotherapy with or without targeted therapy

CHECKMATE-8HW Trial

- In CHECKMATE-8HW, patients were randomized to three regimens.
- The 202 patients in the combination arm received nivolumab 240 mg plus ipilimumab 1 mg/kg every 3 weeks for four doses, followed by nivolumab 480 mg every 4 weeks.
- The 101 patients in the chemotherapy group received investigator's choice of mFOLFOX6 or FOLFIRI with or without bevacizumab or cetuximab. And the nivolumab

It's a good surprise

- The magnitude of the benefit was unexpected, especially considering patients only received four cycles of the immunotherapy combination in the trial. “
- The findings indicate that nivolumab plus ipilimumab should really be "a new standard.
- The combination as well as nivolumab alone has received US Food and Drug Administration's (FDA's) approval to treat MSI-H or dMMR metastatic CRC in the second line, following chemotherapy failure.

FDA Approval

- The FDA also approved pembrolizumab as first-line monotherapy for this CRC indication in 2020.
- The KEYNOTE-177 trial, which led to the pembrolizumab approval, reported a 2-year PFS of 48% among patients receiving the monotherapy.

- To compare PFS results for pembrolizumab and nivolumab alone, the CHECKMATE-8HW trial included a nivolumab monotherapy arm, but these results are pending, as are the overall survival findings,

Important therapeutic targets for all patients with CRC

In all CRC patients we need to do universal biomarker testing including

- KRAS.
- Microsatellite instability (MSI),
- BRAF
- ERBB2 (formerly HER2), represent Accordingly, the

CRC with mismatch repair deficiency(MMRD)

- About 15% to 20% of patients with localized colon cancer and 5% to 7% of patients with rectal cancer have mismatch repair deficiency(MMRD).

- MMRD patients are less responsive to conventional chemotherapy but highly responsive to immunotherapy with checkpoint inhibitors.

World J Gastrointest Oncol 020;12[8]:808-832
),

Immunotherapy alone could induce complete regression of the Localized CRC

- Chalabi et al presented results of the NICHE-2 trial of 107 patients with MMRD localized colon cancer at the 2022 annual meeting of the European Society for Medical Oncology, showing that immunotherapy alone could induce complete regression of the tumors in 67% of patients (abstractLBA7).
- In another study, Cercek et al found that six months of immunotherapy resulted in complete regression ofrectal tumors in 12 patients (N Engl J Med 2022;386[25]:2363-2376}

JUNE 9, 2022

100% Remission Rate 'Thrills' Rectal Cancer Investigators

Chicago, IL—There are positive cancer trials, there presented at the 2022 annual meeting of the Ame possible in oncology (abstract LBA5).



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ORIGINAL ARTICLE

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.

ABSTRACT

BACKGROUND

Neoadjuvant chemotherapy and radiation followed by surgical resection of the rectum is a standard treatment for locally advanced rectal cancer. A subset of rectal cancer is caused by a deficiency in mismatch repair. Because mismatch repair–deficient colorectal cancer is responsive to programmed death 1 (PD-1) blockade in the context of metastatic disease, it was hypothesized that checkpoint blockade could be effective in patients with mismatch repair–deficient, locally advanced rectal cancer.

METHODS

We initiated a prospective phase 2 study in which single-agent dostarlimab, an anti–PD-1 monoclonal antibody, was administered every 3 weeks for 6 months in patients with mismatch repair–deficient stage II or III rectal adenocarcinoma. This treatment was to be followed by standard chemoradiotherapy and surgery. Patients who had a clinical complete response after completion of dostarlimab therapy would proceed without chemoradiotherapy and surgery. The primary end points are sustained clinical complete response 12 months after completion of dostarlimab therapy or pathological complete response after completion of dostarlimab therapy with or without chemoradiotherapy and overall response to neoadjuvant dostarlimab therapy with or without chemoradiotherapy.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Cercek can be contacted at cerceka@mskcc.org or at Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065. Dr. Diaz can be contacted at ldiaz@mskcc.org or at Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065.

This article was published on June 5, 2022, at NEJM.org.

DOI: 10.1056/NEJMoa2201445

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At the 2023 ASCO Gastrointestinal Cancers Symposium

- Data was presented similar MMRD CRC, most of whom could not undergo surgery because of various health conditions unrelated to cancer.
- The patients received immunotherapy with checkpoint inhibitors instead and did not receive any radiation therapy or chemotherapy. Of note, the patients were treated outside of clinical trials.
- In this patient group, the overall response rate was 74%, and 57% of those who responded had complete regression of their tumors.
- Some of the patients continue to enjoy complete remission beyond one year or longer from their diagnoses.
- The data suggest that immunotherapy is an effective treatment for patients who cannot undergo surgery for various reasons, including advanced age or various health problems unrelated to cancer

Treatment of CRC with immunotherapy alone—without radiation, chemotherapy, or surgery.

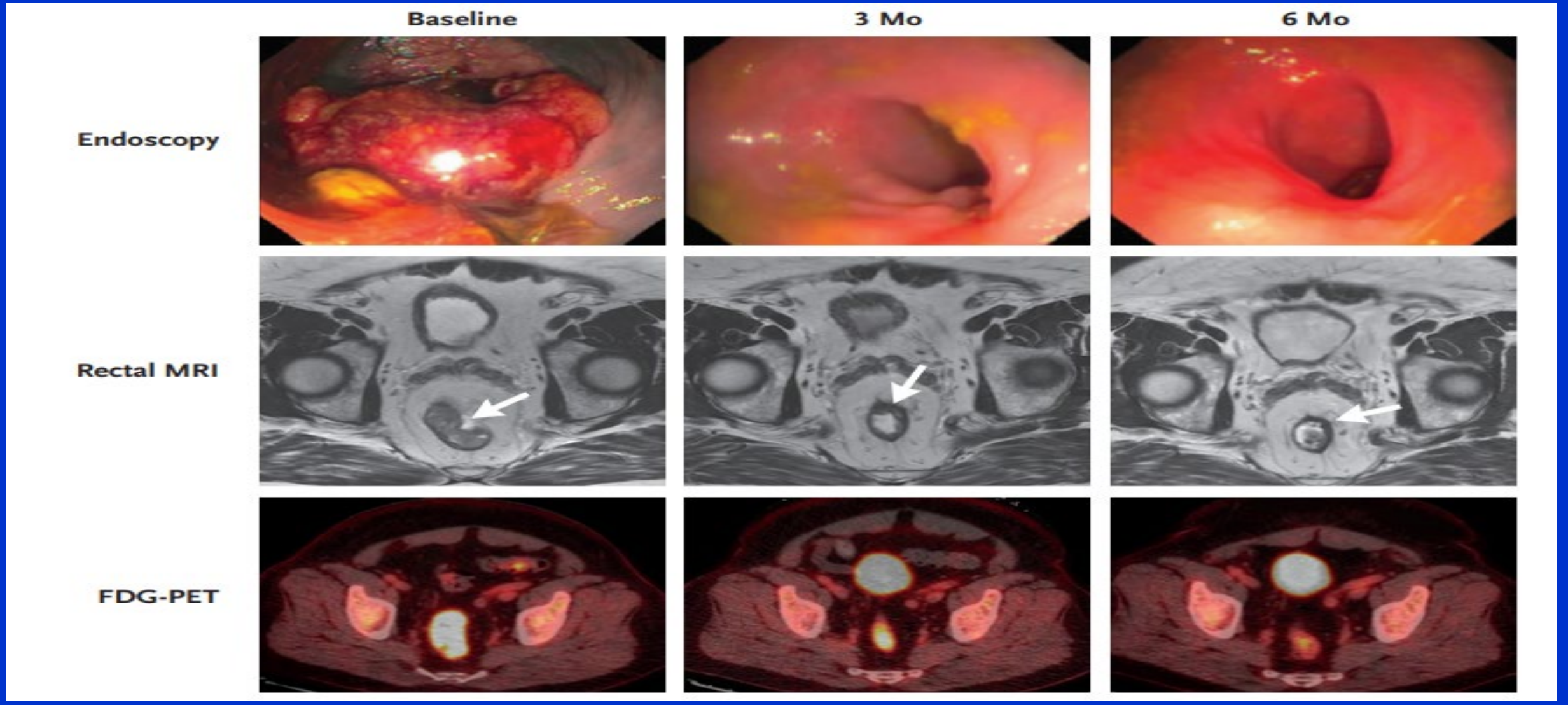
- These real-world data will motivate future studies with immunotherapy in MMRD CRC patients, who can potentially avoid surgery altogether.
- However, more studies are required to optimize immunotherapy for this patient group.
- The optimal immunotherapy agents and duration of therapy are uncertain at this time.
- Well-conducted clinical trials will be needed to standardize the treatment.
- If validated, treating CRC with immunotherapy alone—without radiation, chemotherapy, or surgery—would be a reality that could result in signifi cant quality-of-life improvement for patients.

Immunotherapy in patients with MMRD advanced-stage CRC

- Studies already have shown the benefit of immunotherapy in patients with MMRD advanced-stage CRC (NEJM 2020;383[23]:2207-2218

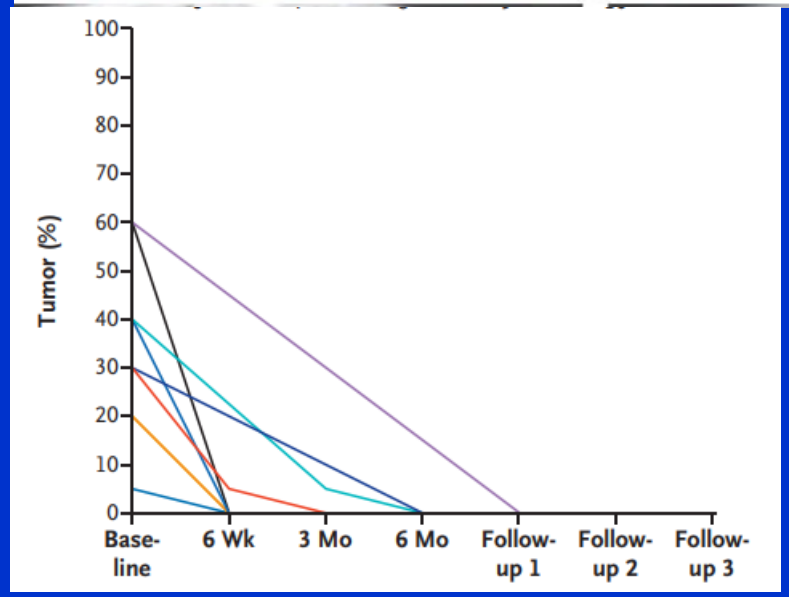
- Recently published data demonstrate that immunotherapy also could be helpful for patients with localized CRC with MMRD, with trials reporting complete regression of such tumors without chemotherapy, radiation therapy or surgery.

Colonoscopy MRI .PET,EUS Follow up



Complete Cure of Advance Rectal cancer by immunologic Therapy





PD-1 Blockade and Viable Tumor Cell Content.

Results

- A total of 12 patients have completed treatment with dostarlimab and have undergone at least 6 months of follow-up.

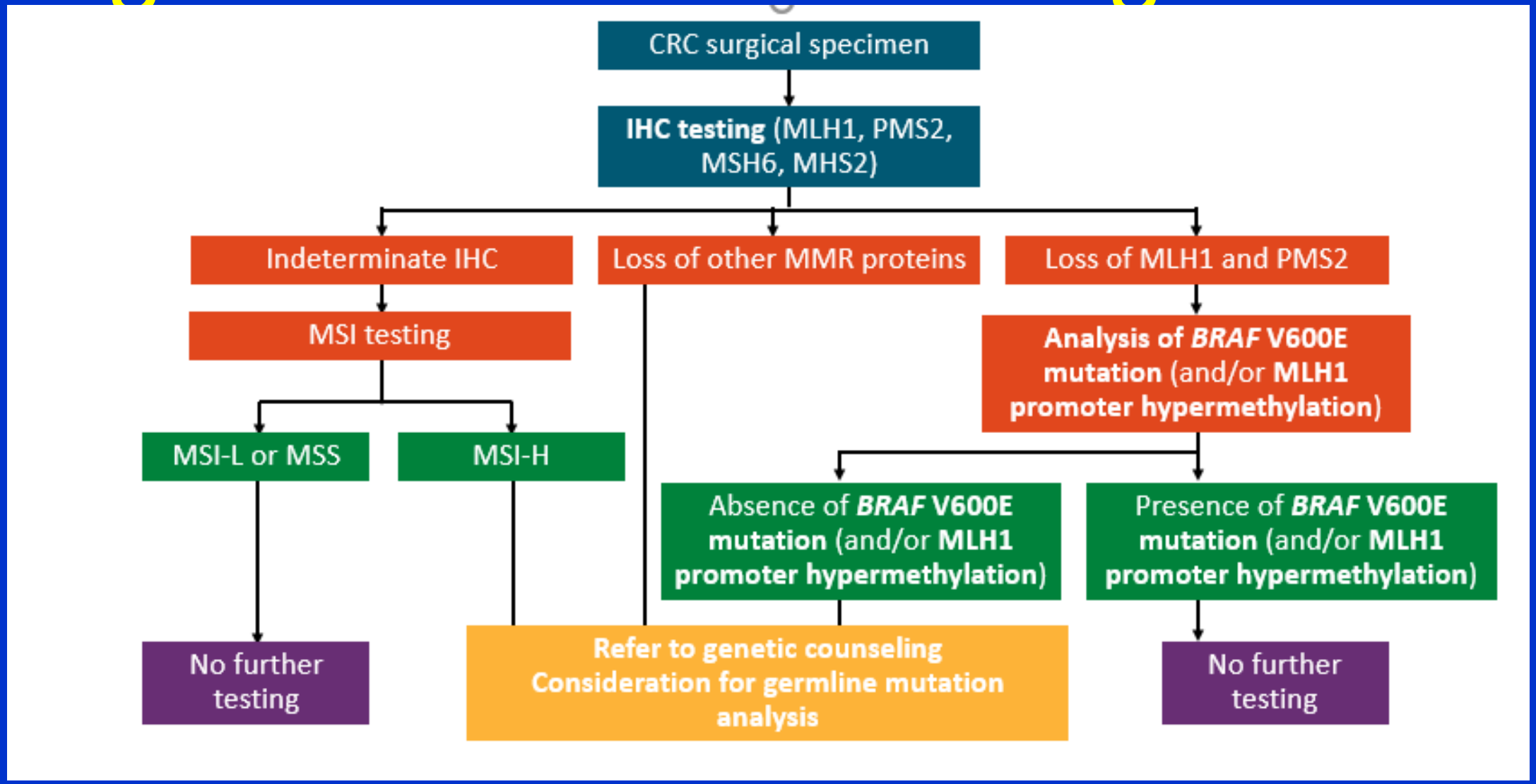
- **All 12 patients (100%; 95% confidence interval, 74 to 100) had a clinical complete response, with no evidence of tumor on MRI .PET,EUS ,Colonoscopy and biopsy**
- At the time of this report, no patients had received chemoradiotherapy or undergone surgery, and
- No cases of progression or recurrence had been reported during follow-up (range, 6 to 25 months).
- No adverse events of grade 3 or higher have been reported.

Conclusions

- Mismatch repair–deficient, locally advanced rectal cancer was highly sensitive to single-agent PD-1 blockade.

- Longer follow-up is needed to assess the duration of response.

Algorithm for MSI Testing in CRC



CRC, colorectal cancer; IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability

Three important Subtypes has been largely driven by well-described up to now.

1- Defective mismatch repair resulting in higher mutation rate.

2- Chromosomal instability with cellular proliferation along with and copy number aberrations.

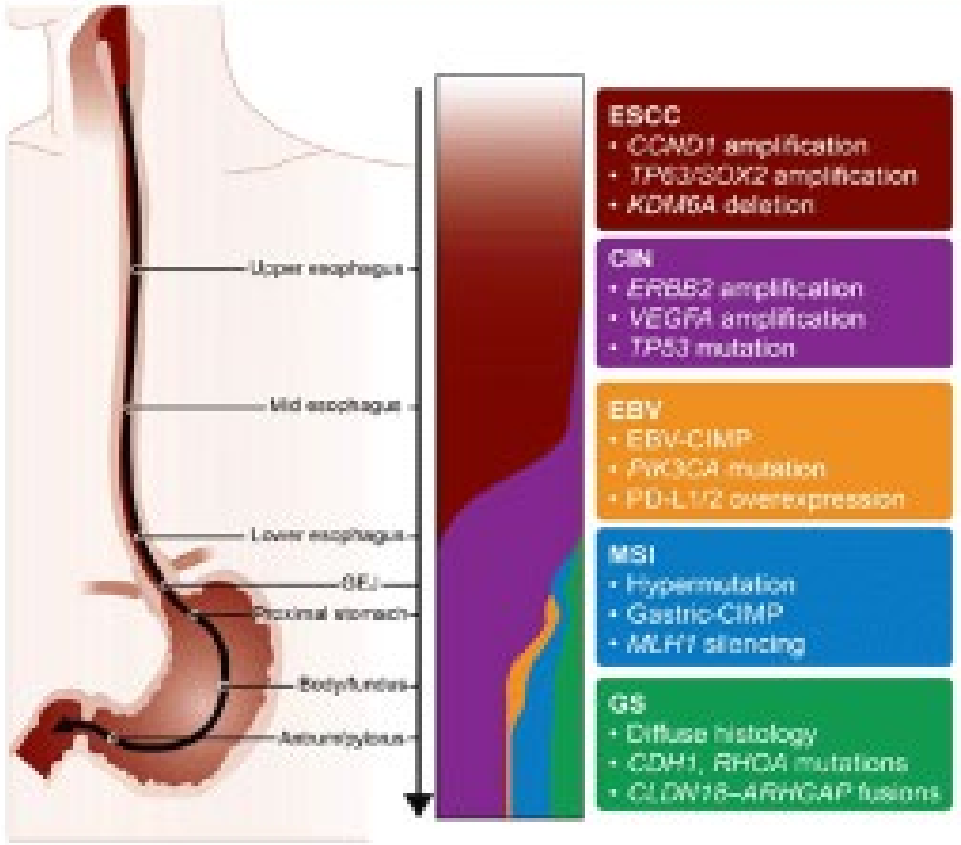
3 An invasive stromal phenotype mainly driven by TGF-beta linked to epithelial-mesenchymal transition

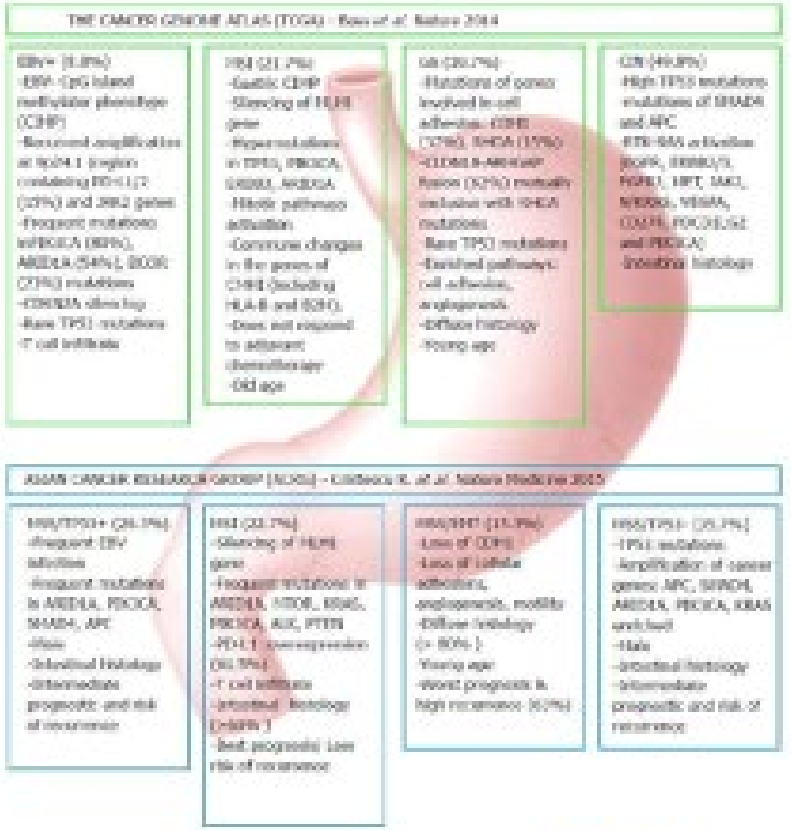
Conclusions

- Mismatch repair–deficient, locally advanced rectal cancer was highly sensitive to single-agent PD-1 blockade.

- Longer follow-up is needed to assess the duration of response.

Gastroesophageal Cancer Is Molecularly Heterogeneous[1,2]





1. Cancer Genome Atlas Network. Nature. 2017;541:169-175. 2. Chivu-Economescu M et al. World J Gastroenterol. 2018;24:1942-1961.

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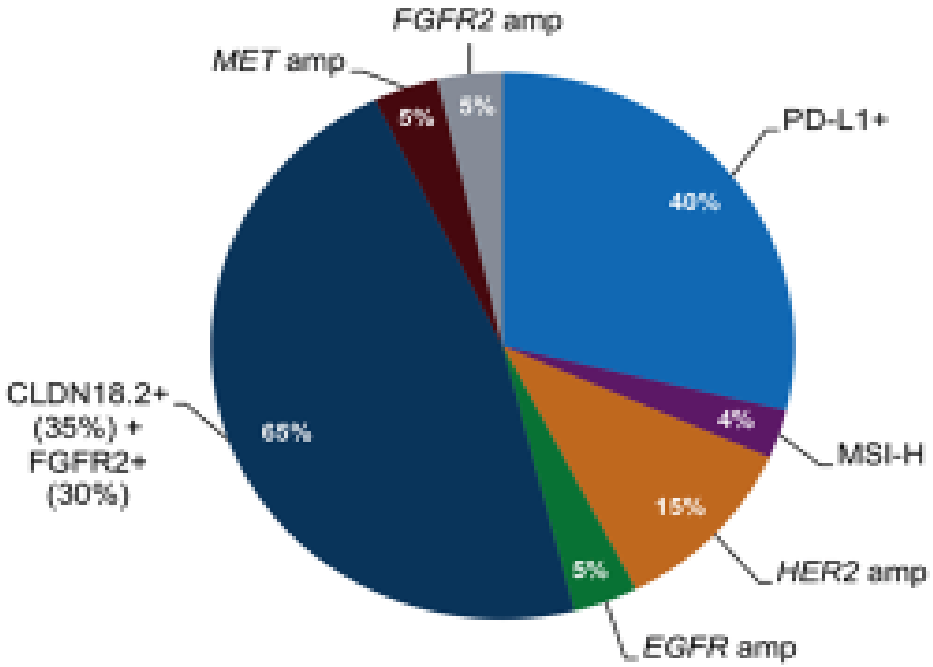
Current and Emerging Biomarkers in Gastroesophageal Cancers[1]



Key required biomarkers in advanced disease

- **HER2+**: 15%-20% of patients, improved survival with chemotherapy + trastuzumab and in 2L with trastuzumab deruxtecan (DS8201)
- **MSI-H**: 3%-5% of patients, high response rates and survival with PD-1 inhibitors
- **PD-L1+**: 30%-50% of patients, identifies those more likely to benefit from immune therapies, likely gradation within PD-L1+

Investigational biomarkers

- **CLDN18.2** high: 30%-35% of patients, response predictor for zolbetuximab (FAST Trial)[2]
- **FGFR2+** (IHC): 30% of patients, response predictor for bemarituzumab (FIGHT Trial)[3]

1. Provided courtesy of Zev A. Wainberg, MD. 2. Sahin U et al. *Ann Oncol*. 2021;32:609-619. 3. Wainberg ZA et al. ASCO GI 2021. Abstract 160.

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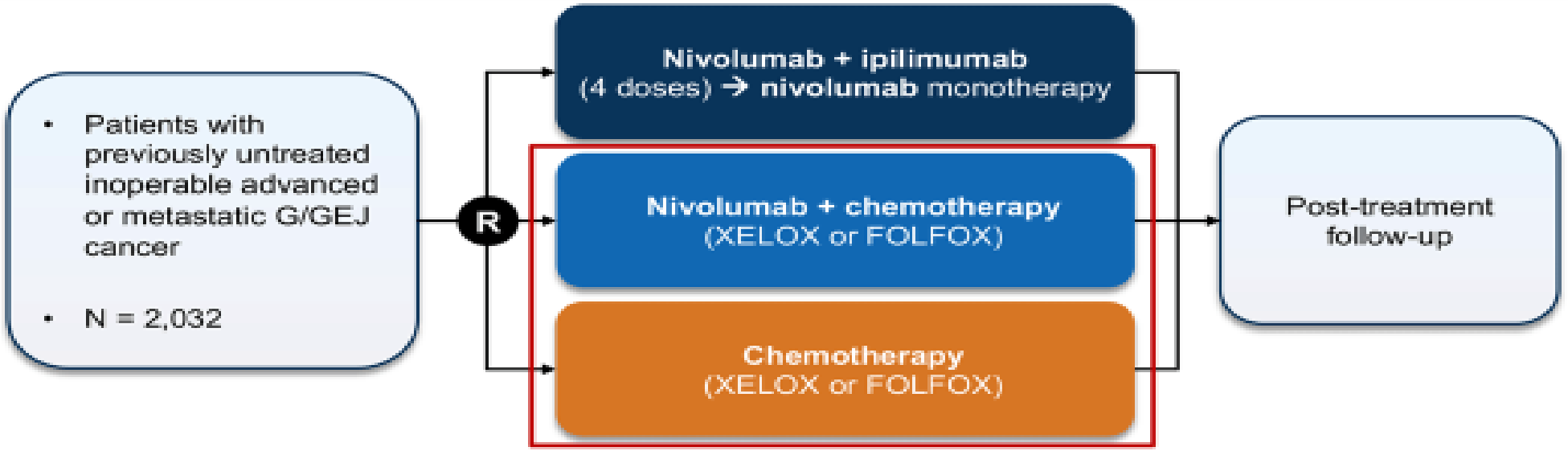
Immunotherapy-based regimens as first-line SoC in advanced ESCC

CheckMate -649: Immunotherapy Combinations for 1L Advanced/Metastatic G/GEJ Cancer[1]



- **Primary endpoints:** OS, PFS in PD-L1+ participants
- **Secondary endpoints:** OS, PFS, ORR, TTSD in all randomized participants

1. https://clinicaltrials.gov/ct2/show/NCT02872116.

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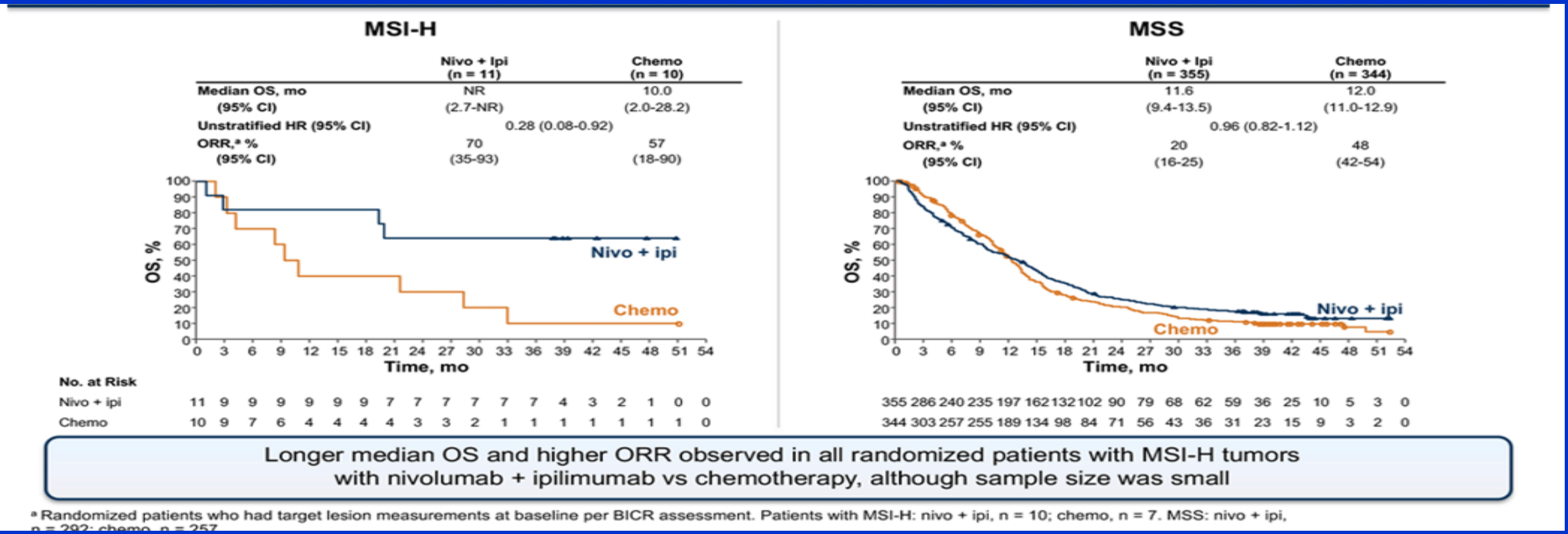
Overall Survival (OS) with Immunotherapy VS chemotherapy



Longer median OS and higher ORR observed in all randomized patients with MSI-H tumors with nivolumab + ipilimumab vs chemotherapy, although sample size was small

[a] Randomized patients who had target lesion measurements at baseline per BICR assessment. Patients with MSI-H: nivo + ipi, n = 10; chemo, n = 7. MSS: nivo + ipi, n = 292; chemo, n = 257

MSI (microsatellite instability) and MSS (microsatellite stability)

Practice-Changing Advances Seen With Immunotherapies in Upper GE Cancers (Adenocarcinoma)

Addressing Gaps and Improving Outcomes With Immunotherapy

- Patients with advanced gastroesophageal cancers have historically had few treatment options and poor outcomes, but within the last few years, ICIs have emerged and changed practice as well as outcomes
  - Standard 1L chemotherapy results in disease progression and death within 1 year in most patients with HER2- gastroesophageal adenocarcinoma
  - ICI-based therapies have demonstrated superior OS vs chemotherapy in numerous phase 3 RCTs and become new standards of care

Approvals in Adenocarcinoma:

- ❑ Nivolumab + chemotherapy approved in the United States for 1L treatment, irrespective of PD-L1 status[1,2]
- ❑ Pembrolizumab + trastuzumab and chemotherapy approved in the United States for HER2+ disease[3]
- ❑ Nivolumab approved in Asia irrespective of PD-L1 status for ≥3L treament[4]
- ❑ Pembrolizumab approval for ≥3L treatment in the United States withdrawn (announced in July 2021)[5]
- ❑ Pembrolizumab approved in TMB ≥10 mut/Mb (United States) or MSI-H tumors (United States and Japan)[3,6]

1. https://packageinserts.bms.com/pi/pi_opdivo.pdf. 2. https://www.bms.com/assets/bms/ca/documents/productmonograph/OPDIVO_EN_PM.pdf.
3. https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. 4. Högner A, Thuss-Patience P. *Pharmaceuticals (Basel)*. 2021;14:151.
5. https://www.merck.com/news/merck-provides-update-on-keytruda-pembrolizumab-indication-in-third-line-gastric-cancer-in-the-us.
6. https://www.merck.com/news/mercks-keytruda-pembrolizumab-significantly-improved-overall-survival-os-versus-placebo-in-certain-patients-with-advanced-hepatocellular-carcinoma-hcc-previously-treated-with-sora.

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FDA-Approved Immunotherapy Options in Advanced/Metastatic Gastroesophageal Cancers



FIRST-LINE TREATMENT

- ✓ Nivolumab with chemotherapy for advanced or metastatic G/GEJ cancer and esophageal adenocarcinoma regardless of PD-L1 status based on CheckMate -649 trial
- ✓ Pembrolizumab with chemotherapy for metastatic or locally advanced esophageal or GEJ carcinoma based on KEYNOTE-590 trial
- ✓ Pembrolizumab with trastuzumab and chemotherapy for HER2+ G/GEJ adenocarcinoma based on KEYNOTE-811 trial
- ✓ Nivolumab with ipilimumab or nivolumab with chemotherapy for advanced or metastatic ESCC based on CheckMate -648 trial

SECOND-LINE TREATMENT

- ✓ Nivolumab for ESCC based on ATTRACTION-3 trial
- ✓ Pembrolizumab for CPS ≥10 ESCC or MSI-H/dMMR and TMB-H (≥10 mut/Mb) tumors based on KEYNOTE-180 trial

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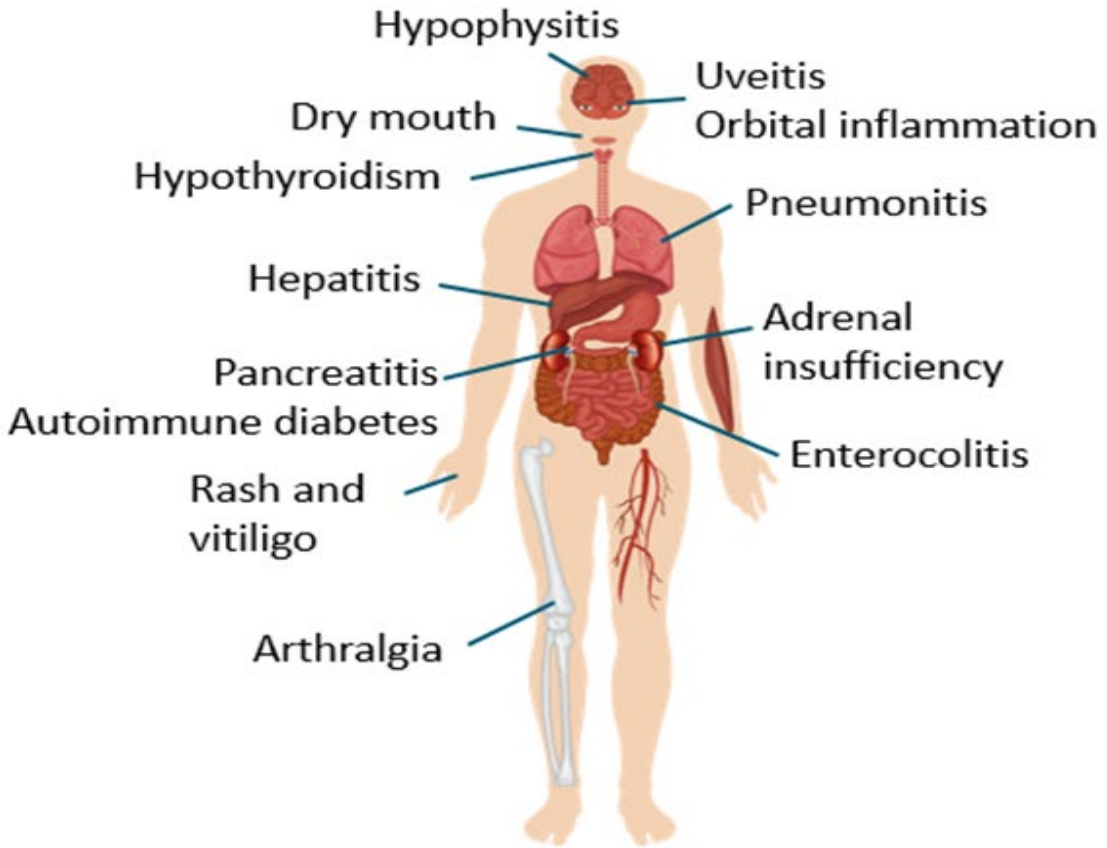
Adverse Evident with Immunotherapy

Immune-Related AEs Seen With Immune Checkpoint Inhibitors



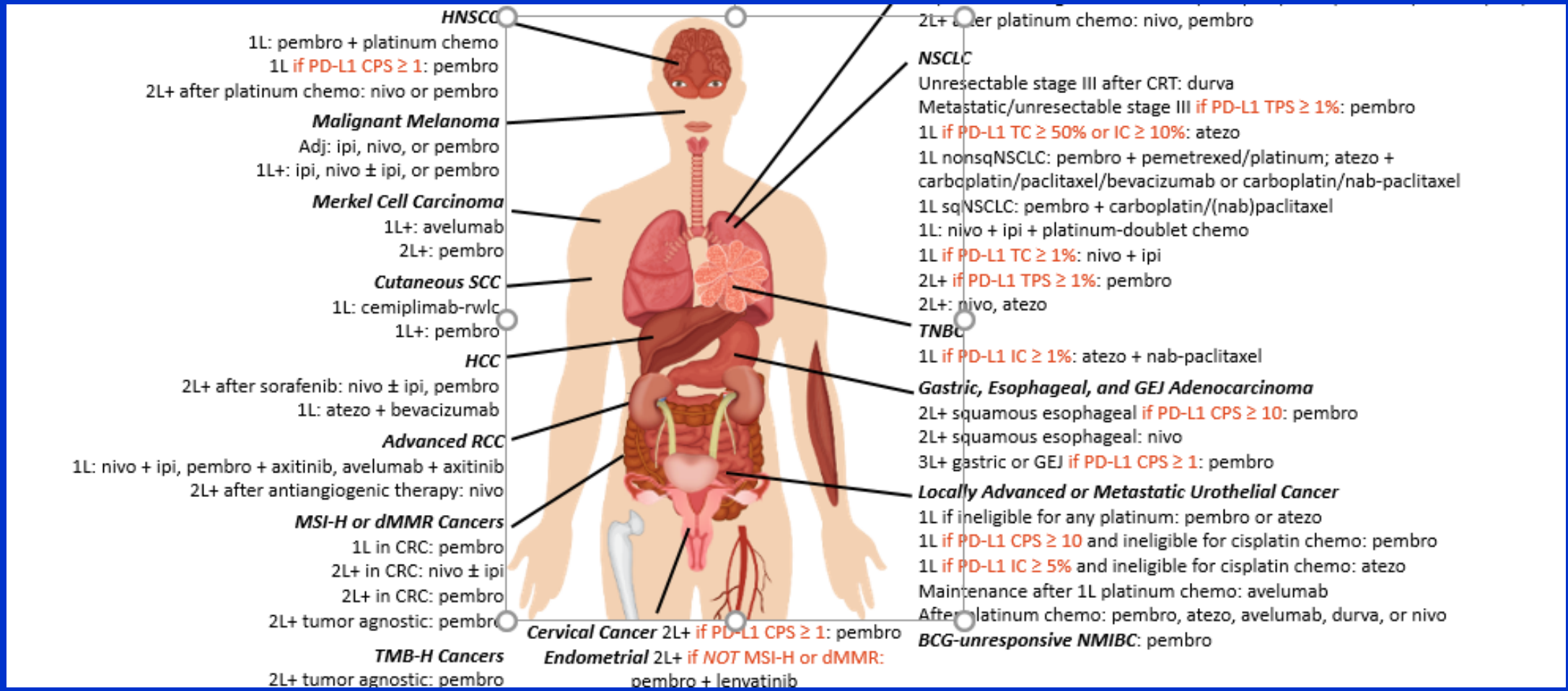
General Principles for Managing AEs

- Management generally based on severity of symptoms
- Mild (grade 1): supportive care, consider holding ICI
- Moderate (grade 2): hold ICI, redose if toxicity improves, consider steroids (prednisone 0.5-1 mg/kg/day)
- Severe (grade 3): discontinue ICI, monitor closely (likely inpatient), start high-dose steroids (prednisone 1-2 mg/kg/day) with a slow taper (≥ 1 mo)
- If not improving in 1-3 days, increase immunosuppression
- Dose reduction of ICI is not a recommended strategy
- Avoid delays in recognition and intervention

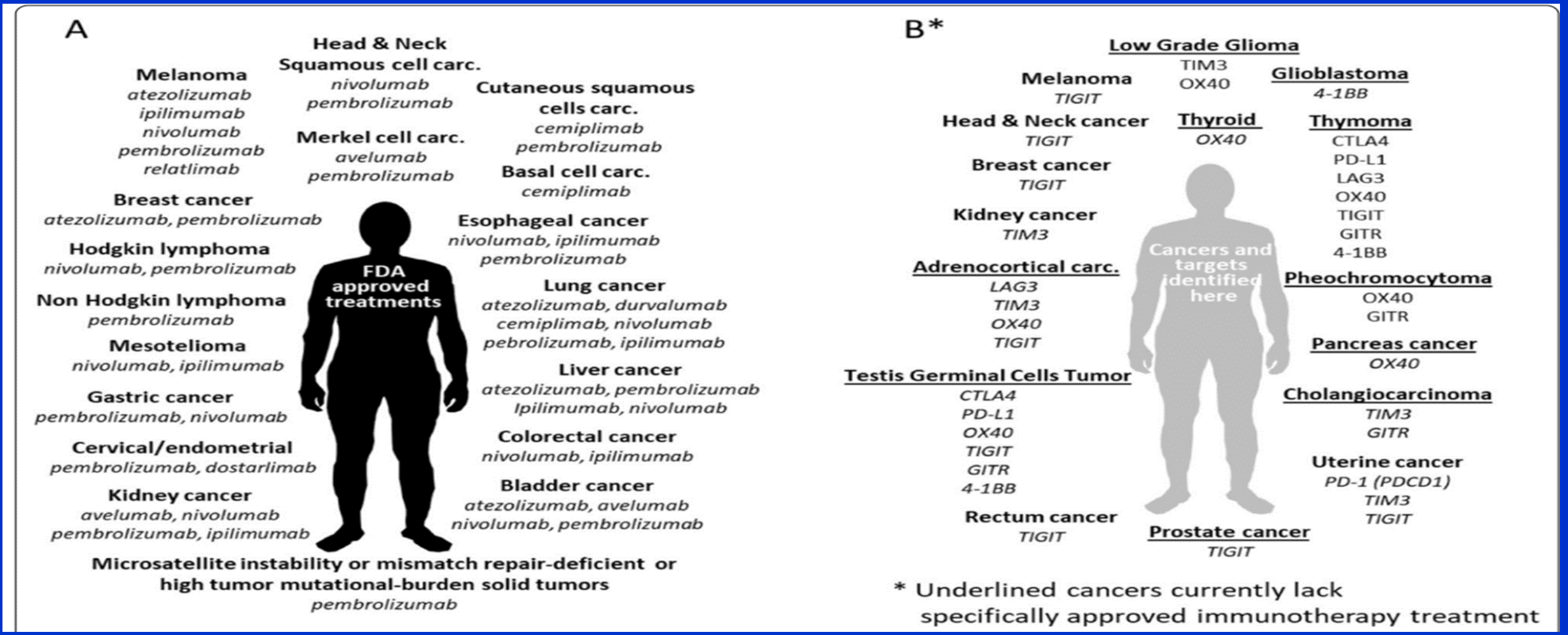
9 most relevant Immune checkpoint (ICR) receptors

- CTLA4,
- PD1,
- PD-L1,
- LAG3,
- TIM3,
- OX40,
- GITR,
- 4-1BB
- TIGIT

FDA-Approved Immune Checkpoint Inhibitor Indications in Solid Tumors



Immunotherapy based treatments approved by FDA (A) and new options under trial



Development of effective salvage therapies for cancers which do not respond to anti-PD-(L)1

- Another vast unmet challenge is the development of effective salvage therapies for individuals whose cancers do not respond to anti-PD-(L)1 despite having a generally ICB-responsive tumor type.

- We have learned that results can be improved by combining immunotherapies with many other kinds of cancer drugs, such as those targeting oncogenic kinases, that were never previously envisioned to play an immunologic role.

Final Thoughts

- Personalization and individualization of treatment for mCRC leads to improved outcomes
- Biomarker analyses in all patients with mCRC is extremely relevant and requires quality assurance and expert knowledge for applying implications of findings
- Relevant markers leading to change in therapeutic strategy in mCRC:
  - MSI-H/MSS—dMMR/pMMR
  - *RAS*
  - *BRAF* V600E mutation
  - HER2: IHC 3+ or amplification
  - *NTRK* fusion
  - Other mutations/alterations: anecdotal reports

Cancer will become a treatable curable and even preventable Disease

- Immunotherapy is already transforming cancer from a death sentence to a chronic disease for some patients.
- By making smart, evidence-based decisions in developing next generation immunotherapies, cancer should become an imminently treatable, curable and even preventable disease


Thank you