Treating Cancers in Lynch Syndrome What have we learned?

Dr. Grainne O'Kane

MB BCh BAO, MRCPI, MD
Assistant Professor University of Toronto
Medical Oncologist, Princess Margaret Cancer Centre

UHN
Toronto General
Toronto Western
Princess Margaret
Toronto Rehab
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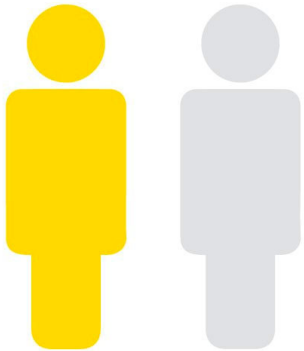
Outline

- Introduction & Cancers associated with Lynch Syndrome
- Prognosis and early stage disease
  - Chemotherapy
  - immunotherapy
- Later stage cancer and
  - chemotherapy
  - immunotherapy
- The Future of treatment

Nearly **1 in 2 Canadians**
will be diagnosed with cancer



cancer.ca/statistics

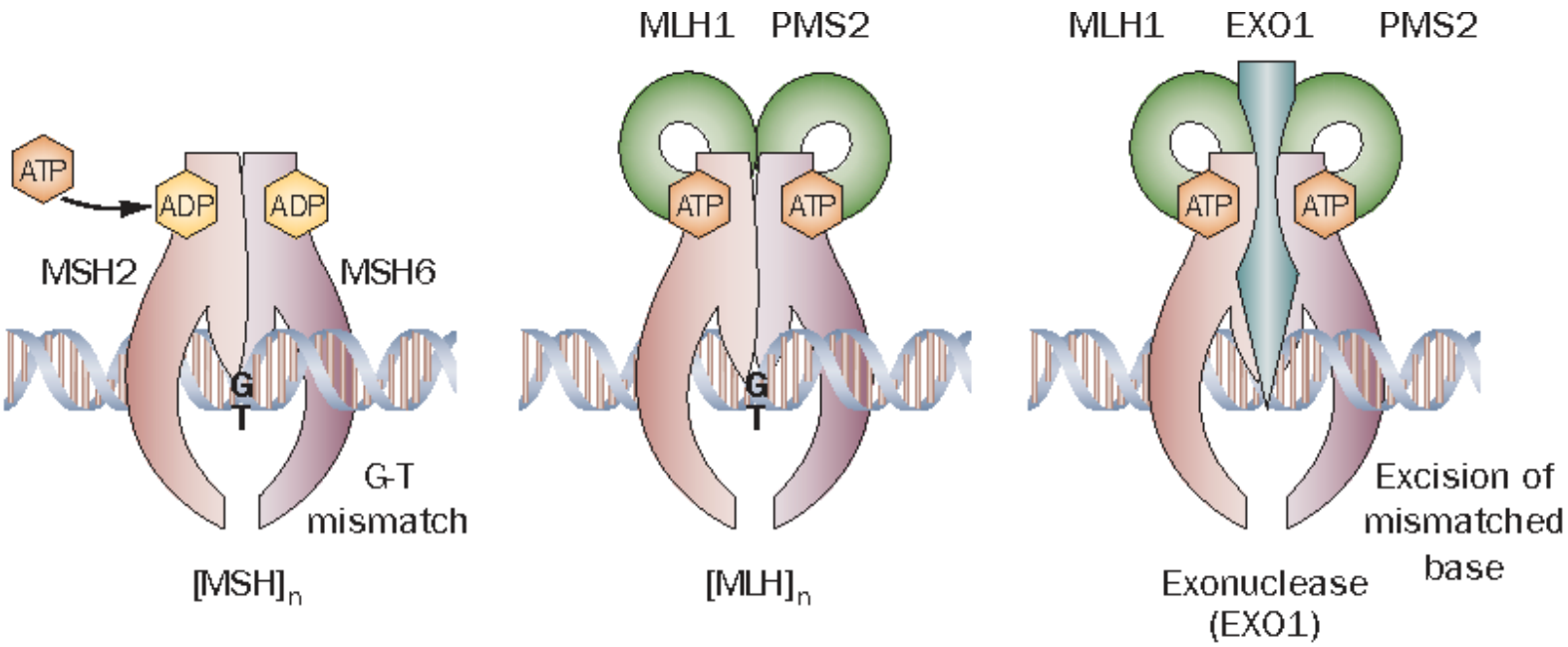
Two- Hit Theory of Cancer Causation

Normal cells typically have two undamaged chromosomes; one inherited from our mother and the other from our father. Each chromosome contains thousands of genes some of which are responsible for controlling cancer.

NON-HEREDITARY CANCER *By Chance – Most Common*

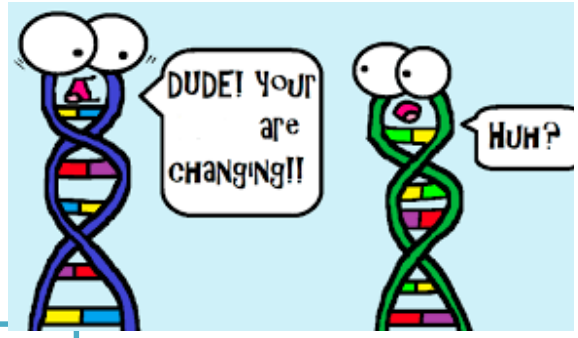
HEREDITARY CANCER *Passed Through Family – Rare*

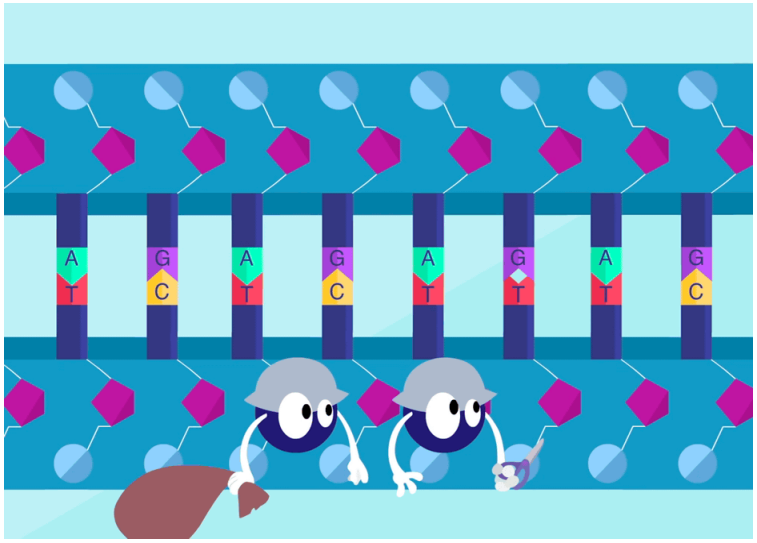
Lynch syndrome a defect in repair of mismatches



Nature Reviews clinical Oncology 2010

Mismatch repair deficient (MMRd) or MSI-H tumours



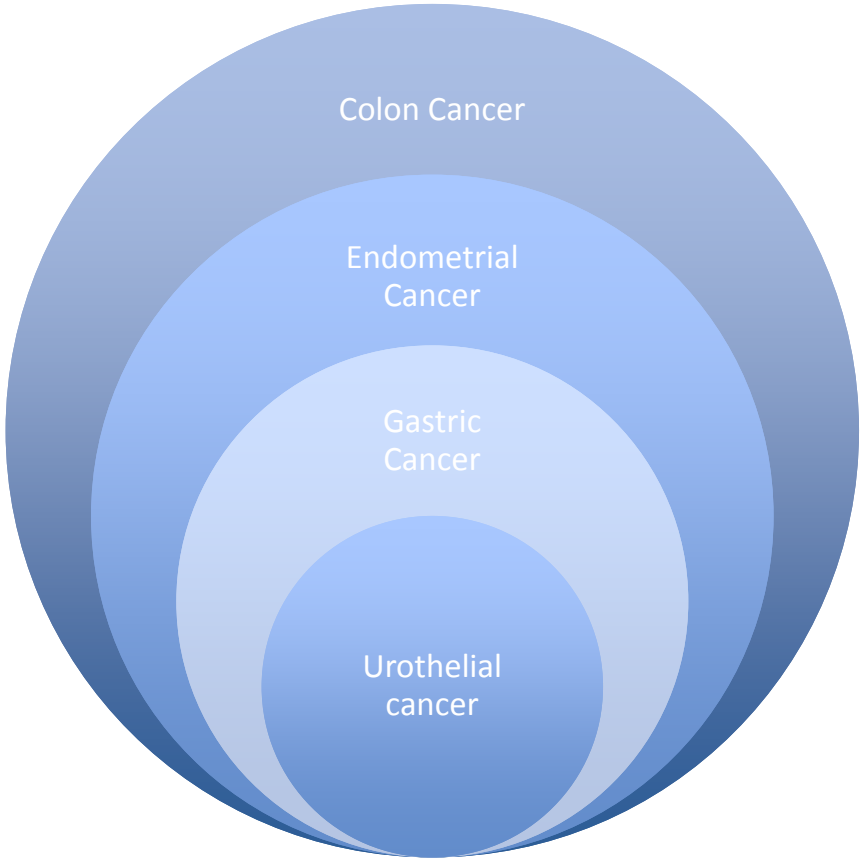


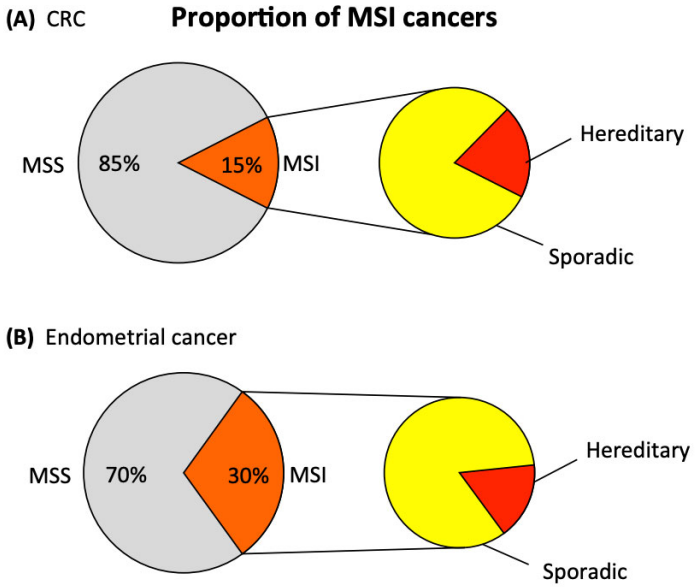
Mutations –
High mutational burden

↓

Abnormal Proteins recognised by Immune cells

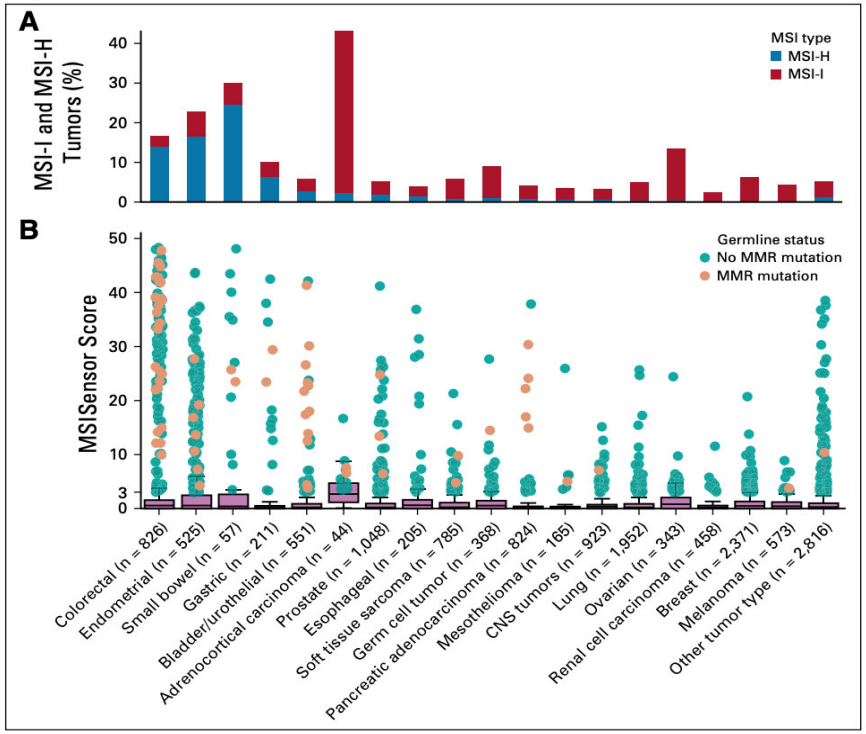
MSI-H cancers- most common cases in LS





Kloor Trends in Cancer 2016

Others? – Role of NGS in oncology
Memorial Sloan Kettering experience



>15,000 tumour samples; >50 types
NGS-panel testing
MSI-sensor: MSS, MSI-I, MSI-H

2.2% - MSI-H (n=326)
Highest in small bowel, CRC, endometrial

103 patients with Lynch
36% had MSS tumours

Lathman JCO 2019

Pearls

- MSI-H cancers are unique because of the failure of the specific mismatch repair pathway
- Lynch syndrome is a smaller portion of all MSI-H cancers
- Not all cancers in setting of known Lynch Syndrome are MSI-H

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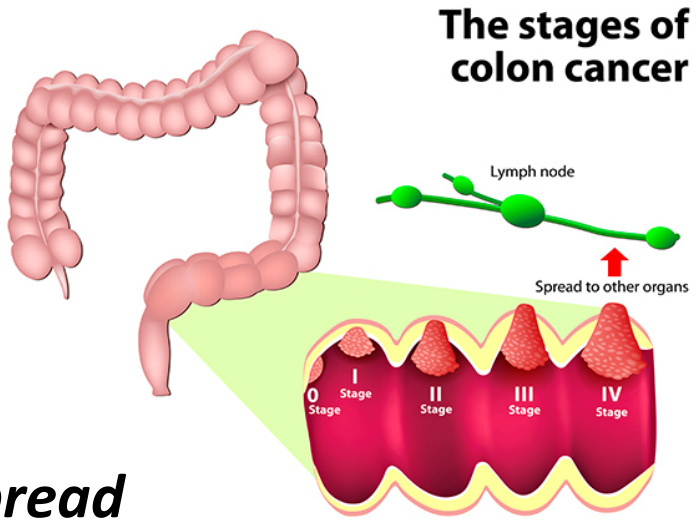
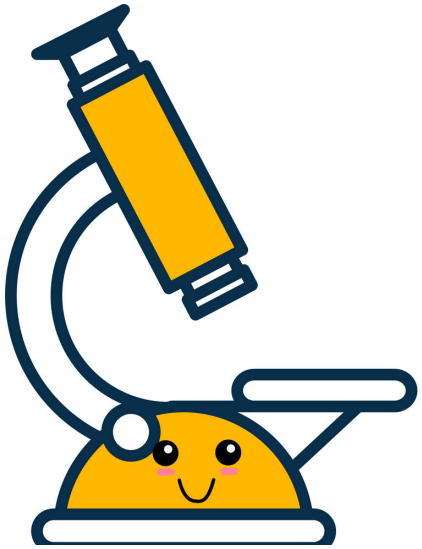
Prognosis and Early stage disease

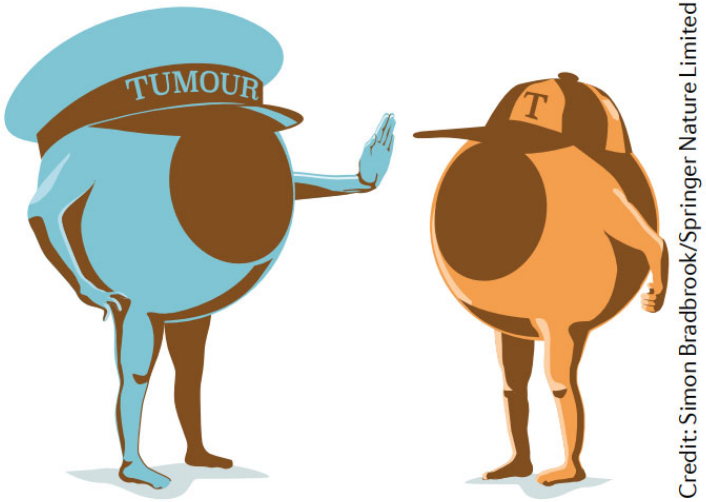
- Colon Cancer - MSI-H tumour %
  - Stage II 22%
  - Stage III 12%
  - Stage IV 3-5%



Less likely to metastasize or spread

In many tumour types MMRd/MSI-H is a marker of good outcome





Credit: Simon Bradbrook/Springer Nature Limited

Otto Nature Reviews Immunology 2018

The stage of the cancer can influence treatment decisions- do we need chemo?

MSI-H tumours have a better prognosis in early stage

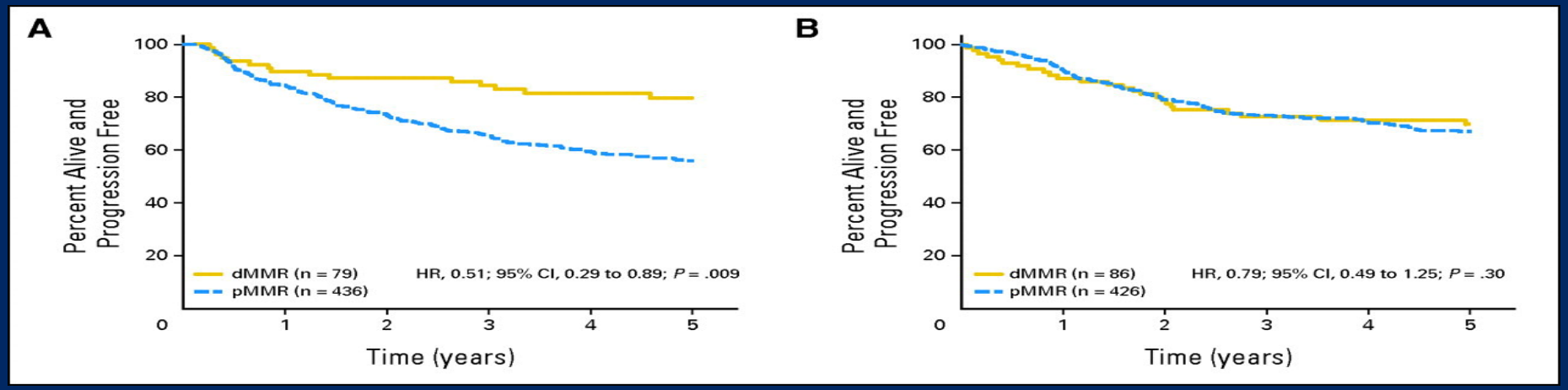


Fig 1. (A) Disease-free survival (DFS) in untreated patients by DNA mismatch repair (MMR) status. (B) DFS in treated patients by MMR. dMMR, defective DNA mismatch repair; pMMR, proficient DNA mismatch repair.

Sargent et al JCO 2010

MSI-H tumours in stage II may not benefit from any additional chemo

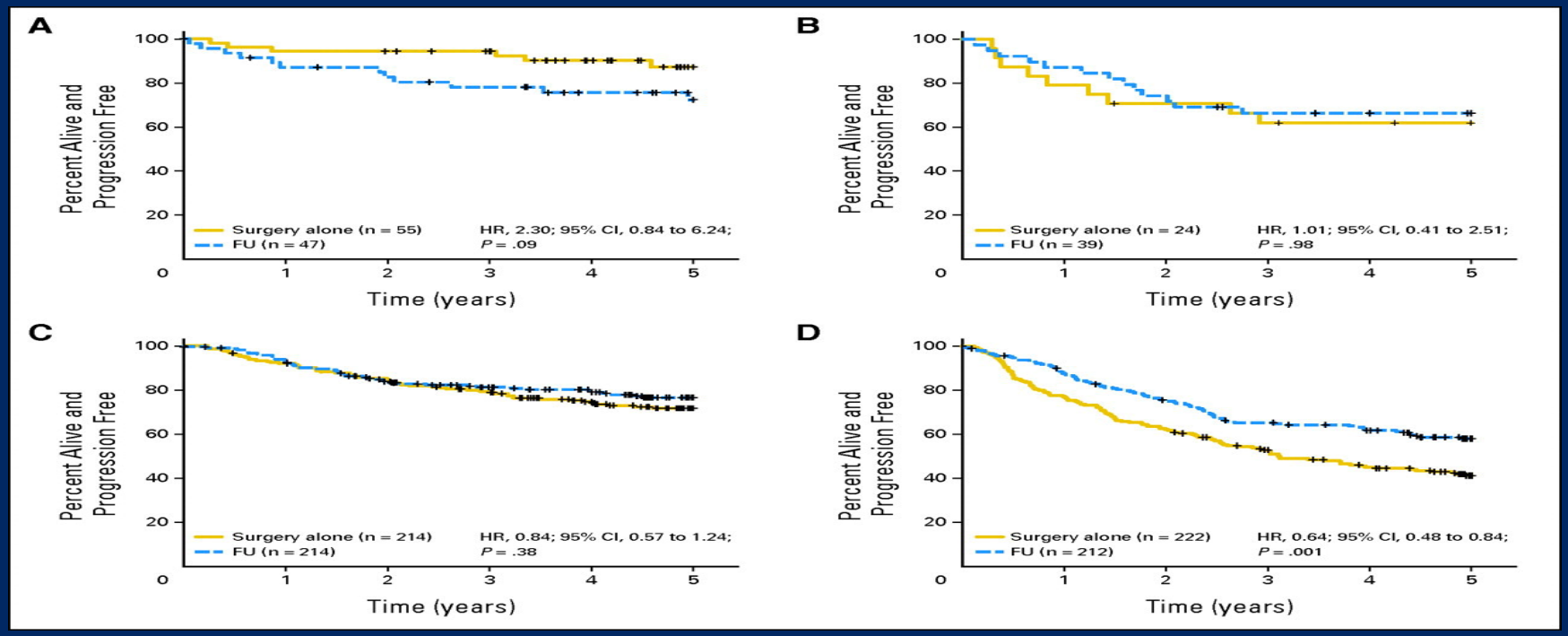


Fig 2. (A) Disease-free survival (DFS) in patients with stage II disease and defective DNA mismatch repair (dMMR) by treatment status. (B) DFS in patients with stage III disease and dMMR by treatment status. (C) DFS in patients with stage II disease and proficient MMR (pMMR) by treatment status. (D) DFS in patients with stage III disease and pMMR by treatment

Sargent et al JCO 2010

Gastric Cancer – Early stage

- 8-10% stomach cancers are MSI-H-better prognosis

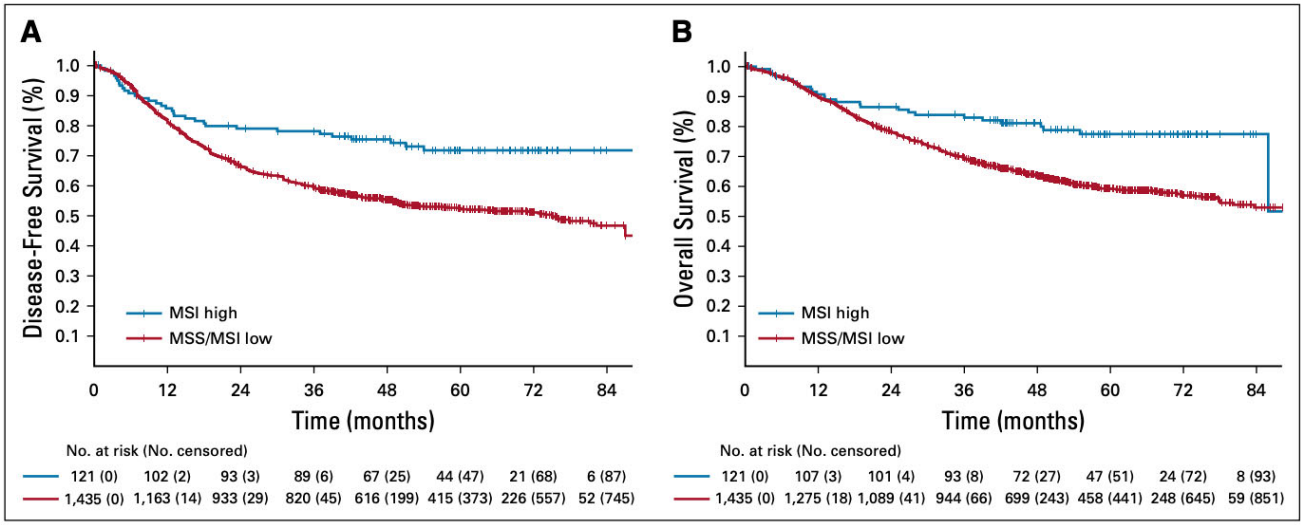


FIG 2. Kaplan-Meier curves of (A) disease-free survival and (B) overall survival according to microsatellite-instability (MSI) status (microsatellite stable [MSS]/MSI-low *v* MSI-high).

Pietrantonio et al
JCO 2019

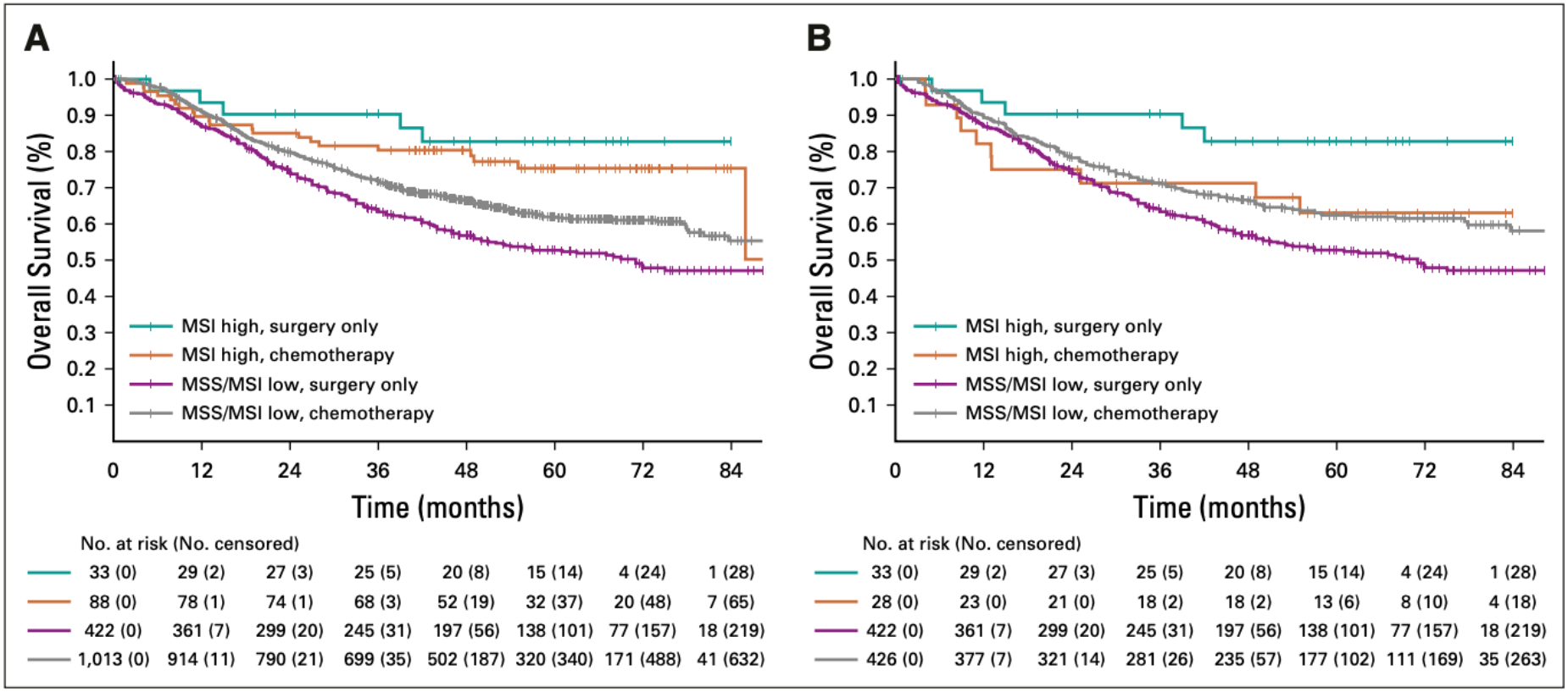


FIG 4. Kaplan-Meier curves of overall survival according to treatment (surgery plus chemotherapy *v* surgery only) and microsatellite-instability (MSI) status (MSI-high *v* microsatellite stable [MSS]/MSI-low) in (A) whole trial population and (B) MAGIC and CLASSIC trials only.

Pietrantonio et al
JCO 2019

Pearls

- Lynch syndrome cancer such as colon cancer have a better prognosis than microsatellite stable cancers that are removed by surgery
- In certain stages additional chemotherapy may cause more harm

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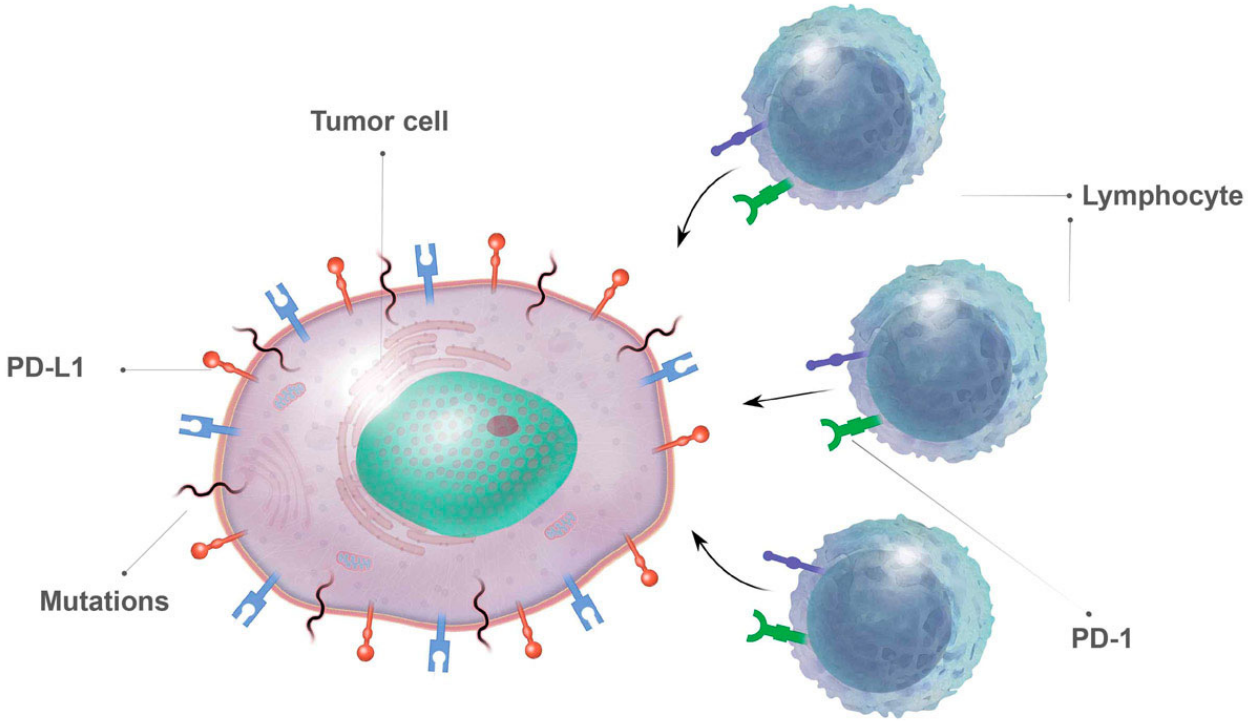
Stage IV cancers- will chemotherapy go?

Immunotherapy could revolutionise care for cancer patients. So is this the end of chemotherapy as we know it?

Cut, burn, poison, aka surgery, radiation and chemotherapy, were the options for cancer sufferers. But one man had other ideas. James Allison pursued his belief in immunotherapy for years when the medical world was doubtful. No longer. Last month he won the Nobel prize for medicine (with help from his brilliant colleagues and brainy wife). Now his research is changing everything we know about treating cancer

What is immunotherapy and why in LS



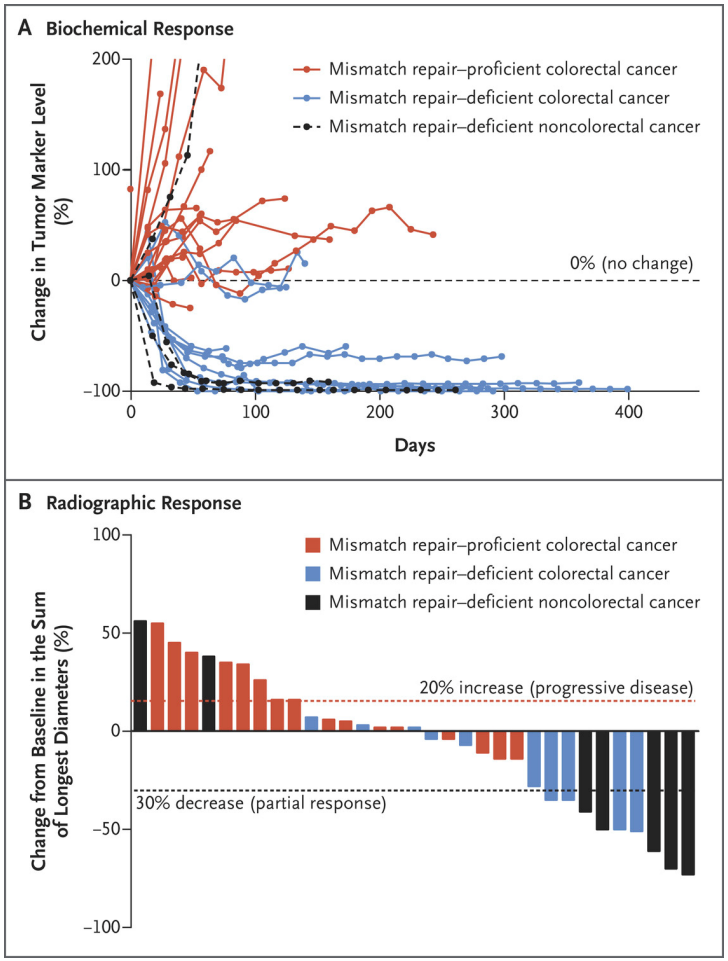
Immune checkpoint inhibitors

Immunotherapy in Lynch Syndrome

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

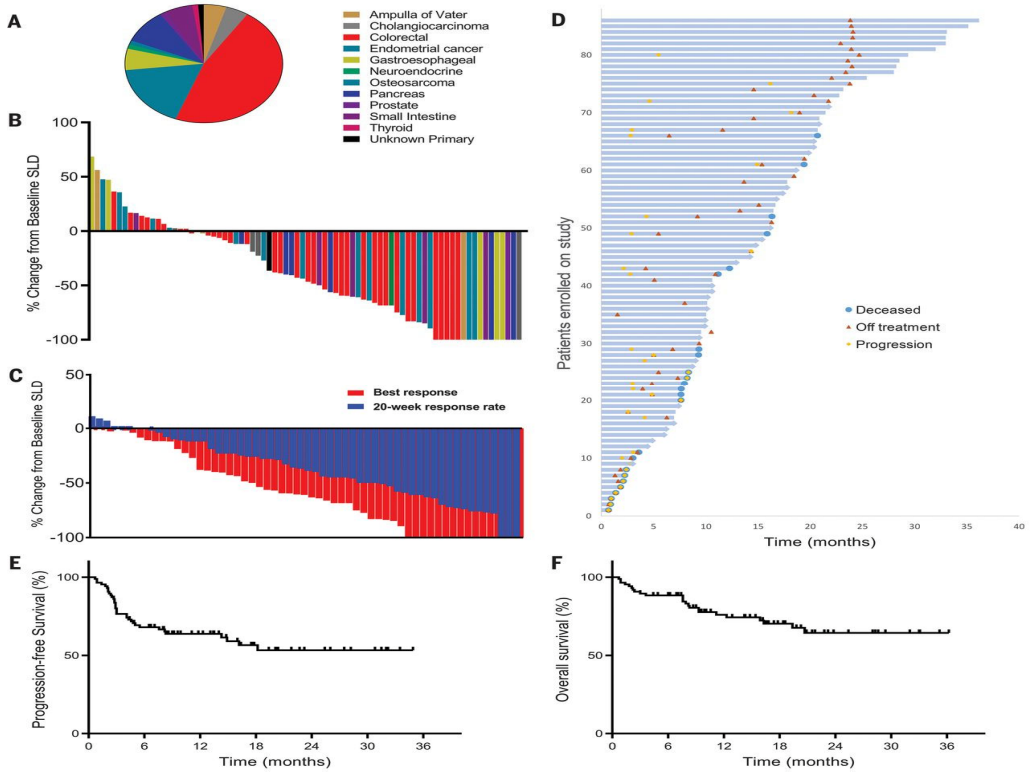
Listen to the FDA D.I.S.C.O. podcast about this approval

On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.



Le NEJM June 2015

Fig. 1 Patient survival and clinical response to pembrolizumab across 12 different tumor types with mismatch repair deficiency.



Dung T. Le et al. Science 2017;357:409-413

Science
AAAS

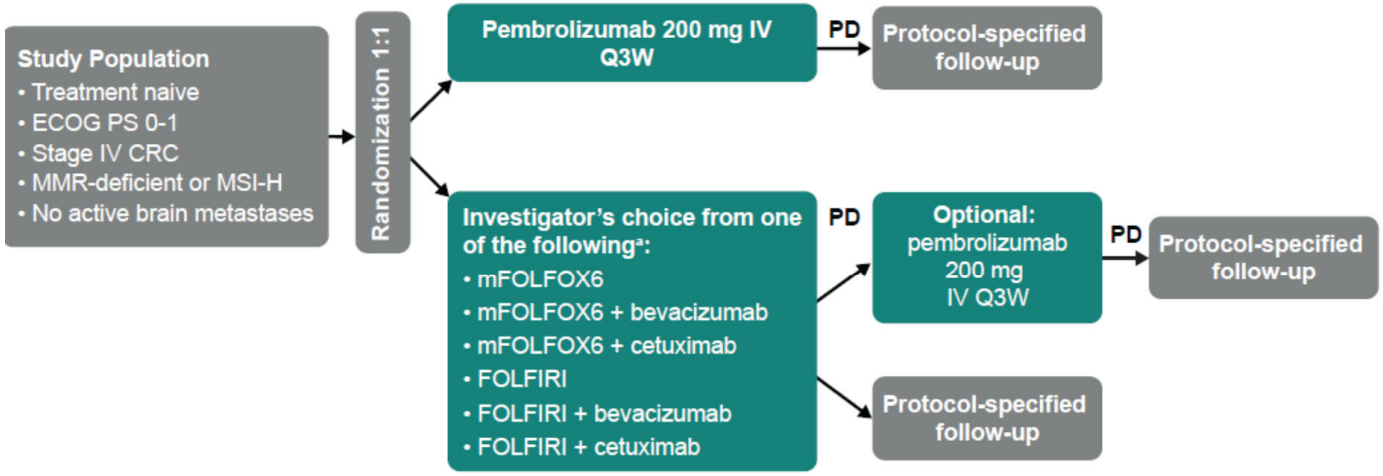
FDA approved Drugs

- Pembrolizumab- regardless of tumour type- Keynote trials (23 May 2017)
- Nivolumab in colorectal cancer after first therapy not worked – Checkmate 142 (July 31st 2017)
- Nivolumab/Ipilimumab in colorectal cancer after first therapy had not worked- Checkmate-142 (10th July 2018)

Should Immunotherapy be used as fist treatment

- **2-arm, randomized, open-label, multisite, phase III trial**

KEYNOTE-177



CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, leucovorin + irinotecan + 5-fluorouracil; IV, intravenously; mFOLFOX6, modified oxaliplatin + leucovorin + 5-fluorouracil; MMR, mismatch repair; MSI-H, microsatellite instability-high; PD, disease progression; Q3W, every 3 weeks; [a]Choice must be determined before randomization.

Diaz Jr LA, et al. *J Clin Oncol.* 2016;34(Suppl 4S): Abstract TPS789.

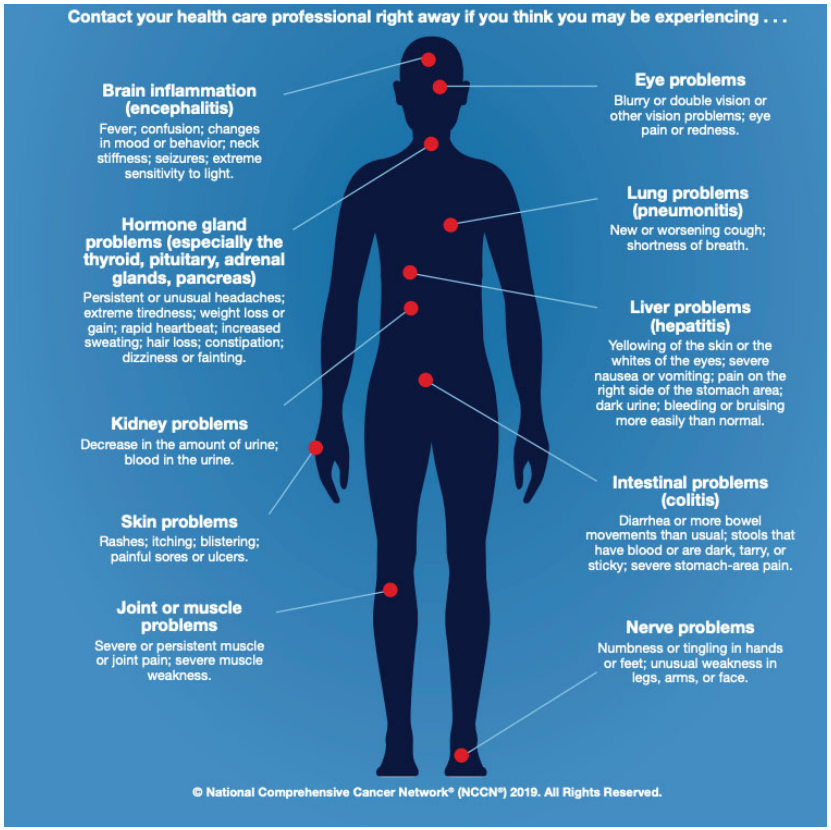
Immunotherapy may become new first line treatment in some metastatic colorectal cancers [ESMO 2018 Press Release]

Date: 22 Oct 2018

Topic: **Gastrointestinal cancers**

Munich, Germany, 22 October 2018 – Immunotherapy with nivolumab and low-dose ipilimumab could become a new first line treatment in patients with some metastatic colorectal cancers following late-breaking results from the CheckMate-142 trial reported at the ESMO 2018 Congress in Munich. (1) The drug combination shrank tumours and had beneficial effects on survival in patients with microsatellite in-stabiliy (MSI)-high metastatic colorectal cancer.

Immunotherapy side effects



Where are we in Canada?

- Access can be challenging
- Relying currently on clinical trials (many)
- Private Health Insurance

- No compassionate access

Pearls

- MMR-d/MSI-H first marker to allow drug approval regardless of where tumour is
- Immunotherapy is not yet **freely** accessible in Canada, but many trials available, insurance companies

The future

The future

- Late Stage
  - Immunotherapy will become standard of care
  - Optimal duration of immunotherapy
  - Resistance and sequence of drugs
- Early Stage
  - Immunotherapy used before or after surgery
- Prevention/Early Detection
  - Can we create a vaccine
  - Blood markers