RECOGNISING TARGETS NEW WEAPONS

Kate Clarke

Medical oncologist

Te Whatu Ora
Health New Zealand

20 MINS WITH A MEDICAL ONCOLOGIST

Recognising targets

- PD-1 blockade as curative-intent therapy in mismatch repair deficient locally advanced rectal cancer
- Next generation sequence utility in cholangiocarcinoma

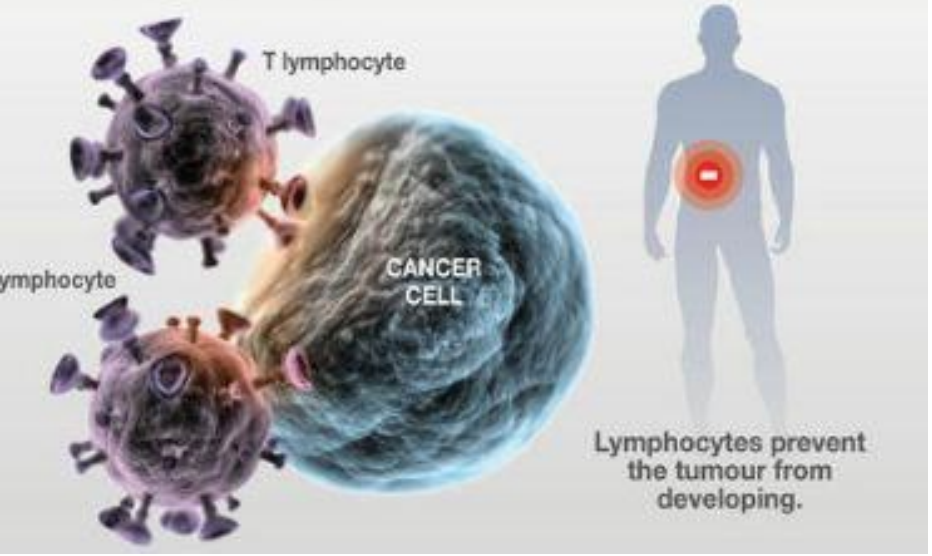
New therapies

- Adjuvant nivolumab in resected oesophageal or gastro-esophageal junction cancer
- Systemic therapy advanced hepato-cellular carcinoma

Disclaimer – although these therapies/tests are licenced and recommended by international expert guidelines; they are not funded for patients in Aotearoa

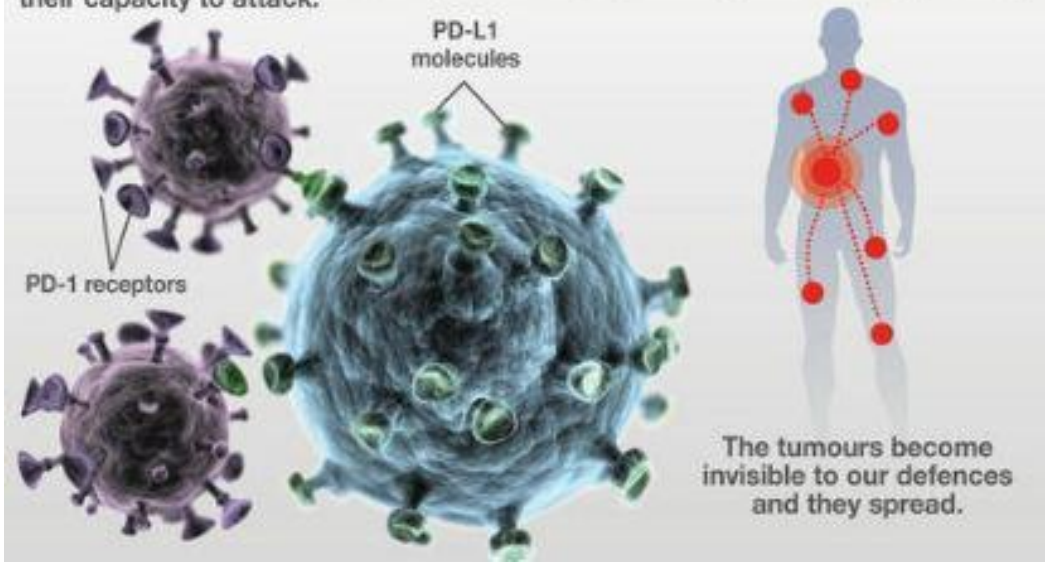
1. Normal work of the immune system

T lymphocytes are the cells of the immune system that identify tumour cells and destroy them.



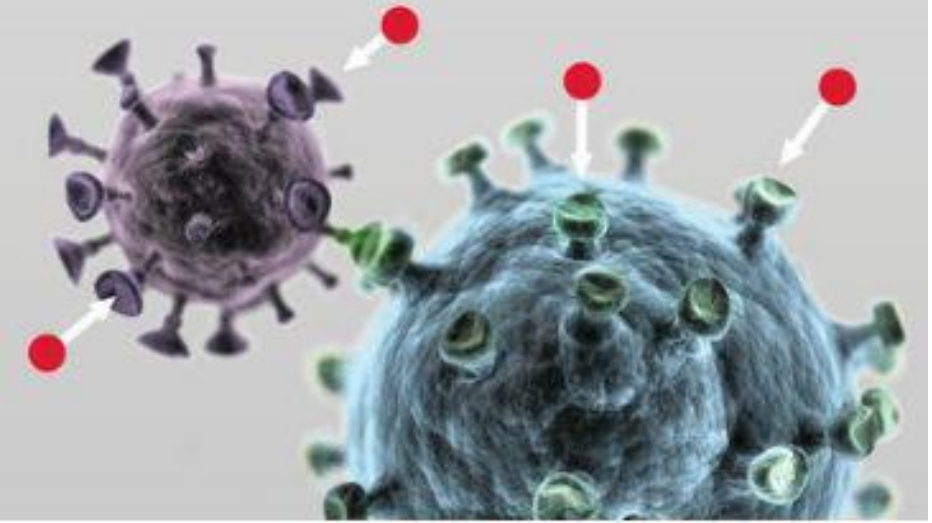
2. Camouflage of tumour cells

Some tumour cells arm themselves with a shield of molecules called PD-L1. Lymphocytes possess PD-1 receptors which, by bonding to these traps, destroy their capacity to attack.



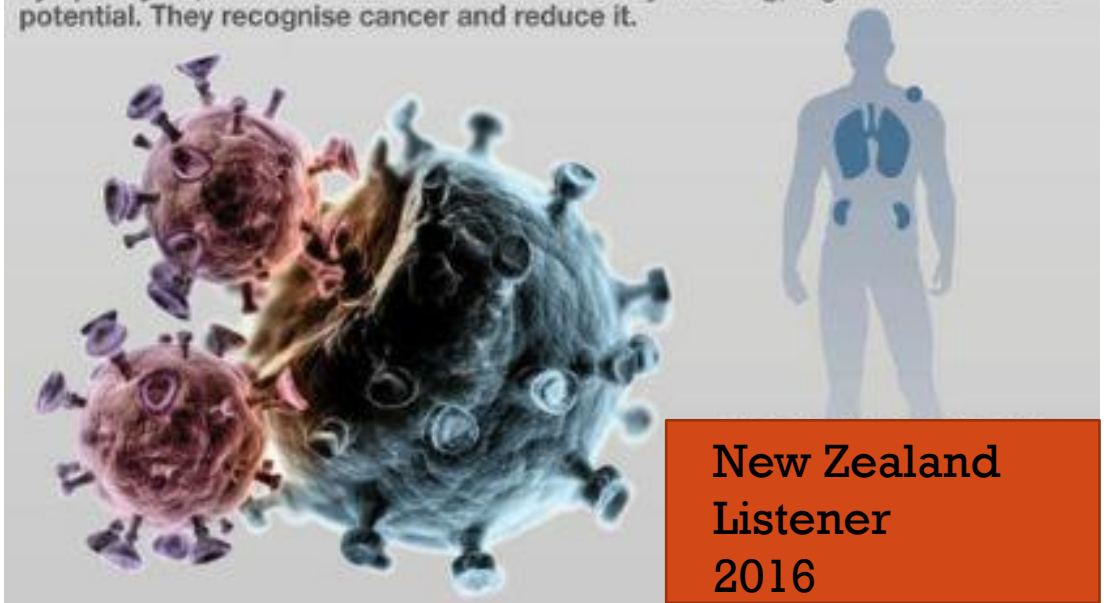
3. Action of the new inhibitor drugs

The new drugs based on antibodies block PD-1 from the cells of the immune system and PD-L1 from tumour cells to prevent their fatal action.



4. Result of immunotherapy

Lymphocytes, once freed from their blindness by the drug, regain their defence potential. They recognise cancer and reduce it.



New Zealand Listener 2016

PD-1 BLOCKADE AS CURATIVE-INTENT THERAPY IN MISMATCH REPAIR DEFICIENT LOCALLY ADVANCED RECTAL CANCER

Cercek et al.,
NEJM 2022; 386: 2363-2376
June 23, 2022

RESEARCH SUMMARY

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

Cercek A et al. DOI: 10.1056/NEJMoa2201445

CLINICAL PROBLEM

Standard treatment for locally advanced rectal cancer includes neoadjuvant chemotherapy and radiation, followed by surgical resection of the rectum. This approach, however, is associated with substantial complications and toxic effects. Research suggests that immune checkpoint blockade alone is highly effective in patients with mismatch repair–deficient metastatic colorectal cancer; whether this strategy is effective in mismatch repair–deficient, locally advanced rectal cancer is unknown.

CLINICAL TRIAL

Design: A prospective, phase 2, single-group study examined the efficacy and safety of neoadjuvant therapy with the programmed death 1 (PD-1) inhibitor dostarlimab in patients with mismatch repair–deficient stage II or III rectal adenocarcinoma.

Intervention: Adult patients received intravenous dostarlimab every 3 weeks for 6 months, to be followed by chemoradiotherapy and total mesorectal excision. Patients with a clinical complete response to dostarlimab could forgo chemoradiotherapy and surgery. A key primary end point was overall response to dostarlimab alone or to dostarlimab plus chemoradiotherapy, determined on the basis of rectal magnetic resonance imaging, endoscopic visualization, and digital rectal examination.

RESULTS

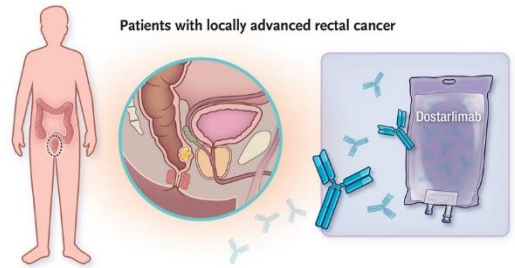
Efficacy: 12 of 16 enrolled patients have already completed 6 months of dostarlimab. All 12 had a clinical complete response, with no evidence of tumor on any diagnostic test. During a median follow-up of 12 months, no patient received chemoradiotherapy or underwent surgery, and none had disease progression or recurrence.

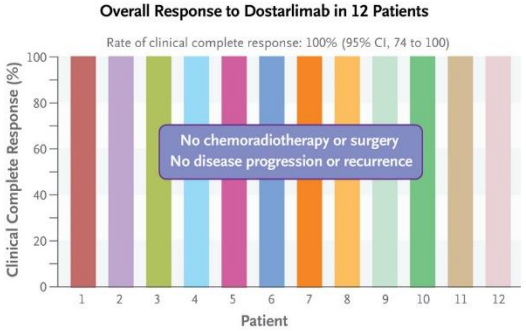
Safety: No adverse events of grade 3 or higher have occurred. The most common adverse events of grade 1 or 2 included rash or dermatitis, pruritus, fatigue, and nausea.

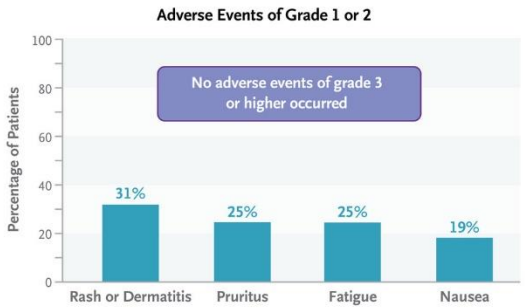
LIMITATIONS AND REMAINING QUESTIONS

- The study was small and limited to a single institution, and most of the patients were White.
- Longer-term follow-up is needed to evaluate the duration of response.

Links: Full Article | NEJM Quick Take | Editorial





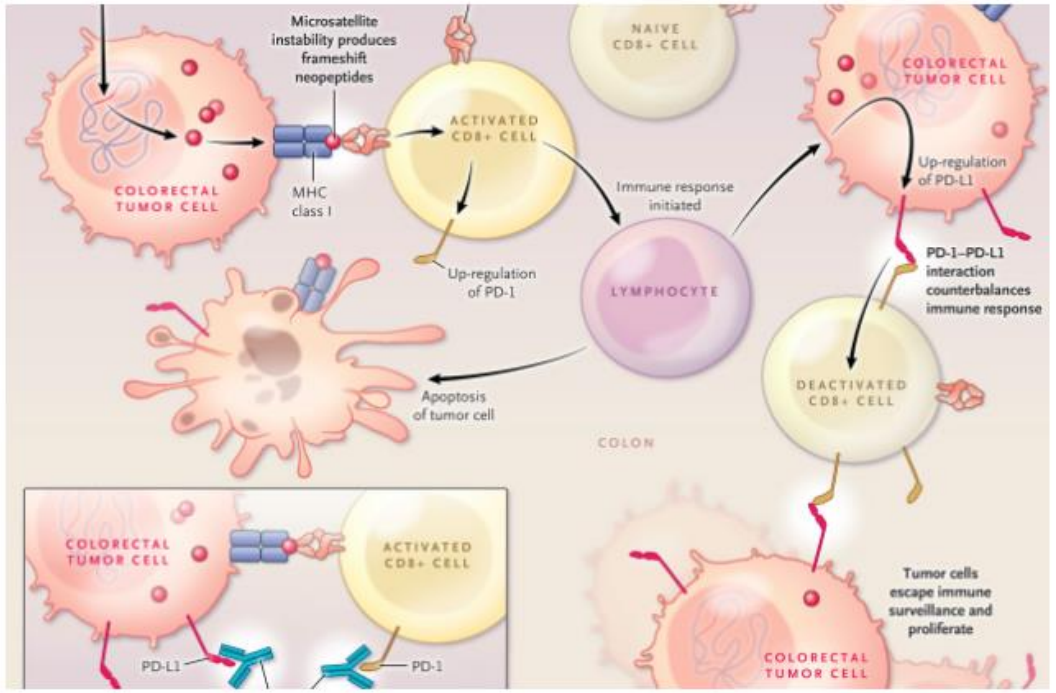


CONCLUSIONS

All patients with mismatch repair–deficient, locally advanced rectal cancer who were treated with the PD-1 inhibitor dostarlimab alone for 6 months had a clinical complete response, although longer follow-up is warranted.

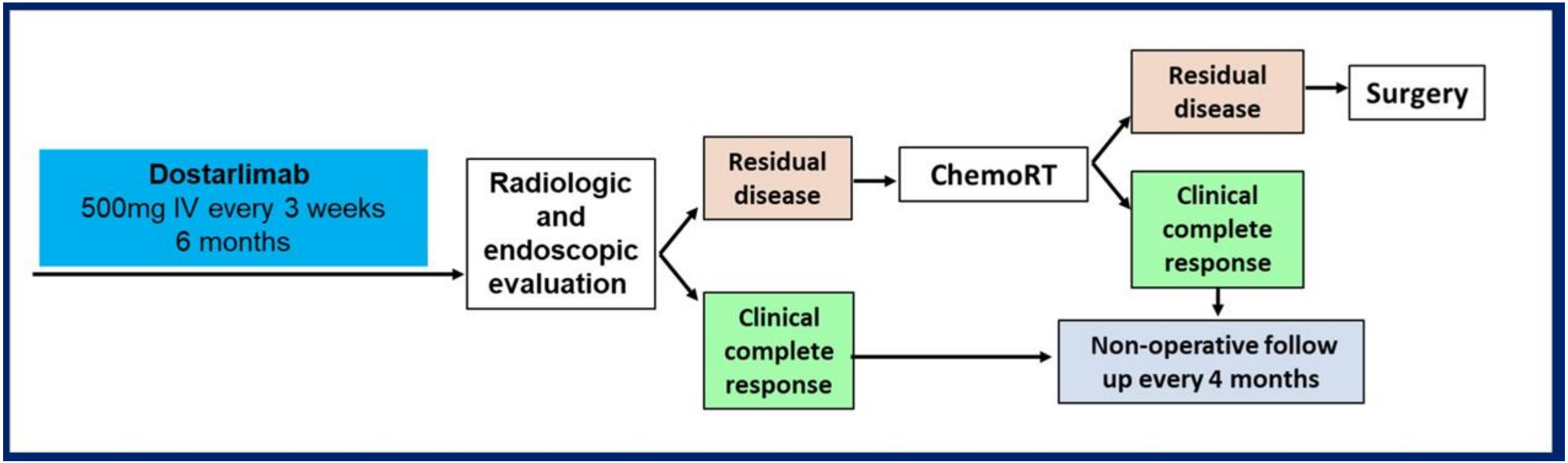
MISMATCH REPAIR DEFICIENT RECTAL CANCER

- AKA dMMR, MSI-H
- 5-10% rectal cancers mismatch repair deficient
- Complete response seen with checkpoint blockade in 10% dMMR metastatic cancers



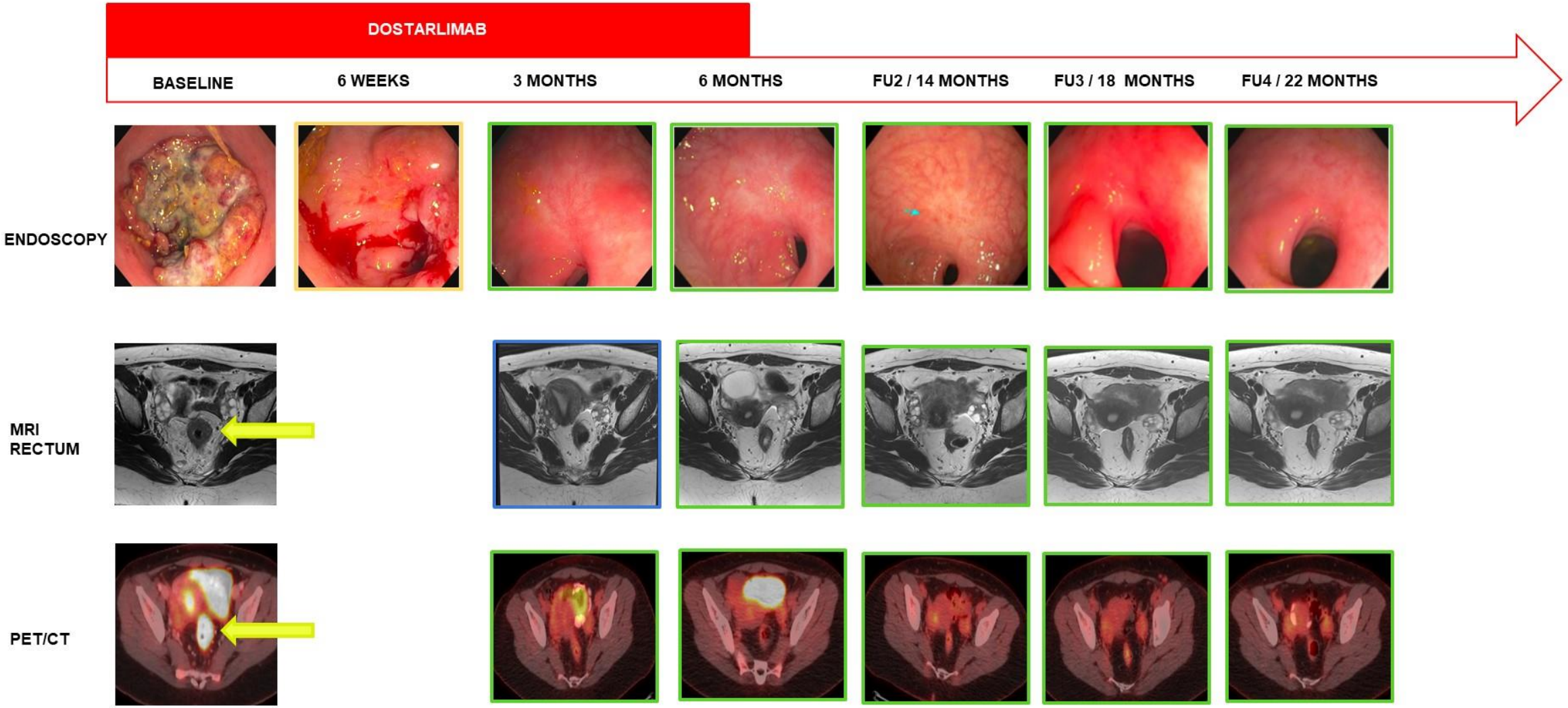
Rothaus, NEJM Resident 360, 2018

PD-1 BLOCKADE AS CURATIVE-INTENT THERAPY IN MMR DEFICIENT LARC



Patient #2

- SD / STABLE DISEASE
- PR / PARTIAL RESPONSE
- NCR / NEAR COMPLETE RESPONSE
- CR / COMPLETE RESPONSE

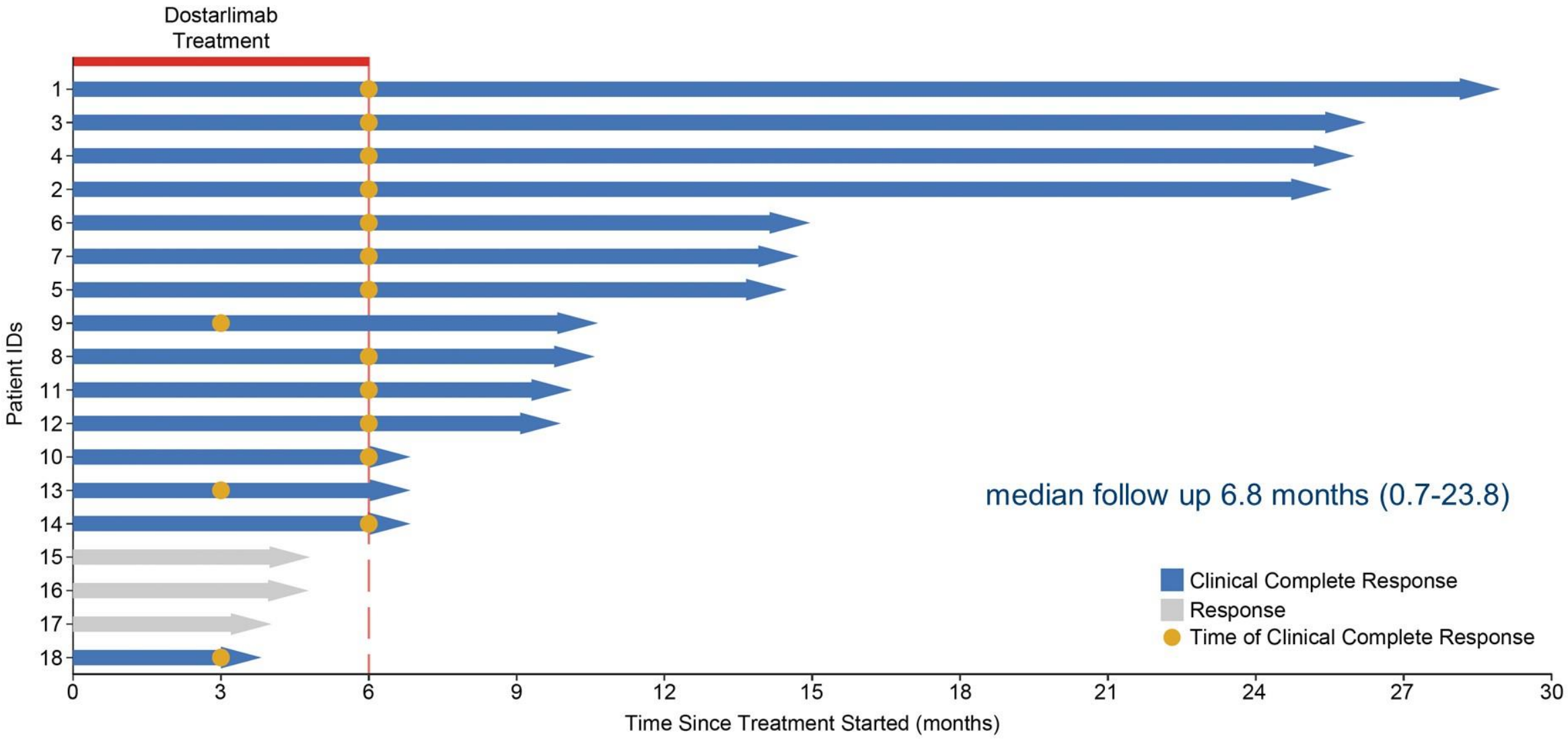


Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-months of dostarlimab

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response 100%
1	38	T4	N+	23.8	CR	CR	CR	**cCR**
2	30	T3	N+	20.5	CR	CR	CR	**cCR**
3	61	T1/2	N+	20.6	CR	CR	CR	**cCR**
4	28	T4	N+	20.5	CR	CR	CR	**cCR**
5	53	T1/2	N+	9.1	CR	CR	CR	**cCR**
6	77	T1/2	N+	11.0	CR	CR	CR	**cCR**
7	77	T1/2	N+	8.7	CR	CR	CR	**cCR**
8	55	T3	N+	5.0	CR	CR	CR	**cCR**
9	68	T3	N+	4.9	CR	CR	CR	**cCR**
10	78	T3	N-	1.7	CR	CR	CR	**cCR**
11	55	T3	N+	4.7	CR	CR	CR	**cCR**
12	27	T3	N+	4.4	CR	CR	CR	**cCR**
13	26	T3	N+	0.8	CR	CR	CR	**cCR**
14	43	T3	N+	0.7	CR	CR	CR	**cCR**

Duration of response



PD-1 BLOCKADE AS CURATIVE-INTENT THERAPY IN MMR DEFICIENT LARC

- 100% clinical complete response in first 14 consecutive patients
  - No evidence of tumour on
    - MRI
    - FDG-PET
    - Endoscopic examination
    - DRE
    - Biopsy
- Median follow-up 12 months (6-25 months)
- No cases of progression or recurrence
- No patients have undergone chemo/radiotherapy or surgery

ADJUVANT NIVOLUMAB IN RESECTED OESOPHAGEAL OR GASTRO-ESOPHAGEAL JUNCTION CANCER

CheckMate 577 Investigators

NEJM 2021; 384:1191-1203

April 1, 2021

RESEARCH SUMMARY

Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

Kelly RJ et al. DOI: 10.1056/NEJMoa2032125

CLINICAL PROBLEM

For patients with locally advanced esophageal or gastroesophageal junction cancer, neoadjuvant chemoradiotherapy followed by surgery is a standard treatment. However, the risk of recurrence is high, especially among the 70 to 75% of patients without a pathological complete response, and clinicians lack proven adjuvant therapies for these patients.

CLINICAL TRIAL

A phase 3, double-blind, randomized, placebo-controlled trial to evaluate the efficacy of the checkpoint inhibitor nivolumab as adjuvant treatment after standard therapy.

794 adults who had received standard therapy for stage II or III esophageal or gastroesophageal junction cancer but had residual pathological disease were assigned within 4 to 16 weeks after surgery to intravenous nivolumab (30-minute infusions of 240 mg every 2 weeks for 16 weeks and then 480 mg monthly) or placebo for a maximum of 1 year. Median follow-up was 24.4 months.

RESULTS

Efficacy:

Median disease-free survival was 22.4 months with nivolumab and 11.0 months with placebo. Adjuvant nivolumab was also associated with longer metastasis-free survival.

Safety:

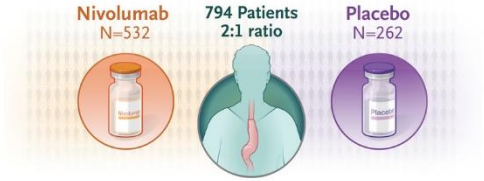
The safety profile of nivolumab was similar to that seen in other types of solid tumors. The most common high-grade nivolumab-related adverse events were pneumonitis and rash.

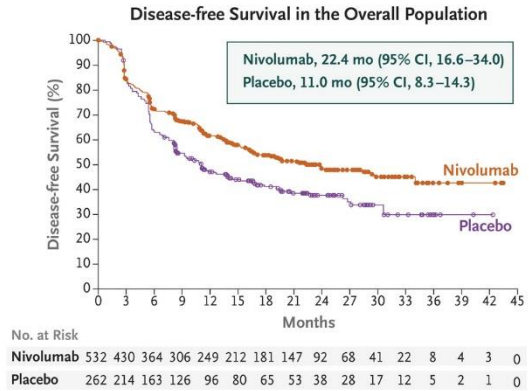
REMAINING QUESTIONS

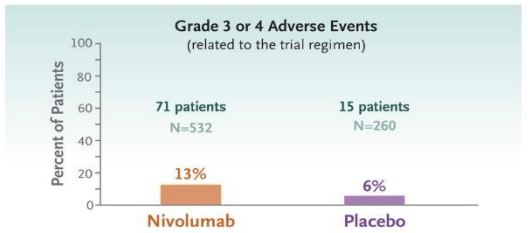
Further study is required to understand the following:

- The longer-term effects of nivolumab on overall survival
- Whether standard chemotherapy would be more effective if given with checkpoint inhibitors

Links: Full article | NEJM Quick Take | Editorial







CONCLUSIONS

Adjuvant nivolumab significantly prolonged disease-free survival among patients with an incomplete pathological response after standard therapy for esophageal or gastroesophageal junction cancer.

CROSS
NEO-ADJUVANT CHEMO-RADIOTHERAPY

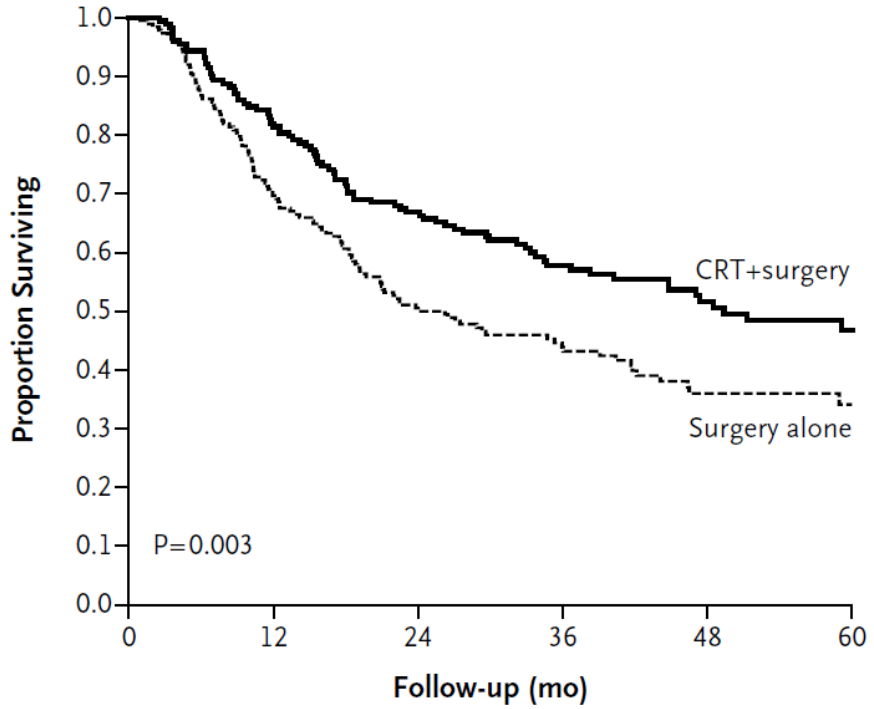
- Van Hagen et al., NEJM 2012; 366:2074-84
- Inclusion
  - Maximum length 8cm, maximum width 5cm
  - T1N1 or T2-3N0-1
  - M0 – NB NOT routinely PET staged
  - 75% adenocarcinoma, 23% squamous, 2% other (mostly de-differentiated)

CROSS
NEO-ADJUVANT CHEMO-RADIOTHERAPY

- Compared "triple-modality" vs surgery alone
- Chemotherapy
  - AUC2 carboplatin and paclitaxel 80mg/m2 weekly x 5
- Radiotherapy
  - 41.4Gy/23#
- Surgery
  - 4-6 weeks after completion radiation
  - Surgery alone arm – immediately after randomisation

CROSS
NEO-ADJUVANT CHEMO-RADIOTHERAPY

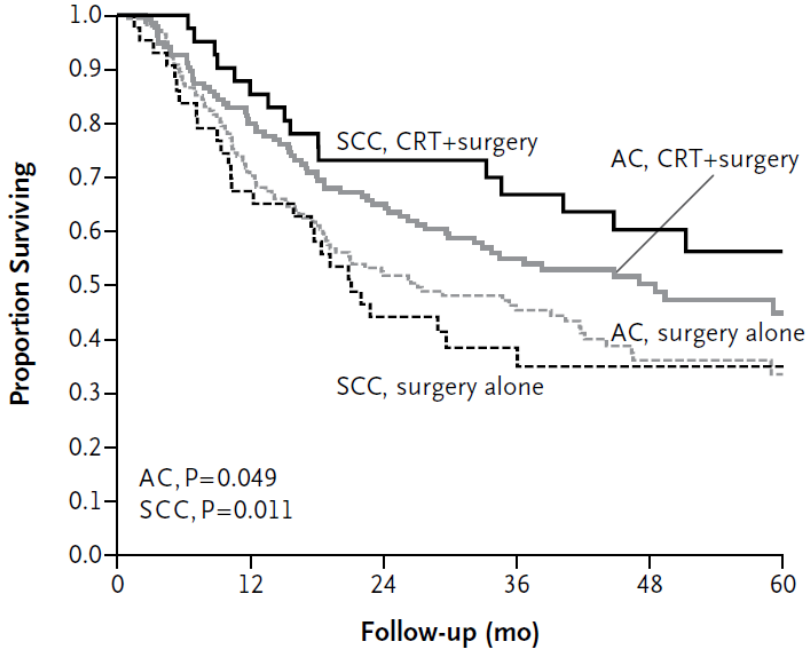
A Survival According to Treatment Group



No. at Risk

CRT+surgery	178	145	119	75	49	28
Surgery alone	188	131	94	62	33	17
Total	366	276	213	137	82	45

B Survival According to Tumor Type and Treatment Group

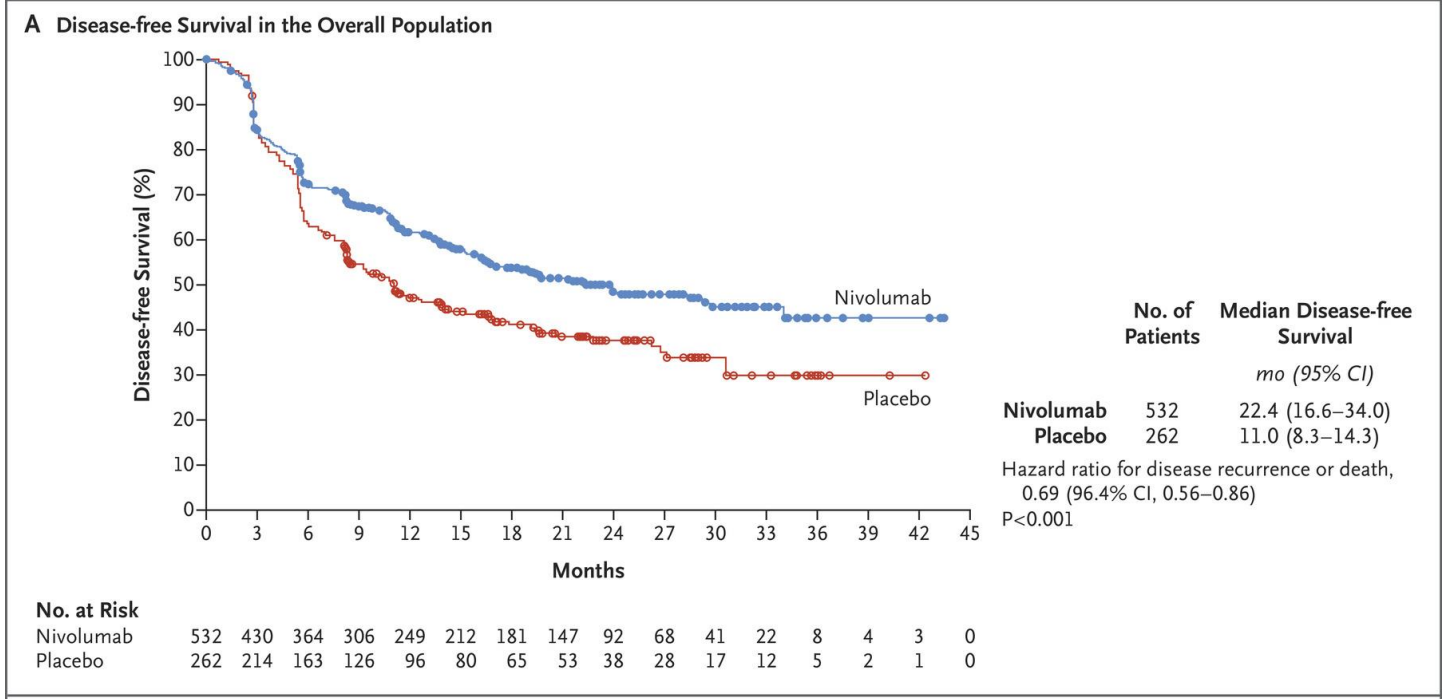


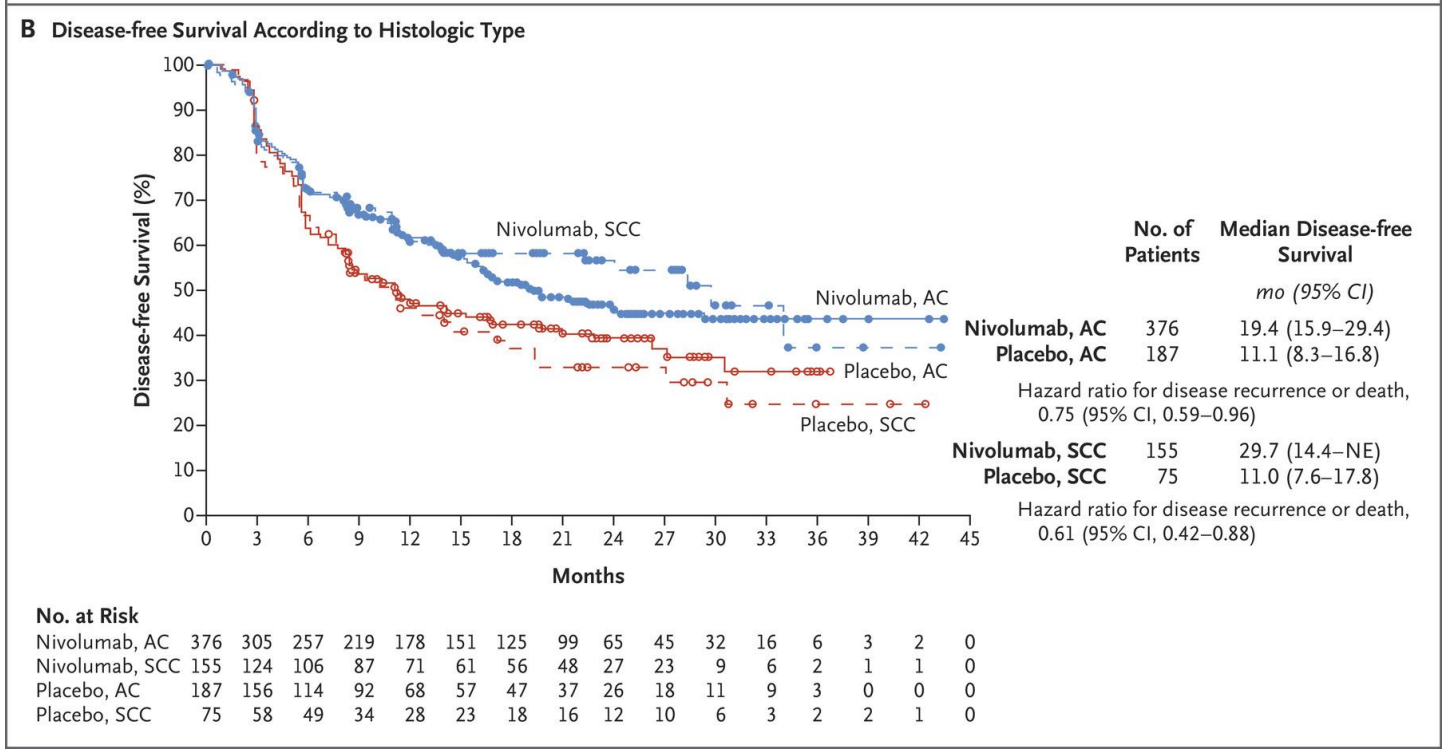
No. at Risk

AC, CRT+surgery	134	107	87	53	34	18
AC, surgery alone	141	99	73	50	25	10
SCC, CRT+surgery	41	35	30	21	15	8
SCC, surgery alone	43	29	19	11	8	4
Total	359	270	209	135	82	40

CHECKMATE 577

- Inclusion
  - Oesophageal or gastro-oesophageal cancer
  - Stage II/III (at time of diagnosis)
  - Adenocarcinoma or squamous cell carcinoma
  - R0 resection after chemo-radiotherapy
  - Residual disease – non-pCR - at least - ypT1 or ypTN1
  - Randomisation within 4-16 weeks of surgery
  - 12 months nivolumab OR placebo





Median DFS
- 22.4m vs 11.0m

Median DFS adenocarcinoma
- 19.4m vs 11.1m

Median DFS SCC
- 29.7m vs 11.0m

SO…

- Giving nivolumab to patients with either SCC/adenocarcinoma oesophagus who have residual invasive malignancy in operative pathology specimens after neo-adjuvant chemo-radiation defers relapse significantly.
- Overall survival benefit awaited
  - Seems likely as median f/u greater than 2 years
  - Beyond "danger period" for relapse
- Although it is unlikely this benefit would be achieved by giving single agent immunotherapy at time of relapse
  - This trial can't/won't answer that question

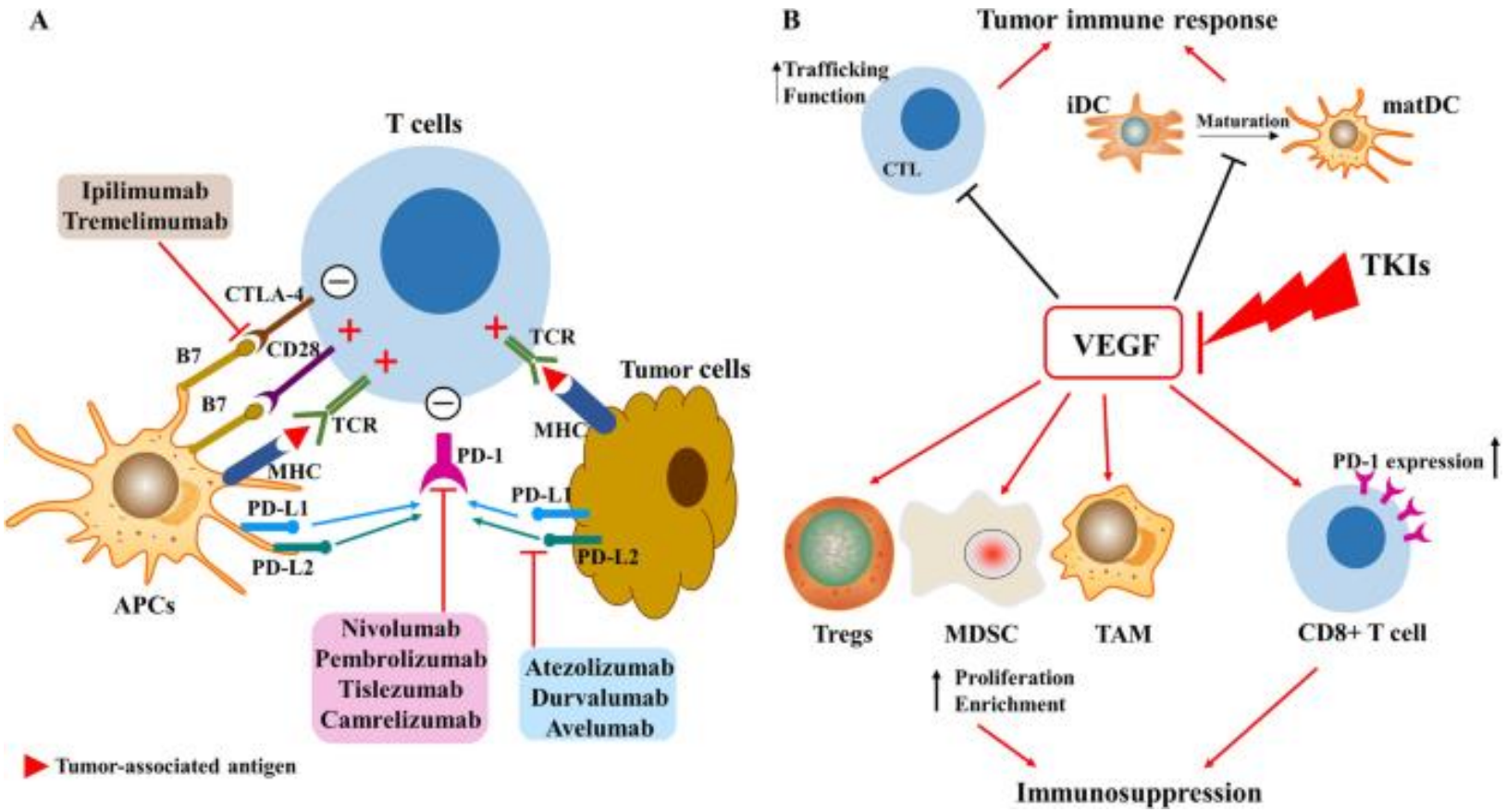
SYSTEMIC THERAPY ADVANCED HEPATO-CELLULAR CARCINOMA

Llovet et al., NEJM 2008; 359: 378-390

Abou-Alfa et al., NEJM Evidence 2022; https://doi.org/10.1056/EVIDoa2100070

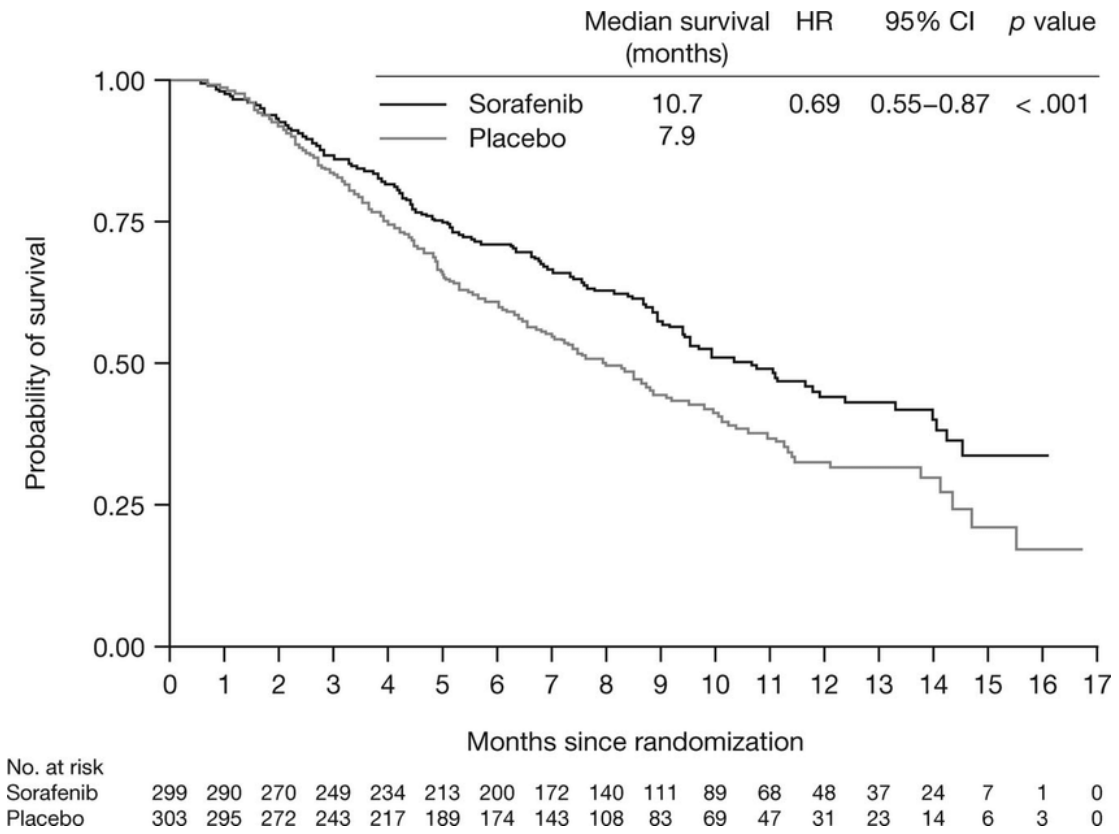
Finn et al., NEJM 2020; 382: 1894-1905

SYSTEMIC THERAPY STRATEGIES



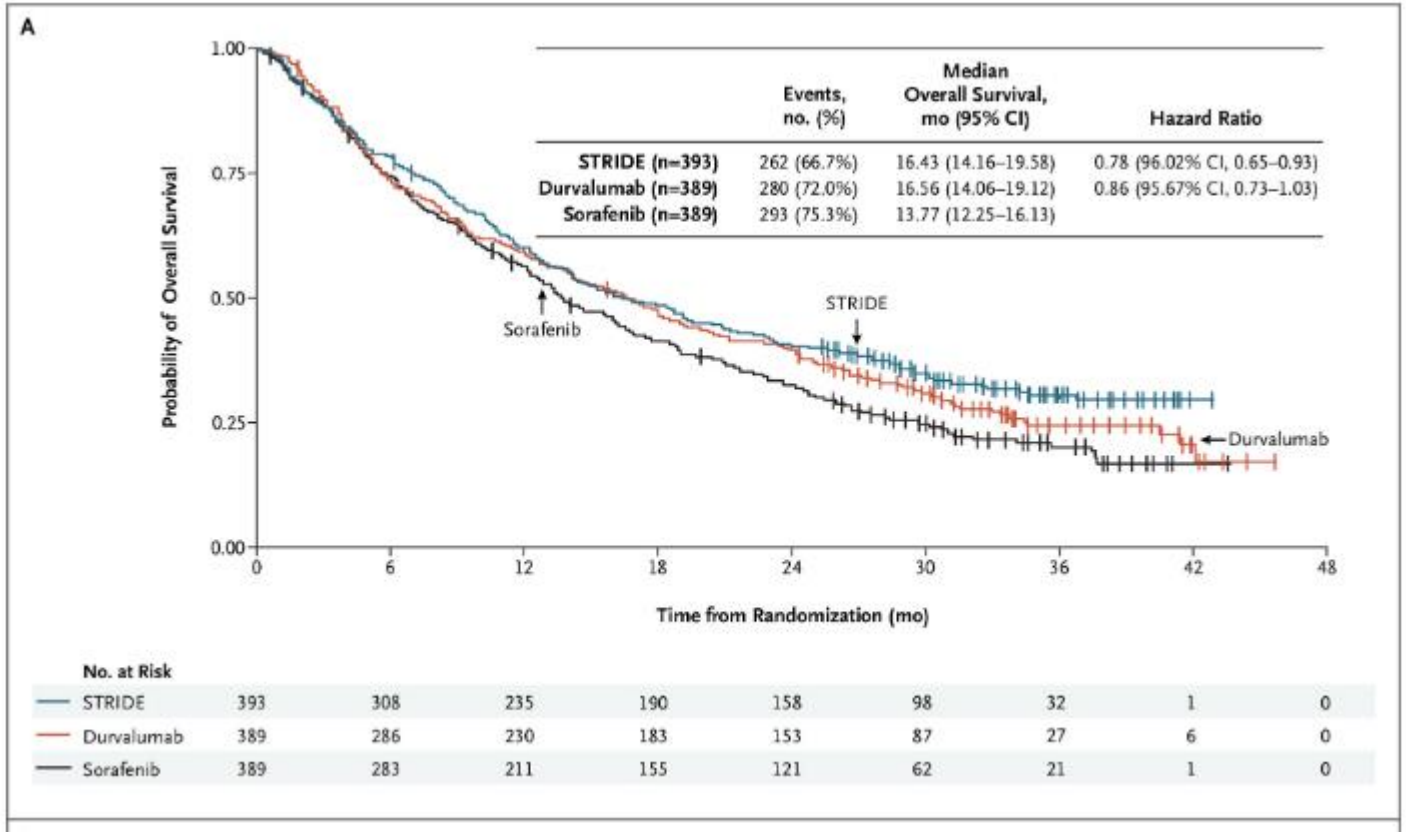
Zhang et al.,
Biomarker Research 10: 3, 2022

SORAFENIB
SHARP TRIAL
LLOVET ET AL., NEJM 2008; 359: 378-390



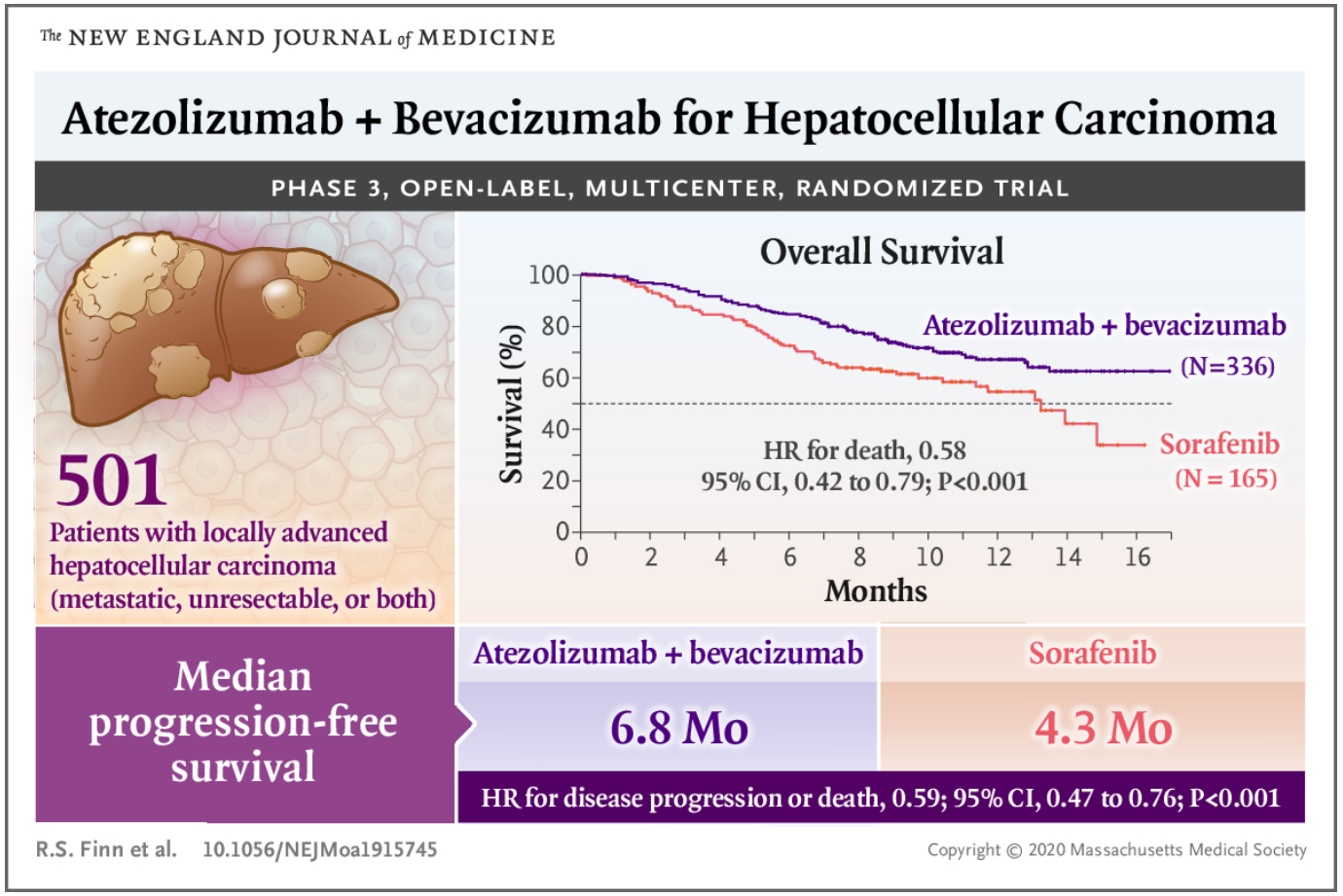
STRIDE
ABOU-ALFA ET AL.,
NEJM EVIDENCE 2022;

- 1 dose anti-CTLA-4 (tremelimumab) followed by anti-PD-1 (durvalumab)

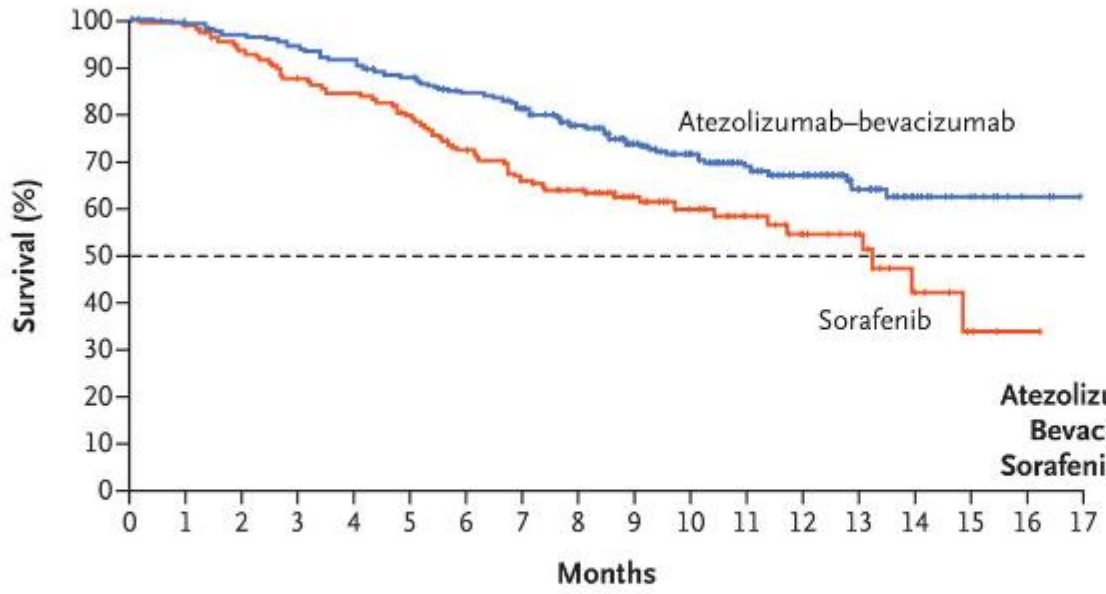


Median OS 16.5m vs 13.7m
Note long tail

ATEZOLIZUMAB/BEVACIZUMAB
IMBRAVE-150
FINN ET AL., NEJM 2020; 382: 1894-1905



A Overall Survival



	No. of Events/ No. of Patients (%)	Median Overall Survival (95% CI)	Overall Survival at 6 Mo
		mo	%
Atezolizumab–Bevacizumab	96/336 (28.6)	NE	84.8
Sorafenib	65/165 (39.4)	13.2 (10.4–NE)	72.2

Stratified hazard ratio for death, 0.58 (95% CI, 0.42–0.79)
P<0.001

No. at Risk

Atezolizumab–bevacizumab	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE

NEXT GENERATION SEQUENCE UTILITY IN CHOLANGIOCARCINOMA

NGS – NEXT GENERATION SEQUENCING

- High rate of actionable mutations found in cholangiocarcinoma
- Panel testing e.g. MSK-IMPACT, FoundationOneCDx
- Targets
  - FGFR2 fusions
  - IDH1 and 2 mutations
  - BRAF V600E
  - Her-2 over-expression
  - TRK fusions
  - dMMR/MSI-H

- DiPeri et al, Expert Review of Gastroenterology and Hepatology, 2021. 15:5, 471-474
- Ross et al., Oncologist. 2014; 19(3):235

NGS – NEXT GENERATION SEQUENCING

- FGFR2 fusions
  - 15-20% intrahepatic cholangiocarcinoma (IHCCA)
  - Less common extrahepatic (EHCCA) or gallbladder carcinoma (GBC)
  - Pemigatinib
    - FIGHT-202 trial
    - Response rate 36%
    - Disease control rate 80%
    - Duration of response 7.5 months
  - Infigratinib
    - Response rate 23%
    - Duration of response 5 months

NGS – NEXT GENERATION SEQUENCING

- IHD1/2 mutations
  - 7-25% IHCCA
  - 12-42% EHCCA
  - 0% GBC
  - Ivosidenib
    - 32% not progressed at six months
    - 22% progression free at twelve months
      - Zhu et al., Jama Oncol. 2021; 7(11):1669

NGS – NEXT GENERATION SEQUENCING

- BRAF V600E
  - 5% IHCCA
  - 3% EHCCA
  - 1% GBC
  - Dabrafenib and trametinib (MEK inhibitor)
    - 47% response rate
    - Some responses prolonged >24 months
      - Salama et al., J Clin Oncol. 2020; 38(33):3895.

NGS – NEXT GENERATION SEQUENCING

- Her-2 over-expression (IHC technically NOT NGS)
  - 3% IHCCA
  - 11% EHCCA
  - 30% GBC
  - Pertuzumab/trastuzumab
    - Dual anti-her 2 antibodies
    - IHC 3+/FISH +ve - Response rate 23%
    - Duration of response 10.8months
      - Javle et al., Lancet Oncol 2021; 22(9):1290.
  - Trastuzumab deruxetan
    - Antibody/drug conjugate
    - IHC 3+ RR 36% - median duration of response 7.4months
    - IHC ½+ RR12.5% - median duration of response 5.1months
      - Ohba et al., ASCO 2022

NGS – NEXT GENERATION SEQUENCING

- TRK fusions
  - 3% IHCCA
  - ?% EHCCA
  - ?% GBC
  - Larotrectinib/entrectinib
    - Response rate 75%
    - Durable responses >12 months
      - Cancer Discov. 2015; 5(1):25.

NGS – NEXT GENERATION SEQUENCING

- dMMR/MSI-H
  - 10% IHCCA
  - 5% EHCCA
  - 5% GBC
- Response to check-point inhibitors
  - E.g. KEYNOTE-158 – phase II – pembrolizumab
    - 41% objective response
    - Median duration of response 4 to >25 months
      - Marabelle et al., J Clin Onc. 2020 Jan 1; 38(1):1-10

20 MINS WITH A MEDICAL ONCOLOGIST

New weapons

- Adjuvant nivolumab in resected oesophageal or gastro-esophageal junction cancer

Take home

- Post CROSS neo-adjuvant CRTx
- Resected - non-pCR
- 12 months nivolumab (anti-PD-1)
- Median DFS 11m to 22.4m
  - HR 0.69 all-comers
  - HR=0.61 SCC
  - HR = 0.75 adenocarcinoma

Disclaimer – although these therapies/tests are licenced and recommended by international expert guidelines; they are not funded for patients in Aotearoa

20 MINS WITH A MEDICAL ONCOLOGIST

New weapons

- Systemic therapy advanced hepato-cellular carcinoma

Take home

- Watch this space
- Lots of agents/combinations in trials
- NOTHING funded in Aotearoa
- Focus on Childs-Pugh A

Disclaimer – although these therapies/tests are licenced and recommended by international expert guidelines; they are not funded for patients in Aotearoa

20 MINS WITH A MEDICAL ONCOLOGIST

Take Home

- dMMR testing SHOULD be ubiquitous in colorectal cancer
- Early days but this is unprecedented data
- Can we extend out to more affordable anti-PD-1 drugs??

Recognising targets

- PD-1 blockade as curative-intent therapy in mismatch repair deficient locally advanced rectal cancer

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20 MINS WITH A MEDICAL ONCOLOGIST

Take Home

- Motivated good performance status patient after first line cytotoxics (cisplatin/gemcitabine)
- NGS via tissue/cTC/cDNA
- Target provide meaningful responses
- Watch this space – more coming

Recognising targets

- Next generation sequence utility in cholangiocarcinoma

Disclaimer – although these therapies/tests are licenced and recommended by international expert guidelines; they are not funded for patients in Aotearoa