# Advances in targeted therapy including immunotherapy

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Kaysia Ludford M.D.
The University of Texas MD Anderson Cancer Center
April 27, 2024

# Objectives

1) Definition of chemotherapy, targeted therapy and immunotherapy

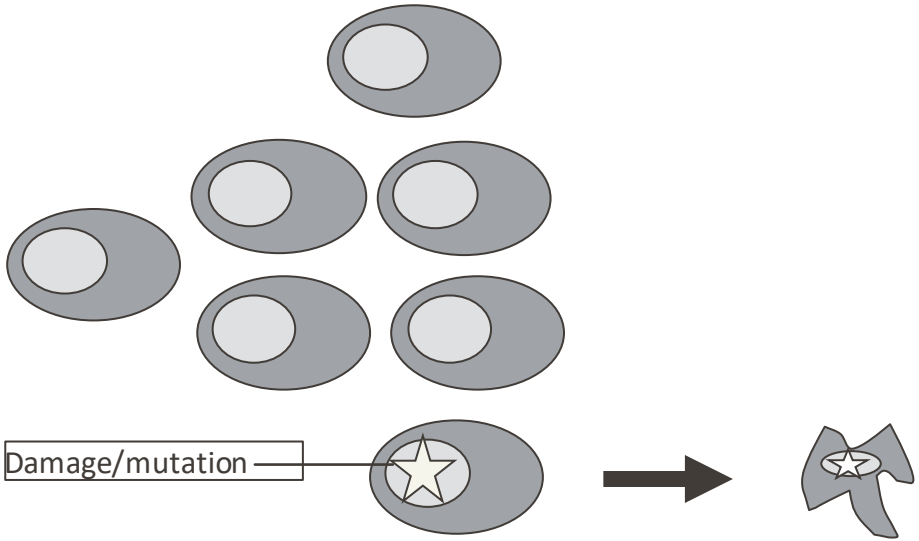
2) Updates in immunotherapy (local and metastatic)

3) Updates in other targeted therapies (metastatic):
    a) HER-2 directed therapy
    b) BRAF-directed therapy
    c) RAS directed therapy

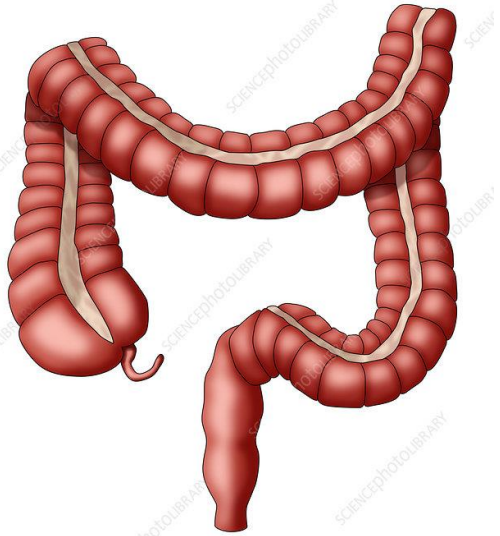
4) Summary

# How do cancer therapeutics work?

# Normal physiology

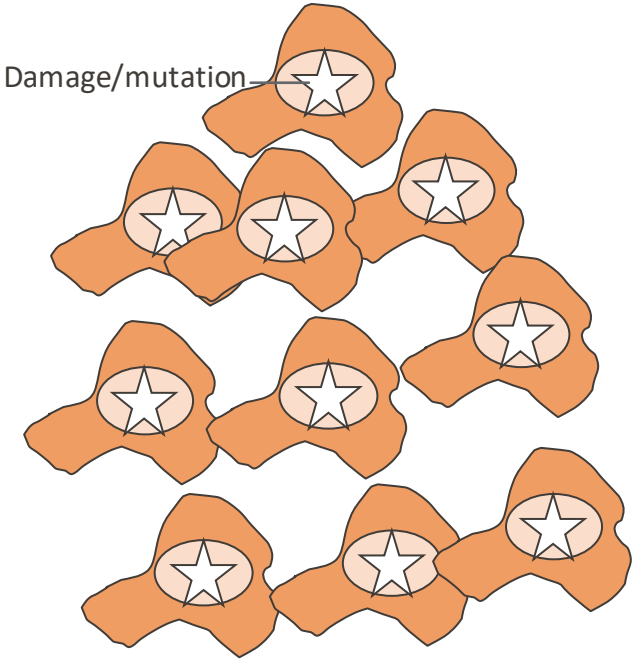



Normal cells

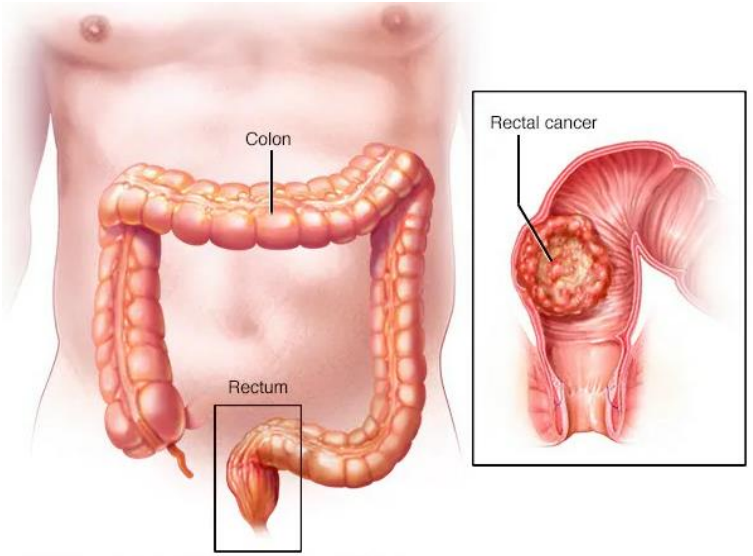


https://www.sciencephoto.com/media/861328/view/healthy-large-intestine-illustration

# Cancer

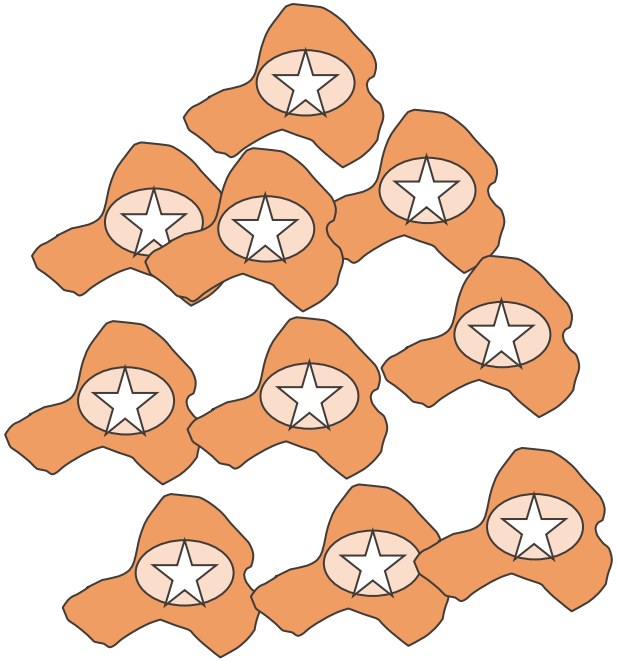



Cancer cells

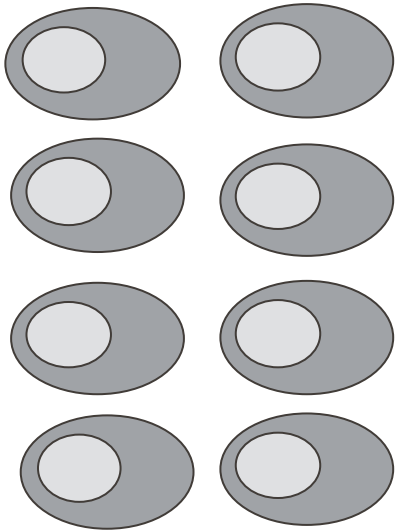



Mayo Foundation for Medical Education and Research

# How does chemotherapy work?

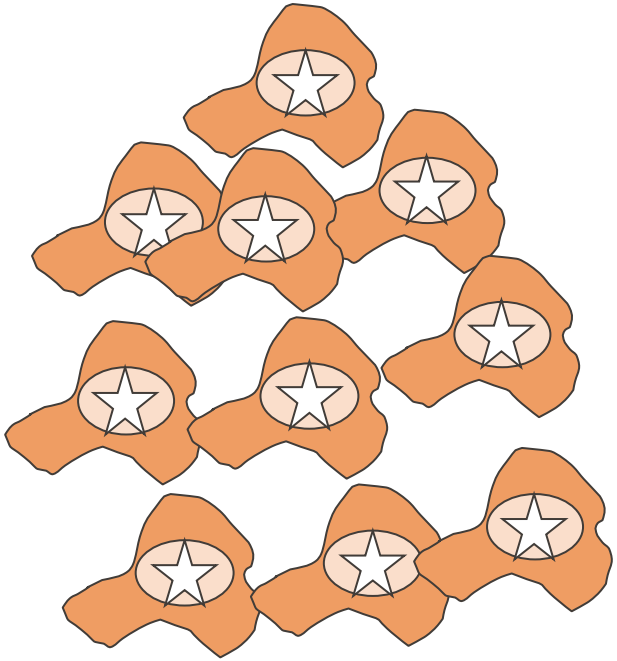


Cancer cells

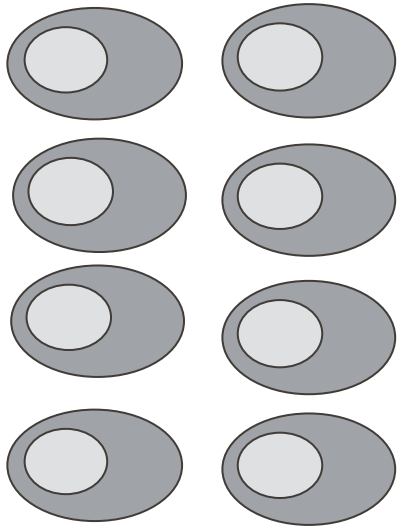


Normal cells

# How does chemotherapy work?

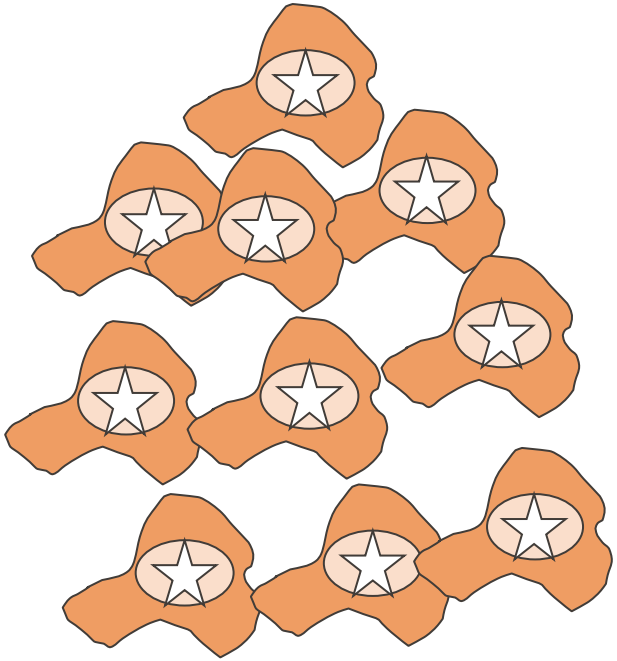


Cancer cells

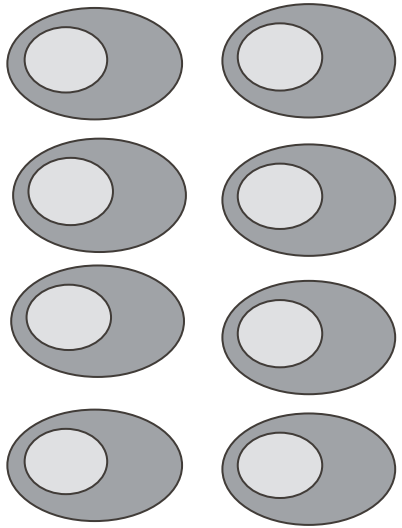


Normal cells

# How does targeted therapy work?

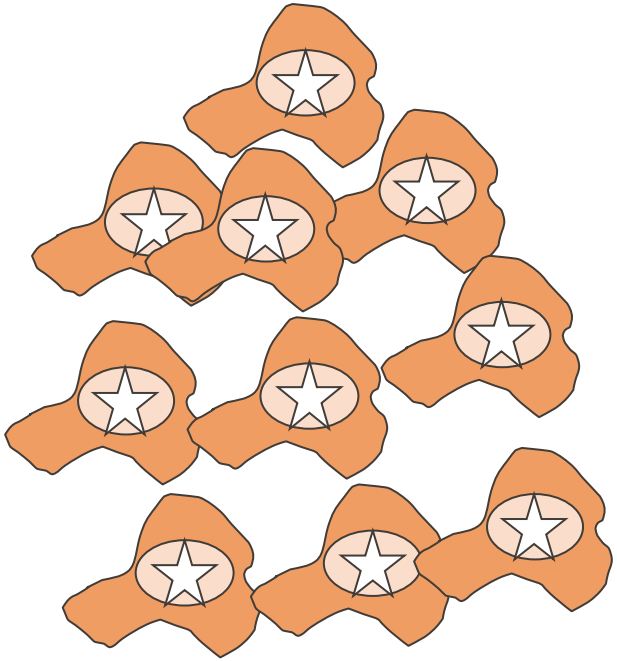


Cancer cells with driver mutations
BRAF/KRAS/HER2

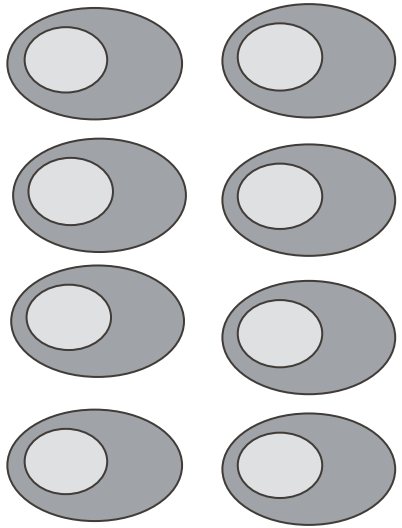


Normal cells

# How does targeted therapy work?



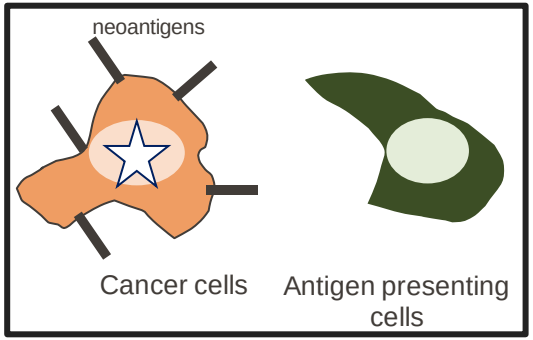
Cancer cells with driver mutations
BRAF/KRAS/HER2

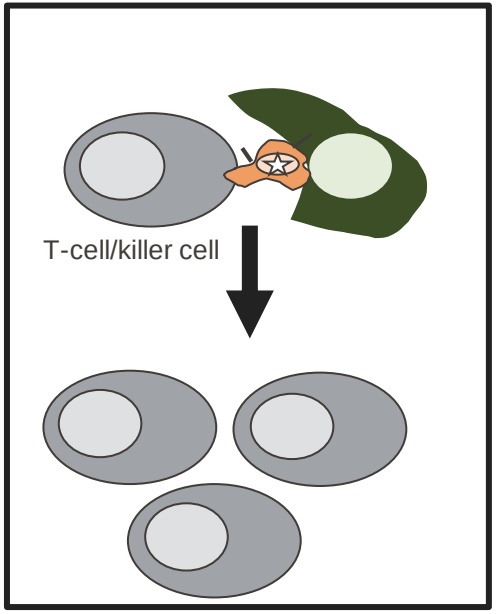


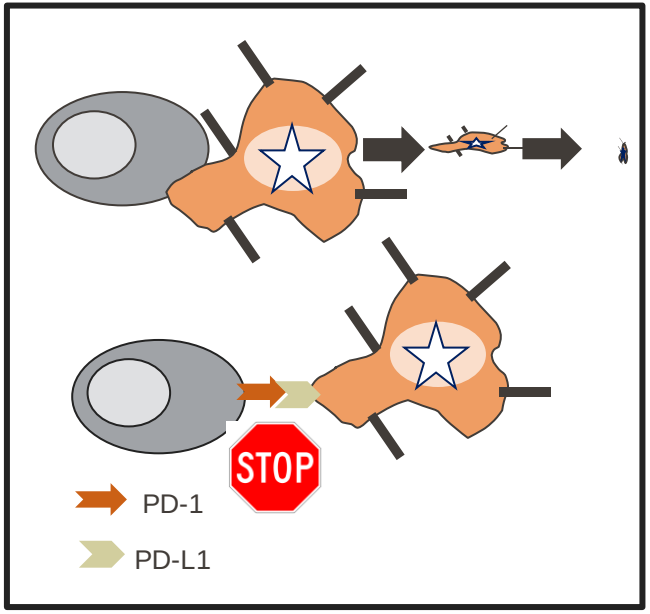
Normal cells

# How does immunotherapy work?

- https://m.youtube.com/watch?v=CwaMZCu4kpI&pp=ygU0aG93IGRvIGltbXVuZSBjaGVja3BvaW50IGluaGliaXRvcnMgd29yayBtZCBhbmRlcnNvbg%3D%3D

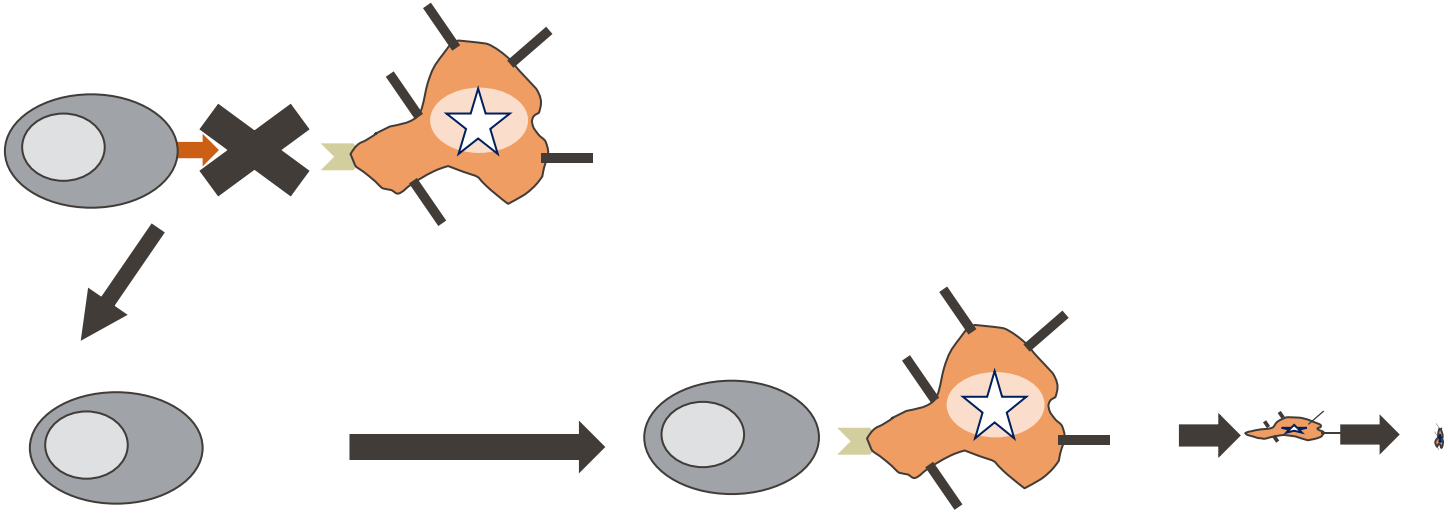


# How does immunotherapy work?

- https://m.youtube.com/watch?v=CwaMZCu4kpI&pp=ygU0aG93IGRvIGltbXVuZSBjaGVja3BvaW50IGluaGliaXRvcnMgd29yayBtZCBhbmRlcnNvbg%3D%3D



# Updates in Immunotherapy

# Immunotherapy can be beneficial for a subset of patients with colorectal cancer

- Works in patients with microsatellite instability high (MSI-H) colon cancers
- Up to 15% of all colorectal cancer are MSI- H
- Only 3-5% of stage IV colorectal cancers are MSI-H
- All patients are tested for MSI-H
- Loss/dysfunction of mismatch repair genes result in cancer cells being unable to recognize and repair spontaneous mutations. This results in high tumor mutation burden/neoantigens, tumor infiltrating lymphocytes and efficacy of immunotherapy

# Immunotherapy for patients with MSI-H metastatic CRC

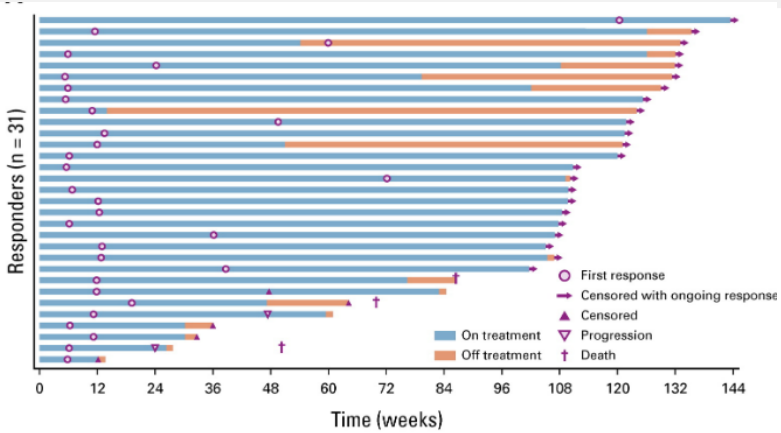
| Agent/Regimen | Key Trials | Key Findings |
|---|---|---|
| Pembrolizumab | Keynote 177<br>▪ Phase III (randomized 307 pts: firstline pembrolizumab or chemotherapy) | ▪ Response rate: 43.8% vs 33.1% (11% vs 4% CR)<br>▪ Progression free survival: mPFS 16.5 months vs 8 months. 36month PFS: 42.3% vs 11.1%<br>▪ Overall Survival: not reached vs 36.7 months*<br>▪ Adverse events (G3+): 56% vs 78% |

*Did not met one-sided alpha boundary of 0.025 required for superiority

Diaz LA Jr, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, Smith D, Garcia-Carbonero R, Benavides M, Gibbs P, de la Fourchardiere C, Rivera F, Elez E, Le DT, Yoshino T, Zhong WY, Fogelman D, Marinello P, Andre T; KEYNOTE-177 Investigators. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. Lancet Oncol. 2022 May;23(5):659-670.

# Immunotherapy for patients with MSI-H metastatic CRC

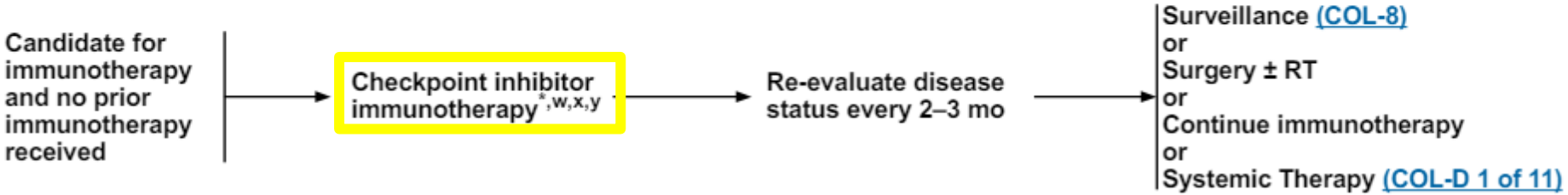
| Agent/Regimen | Key Trials | Key Findings |
|---|---|---|
| Nivolumab + ipilimumab | Checkmate 142<br>▪ Phase II (non-randomized 45 pts: firstline ipilimumab + nivolumab | ▪ Response rate: 69%<br>▪ Progression free survival: mPFS not reached. 24 month PFS 73.6%<br>▪ Overall Survival: not reached. 24 month OS 79.4%<br>▪ Adverse events (G3+): 22% |




Lenz HJ, Van Cutsem E, Luisa Limon M, Wong KYM, Hendlisz A, Aglietta M, García-Alfonso P, Neyns B, Luppi G, Cardin DB, Dragovich T, Shah U, Abdullaev S, Gricar J, Ledeine JM, Overman MJ, Lonardi S. First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 St

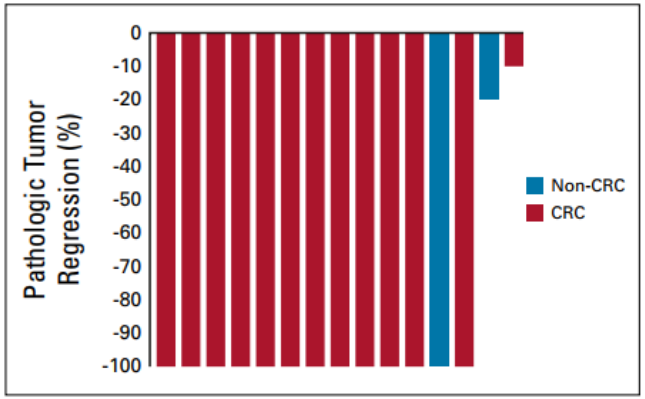
# Immunotherapy for metastatic MSI-H CRC

**dMMR/MSI-H or *POLE/POLD1* mutation**
**Any line of therapy**



# Immunotherapy for localized MSI-H CRC

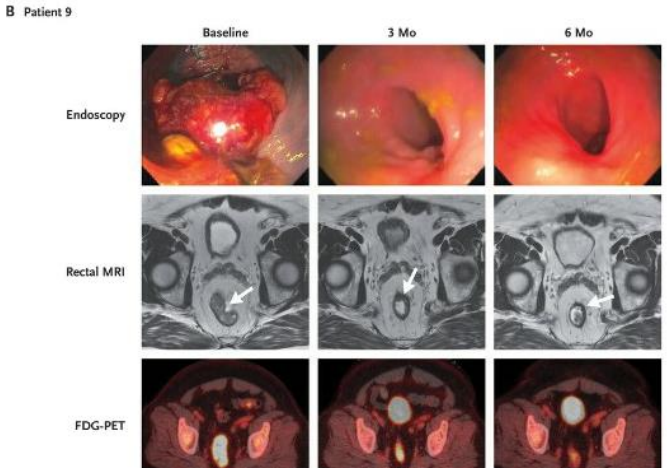
| Agent/Regimen | Key Trials | Key Findings |
|---|---|---|
| Pembrolizumab | MDACC<br>▪ Phase II (non-randomized, 35 patients (27 CRC), localized solid cancers, MSI-H) | ▪ Pathologic complete response rate: 65% in all patients, 79% in CRC<br>▪ Radiographic response rate: 82% (CR 30%)<br>▪ Endoscopic complete response: 63%<br>▪ Non-operative approach: n=18<br>▪ Adverse events (G3+): 6% |




Ludford K, Ho WJ, Thomas JV, Raghav KPS, Murphy MB, Fleming ND, Lee MS, Smaglo BG, You YN, Tillman MM, Kamiya-Matsuoka C, Thirumurthi S, Messick C, Johnson B, Vilar E, Dasari A, Shin S, Hernandez A, Yuan X, Yang H, Foo WC, Qiao W, Maru D, Kopetz S, Overman MJ. Neoadjuvant Pembrolizumab in Localized Microsatellite Instability High/Deficient Mismatch Repair Solid Tumors. J Clin Oncol. 2023 Apr 20;41(12):2181-2190

# Immunotherapy for localized MSI-H CRC

| Agent/Regimen | Key Trials | Key Findings |
|---|---|---|
| Dostarlimab | MSKCC<br>▪ Phase II (non-randomized, 12 patients, localized rectal cancer, MSI-H) | ▪ Clinical complete response: 100%<br>▪ Non-operative approach: n=12<br>▪ Adverse events (G3+): 0% |




Cercek A, Lumish M, Sinopoli J, Weiss J, Shia J, Lamendola-Essel M, El Dika IH, Segal N, Shcherba M, Sugarman R, Stadler Z, Yaeger R, Smith JJ, Rousseau B, Argiles G, Patel M, Desai A, Saltz LB, Widmar M, Iyer K, Zhang J, Gianino N, Crane C, Romesser PB, Pappou EP, Paty P, Garcia-Aguilar J, Gonen M, Gollub M, Weiser MR, Schalper KA, Diaz LA Jr. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. N Engl J Med. 2022 Jun 23;386(25):2363-2376

# Immunotherapy for localized MSI-H CRC

| Agent/Regimen | Key Trials | Key Findings |
|---|---|---|
| Pembrolizumab | MDACC<br>▪ Phase II (non-randomized, 35 patients (27 CRC), localized solid cancers, MSI-H) | ▪ Pathologic complete response rate: 65% in all patients, 79% in CRC<br>▪ Radiographic response rate: 82% (CR 30%)<br>▪ Endoscopic complete response: 63%<br>▪ Non-operative approach: n=18<br>▪ Adverse events (G3+): 6% |
| Dostarlimab | MSKCC<br>▪ Phase II (non-randomized, 12 patients, localized rectal cancer, MSI-H) | ▪ Clinical complete response: 100%<br>▪ Non-operative approach: n=12<br>▪ Adverse events (G3+): 0% |

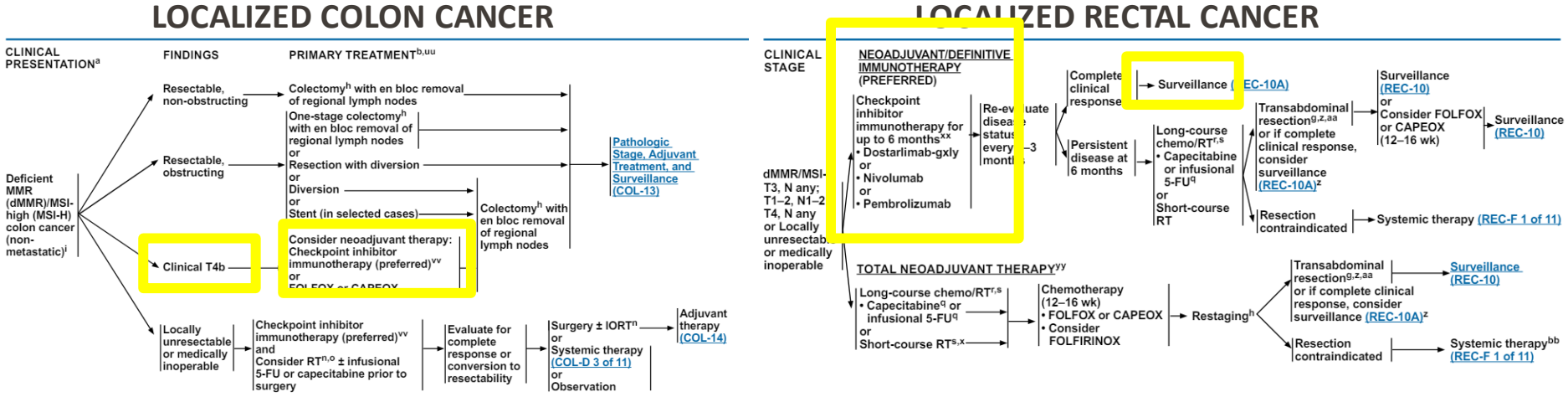
Ludford K, Ho WJ, Thomas JV, Raghav KPS, Murphy MB, Fleming ND, Lee MS, Smaglo BG, You YN, Tillman MM, Kamiya-Matsuoka C, Thirumurthi S, Messick C, Johnson B, Vilar E, Dasari A, Shin S, Hernandez A, Yuan X, Yang H, Foo WC, Qiao W, Maru D, Kopetz S, Overman MJ. Neoadjuvant Pembrolizumab in Localized Microsatellite Instability High/Deficient Mismatch Repair Solid Tumors. J Clin Oncol. 2023 Apr 20;41(12):2181-2190

Cercek A, Lumish M, Sinopoli J, Weiss J, Shia J, Lamendola-Essel M, El Dika IH, Segal N, Shcherba M, Sugarman R, Stadler Z, Yaeger R, Smith JJ, Rousseau B, Argiles G, Patel M, Desai A, Saltz LB, Widmar M, Iyer K, Zhang J, Gianino N, Crane C, Romesser PB, Pappou EP, Paty P, Garcia-Aguilar J, Gonen M, Gollub M, Weiser MR, Schalper KA, Diaz LA Jr. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. N Engl J Med. 2022 Jun 23;386(25):2363-2376

# Immunotherapy for localized MSI-H CRC

| Agent/Regimen | Key Trials | Key Findings |
|---|---|---|
| Pembrolizumab | MDACC<br>▪ Phase II (non-randomized, 35 patients (27 CRC), localized solid cancers, MSI-H) | ▪ Pathologic complete response rate: 65% in all patients, 79% in CRC<br>▪ Radiographic response rate: 82% (CR 30%)<br>▪ Endoscopic complete response: 63%<br>▪ Non-operative approach: n=18<br>▪ Adverse events (G3+): 6% |
| Dostarlimab | MSKCC<br>▪ Phase II (non-randomized, 12 patients, localized rectal cancer, MSI-H) | ▪ Clinical complete response: 100%<br>▪ Non-operative approach: n=12<br>▪ Adverse events (G3+): 0% |
| Ipilimumab + nivolumab | NICHE (Amsterdam)<br>▪ Phase II non-randomized, 112 patients, localized colon cancer, MSI-H) | ▪ Pathologic complete response: 67%<br>▪ Duration of response: median follow up 13 months (1-57mo): no recurrences<br>▪ Adverse events (G3+) 3% |

# Immunotherapy for localized MSI-H CRC



# HER-2 directed therapy for mCRC (2-3 % of individuals with CRC)

| Agent/Regimen | Key Trials | Key Findings |
|---|---|---|
| Tucatinib + trastuzumab | MOUNTAINEER<br>▪ For previously treated HER2+ mCRC (phase II; N = 84) | ▪ ORR: 38.1%<br>▪ Median PFS: 8.2 mo<br>▪ Median OS: 24.1 mo |
| Trastuzumab deruxtecan | DESTINY-CRC01<br>▪ Advanced CRC of varied HER2 expression with ≥2 prior regimens (phase II; N = 78) | ▪ ORR: 45.3% if HER2 IHC 3+<br>▪ Median PFS: 6.9 mo<br>▪ Median OS: 15.5 mo |
| Trastuzumab + lapatinib | HERACLES<br>▪ HER2+ mCRC with PD after standard treatment (phase II; N = 35) | ▪ ORR: 28% (n = 1 CR; 9 PR)<br>▪ Median PFS: 4.7 mo<br>▪ Median OS: 10.0 mo |
| Trastuzumab + pertuzumab | MyPathway Basket Trial<br>▪ HER2+ mCRC refractory to standard treatment (phase II; N = 84) | ▪ ORR: 26.2%<br>▪ ORR w WT *KRAS*: 31%<br>▪ Median DoR: 5.9 mo |

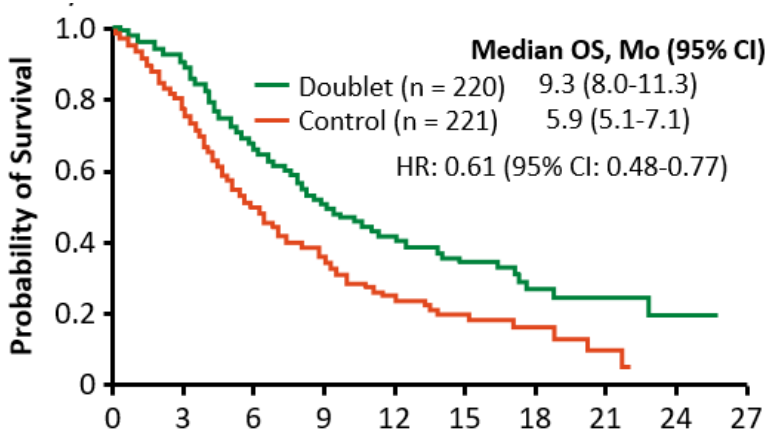
- **Tucatinib** + **trastuzumab** and T**rastuzumab deruxtecan** approved

Slide adapted from Clinicaloptions.com

Meric-Bernstam F, Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. J Clin Oncol. 2024 Jan 1;42(1):47-58.Siena. Lancet Oncol. 2021;22:779. Strickler. Lancet Oncol. 2023;24:496. Tosi. Clin Colorectal Cancer. 2020;19:256. Yoshino. JCO. 2022;40:Abstr. 119. Tucatinib PI.

# BRAF- directed therapy for mCRC (10% of individuals with CRC)

| Agent/Regimen | Key Trials | Key Findings |
|---|---|---|
| Encorafenib,binimetinib, cetuximab | Beacon<br>▪ Phase III (randomized, 665 patients with V600E mutation with progression of disease after 1-2 lines of therapy)<br>▪ Encorafenib/binimetinib/ccetuximab vs encorafenib/cetuximab vs cetuximab/chemo | ▪ ORR: 26 vs 20 vs 2%<br>▪ mOS: 9 vs 8.4 vs 5.4 months<br>▪ mPFS: 4.3 vs 4.2 vs 1.5 months<br>▪ Adverse events (G3+): 58 vs 50 vs 61% |




Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, Wasan H, Ciardiello F, Loupakis F, Hong YS, Steeghs N, Guren TK, Arkenau HT, Garcia-Alfonso P, Pfeiffer P, Orlov S, Lonardi S, Elez E, Kim TW, Schellens JHM, Guo C, Krishnan A, Dekervel J, Morris V, Calvo Ferrandiz A, Tarpgaard LS, Braun M, Gollerkeri A, Keir C, Maharry K, Pickard M, Christy-Bittel J, Anderson L, Sandor V, Tabernero J. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. N Engl J Med. 2019 Oct 24;381(17):1632-1643.

# BRAF- directed therapy for mCRC (10% of individuals with CRC)

| Agent/Regimen | Key Trials | Key Findings |
|---|---|---|
| Encorafenib,binimetinib, cetuximab | Beacon<br>▪ Phase III (randomized, 665 patients with V600E mutation with progression of disease after 1-2 lines of therapy)<br>▪ Encorafenib/binimetinib/ccetuximab vs encorafenib/cetuximab vs cetuximab/chemo | ▪ ORR: 26 vs 20 vs 2%<br>▪ mOS: 9 vs 8.4 vs 5.4 months<br>▪ mPFS: 4.3 vs 4.2 vs 1.5 months<br>▪ Adverse events (G3+): 58 vs 50 vs 61% |
| Encorafenib,cetuximab | Breakwater<br>▪ Phase III (randomized, 1L BRAF V600E, goal 620pts)<br>▪ Encorafenib/cetuximab +/-chemotherapy vs SOC chemotherapy | ▪ Ongoing |

Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, Wasan H, Ciardiello F, Loupakis F, Hong YS, Steeghs N, Guren TK, Arkenau HT, Garcia-Alfonso P, Pfeiffer P, Orlov S, Lonardi S, Elez E, Kim TW, Schellens JHM, Guo C, Krishnan A, Dekervel J, Morris V, Calvo Ferrandiz A, Tarpgaard LS, Braun M, Gollerkeri A, Keir C, Maharry K, Pickard M, Christy-Bittel J, Anderson L, Sandor V, Tabernero J. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. N Engl J Med. 2019 Oct 24;381(17):1632-1643.

# KRAS G12C- directed therapy for mCRC (3-4% of pts with CRC)

| Agent | Key Trials | Key Findings |
|---|---|---|
| Sotorasib | Phase III study of sotorasib + panitumumab vs thirdline chemotherapy (n = 160) | ORR: 26 vs 0%<br>mPFS: 5.6 vs 3.9months<br>mOS: immature<br>Adverse events (G3+): 35.8 vs 43% |

Fakih MG. Sotorasib plus Panitumumab in Refractory Colorectal Cancer with Mutated KRAS G12C. N Engl J Med. 2023 Dec 7;389(23):2125-2139;

# KRAS G12C- directed therapy for mCRC (3-4% of pts with CRC)

| Agent | Key Trials | Key Findings |
|---|---|---|
| Sotorasib | Phase III study of sotorasib + panitumumab vs thirdline chemotherapy (n = 160) | ORR: 26 vs 0%<br>mPFS: 5.6 vs 3.9months<br>mOS: immature<br>Adverse events (G3+): 35.8 vs 43% |
| Adagrasib | Phase III study of adagrasib + cetuximab vs adagrasib in pre-treated patients (n=76) | ORR: 46 vs 23%<br>mPFS: 6.9 vs 5.6 months<br>mOS: 13.4 vs 19.8 months<br>Adverse events (G3+): 16 vs 34% |

Fakih MG. Sotorasib plus Panitumumab in Refractory Colorectal Cancer with Mutated KRAS G12C. N Engl J Med. 2023 Dec 7;389(23):2125-2139;
Yaeger R. Adagrasib with or without Cetuximab in Colorectal Cancer with Mutated KRAS G12C. N Engl J Med. 2023 Jan 5;388(1):44 -54

# SUMMARY OF TARGETED THERAPIES FOR mCRC

| MSI-H/dMMR | *HER2+* | *BRAF* V600E | *KRAS G12c* | Other mutations |
|---|---|---|---|---|
| ▪ Nivolumab ± ipilimumab<br>▪ Pembrolizumab<br>▪ Dostarlimab | ▪ Trastuzumab + tucatinib<br>▪ Trastuzumab deruxtecan | ▪ Encorafenib + cetuximab | ▪ Sotorasib<br>▪ Adagrasib | ▪ Clinical Trials |

# QUESTIONS