ENGAGE Webinar
06.12.2023

Endometrial cancer and immunotherapies

New Hope?

JUNGE AKADEMIE
GYNÄKOLOGISCHE
ONKOLOGIE

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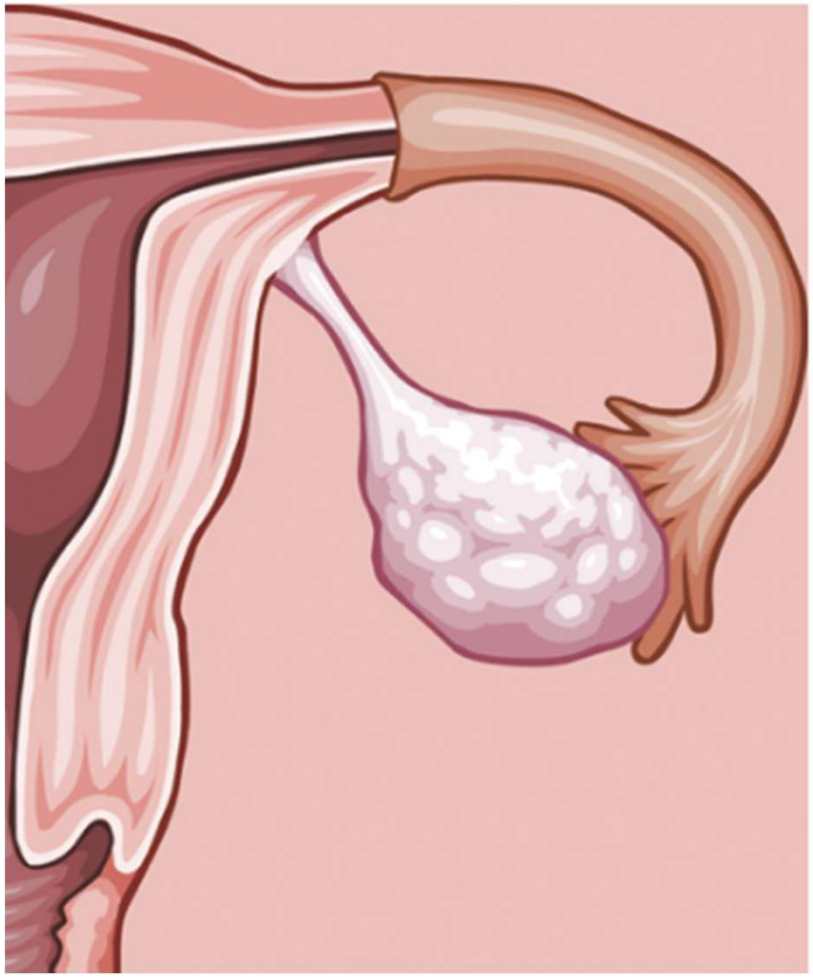
Department for Gynecologic Oncology
Charité-University Medicine of Berlin

CHARITÉ

Endometrial cancer

What fields do we need to cover with this talk?



1

Basics cancer

Why does cancer develop?

Why is cancer difficult to kill?

2

Basics immunotherapy

How does the immune system work?

How does immunotherapy work?

3

New hope in endometrial cancer

New data for immunotherapy

New therapies on the horizon

Endometrial cancer

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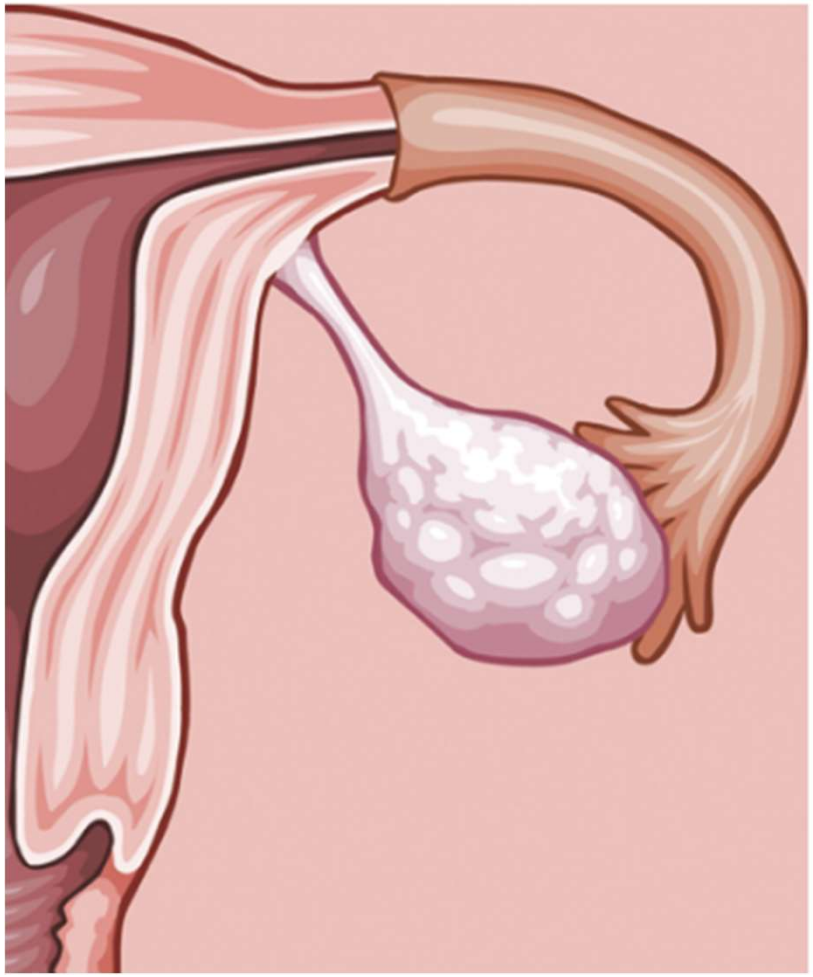

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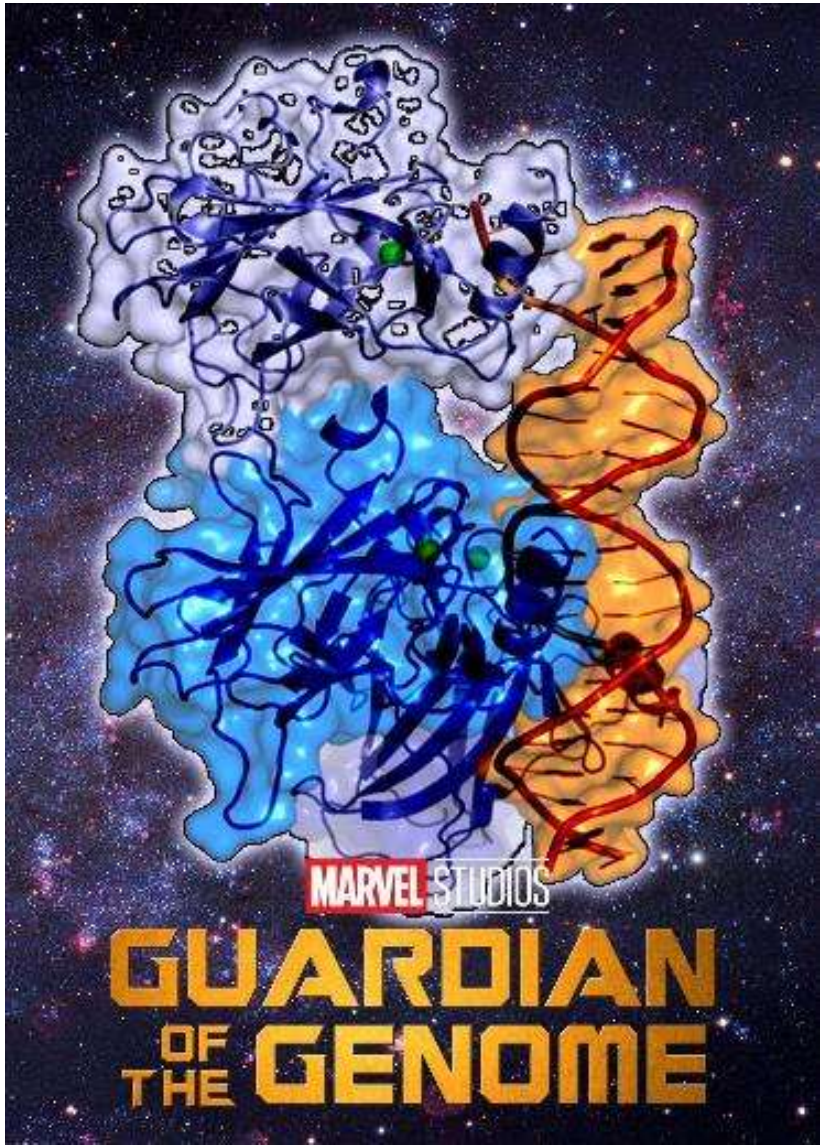
Why do cells turn into cancer cells?



Using the example of
p53 tumor suppressor gene

- If the DNA is damaged, p53 builds up in the cell
- P53 protects the cell from becoming a tumor cell by arresting the cell in it´s growth cycle or killing it
- If the cell is arrested/frozen or killed - depends on which part of the cell cycle the cell is currently in
- Special forms of viruses like HPV can cause cancer by switching off the p53-tumor suppressor

Basics immune system: A complex balance

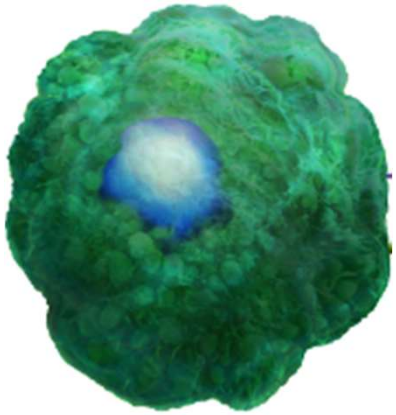
Infection/Cancer:

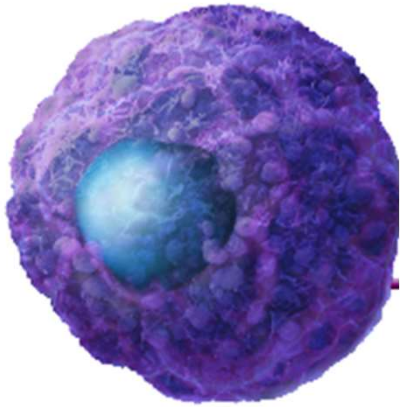
If the immune system is not aggressive, infection or cancer can develop

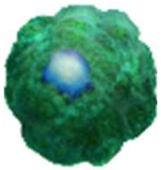
Auto-immune disease:

If the immune system is too agressive, normal cells of the body can be destroyed

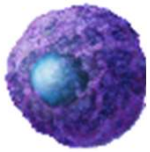
Replicating and sleeping tumor cells





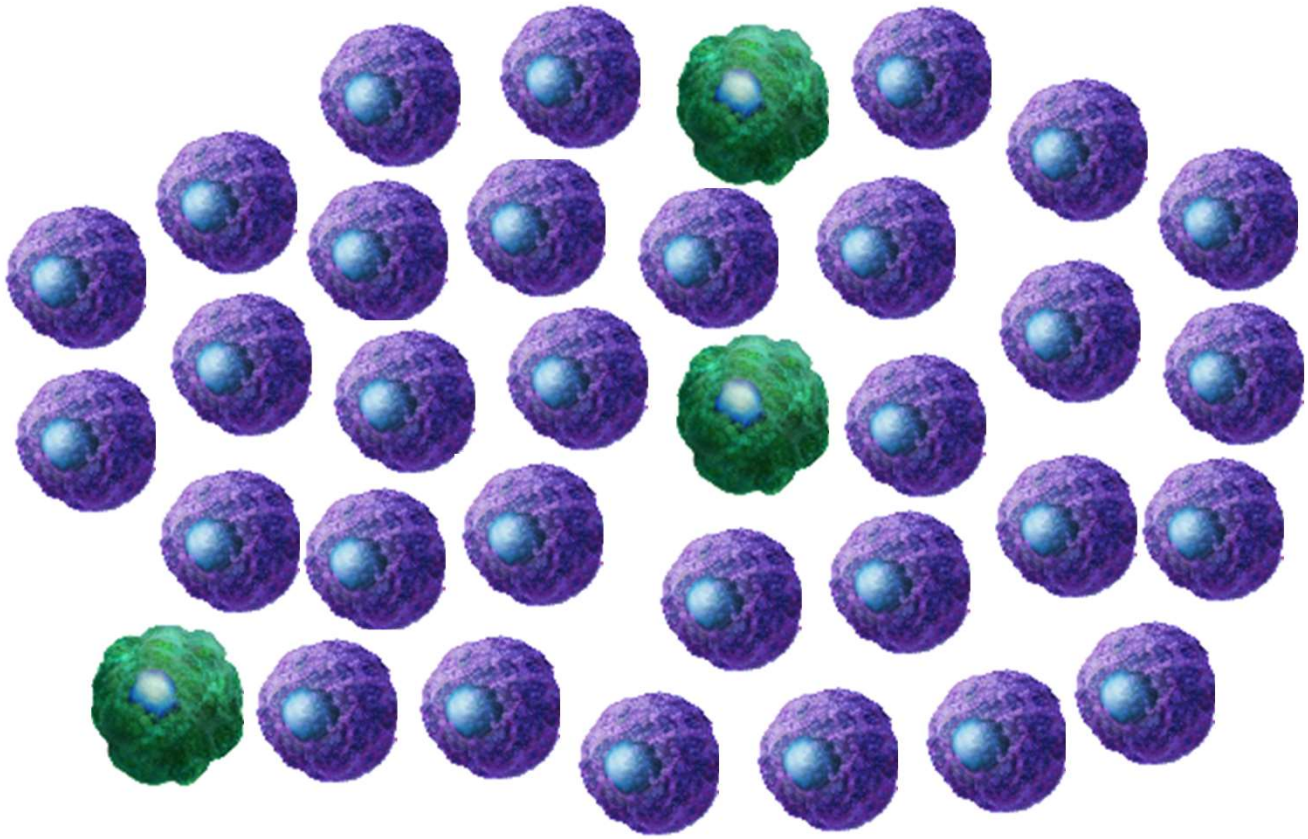


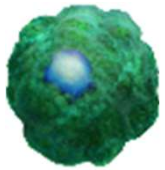
Green cell= Sleeping cell



Blue cell= Replicating cell

Fast-growing tumors





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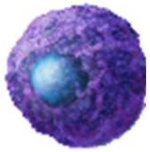

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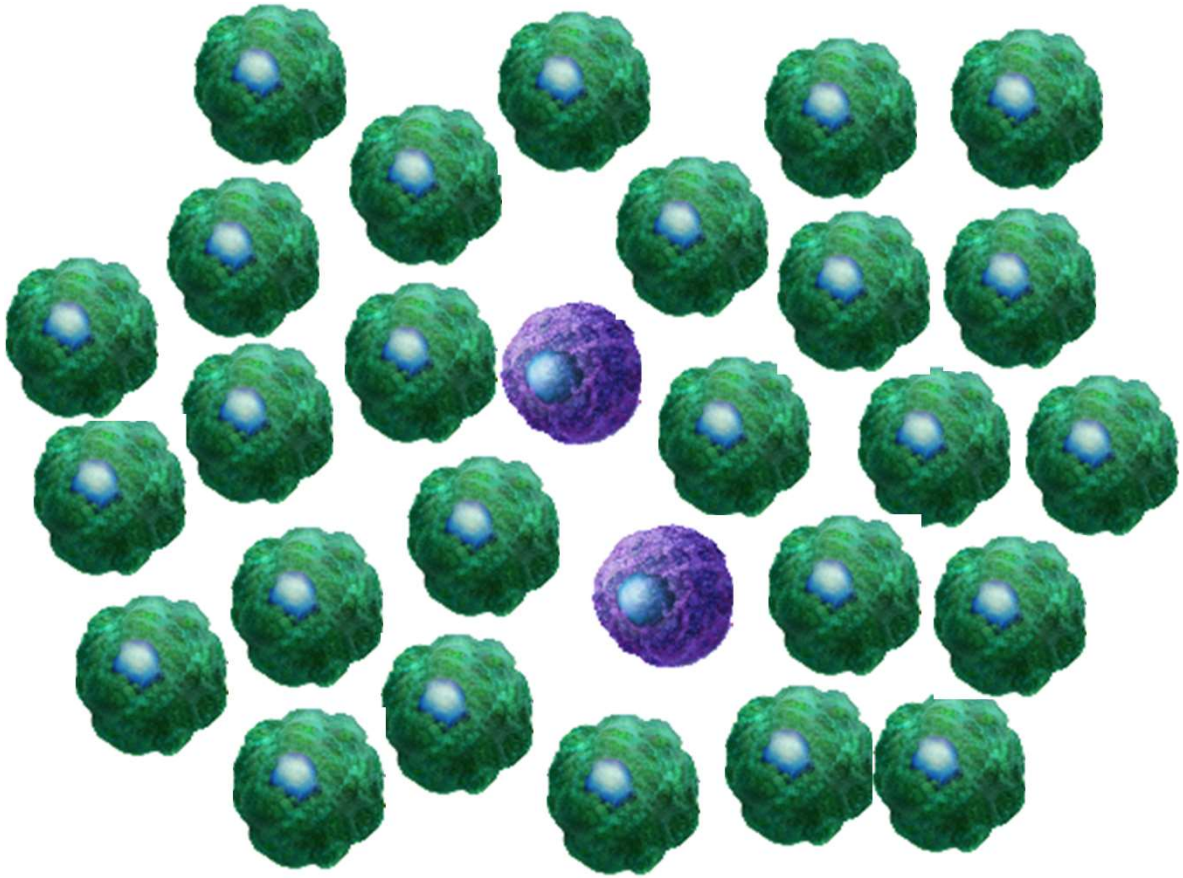
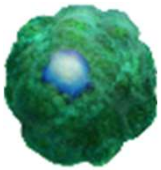
Slow-growing tumors





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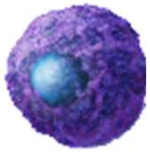

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Why is cancer not easy to kill?

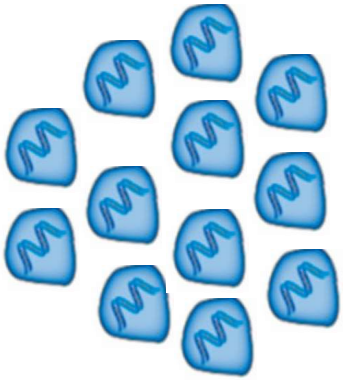
Cancer cells

Targeted therapy

Cancer cells

Targeted therapy

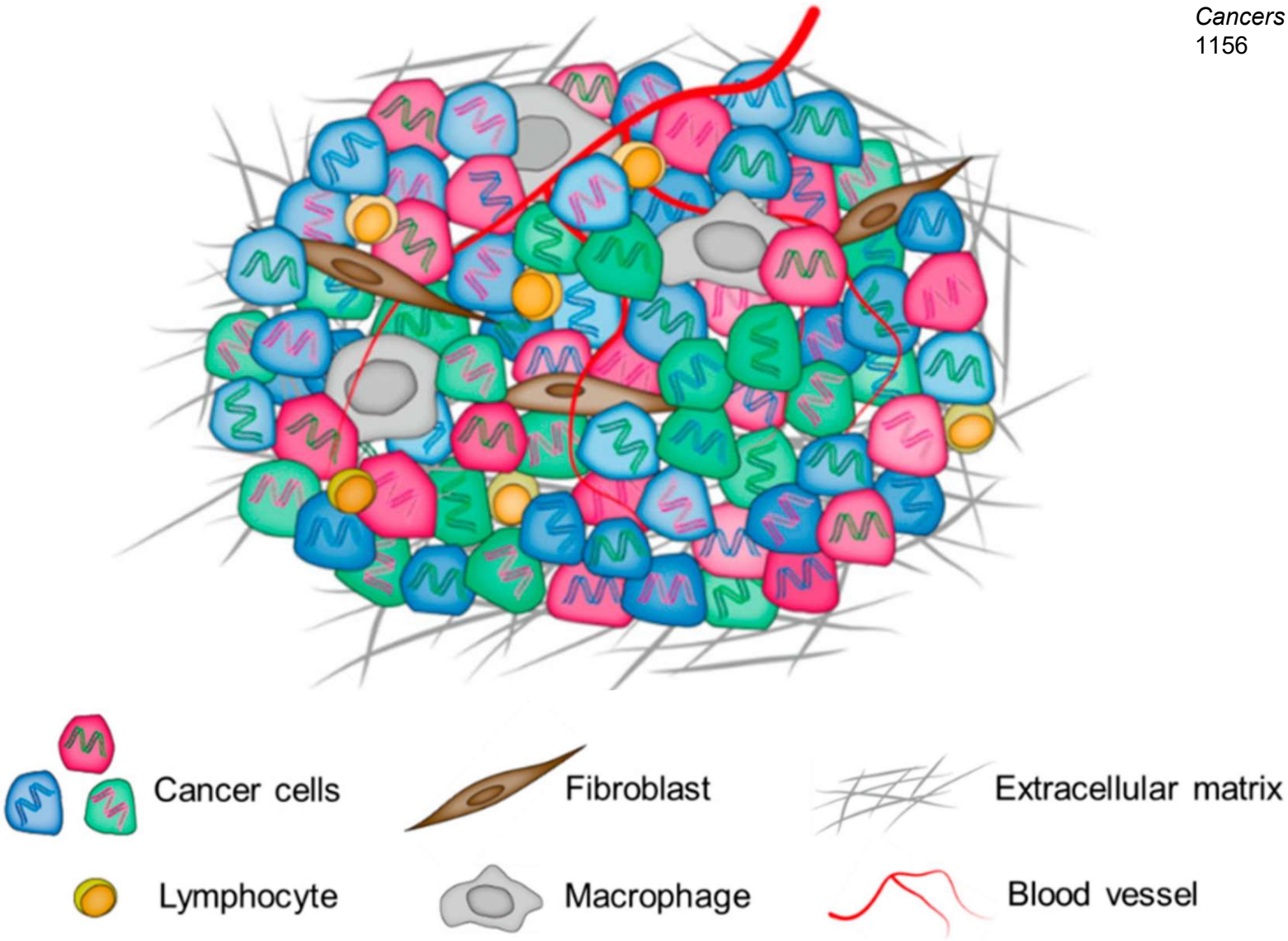
Cancer cells



Targeted therapy

What is intratumor heterogeneity?

Modified from: Lin et al: *Cancers* **2019**, *11*(8), 1156



Endometrial cancer

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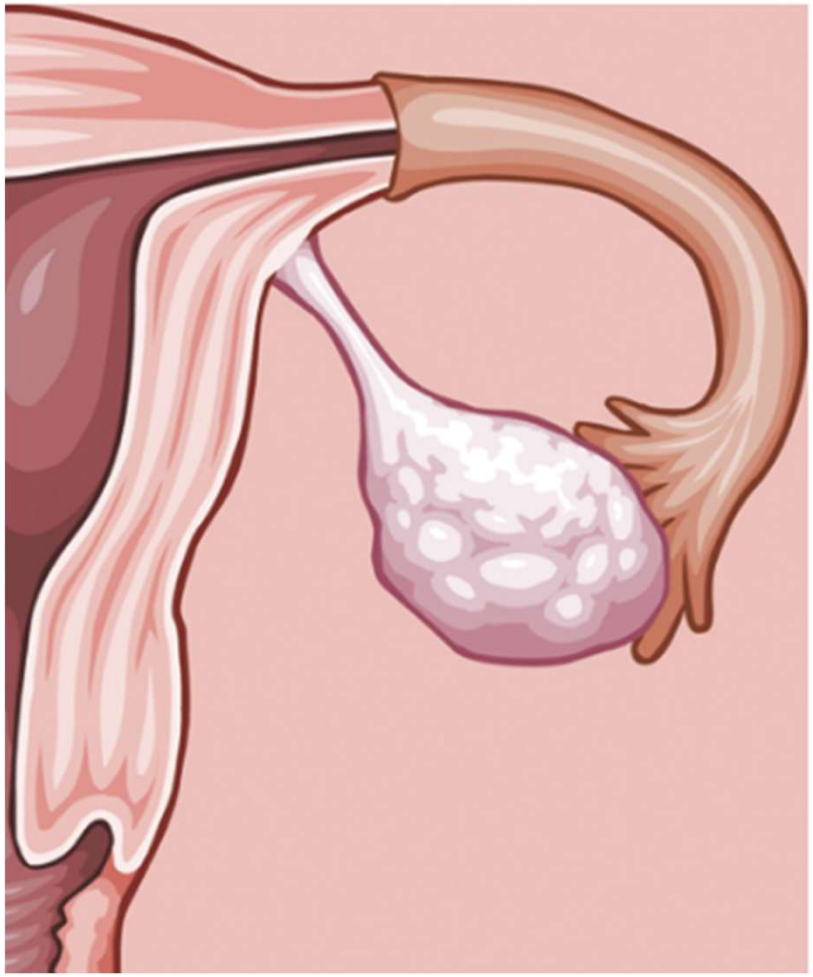

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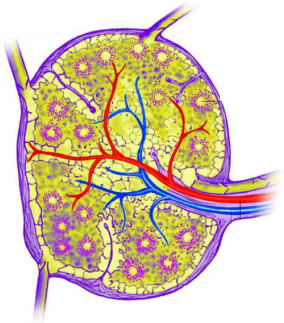
New data for immunotherapy

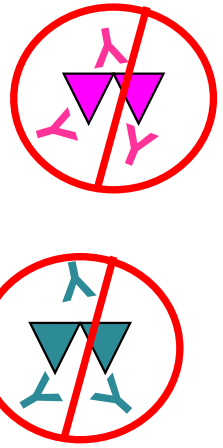
New therapies on the horizon

How does the immune system work? Antibodies

Lymph node

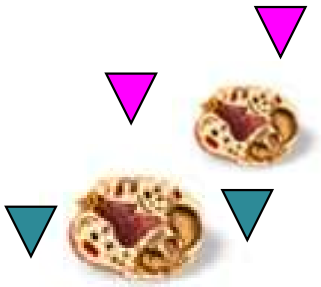


Dendritic cells / T-Helper Cells



White Blood Cells (B-Lymphozyte)

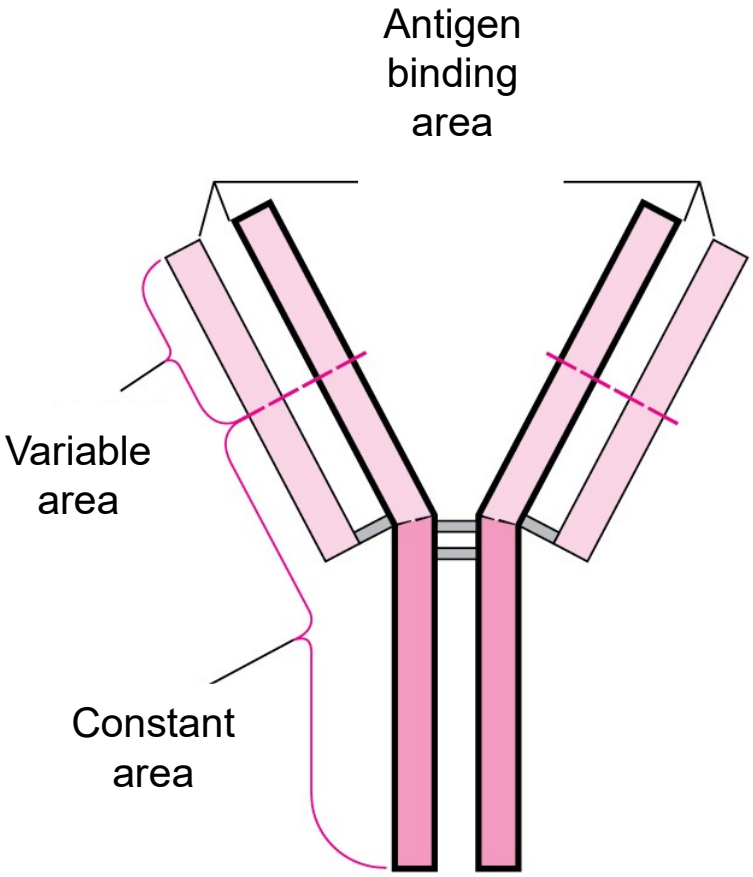
Antigen

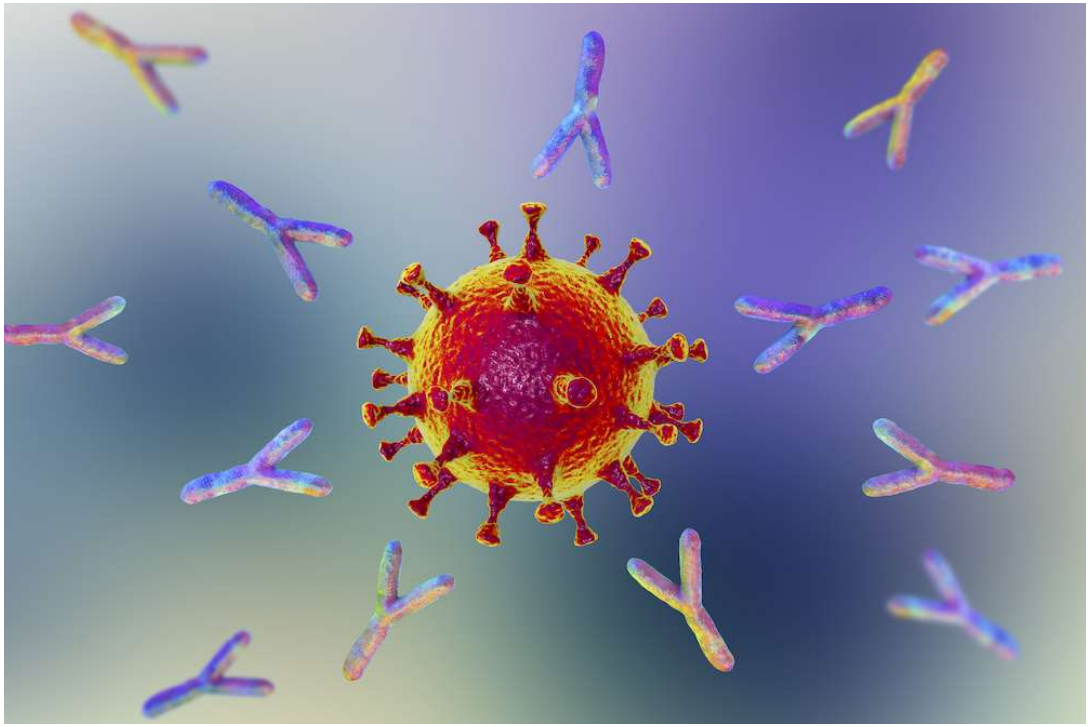


White Blood Cells (Macrophages)

Antigen-Presentation

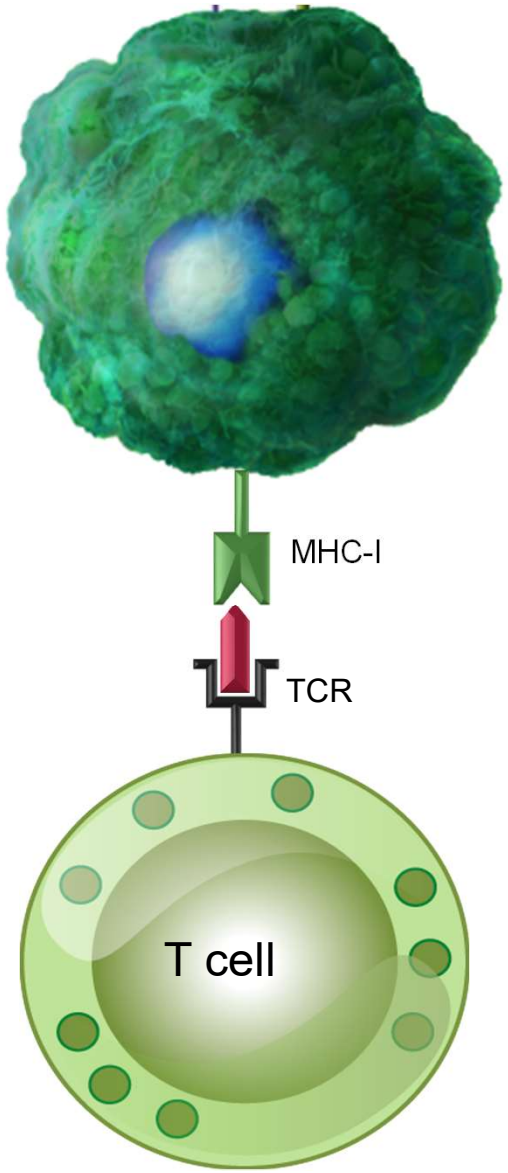
Basics: Antibody





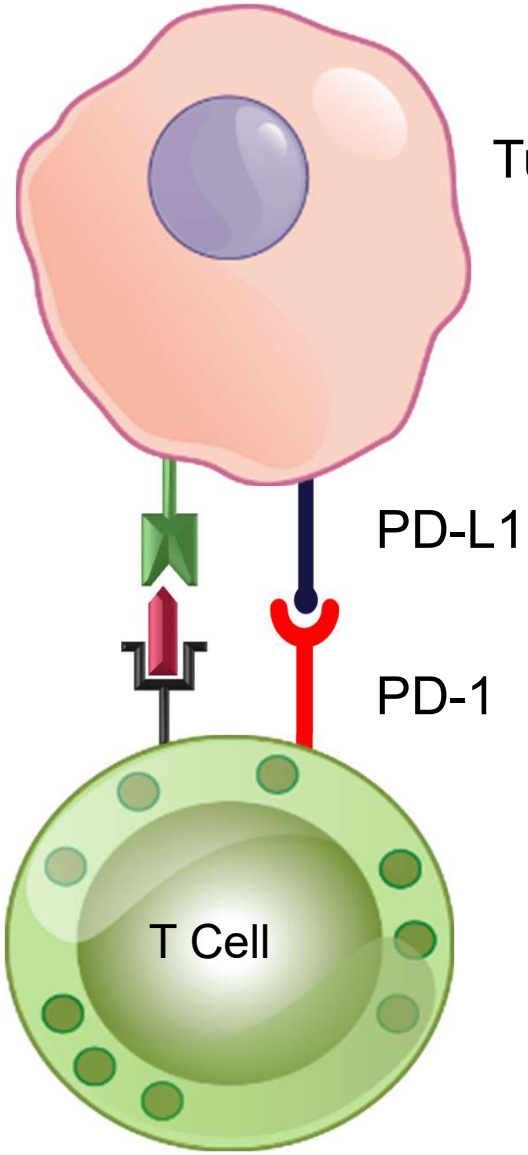
All substances ending with „-mab“ are antibodies (monoclonal antibody)

How does the immune system work? T cells

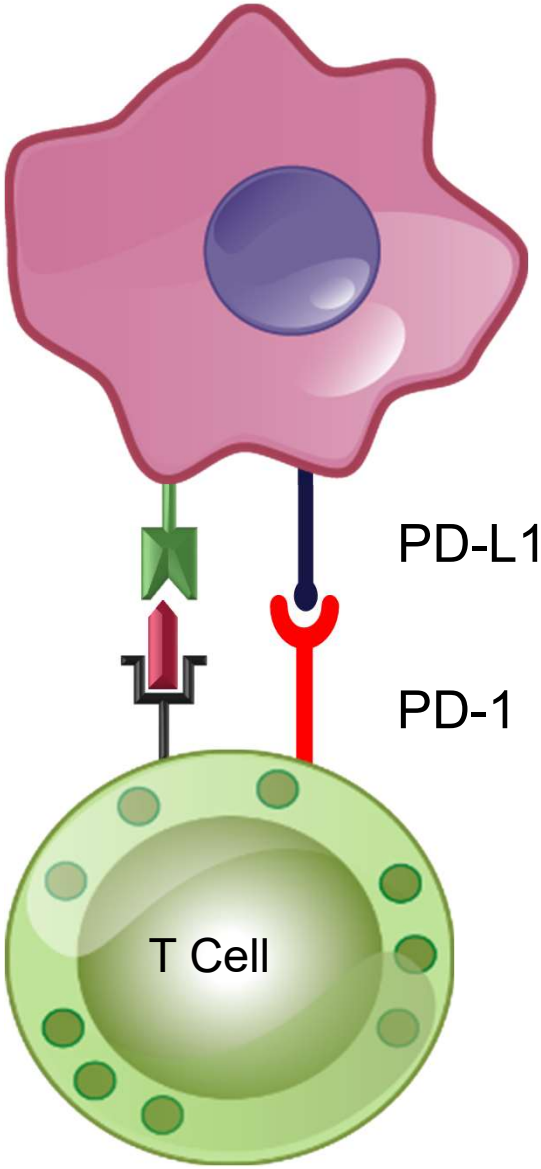


- T cells check the „barcode“ (MHC I-complex) of every cell in the human body
- If the barcode (MHC-I) indicates a virus infected cell or **tumor cell** –this cell will be killed
- T cells have the ability to kill cells directly- or by starting their built-in suicide programme (apoptosis induction)

Immun-checkpoint is also important in pregnancy



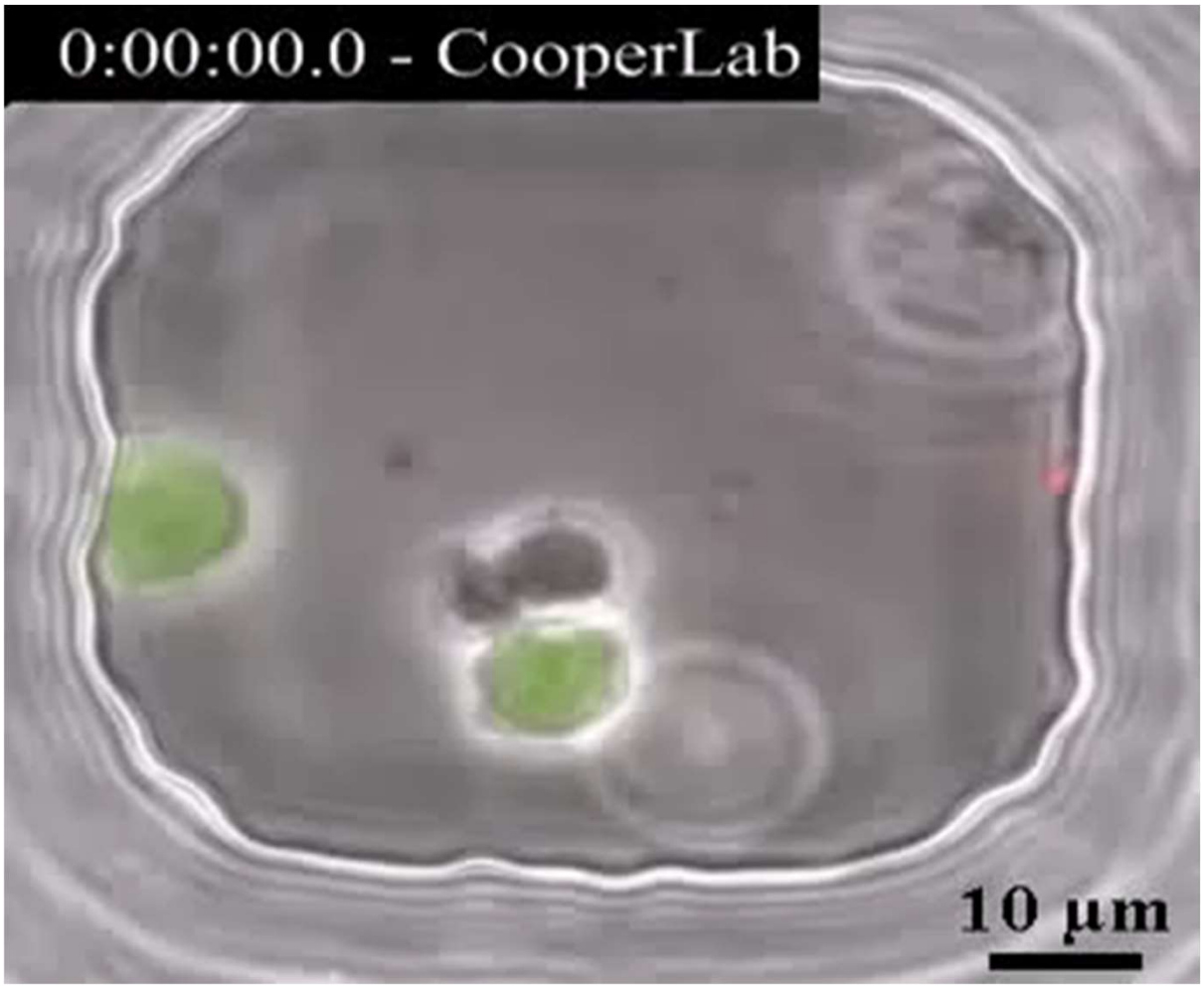
Fetal cell
of the placenta



Pregnancy and cancer both use the immune-checkpoint to avoid/turn-off the immune system

Checkpoint-immune escape: Does it really work?

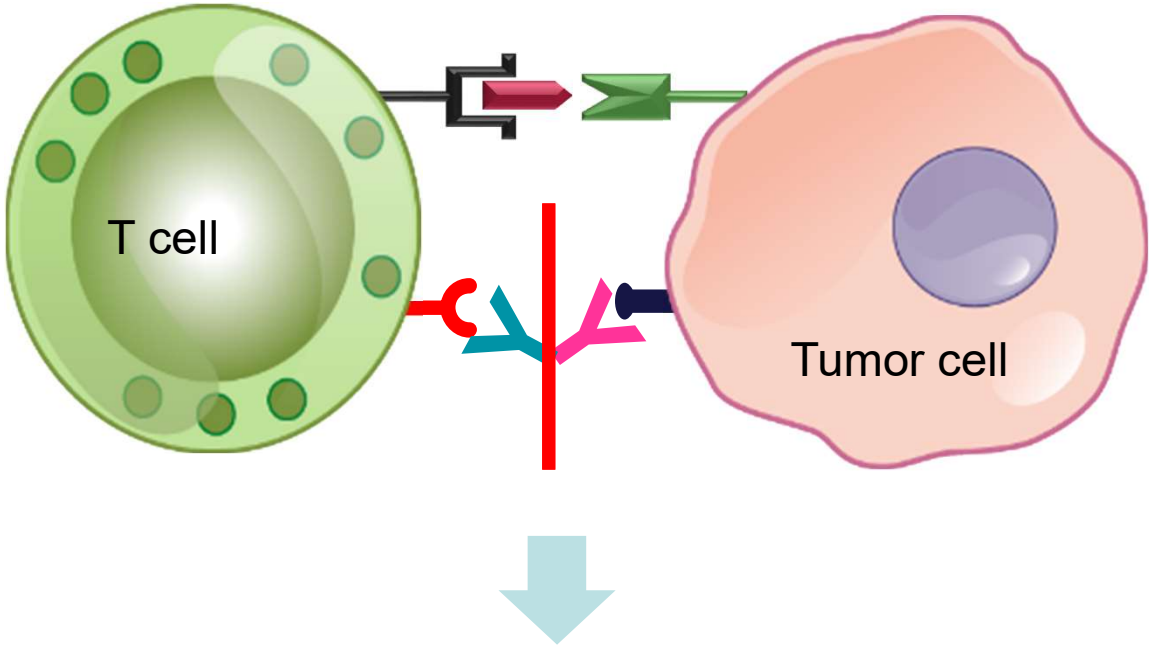
Green = 2 Tumor cells
Red = Tumor cell death
Unmarked = Human T cell



Thanks to: **Dr. Navin Varadarajan** (Laurence Cooper laboratory), MD Anderson Cancer Center

A new idea: Checkpoint-Inhibitors

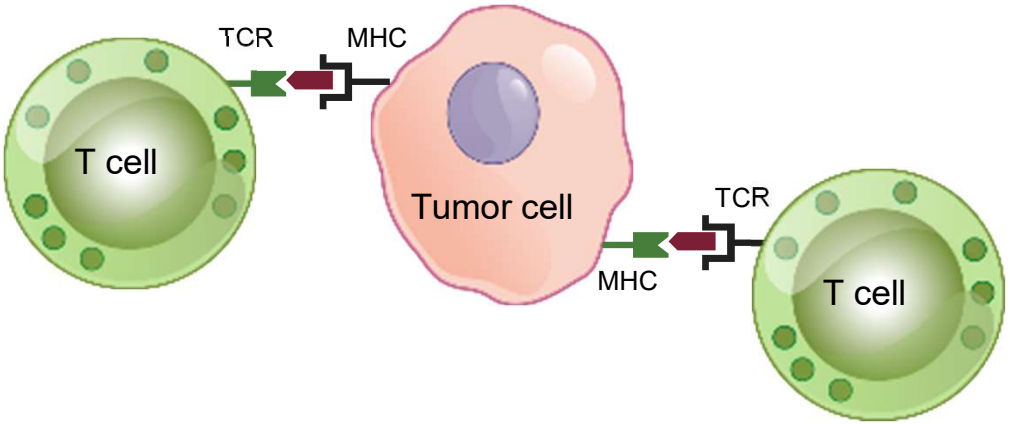
Antibodies are use to block the docking site of the immune-checkpoint



The T cell can do it`s job again- to recognize and then kill the tumor cell

Protection for the police of your immune system

PD-1
PD-L1

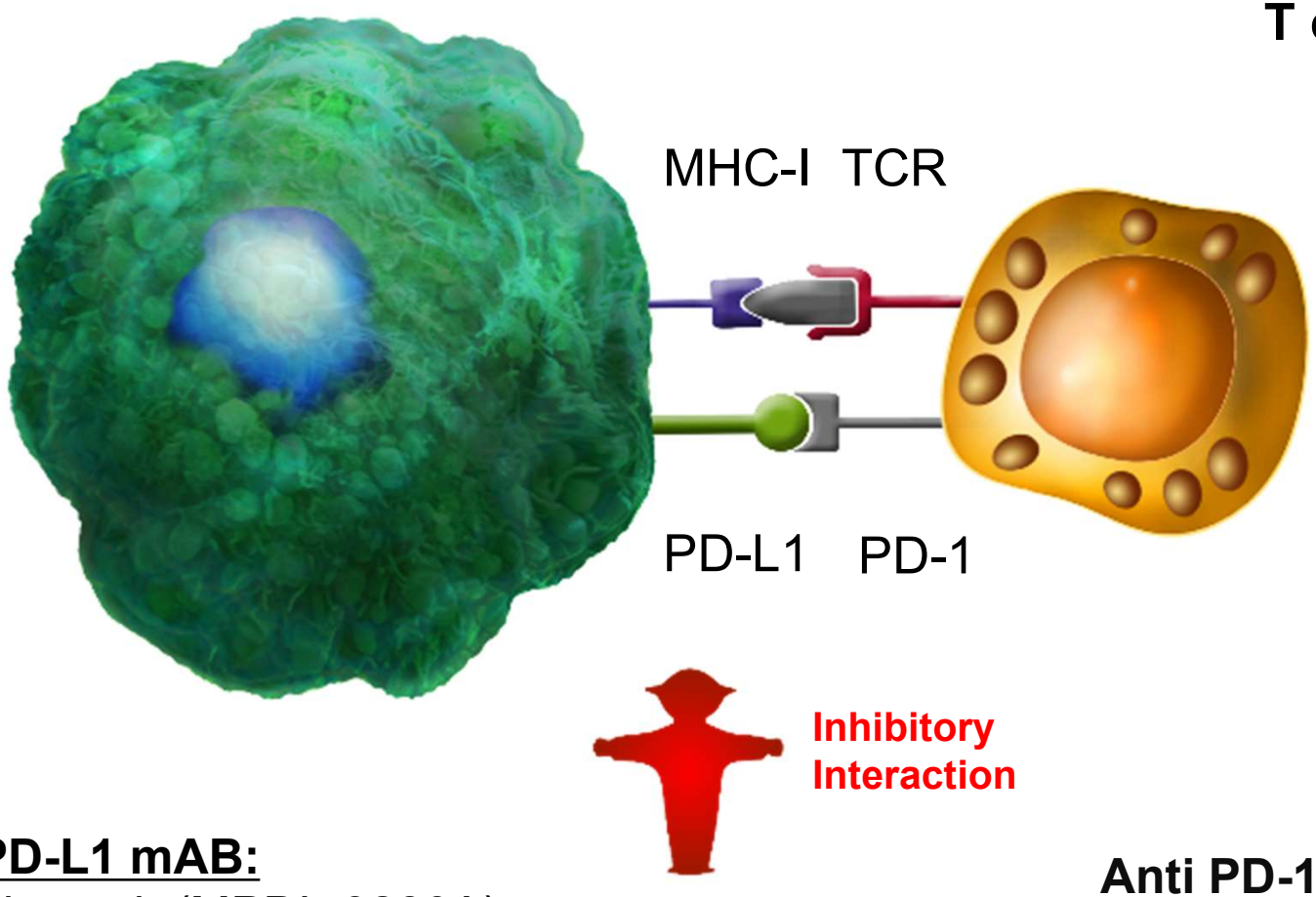


Check-Point-Inhibitor

Checkpoint-Inhibitors: Different substances

Tumor cell

T cell



<u>Anti PD-L1 mAB:</u>
Atezolizumab (MPDL-3280A)
Durvalumab (MEDI-4736)
Avelumab (MSB0010718C)

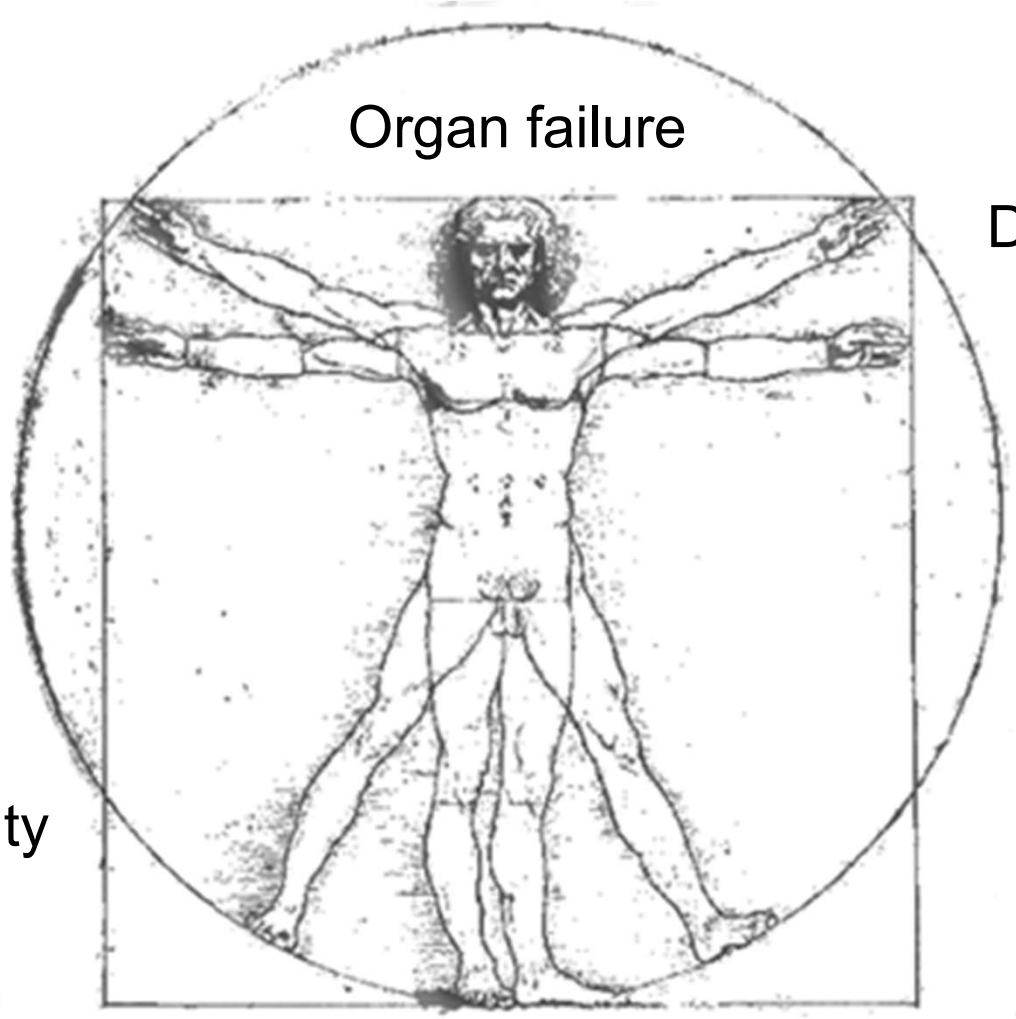
<u>Anti PD-1 mAB:</u>
Nivolumab
Pembrolizumab (MK-3475)
Dostarlimab

Side effects: Checkpoint-Inhibitors

Organ failure

Gastrointestinal side-effects

Dermatologic toxicity

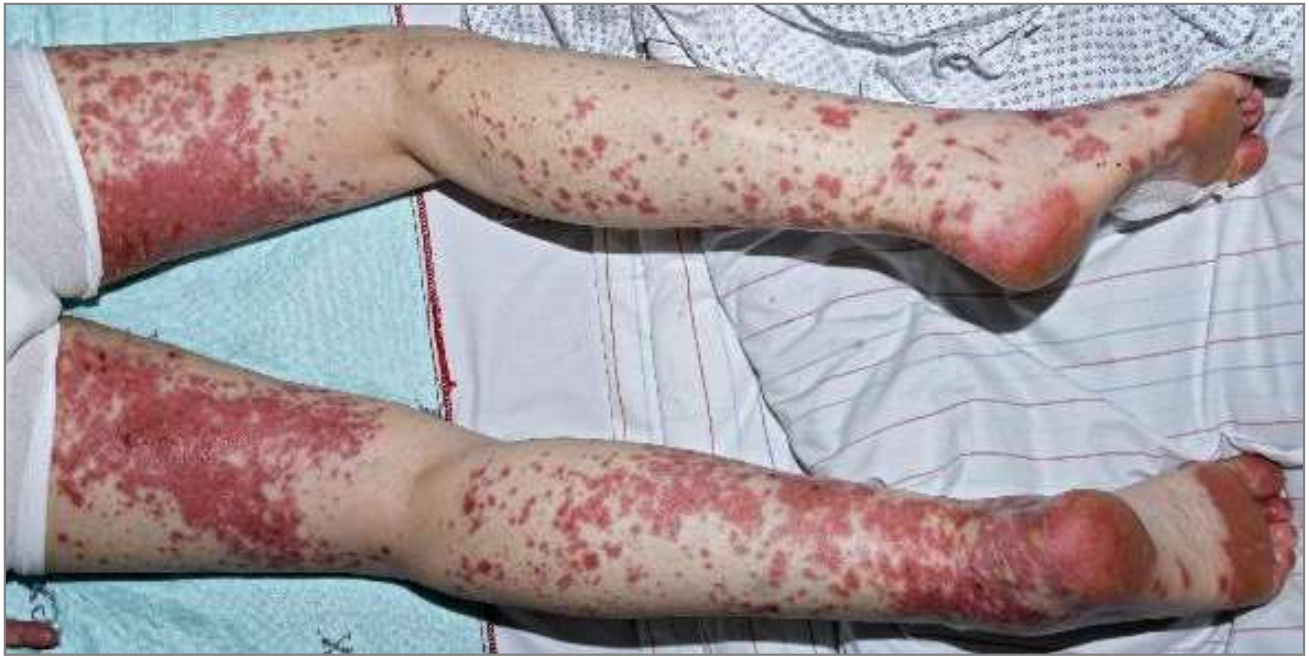


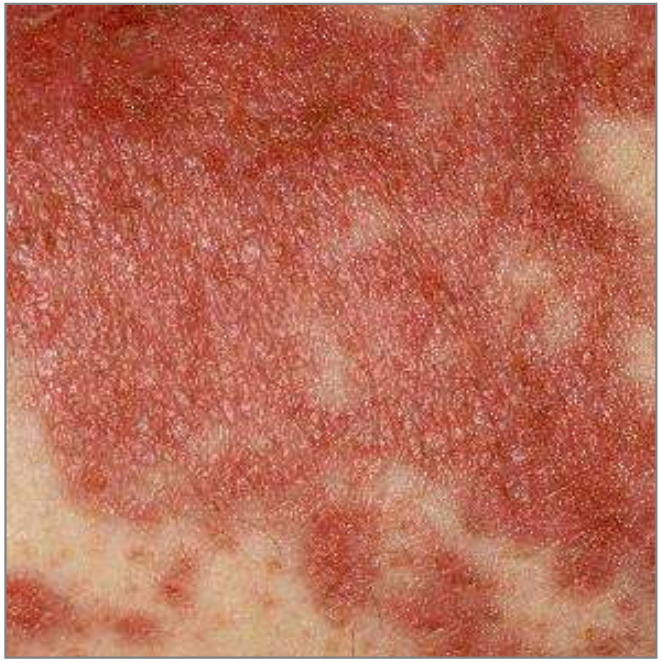
Hepatic toxicity

Neurologic side-effects

Endocrine side-effects

Example of massive skin reaction under immunotherapy

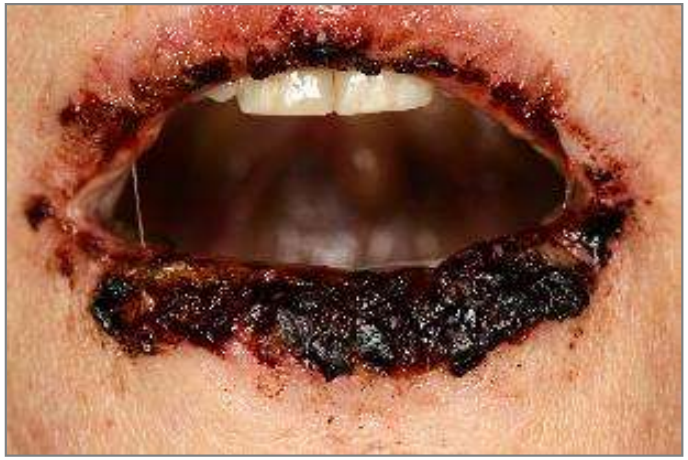
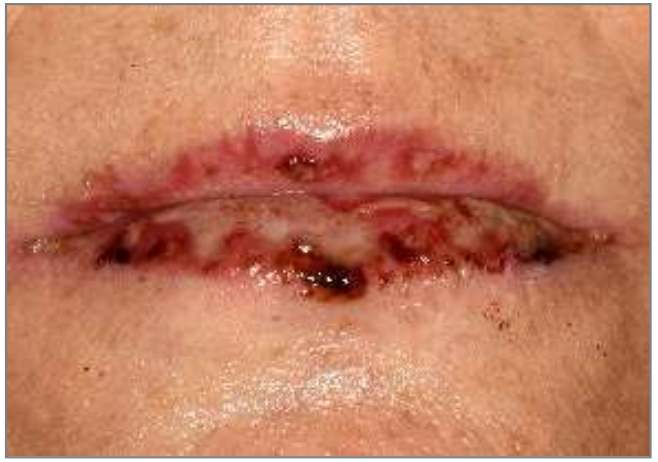


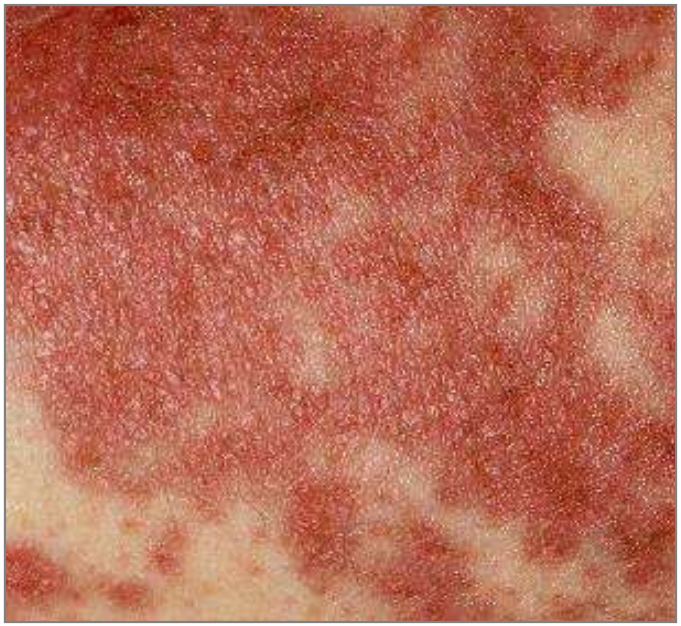
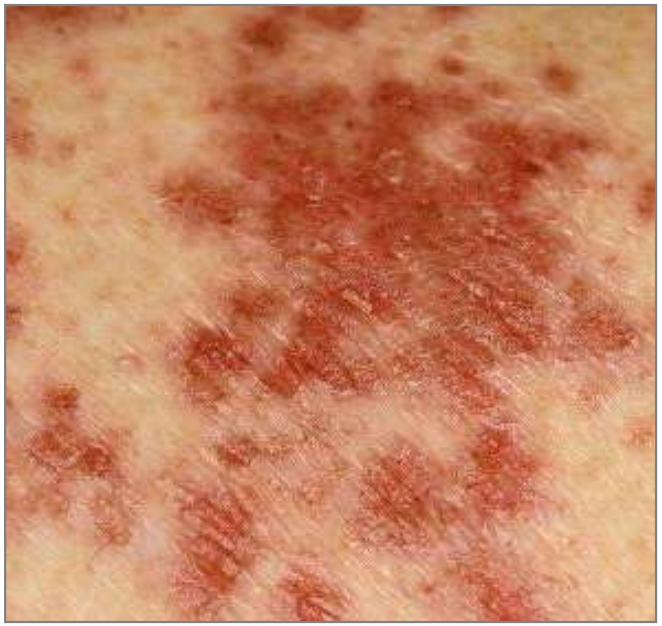
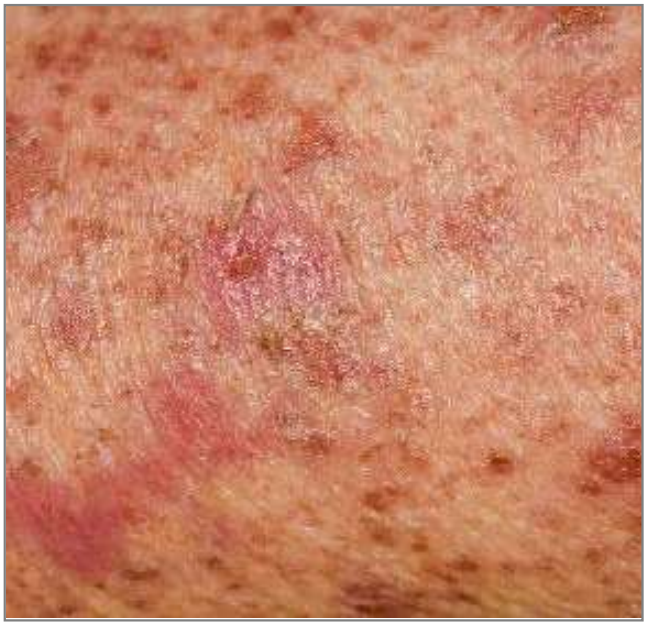


- 57-year old patient with cervical cancer
- Massive skin reaction under therapy with Pembrolizumab

The patient gave written consent for these pictures to be shown in a presentation

Skin reactions resolve under corticosteroid-therapy

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Endometrial cancer

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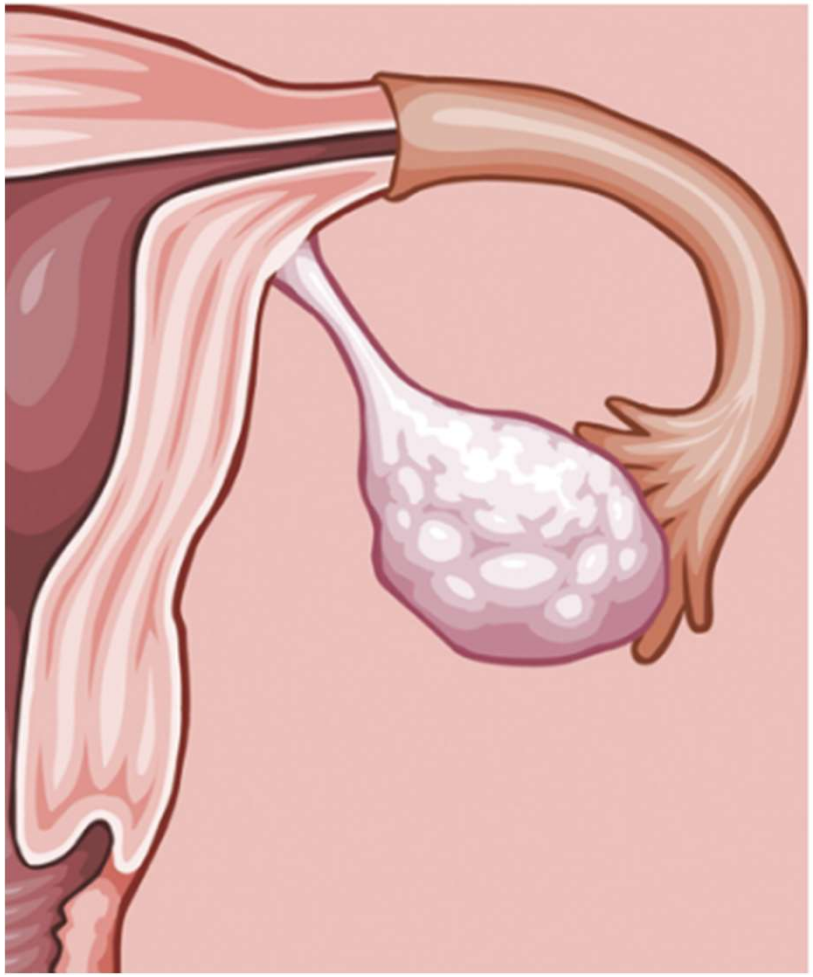

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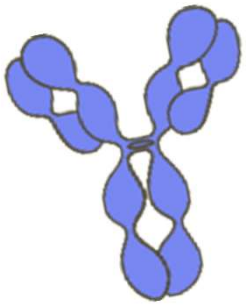
New hope in endometrial cancer

New data for immunotherapy

New therapies on the horizon

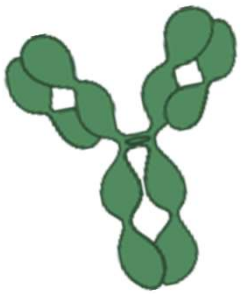
Dostarlimab is available in the EU since April



Dostarlimab
(Anti-PD-1 Antikörper)

Dostarlimab can be used for patients with recurrent **(EC) with Mismatch-Repair-Defiziency (dMMR) / microsatellite instability (MSI-H)** when the disease progresses after Carboplatin –based Chemotherapy

Pembrolizumab+Lenvatinib is available since Nov. 2021/Pembrolizumab Mono since April 2022 in the EU



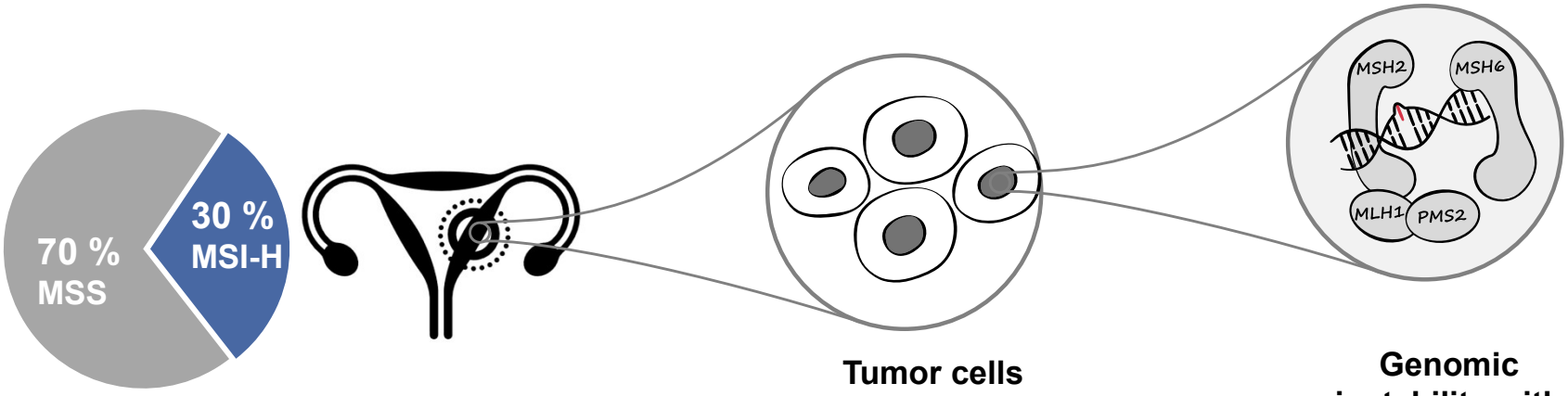
Pembrolizumab
(Anti-PD-1 Antikörper)

Pembrolizumab+Lenvatinib can be used for all patients with recurrent **(EC)** when the disease progresses after Carboplatin –based Chemotherapy

Pembrolizumab Monotherapie can be used for patients with recurrent **(EC) with Mismatch-Repair-Defiziency (dMMR) / microsatellite instability (MSI-H)** when the disease progresses after Carboplatin –based Chemotherapy

1. JEMPERLI, Fachinformation. Stand April 2021 2. KEYTRUDA Fachinformation, Stand Juli 2021

About 30 % of patients show dMMR/MSI-H



dMMR, Mismatch-Reparatur-Defizienz; MSI, Mikrosatelliteninstabilität; MSI-H, hohe Mikrosatelliteninstabilität; MSS, Mikrosatelliten stabil..

1. Bonneville R, Krook MA, Kautto EA et al.JCO Precis Oncol 2017; 2017; 2. Kloor M et al. *Trends Cancer.* 2016;2:121–133.

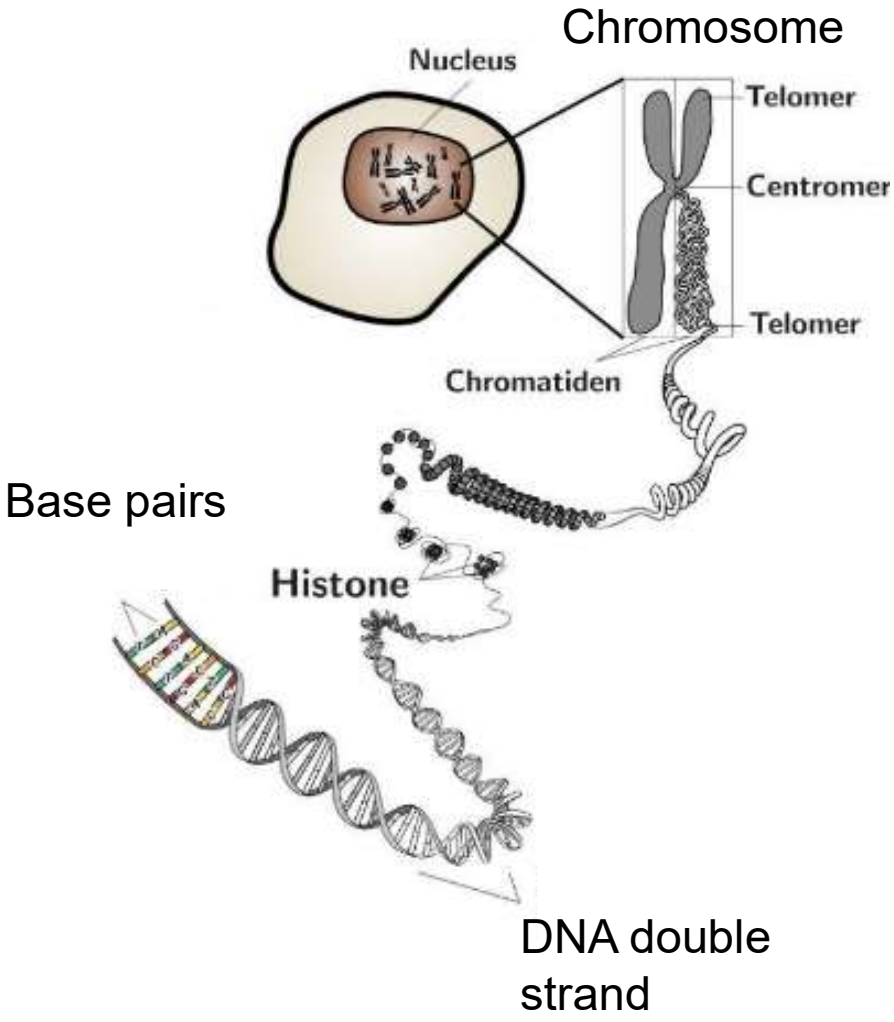
What is a microsatelite instability?

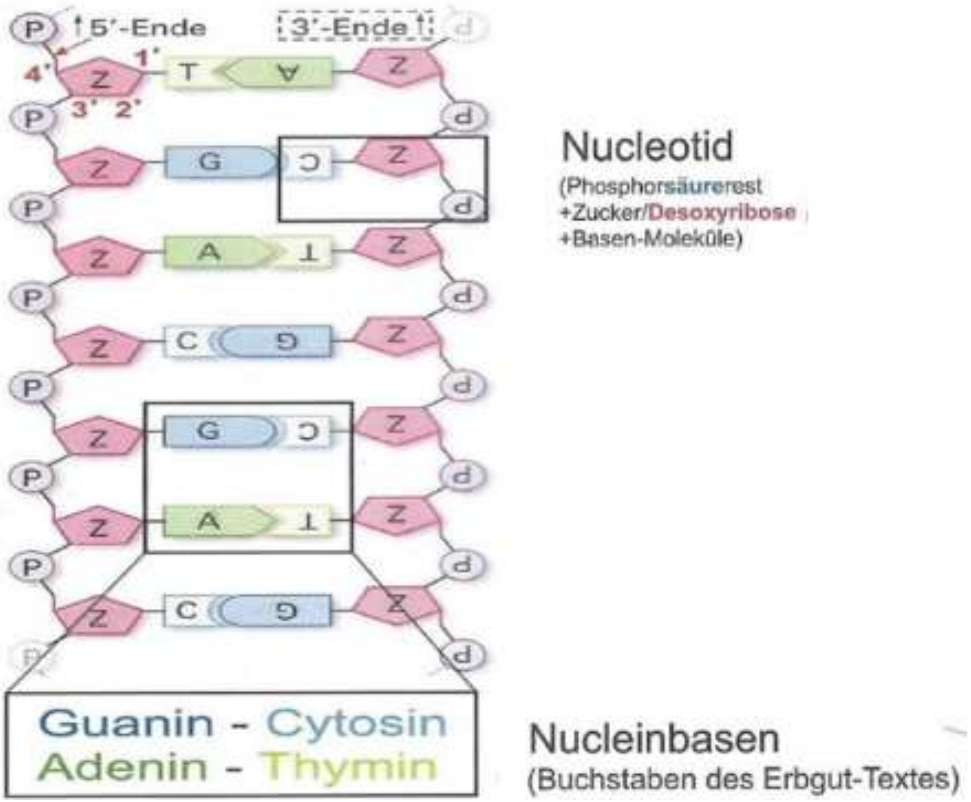
Microsatelites

Deficient Missmatch Repair (dMMR)

Microsatelite-Instability (MSI-H)

How are chromosomes and DNA built?

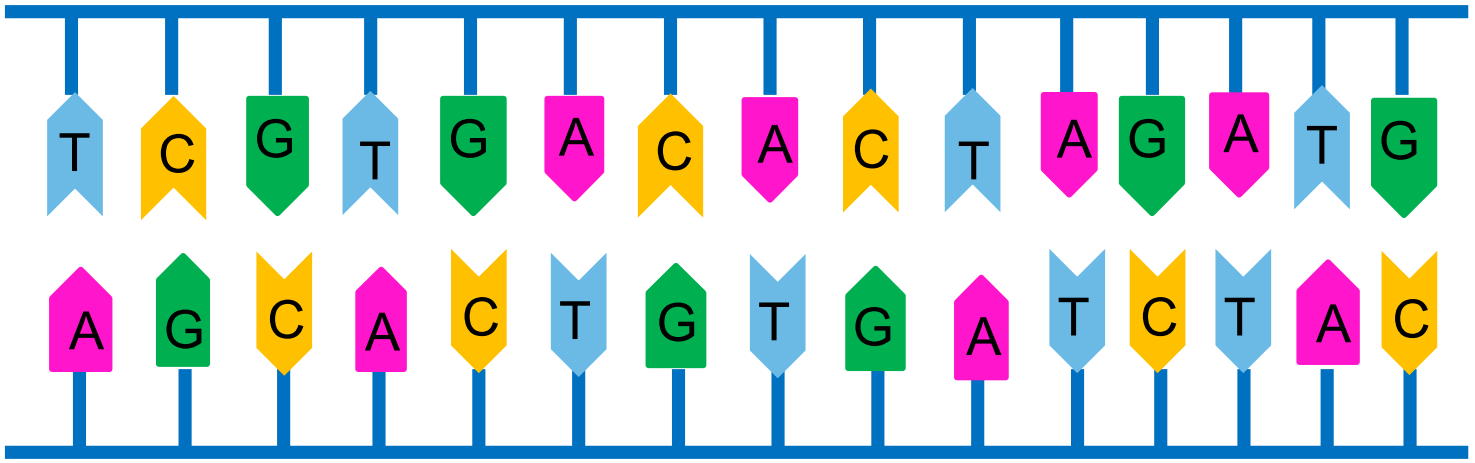




Modifziert nach https://www.springer.com/de/book/9783642049996

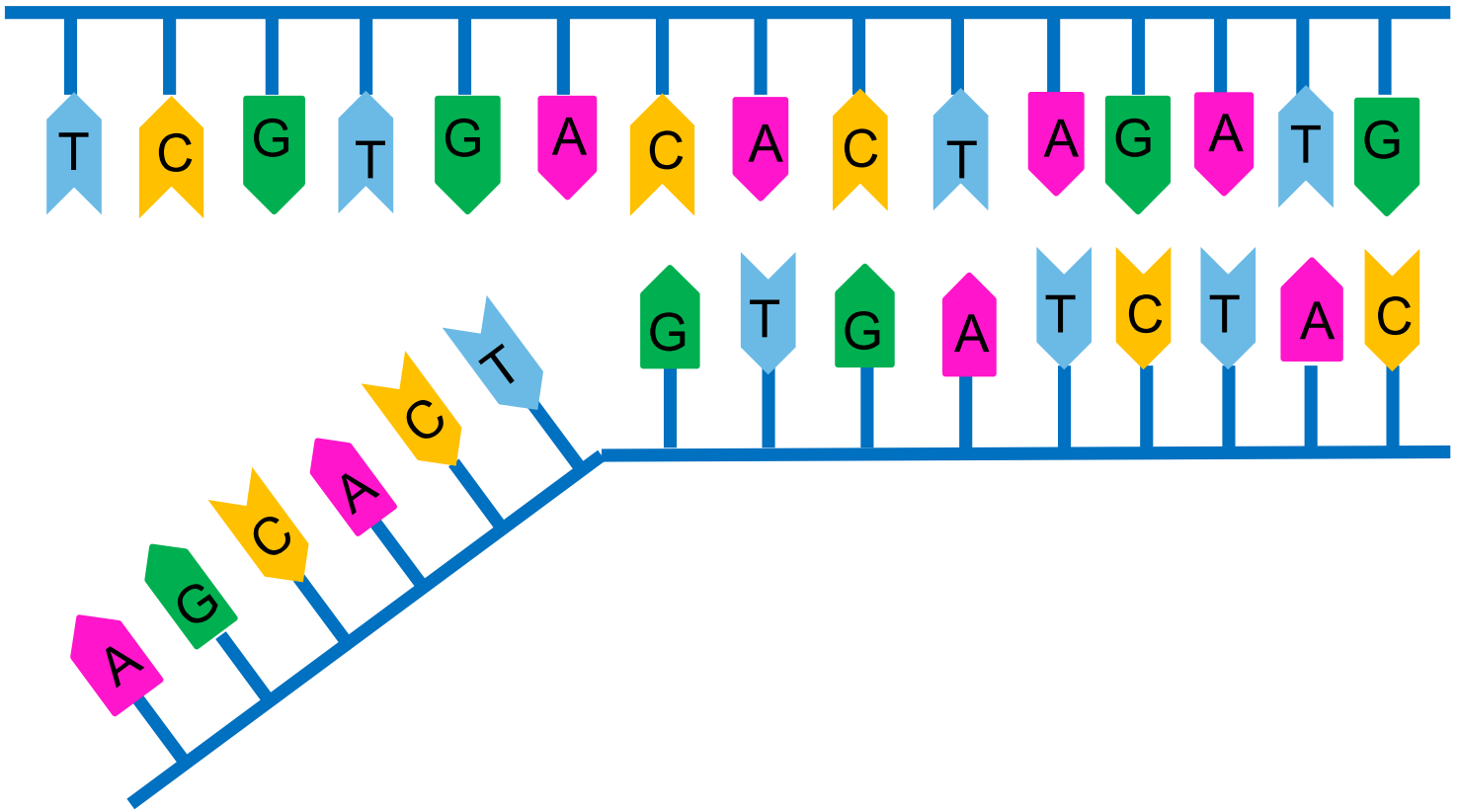
Healthy DNA

DNA is built from base pairs

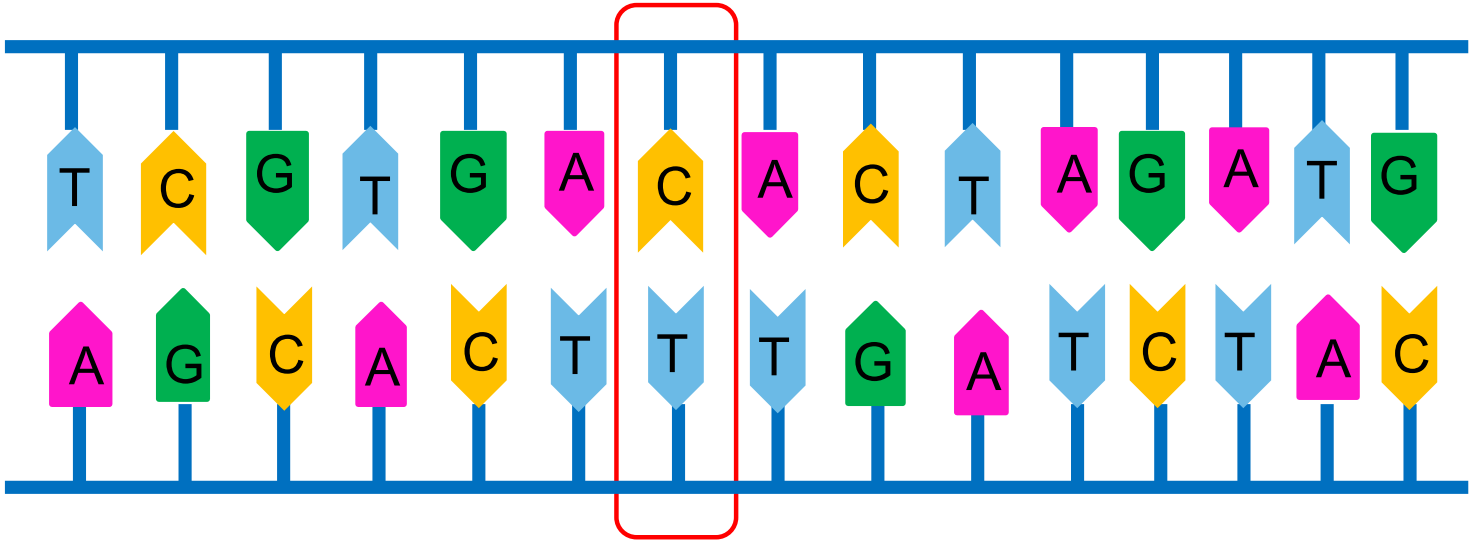


Adenin-Thymin
Guanin-Cytosin

Healthy DNA: Replication



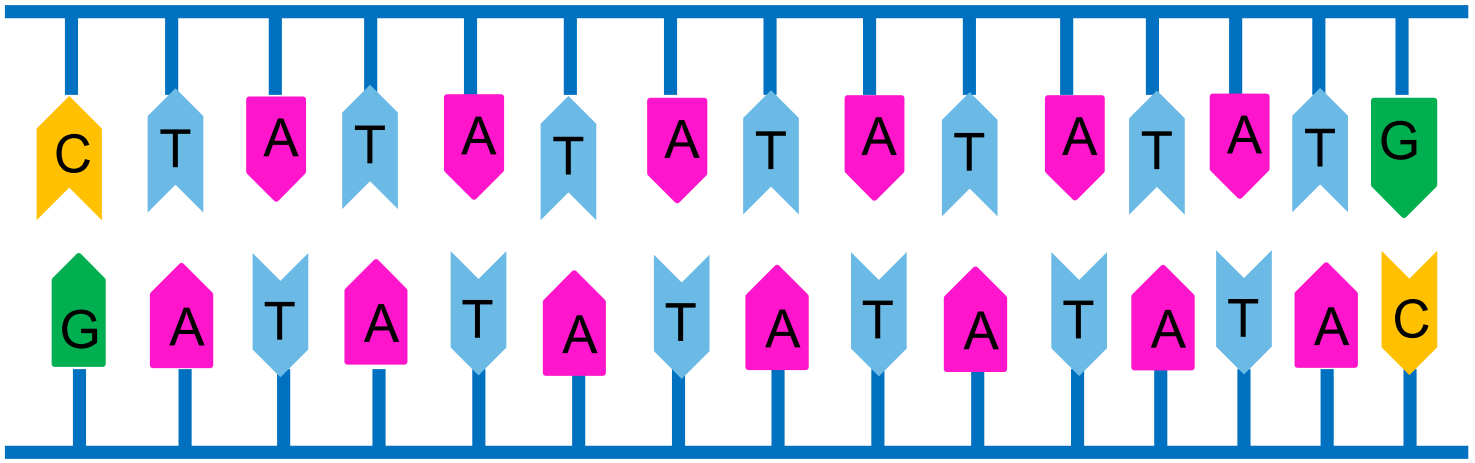
DNA Missmatch



Missmatch-Repair Proteins:
MLH 1, MSH2, MSH6, PMS2

What are Mikrosatelites?

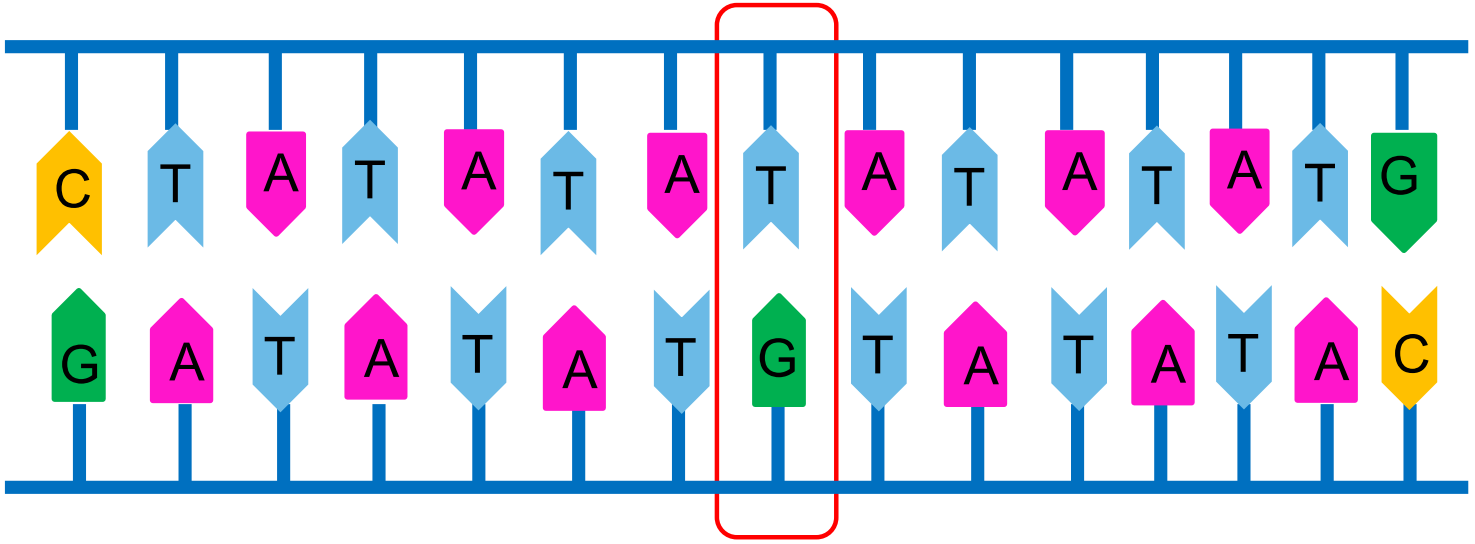
Mikrosatelites = Repetetive DNA sequences



6-10 repeats/stutters = Microsatelite
10-100 repeats/stutters = Minisatelite

What is MSI?

Base pair missmatch in repetetive DNA sequence



The microsatelite becomes unstable and the cell might mutate to become a cancer cell

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

Ramez N. Eskander, M.D., Michael W. Sill, Ph.D., Lindsey Beffa, M.D., Richard G. Moore, M.D., Joanie M. Hope, M.D., Fernanda B. Musa, M.D., Robert Mannel, M.D., Mark S. Shahin, M.D., Guilherme H. Cantuaria, M.D., Eugenia Girda, M.D., Cara Mathews, M.D., Juraj Kavecansky, M.D., Charles A. Leath III, M.D., M.S.P.H., Lilian T. Gien, M.D., Emily M. Hinchcliff, M.D., M.P.H., Shashikant B. Lele, M.D., Lisa M. Landrum, M.D., Floor Backes, M.D., Roisin E. O'Cearbhaill, M.D., Tareq Al Baghdadi, M.D., Emily K. Hill, M.D., Premal H. Thaker, M.D., Veena S. John, M.D., Stephen Welch, M.D., Amanda N. Fader, M.D., Matthew A. Powell, M.D., and Carol Aghajanian, M.D.

Ramez N. Eskander / University of California

ORIGINAL ARTICLE

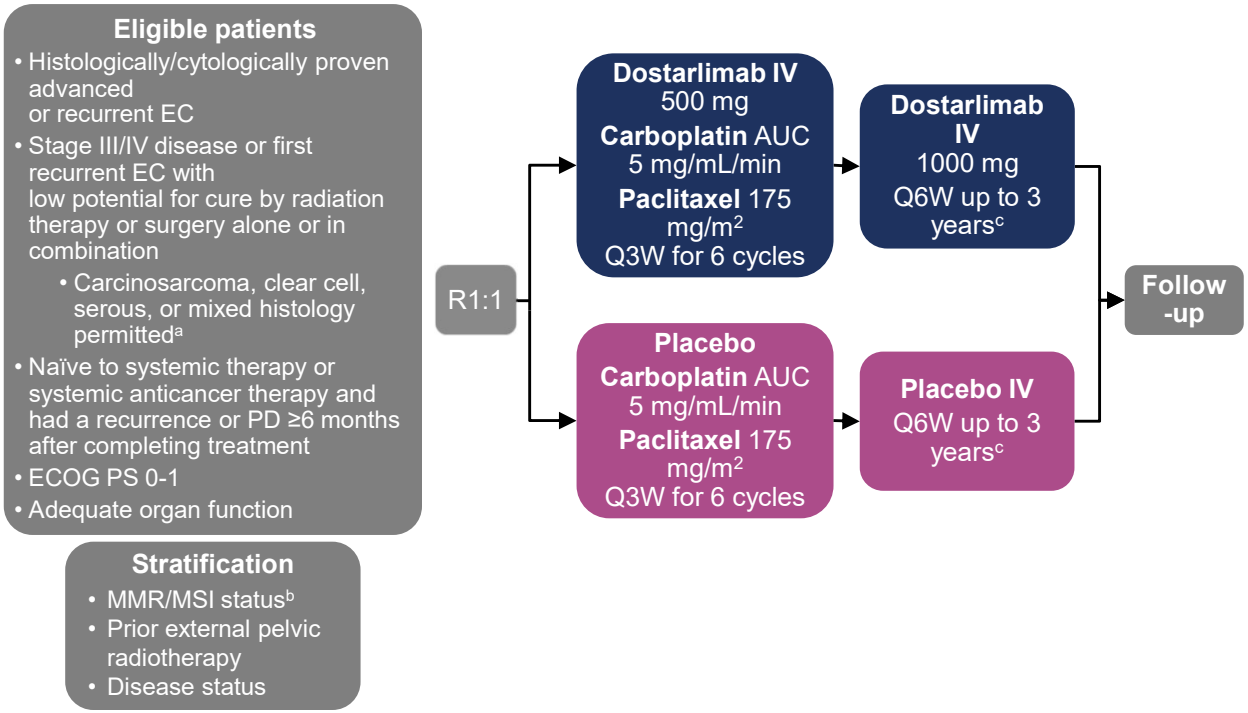
Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

M.R. Mirza, D.M. Chase, B.M. Slomovitz, R. dePont Christensen, Z. Novák, D. Black, L. Gilbert, S. Sharma, G. Valabrega, L.M. Landrum, L.C. Hanker, A. Stuckey, I. Boere, M.A. Gold, A. Auranen, B. Pothuri, D. Cibula, C. McCourt, F. Raspagliesi, M.S. Shahin, S.E. Gill, B.J. Monk, J. Buscema, T.J. Herzog, L.J. Copeland, M. Tian, Z. He, S. Stevens, E. Zografos, R.L. Coleman, and M.A. Powell, for the RUBY Investigators*

Mansoor R. Mirza / University of Copenhagen

ENGOT-EN6-NSGO/GOG-3031/RUBY study

Phase 3, randomized, double-blind, multicenter study of dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin/paclitaxel in patients with primary advanced or recurrent EC



Primary endpoint
- PFS by INV
- OS

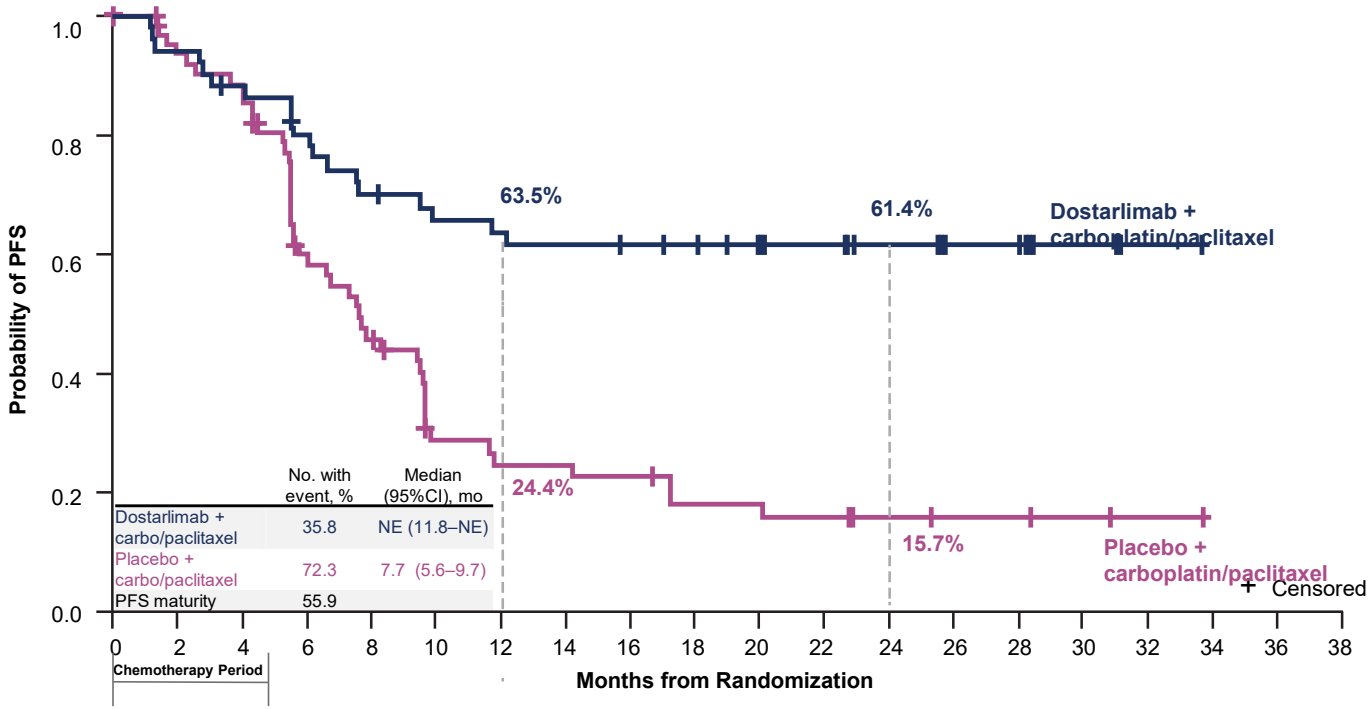
Secondary endpoints
- PFS by BICR
- PFS2
- ORR
- DOR
- DCR
- HRQOL/PRO
- Safety

On-study imaging assessments are to be performed Q6W (±7 days) from the randomization date until Week 25 (Cycle 8), followed by Q9W (±7 days) until Week 52. Subsequent tumor imaging is to be performed every 12 weeks (±7 days) until radiographic PD is documented by investigator assessment per RECIST v1.1 followed by one additional imaging 4-6 weeks later,or subsequent anticancer therapy is started, whichever occurs first. Thereafter, scans may be performed per standard of care.
[a]Mixed histology containing at least 10% carcinosarcoma, clear cell, or serous histology. [b]Patients were randomized based on either local or central MMR/MSI testing results. Central testing was used with local results were not available. For local determination of MMR/MSI status, IHC, next generation sequencing, and polymerase chain reaction assays were accepted. For central determination of MMR/MSI status IHC per Ventana MMR RxDx panel was used. [c]Treatment ends after 3 years, PD, toxicity, withdrawal of consent, investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the Sponsor and the Investigator.
AUC = area under the plasma or serum concentration-time curve; BICR = blinded independent central review; DCR = disease control rate; DOR = duration of response, EC = endometrial cancer; IV = administered intravenously; INV = investigator assessment; MMR = mismatch repair; MSI = microsatellite instability; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome.

Primary Endpoint: PFS in dMMR/MSI-H Population

HR 0.28
(95% CI, 0.162–0.495)
***P*<0.0001**

Median duration of follow-up 24.79 months.



Dostarlimab + carboplatin/paclitaxel	53 (0)	48 (3)	44 (6)	39 (10)	34 (15)	31 (17)	30 (18)	29 (19)	28 (19)	27 (19)	25 (19)	19 (19)	13 (19)	9 (19)	9 (19)	4 (19)	1 (19)	0 (19)
Placebo + carboplatin/paclitaxel	65 (0)	57 (4)	54 (7)	34 (24)	26 (32)	14 (41)	12 (43)	12 (43)	11 (44)	8 (46)	8 (46)	7 (47)	4 (47)	3 (47)	3 (47)	2 (47)	1 (47)	0 (47)

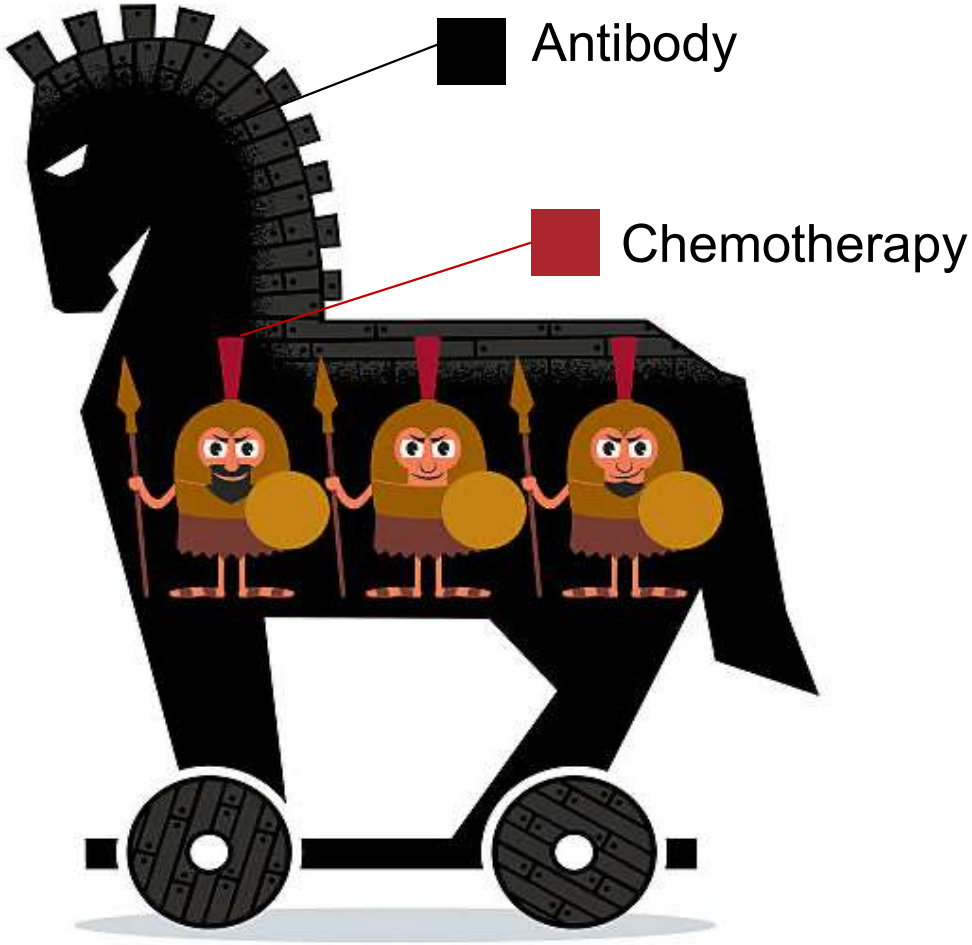
CP = carboplatin/paclitaxel; dMMR = mismatch repair deficient; HR = hazard ratio; MSI-H = microsatellite instability-high; NE = not estimable; PFS = progression-free survival

NX-DE-DST-PPT-230008; March 2023

The view into the future

What´s the next hype in endometrial cancer?

Antibody-Drug-Conjugates (ADCs): Basics



- A highly toxic chemotherapy is linked to an antibody
- In the linked form it is not so toxic
- Once the antibody is brought into the cell, the toxic chemotherapy gets „unpacked“ and becomes very toxic and kills the tumor cell

Ending „-mab“ with „double name“ (e.g.Trastuzumab Deruxtecan): ADC

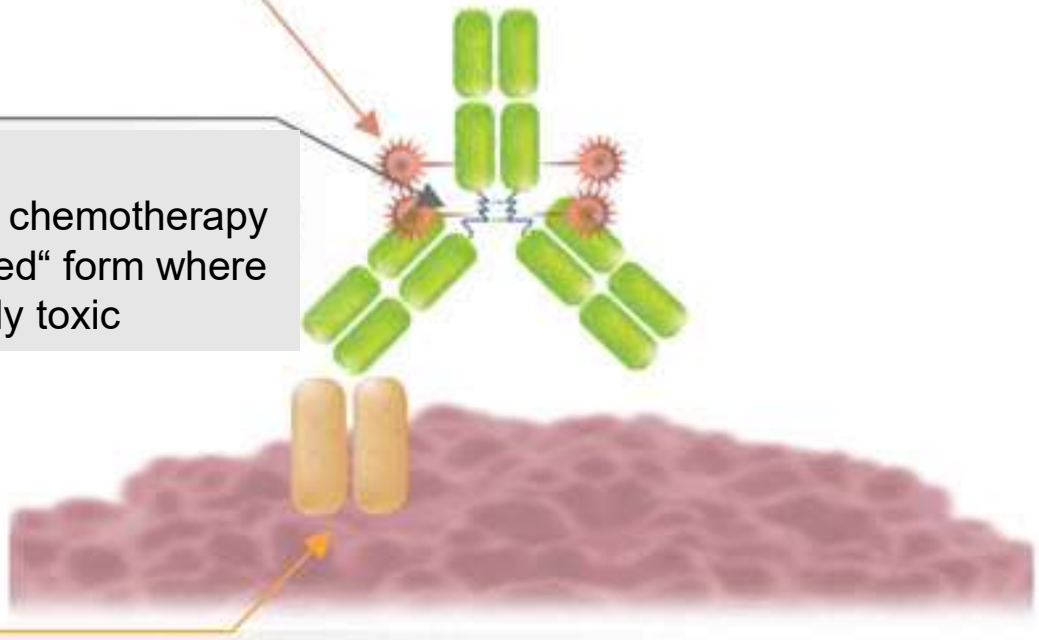
TALENT WINS GAMES,
BUT TEAMWORK
WINS CHAMPIONSHIPS.

Michael Jordan

ADCs: Basics

Antibody
Binds to the specific target structure

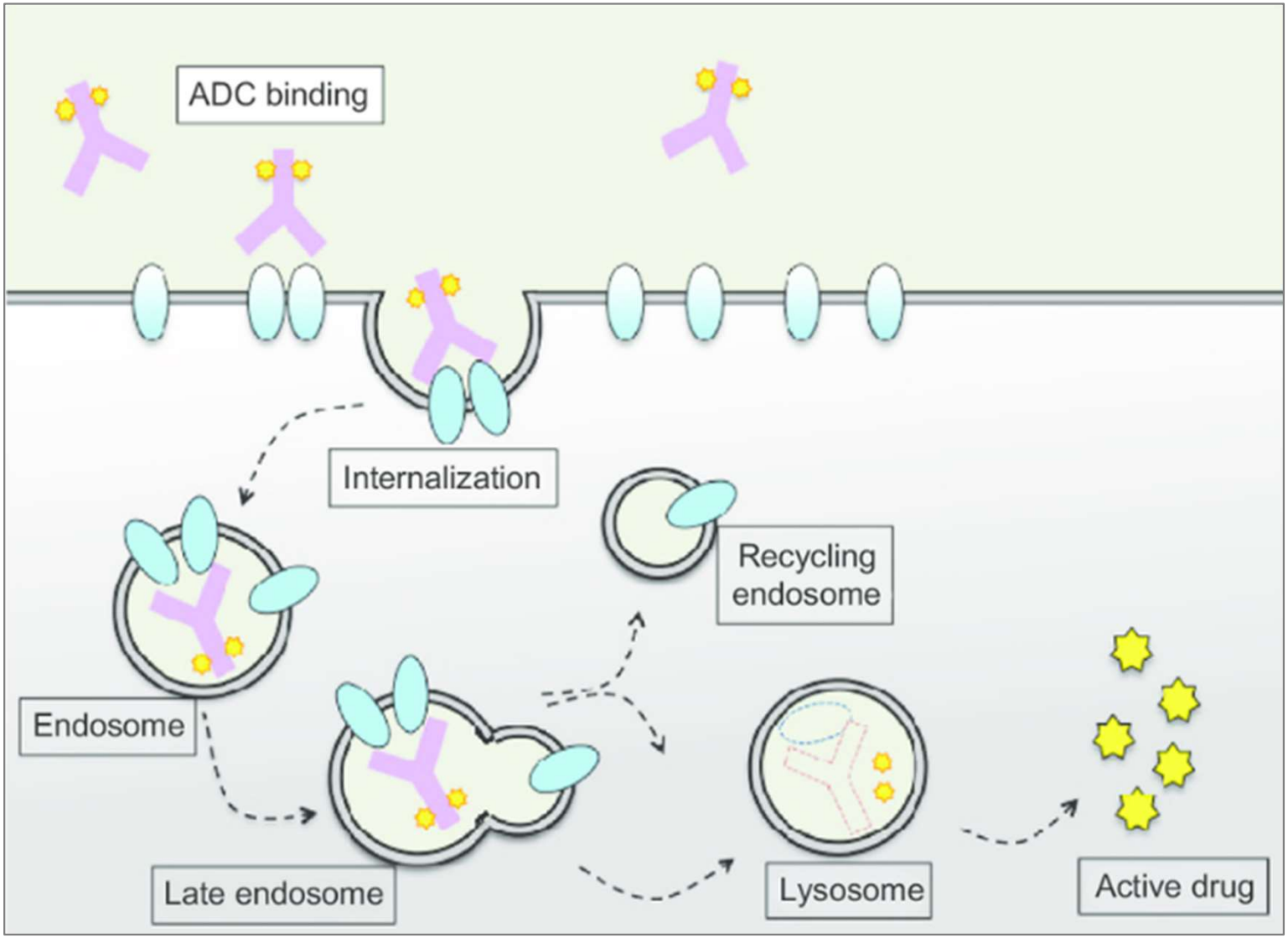
Payload
A very toxic chemotherapy molecule



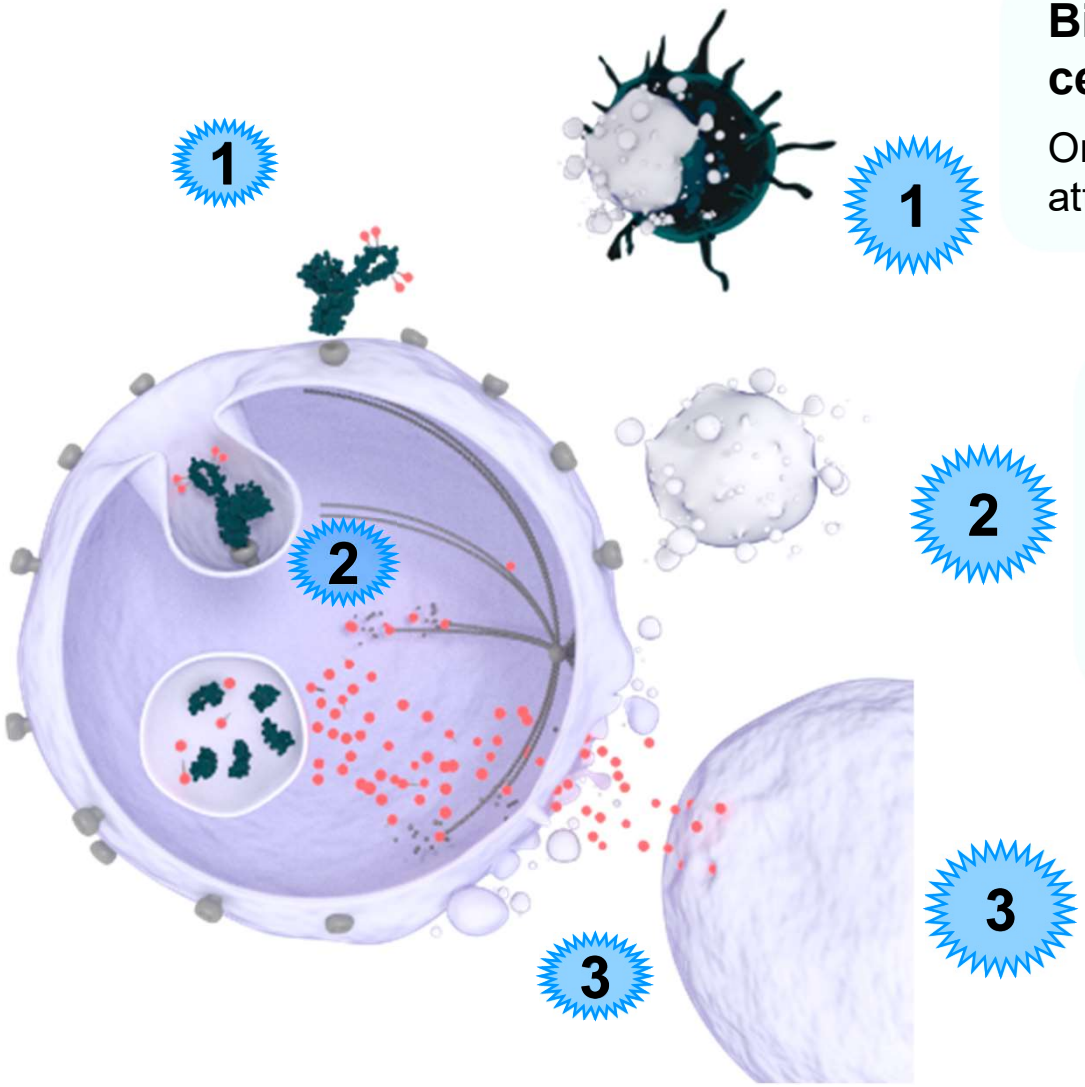
Linker
Packs the toxic chemotherapy into the „wrapped“ form where it is not so highly toxic

Target structure
Structure on the tumor cell, where the antibody can bind- e.g. HER2-neu or Folate-recteptor alpha

ADCs: Basics


ADC binding
Internalization
Recycling endosome
Endosome
Late endosome
Lysosome
Active drug

ADCs: What is a Bystander-Effect?



Binding structure to the tumor cell

Only cells with a target structure can be attacked

Death of the tumor cells with target structure

Only cells that carry the target structure (such as HER-2 neu) will be killed in the first phase

Death of neigbouring cells

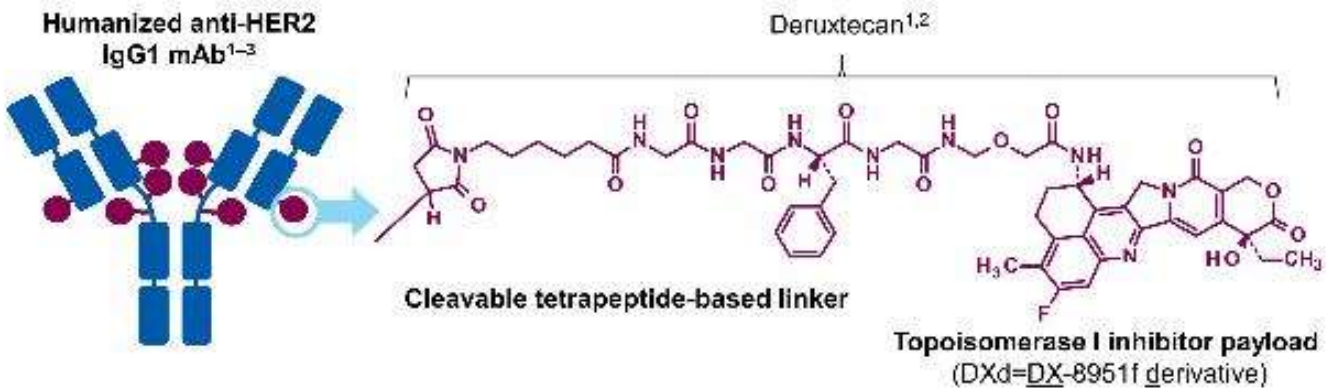
When the tumor cell dies, the highly toxic chemotherapy gets spilled and kills tumor cells in the close proximity- that don´t even have the target structure

DESTINY-PanTumor02

Trastuzumab Deruxtecan (T-DXd) was Designed with Seven Key Attributes

T-DXd is an ADC with three components:

1. A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
2. A topoisomerase I inhibitor payload, an exatecan derivative
3. A tetrapeptide-based cleavable linker



Seven Key Attributes[a,1–5]
Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug-to-antibody ratio ≈8
Payload with short systemic half-life
Stable linker payload
Tumor-selective cleavable linker
Bystander antitumor effect

[a]The clinical relevance of these features is under investigation.
ADC, antibody–drug conjugate; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; mAb, monoclonal antibody; T-DXd, trastuzumab deruxtecan.
1. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173–185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097–5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;[illegible]:126–142.
4. Okamoto K, et al. *Xenobiotica*. 2020;50(10):1242–1250. 5. Nagai Y, et al. *Xenobiotica*. 2019;49(9):1086–1096.

DESTINY-PanTumor02

DESTINY-PanTumor02: A Phase 2 Study of T-DXd for HER2-Expressing Solid Tumors

An open-label, multicenter study (NCT04482309)

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

T-DXd
5.4 mg/kg
q3w

n≈40 per cohort planned

(Cohorts with no objective responses in the first 15 patients were to be closed)

- Cervical cancer
- Endometrial cancer
- Ovarian cancer
- Biliary tract cancer
- Pancreatic cancer
- Bladder cancer
- Other tumors[b]

Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

Data cut-off for analysis:

- Nov 16, 2022

[a]Patients were eligible for either test. All patients were centrally confirmed. [b]Patients with tumors that express HER2, excluding tumors in the tumor specific cohorts, and breast cancer, non small cell lung cancer, gastric cancer, and colorectal cancer. [c]Investigator-assessed per Response Evaluation Criteria in Solid Tumors version 1.1.

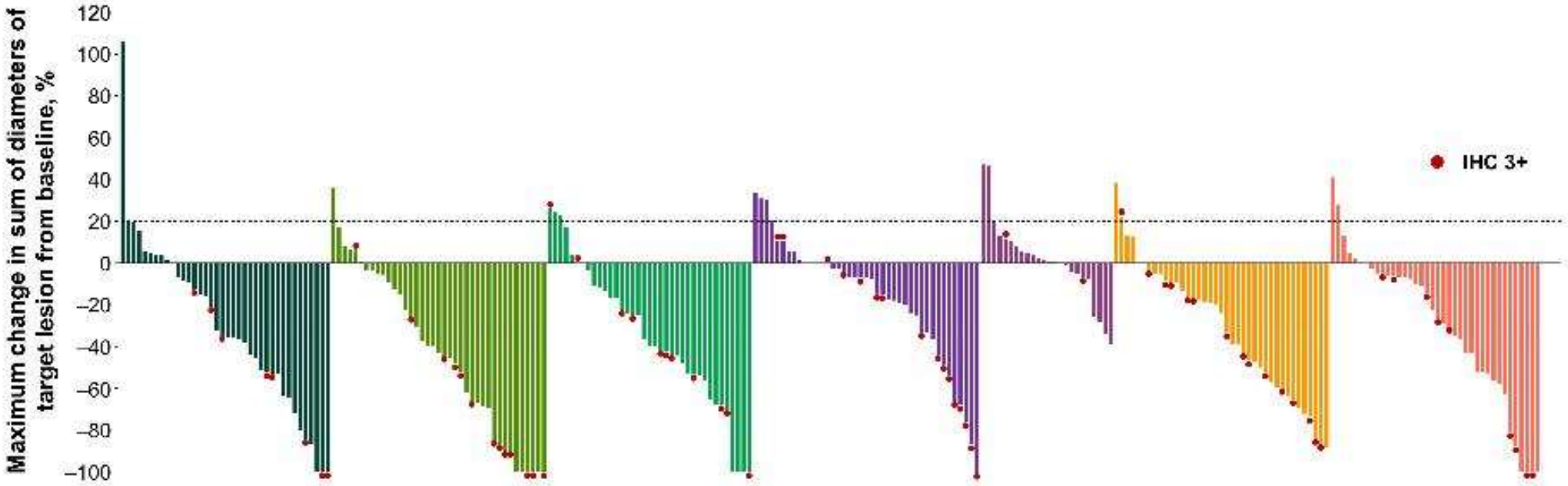
2L, second-line; ASCO, American Society of Clinical Oncology; DCR, disease control rate; CAP, College of American Pathologists; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.

1. Hofmann M, et al. Histopathology 2008;52(7):797–805.

PRESENTED BY: Funda Meric-Bernstam, MD

DESTINY-PanTumor02

Best Percentage Change in Target Lesion From Baseline



ORR in IHC 3+	Cervical (n=8)	Endometrial (n=13)	Ovarian (n=11)	BTC (n=16)	Pancreatic (n=2)	Bladder (n=16)	Other[a] (n=9)
n (%)	6 (75.0)	11 (84.6)	7 (63.6)	9 (56.3)	0	9 (56.3)	4 (44.4)

Analyses were performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of ORR in IHC 3+ was performed in patients with centrally confirmed HER2 status (n=79).
[a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; IHC, immunohistochemistry; ORR, objective response rate.

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