



Updates In Cervix and Vulva Cancer

Raanan Alter MD



Cervical Cancer Statistics

- Third most common GYN cancer in the US
- Most common GYN cancer worldwide
- Estimated 14,000 cases in 2023 in the USA

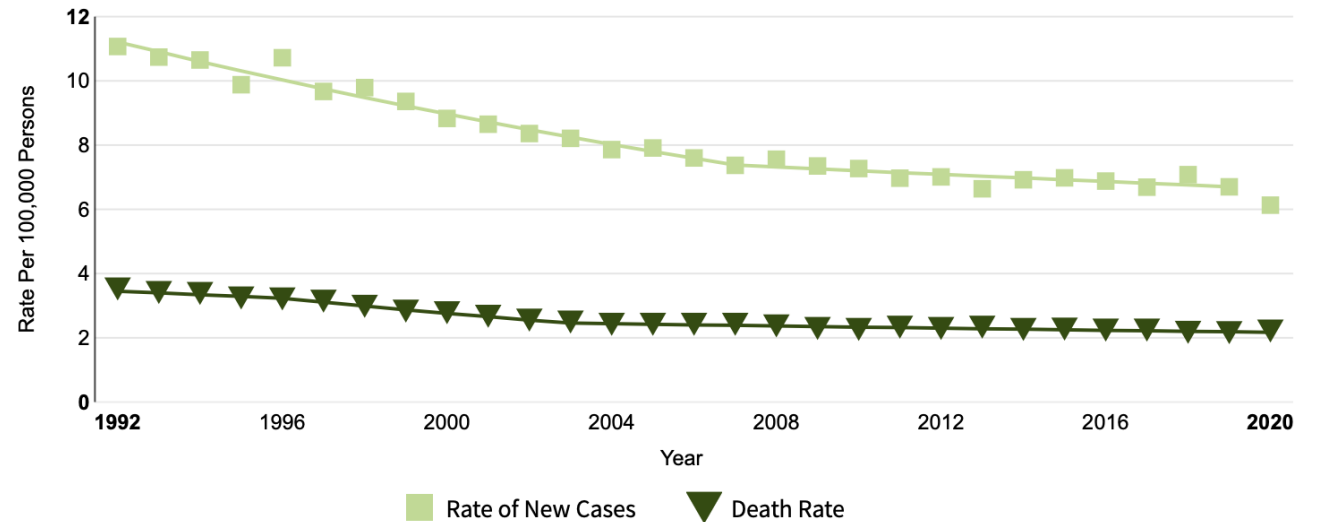
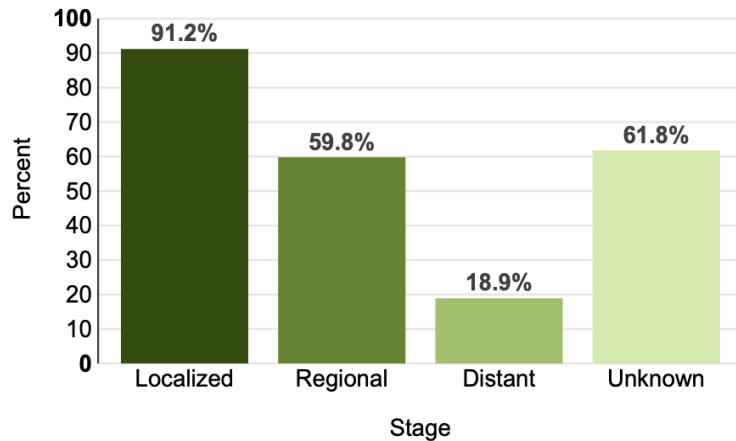
At a Glance

Estimated New Cases in 2023	13,960
% of All New Cancer Cases	0.7%

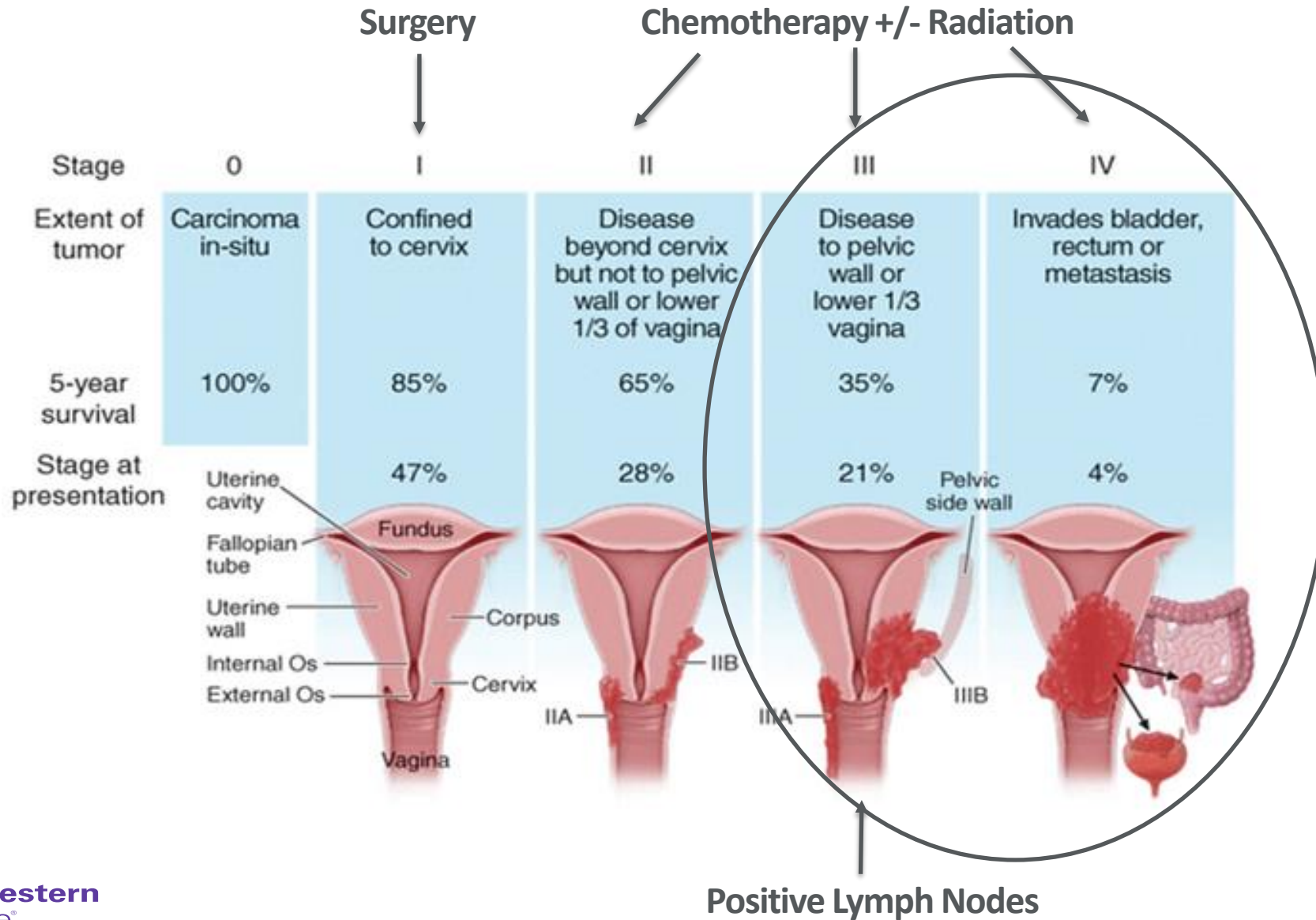
Estimated Deaths in 2023	4,310
% of All Cancer Deaths	0.7%

5-Year Relative Survival
67.2%
2013–2019

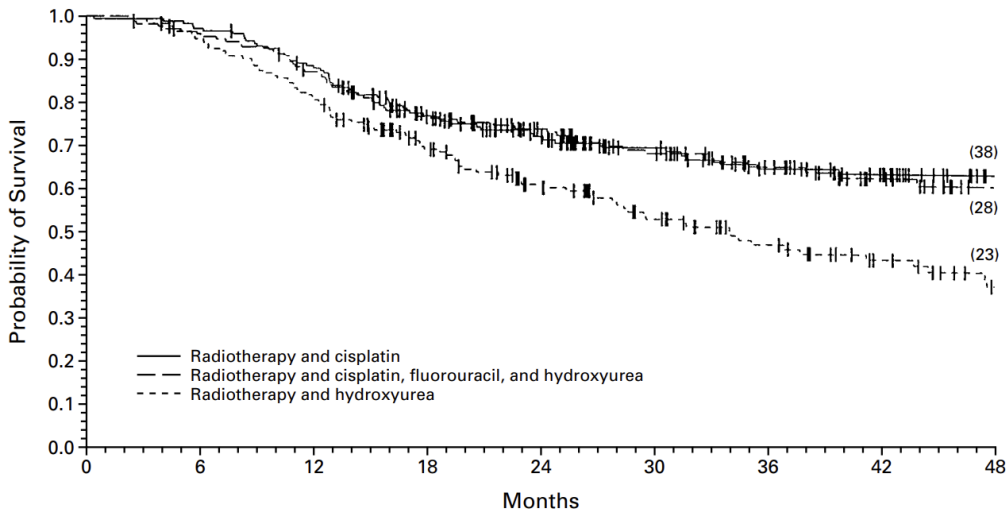
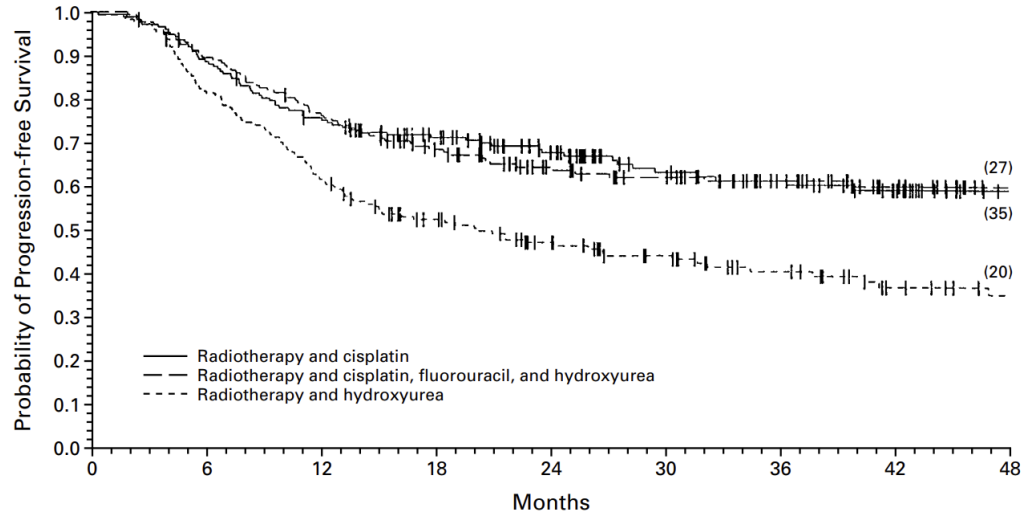
5-Year Relative Survival



Cervical Cancer Staging



Standard of Care for Locally Advanced Cervical Cancer



- **Radiation**
 - External Beam Radiation
 - Internal Radiation
- **Chemotherapy**
 - Cisplatin

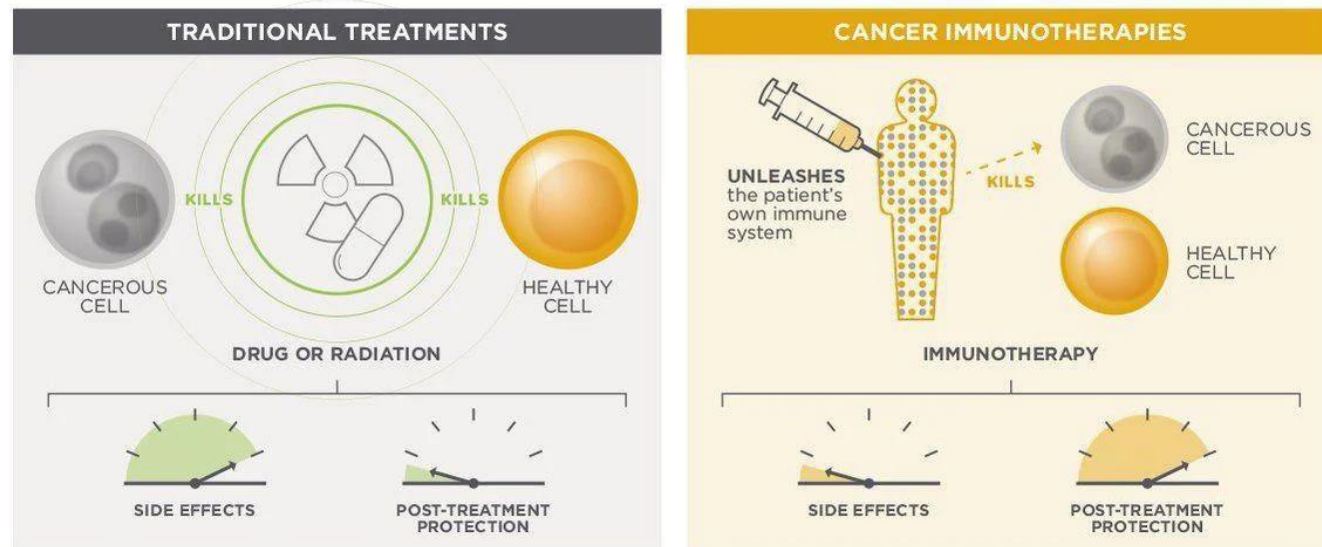


Immune Therapies

Immunotherapy

- Checkpoint Inhibitors
- Adoptive Cell Therapy
- Cytokine Therapy
- Vaccine Therapy
- Oncolytic Virus Therapy

IMMUNOTHERAPY VS. CHEMOTHERAPY



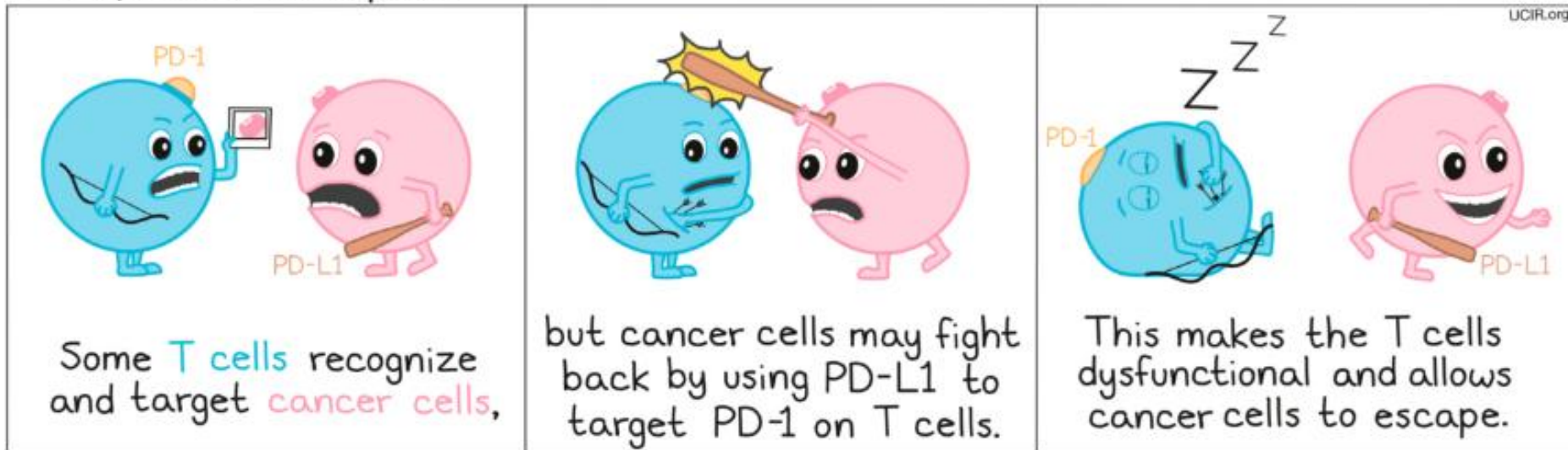
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Immune Checkpoint Blockade (ICB)

Pembrolizumab, Nivolumab, Durvalumab, Dostarlimab, Atezolizumab, Avelumab

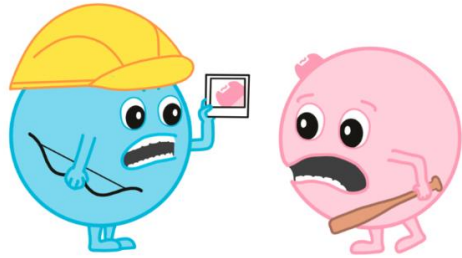
PD-1/PD-L1 checkpoint



Immune Checkpoint Blockade (ICB)

Pembrolizumab, Nivolumab, Durvalumab, Dostarlimab, Atezolizumab, Avelumab

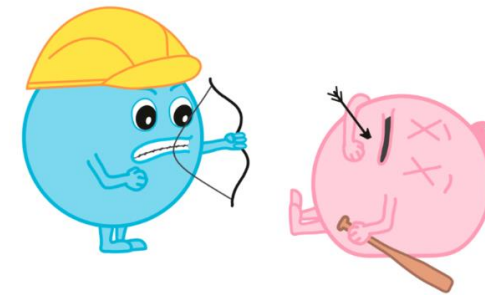
PD-1 checkpoint blockade



PD-1 blockade is like a helmet for T cells.

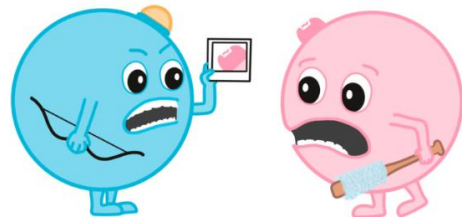


It blocks PD-L1 and prevents interactions with PD-1,

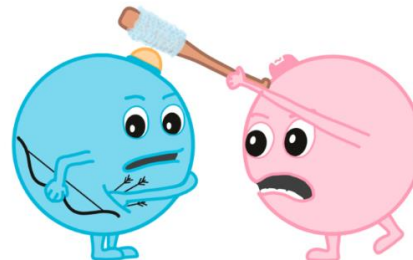


allowing T cells to maintain function and fight the cancer.

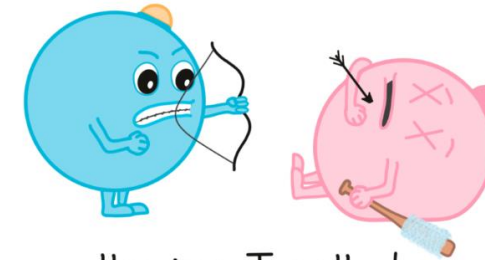
PD-L1 checkpoint blockade



PD-L1 blockade is like bubble wrapping the cancer's best weapon.



It protects PD-1 and prevents interactions with PD-L1,



allowing T cells to maintain function and fight the cancer.

UCIR.org

- PDL1 Expression can predict response to immune checkpoint inhibitor therapy

Precise™ Tumor

Molecular Profile Test

Myriad Genetics
320 Wakara Way
Salt Lake City, UT 84108



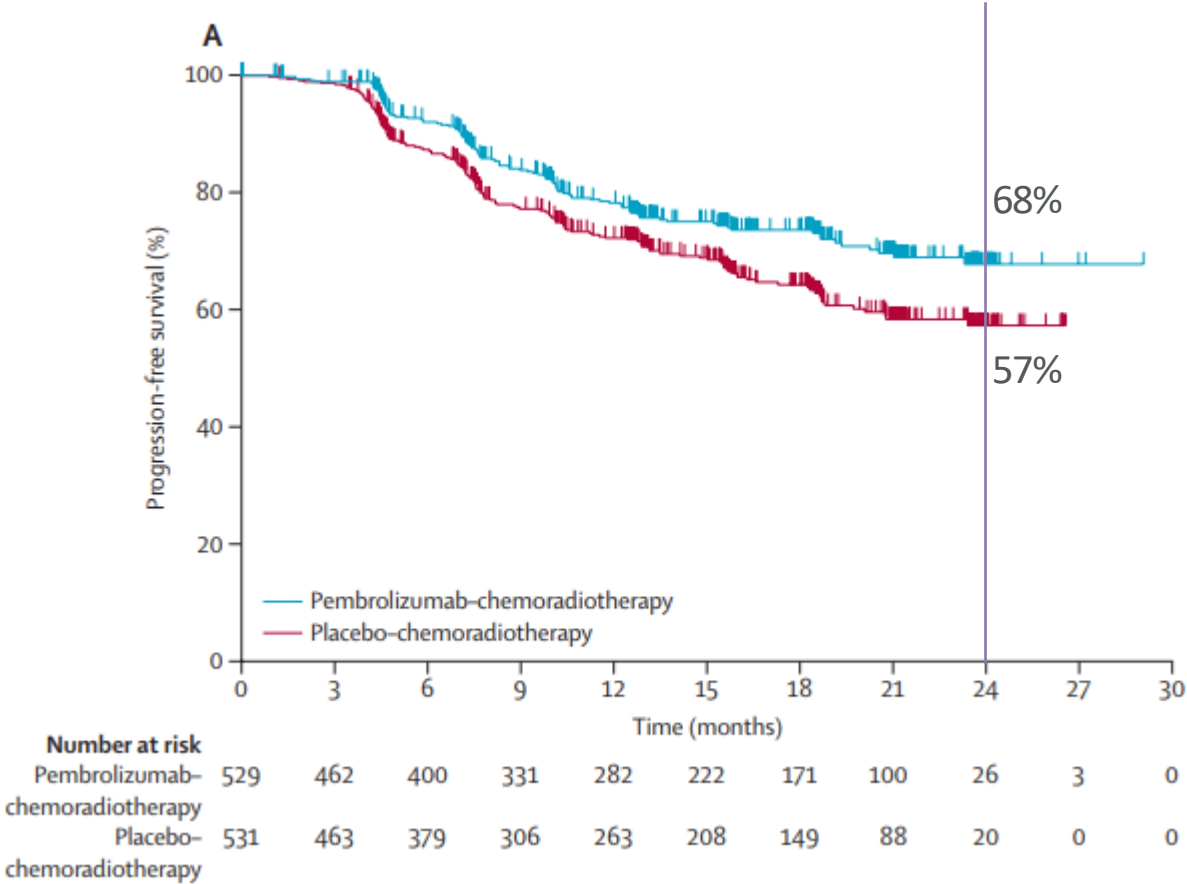
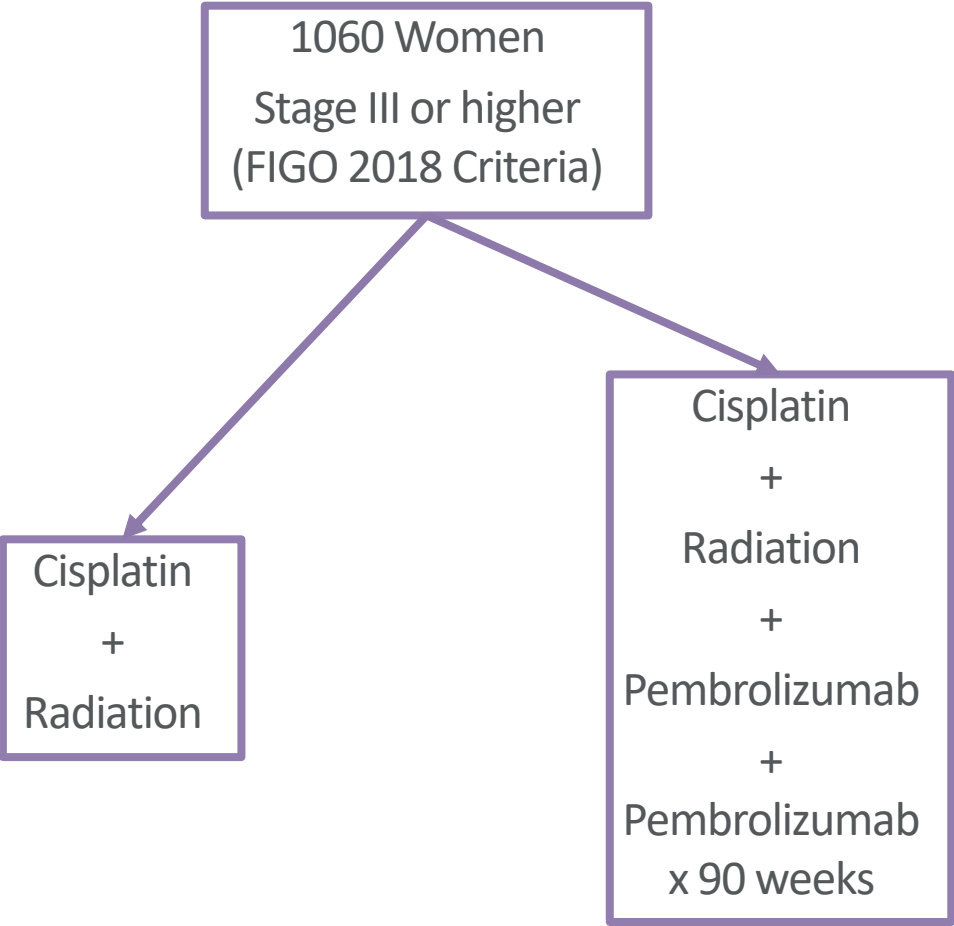
PATIENT		PHYSICIAN	SPECIMEN	CASE
PATIENT Example Fallopian	SEX Female	ORDERING PHYSICIAN Example Doctor	SPECIMEN TYPE Formalin-fixed paraffin-embedded tissue specimen	ACCESSION# FallopianTube-Precise
DISEASE Primary malignant neoplasm of fallopian tube			DATE COLLECTED 01/17/2023	DATE REPORTED
			DATE RECEIVED 01/17/2023	REVIEW STATUS Final
MRN# MRN-1234				DATE ORDERED 01/08/2023
DATE OF BIRTH 06/14/1966				

Interpretive Comments

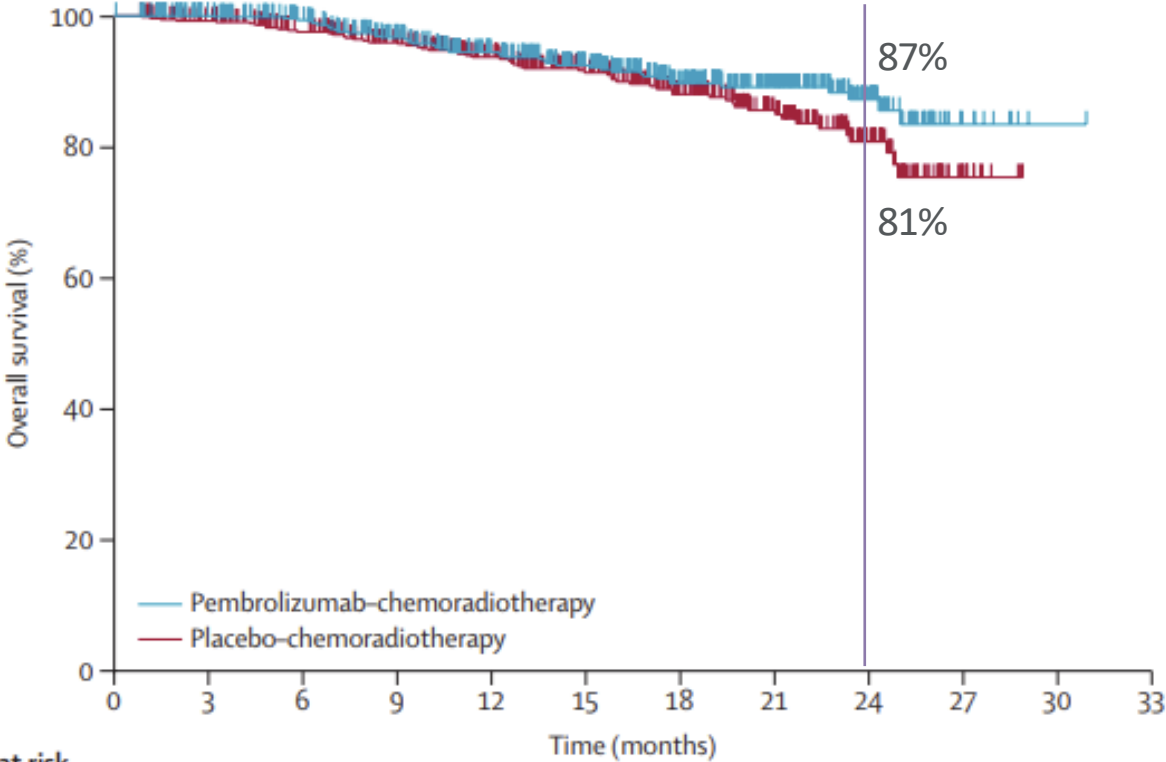
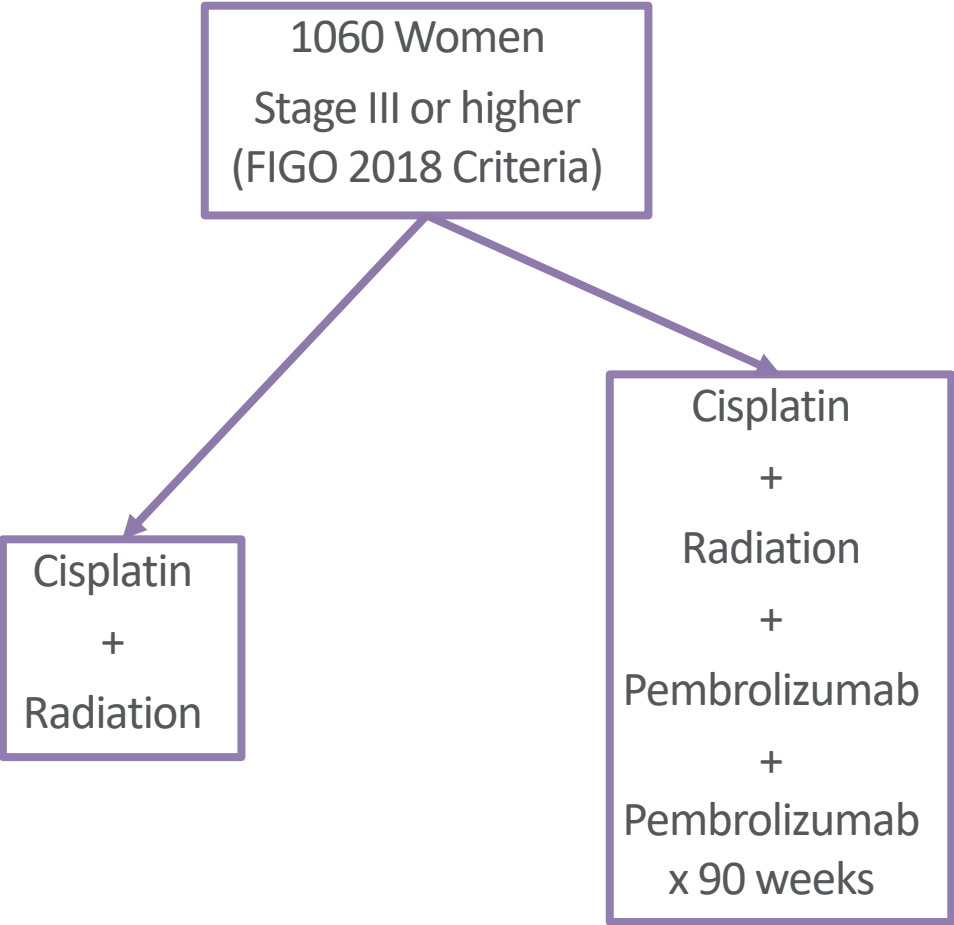
Refer to the Clinically Relevant Results section of the report for a discussion of potential treatment approaches. Given the patient's age, if clinically indicated and not already ordered, consider genetic consultation for hereditary cancer syndromes due to the presence of the possible germline BRCA2 variant p.R2336P/c.7007G>C at VAF of 45%. Based on histopathologic review, the tumor cell percentage in the sequenced sample is 85%.

IA	IB	IIC	IID	TMB	MSI	PD-L1	Trials
1	0	1	0	Low 1.6 muts/Mb	Stable 2.4% Unstable Sites	Positive TPS: 3% unit	34

ENGOT-cx11/ GOG-3047/KEYNOTE-A18



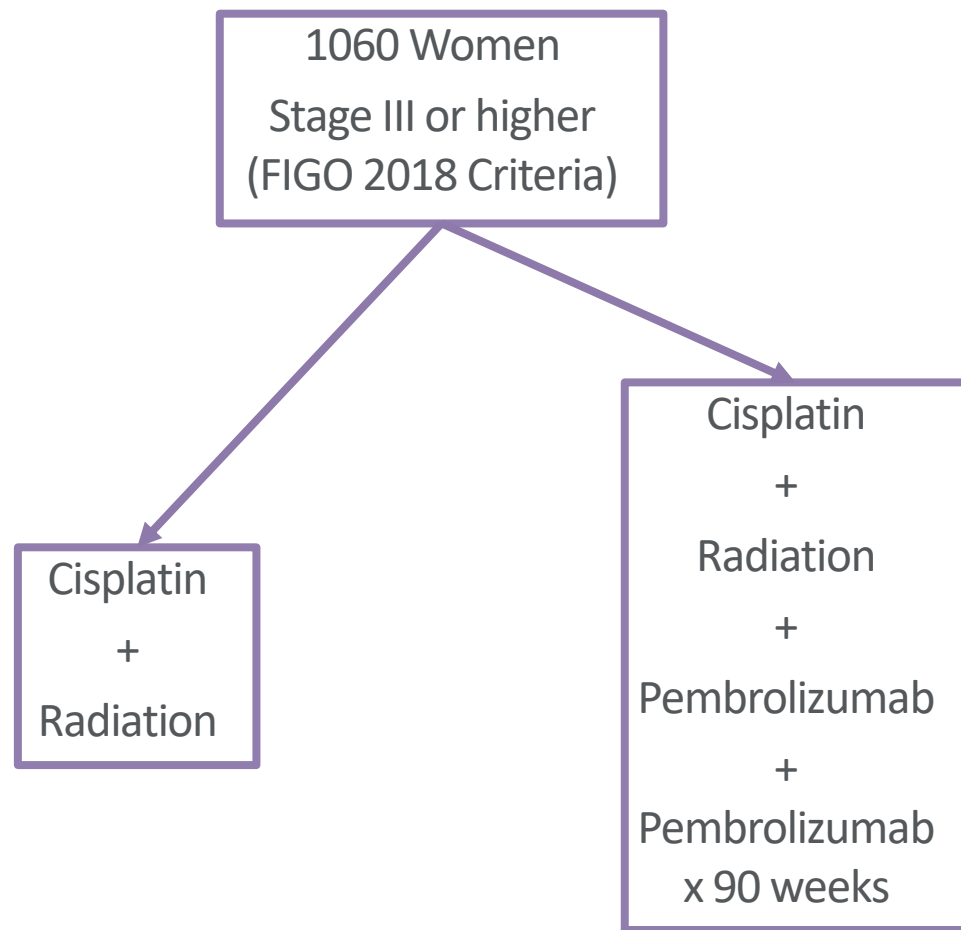
ENGOT-cx11/ GOG-3047/KEYNOTE-A18



Number at risk

Pembrolizumab-chemoradiotherapy	529	496	456	405	351	294	223	151	67	10	1	0
Placebo-chemoradiotherapy	531	498	449	402	339	278	214	139	62	12	0	0

ENGOT-cx11/ GOG-3047/KEYNOTE-A18



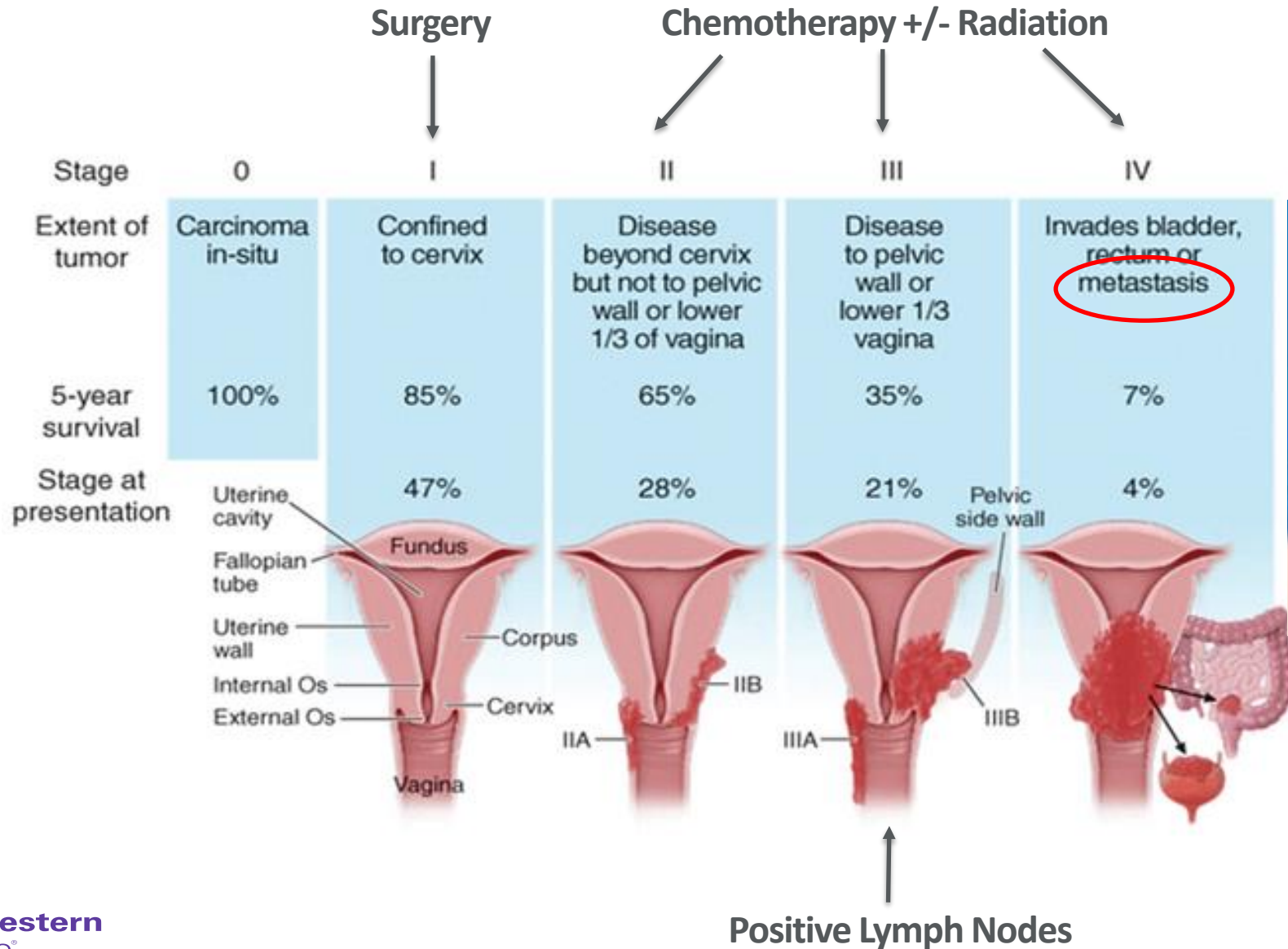
	Pembrolizumab- chemoradiotherapy (n=528)		Placebo-chemoradiotherapy (n=530)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event*	525 (99%)	394 (75%)	526 (99%)	364 (69%)
Treatment-related adverse event†	507 (96%)	354 (67%)	509 (96%)	321 (61%)
Anaemia	313 (59%)	99 (19%)	292 (55%)	84 (16%)
Nausea	302 (57%)	7 (1%)	315 (59%)	9 (2%)
Diarrhoea	266 (50%)	22 (4%)	271 (51%)	23 (4%)
White blood cell count decreased	172 (33%)	102 (19%)	181 (34%)	111 (21%)
Neutrophil count decreased	153 (29%)	77 (15%)	148 (28%)	78 (15%)
Vomiting	132 (25%)	3 (<1%)	150 (28%)	7 (1%)
Leukopenia	125 (24%)	67 (13%)	92 (17%)	57 (11%)
Platelet count decreased	116 (22%)	25 (5%)	108 (20%)	13 (2%)
Neutropenia	113 (21%)	56 (11%)	92 (17%)	51 (10%)
Immune-mediated adverse event‡	167 (32%)	21 (4%)	54 (10%)	5 (<1%)
Hypothyroidism	102 (19%)	3 (<1%)	24 (5%)	0
Hyperthyroidism	60 (11%)	2 (<1%)	11 (2%)	0
Colitis	14 (3%)	4 (<1%)	9 (2%)	4 (<1%)
Thyroiditis	11 (2%)	1 (<1%)	1 (<1%)	0



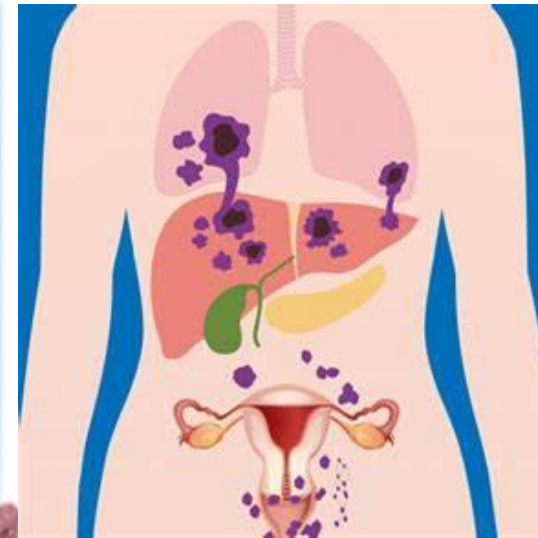
Conclusions

Adding immunotherapy to chemo/radiation for locally advanced cervical cancer can improve outcomes

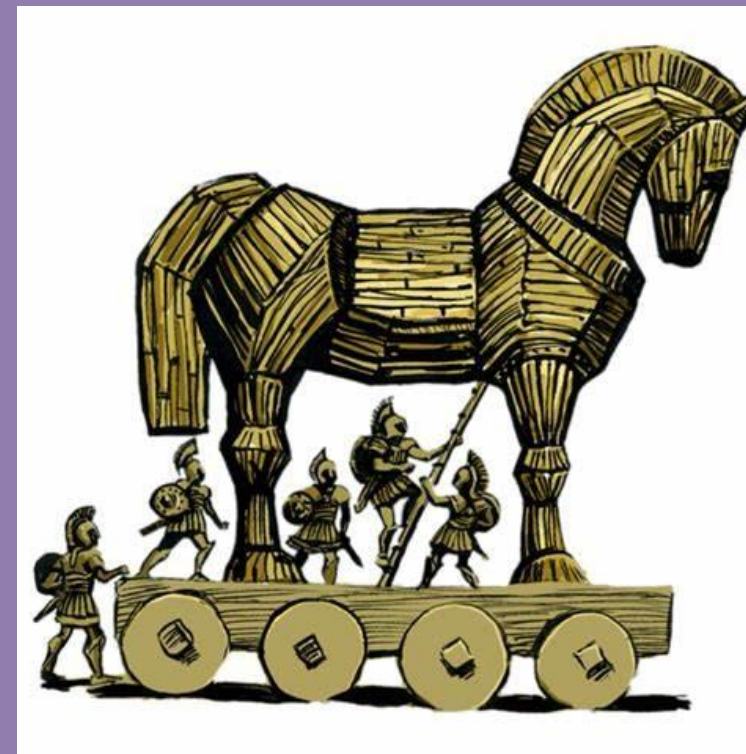
Cervical Cancer Staging



Chemotherapy
Immunotherapy

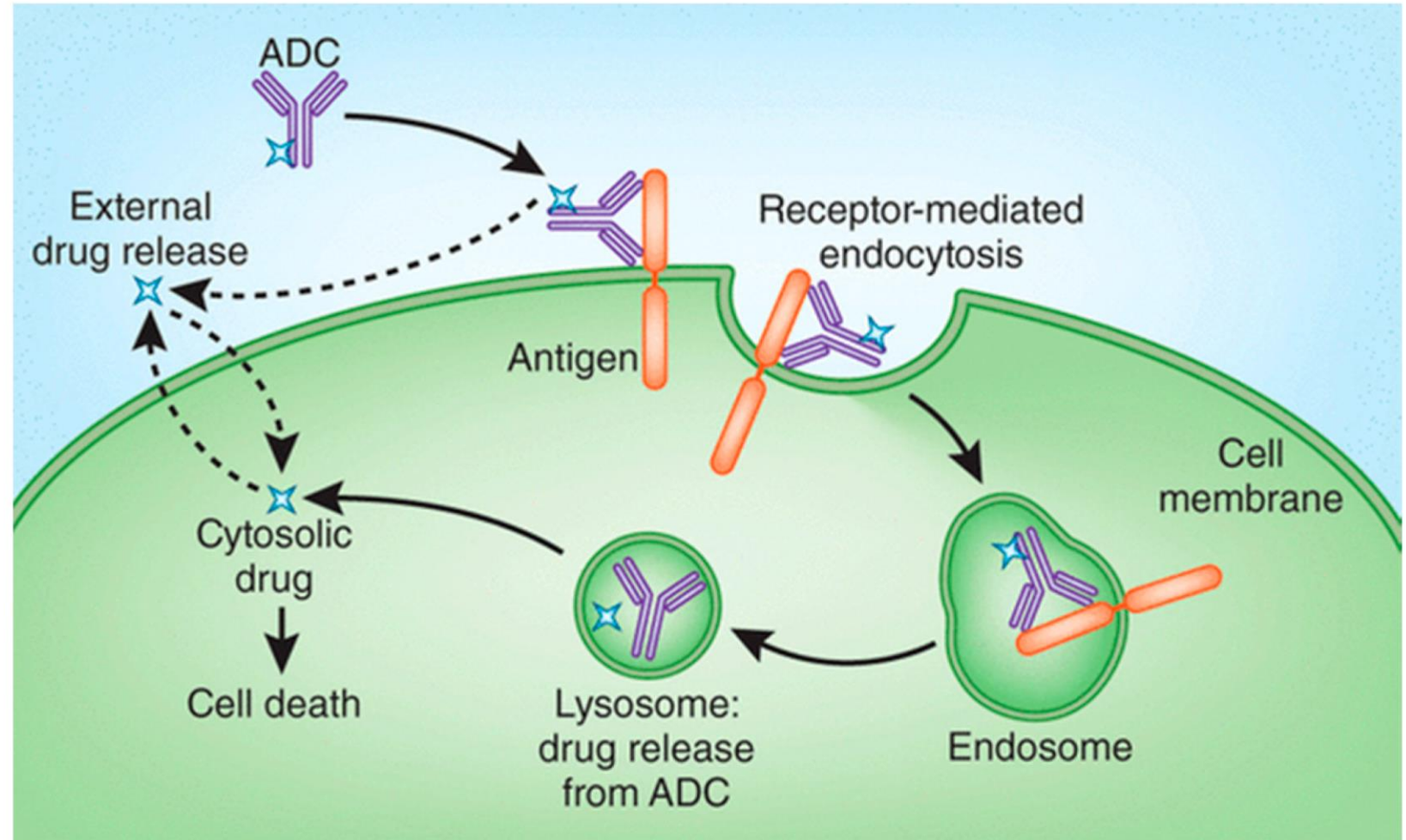


Antibody Drug Conjugates



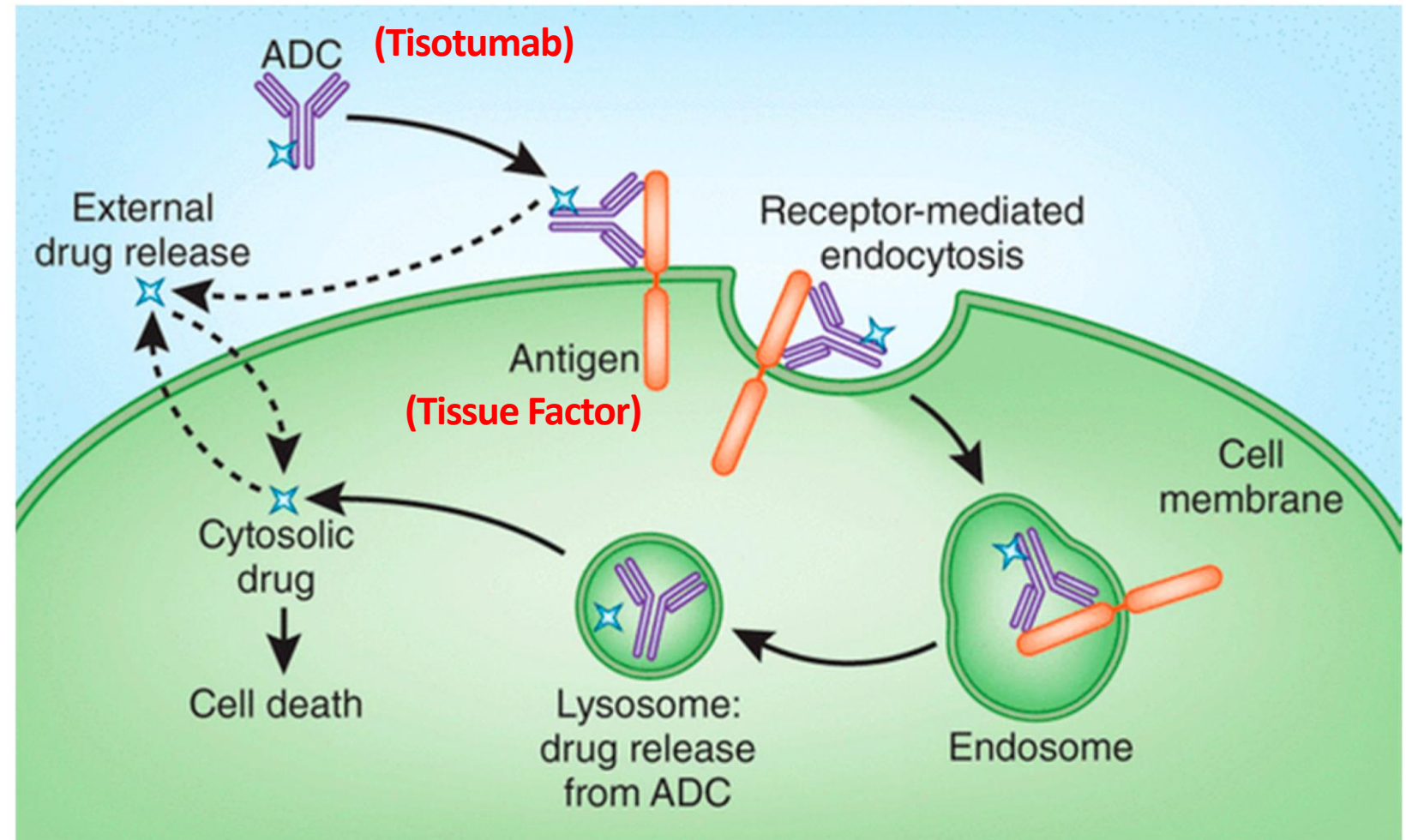
What is an Antibody Drug Conjugate (ADC)

- **Antibody** – selectively homes on a target (Antigen) on a cancer cell
- **Drug** – “payload” that selectively kills the cancer cell



Tisotumab Vedotin Binds to Tissue Factor

- **Antibody** – selectively homes on a target (Antigen) on a cancer cell
- **Drug** – “payload” that selectively kills the cancer cell



THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisotumab Vedotin as Second- or Third-Line Therapy for Recurrent Cervical Cancer

I. Vergote, A. González-Martín, K. Fujiwara, E. Kalbacher, A. Bagaméri, S. Ghamande, J.-Y. Lee, S. Banerjee, F.C. Maluf, D. Lorusso, K. Yonemori, E. Van Nieuwenhuysen, L. Manso, L. Woelber, A. Westermann, A. Covens, K. Hasegawa, B.-G. Kim, M. Raimondo, M. Bjurberg, F.M. Cruz, A. Angelergues, D. Cibula, L. Barraclough, A. Oaknin, C. Gennigens, L. Nicacio, M.S.L. Teng, E. Whalley, I. Soumaoro, and B.M. Slomovitz, for the innovaTV 301/ENGOT-cx12/GOG-3057 Collaborators*

Tisotumab Vedotin for Metastatic/Recurrent Cervical Cancer

- 502 patients
- Progressed after first line treatment
- Randomized 1:1
 - 1) Tisotumab Vedotin
 - 2) Investigators Choice of Chemotherapy

Objective Response Rates:

- Tisotumab: 17.8%
- Chemotherapy: 5.2%

Clinical Benefit for > 5 weeks

- Tisotumab: 76%
- Chemotherapy: 58%

Tisotumab Vedotin for Metastatic/Recurrent Cervical Cancer

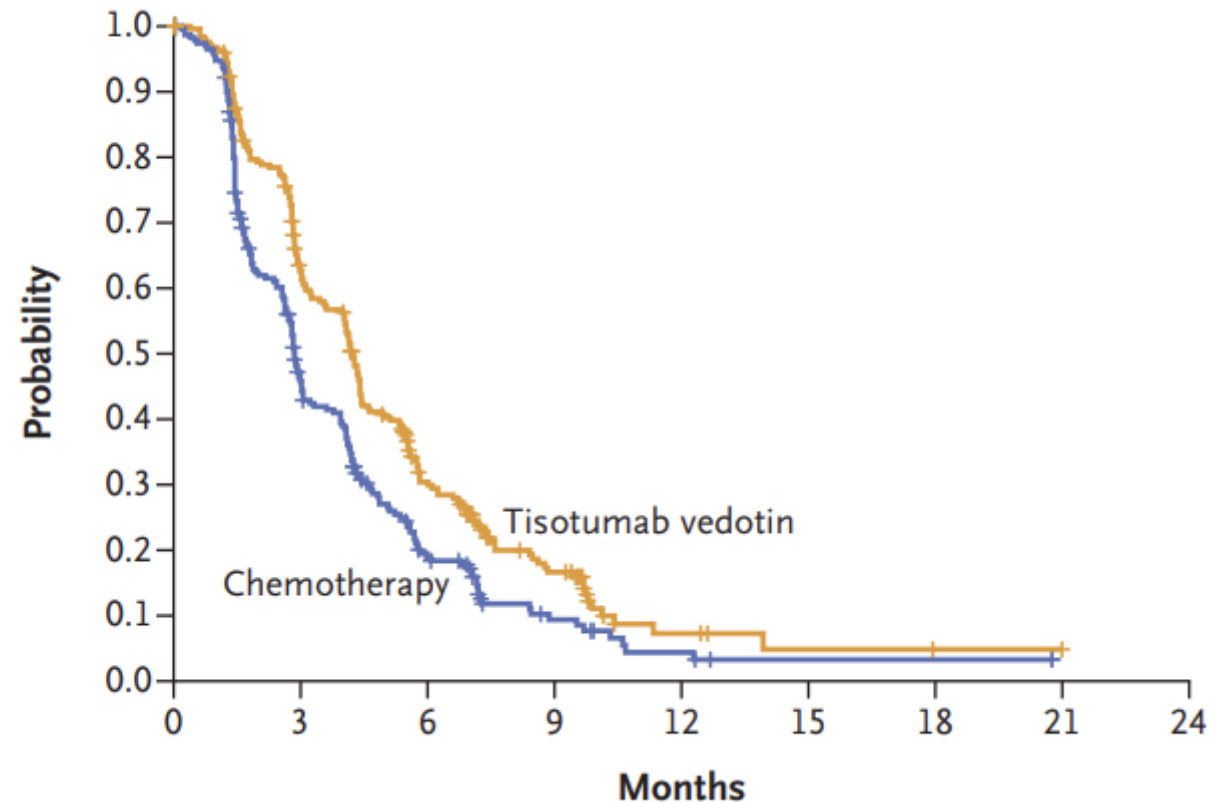
- 502 patients
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 - 1) Tisotumab Vedotin
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Median Progression Free Survival:

4.2 months vs 2.9 months

Representing a **33% reduction in risk of progression or death**

A Progression-free Survival

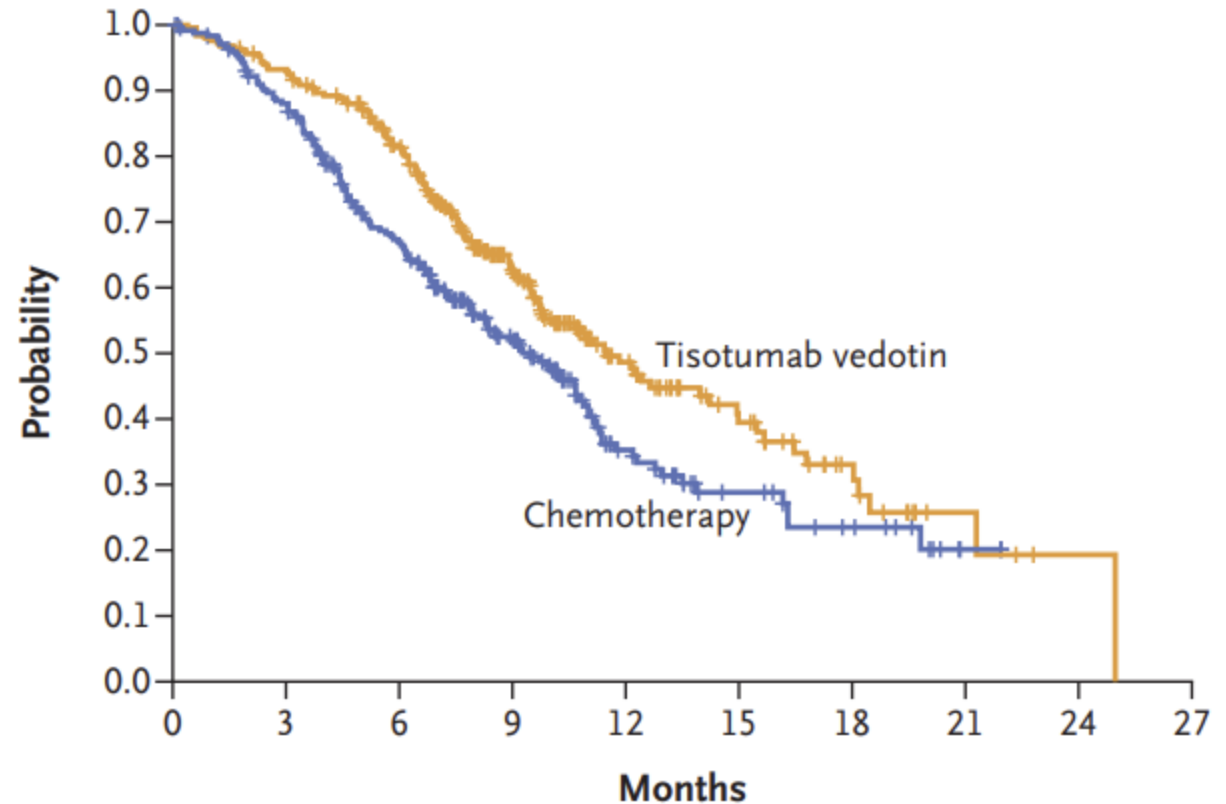


Tisotumab Vedotin for Metastatic/Recurrent Cervical Cancer

- 502 patients
- Progressed after first line treatment
- Randomized 1:1
 - 1) Tisotumab Vedotin
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Median Overall Survival: 11.5 months vs 9.5 months
Representing a **30% reduction in risk of death**

A Overall Survival



- Tisotumab toxicities
 - Ocular toxicity
 - Neuropathy
 - Bleeding

Table 2. Adverse Events That Occurred during the Treatment Period.*

Event	Tisotumab Vedotin (N = 250)		Chemotherapy† (N = 239)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	<i>number of patients (percent)</i>			
Any event	246 (98.4)	130 (52.0)	237 (99.2)	149 (62.3)
Nausea	83 (33.2)	1 (0.4)	96 (40.2)	5 (2.1)
Conjunctivitis	78 (31.2)	0	1 (0.4)	0
Peripheral sensory neuropathy	71 (28.4)	7 (2.8)	6 (2.5)	0
Epistaxis	65 (26.0)	0	6 (2.5)	0
Constipation	62 (24.8)	3 (1.2)	39 (16.3)	0
Alopecia	61 (24.4)	0	7 (2.9)	0
Decreased appetite	59 (23.6)	2 (0.8)	42 (17.6)	1 (0.4)
Anemia	58 (23.2)	21 (8.4)	125 (52.3)	66 (27.6)
Diarrhea	54 (21.6)	4 (1.6)	36 (15.1)	3 (1.3)
Vomiting	44 (17.6)	4 (1.6)	44 (18.4)	3 (1.3)
Pyrexia	42 (16.8)	1 (0.4)	50 (20.9)	2 (0.8)
Asthenia	40 (16.0)	5 (2.0)	38 (15.9)	5 (2.1)
Keratitis	39 (15.6)	5 (2.0)	0	0
Abdominal pain	34 (13.6)	10 (4.0)	23 (9.6)	4 (1.7)



Vulva Cancer Updates

Vulva Cancer

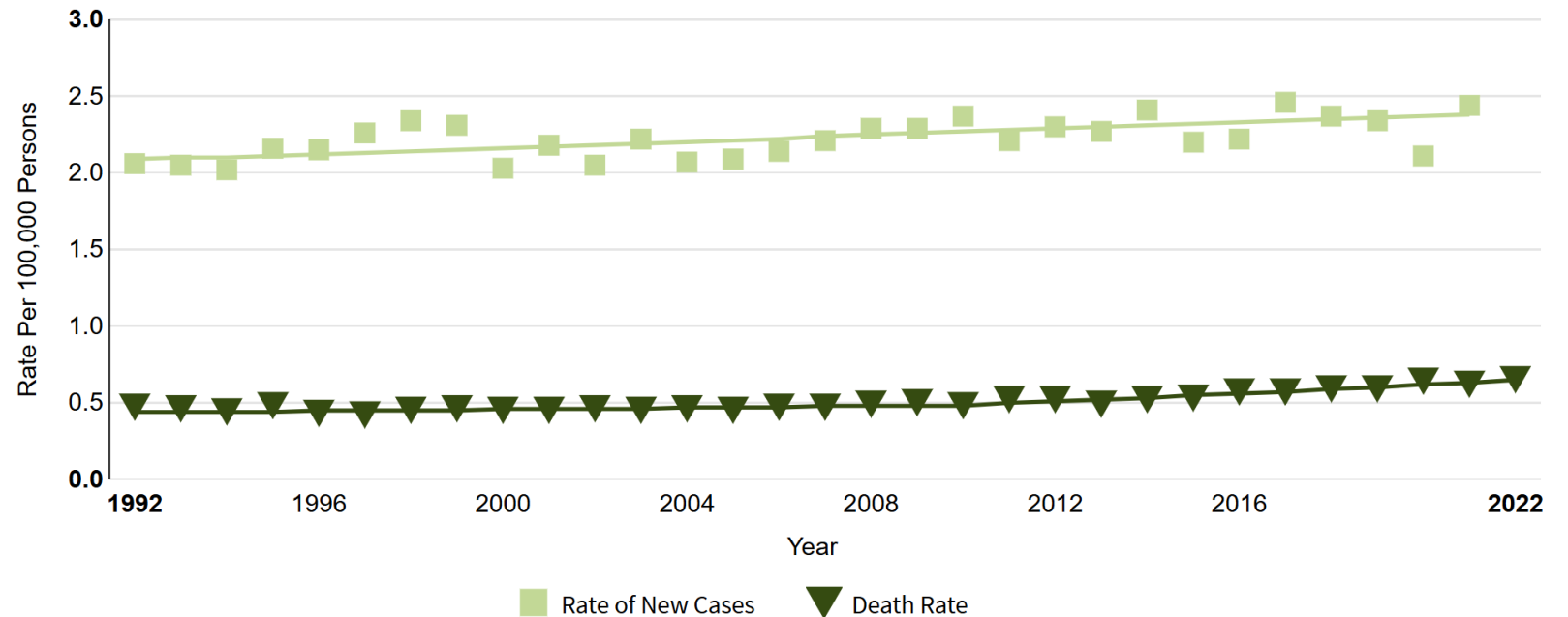
- Rare Malignancy
- Challenging for good quality studies

At a Glance

Estimated New Cases in 2024	6,900
% of All New Cancer Cases	0.3%

Estimated Deaths in 2024	1,630
% of All Cancer Deaths	0.3%

5-Year Relative Survival
69.6%
2014-2020



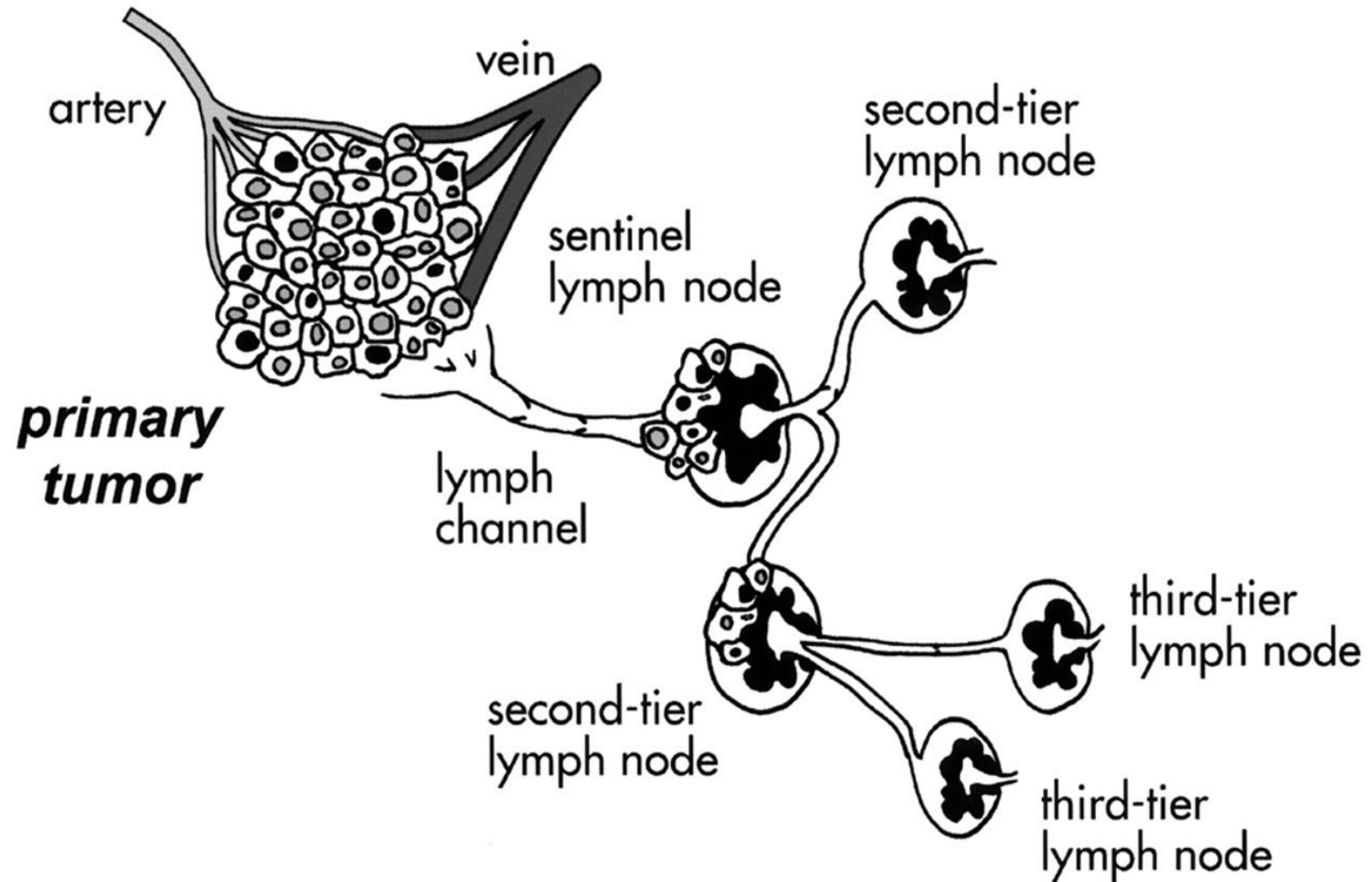
Management and Staging for Vulva Cancer

- Historically:
 - Radical Tumor Excision (negative margins)
 - Full Inguinofemoral Lymphadenectomy



Higher Rates of Lymphedema and Wound Infections

Sentinel Lymph Node Mapping



Management and Staging for Vulva Cancer

- Historically:
 - Radical Tumor Excision (negative margins)
 - Full Inguinofemoral Lymphadenectomy

} Higher Rates of Lymphedema and Wound Infections

GROINSS-V (2008)

- 403 women. <4cm
- Sentinel Lymph Nodes Mapped
- 276 patients had negative Sentinel Lymph Nodes
- Groin Recurrence 2.5%

} If SLN Negative – ok to observe

What if SLN is positive?



Full Lymph node removal +/- Radiation

Management and Staging for Vulva Cancer

- Do All Positive SLN require surgery?

- **GROINSS-V II (2021)**

- 160 Patients with positive SLN
- Treated with 50Gy Radiation

**After 91 patients, 10 had groin recurrences

- 9/10 had **macrometastasis** (>2mm)
- Protocol amended and radiation only offered to **micrometastasis** (<2mm)
- Groin recurrence rate to micrometastasis = 1.6%

If SLN has micrometastasis – ok for radiation

What if SLN is >2mm?

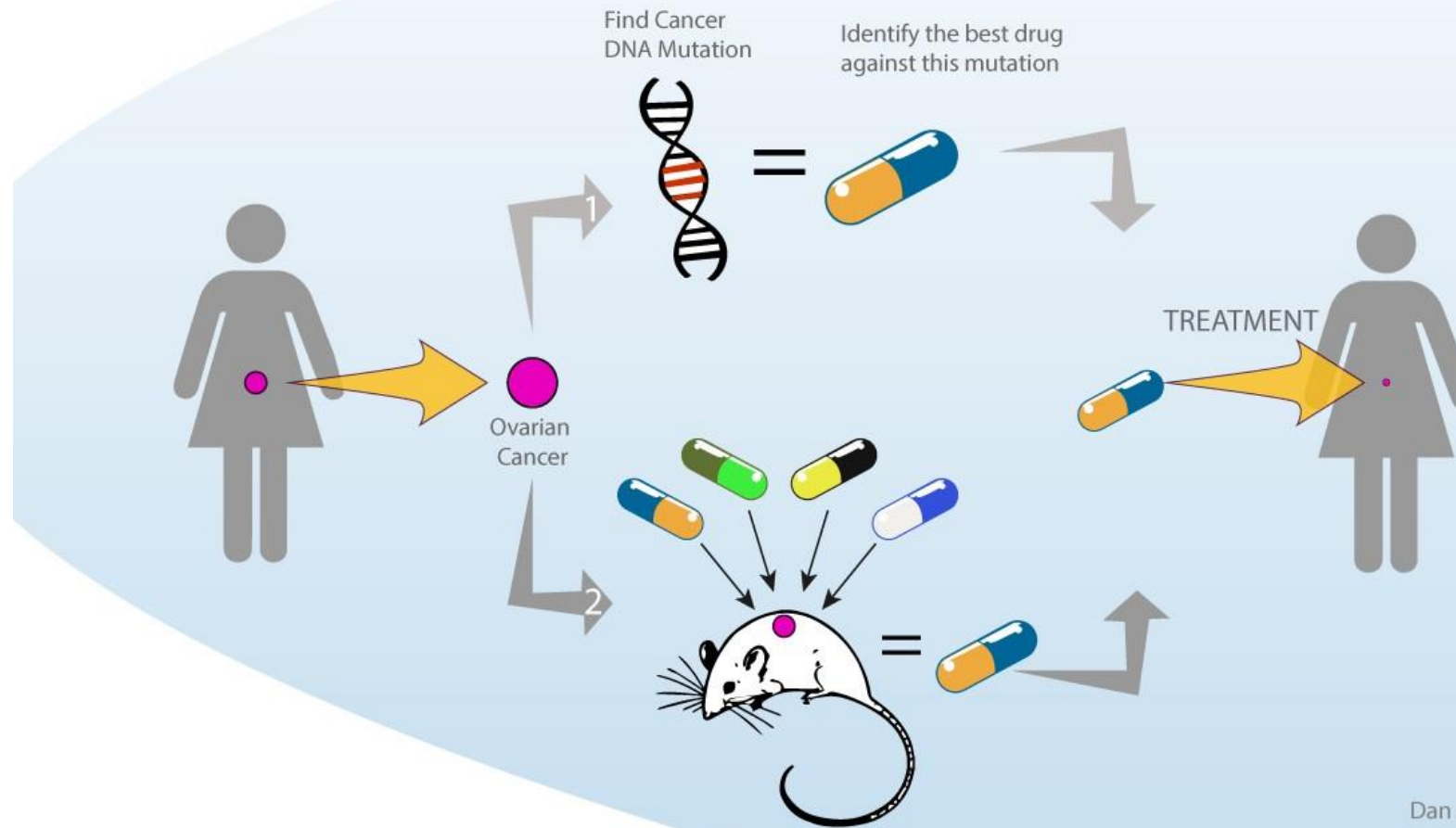
Full Lymph node removal +/- Radiation

Management of Vulvar Cancer

- Are there alternative ways to treat **macrometastases**?
- **GROINSS-V III**
 - Prospective phase II trial for patients with macrometastases on SLN
 - Adjuvant RT (56Gy) + weekly chemotherapy
 - Hypothesis: increasing dose of radiation and adding chemotherapy will reduce groin recurrences and safely omit full lymphadenectomy
 - Currently enrolling

The Age of Personalized Medicine

PERSONALIZED CANCER MEDICINE



Dan Cojocari, 2015

Examples of Personalized Medicines

Target	Drug	Brand	Status
Her2	Fam-Trastuzumab deruxtecan	Enhertu	Available for Her2+ tumors
Tissue Factor	Tisotumab vedotin	Tivdak	Available for cervix cancer
Folate Receptor Alpha	Mirvetuxumab soravtansine	Elahere	Available for ovarian cancer with high FRa expression
NaPi2b	Upifitamab Rilsodotin		In trials
Mismatch Repair Proteins	Immune checkpoint inhibitors (pembrolizumab etc...)	many	Available for all MMR deficient tumors



Thank you!