

Cervical Cancer and the Immune System

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Objectives

- Primary Prevention

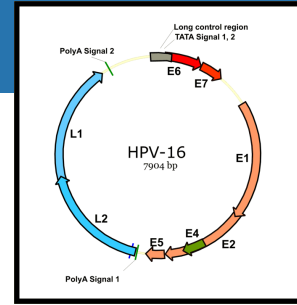
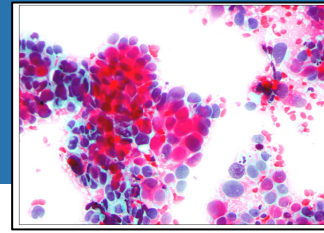
- Screening recommendations
- Vaccination

- Treatment

- Recurrent treatment
- Frontline
 - Advanced/Metastatic
 - Chemoradiation
- Novel combinations

Cervical Cancer HPV Infection

Cervical Cancer Screening

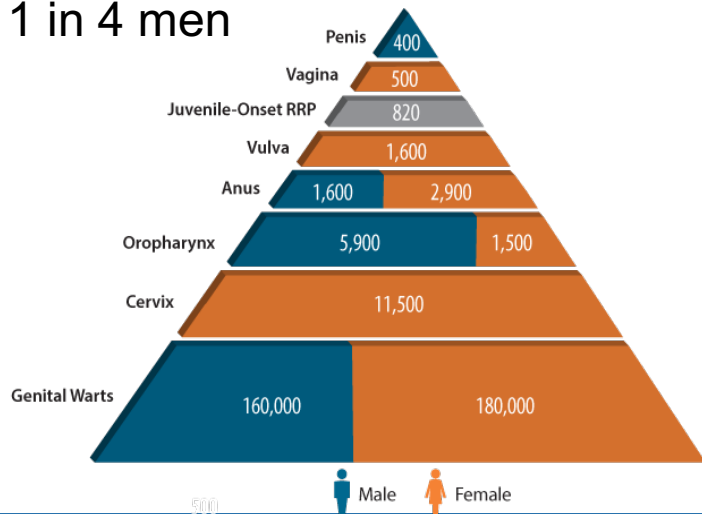


- Cervical cytology: at age 21
- HPV: at age 25 (primary or co-testing)
 - Can discontinue at age 65 if appropriate negative screening
 - Still accounts for ~20% of cases (more advanced stages)
 - \$83 million (unnecessary) cost attributed to screening in this population
- Screening detects 52% of cases
 - Failure to screen, failure to detect or failure to follow up
 - Disparities

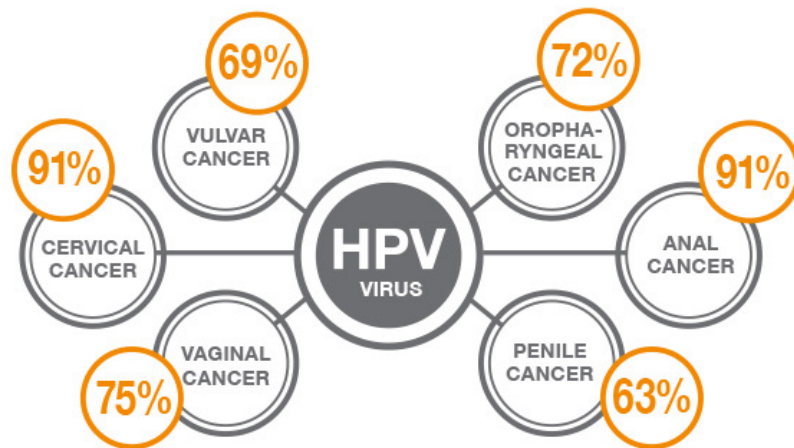
HPV Infection

- Cancer causing HPV infection

- 1 in 5 women
- 1 in 4 men

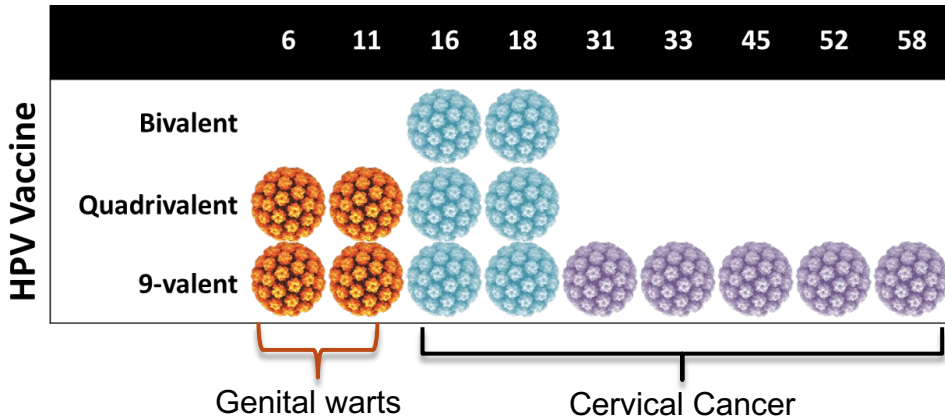


HPV CAUSES SIX TYPES OF CANCER

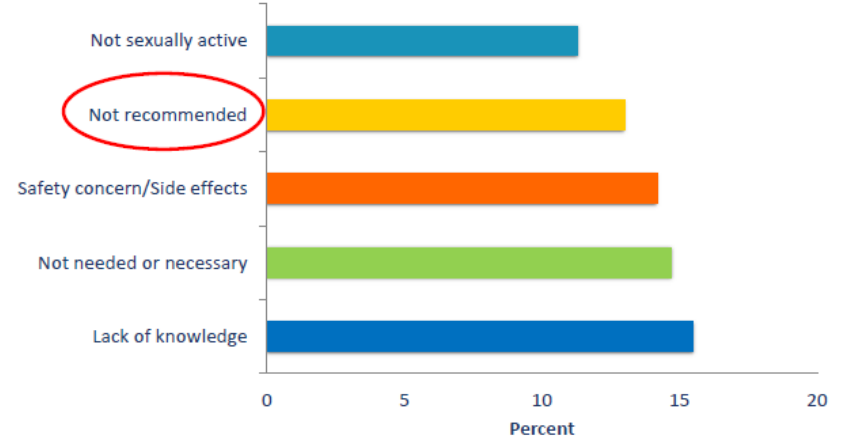


HPV Vaccination

- Ages 9-45 years eligible
 - 11-12 years (ideal)
- Over 300 million doses given



Vaccine hesitancy

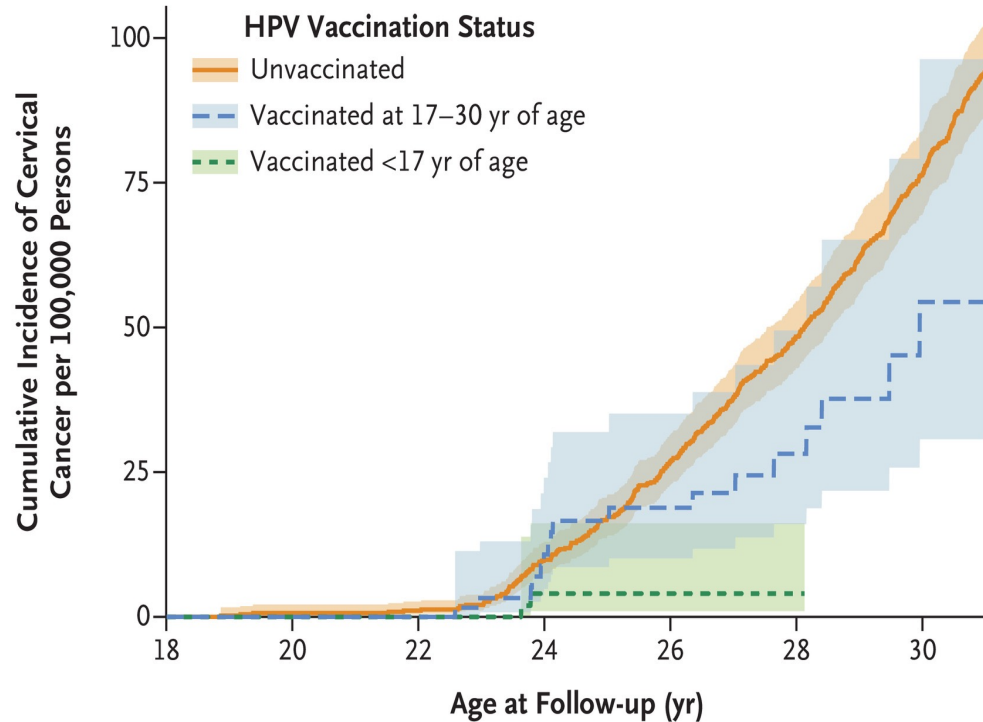


- Study of young cancer survivors
 - 71% refuse vaccine
 - Safety, disinterest, knowledge

Cervical Cancer and HPV Vaccination

- Study of 1,672,983 girls and women ages 10-30
 - 527,871 received at least one dose of HPV vaccine

HPV vaccine	Incidence rate ratio
Before age 17	0.12
Ages 17-30	0.47



WHO Global Call for Action 2018: Eliminate Cervical Cancer

- Vaccinate 90% of girls by age 15
- Screen 70% of women with high performance test by age 35
- Maintain an incidence rate below 4 per 100,000 women
- Treat 90% women with precancerous and invasive cancer
- These interventions will lower incidence by 97% by 2120
 - 62 million deaths averted

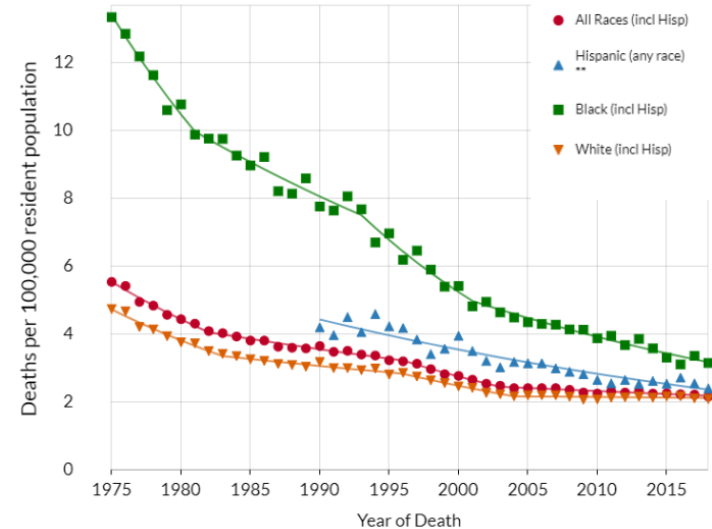
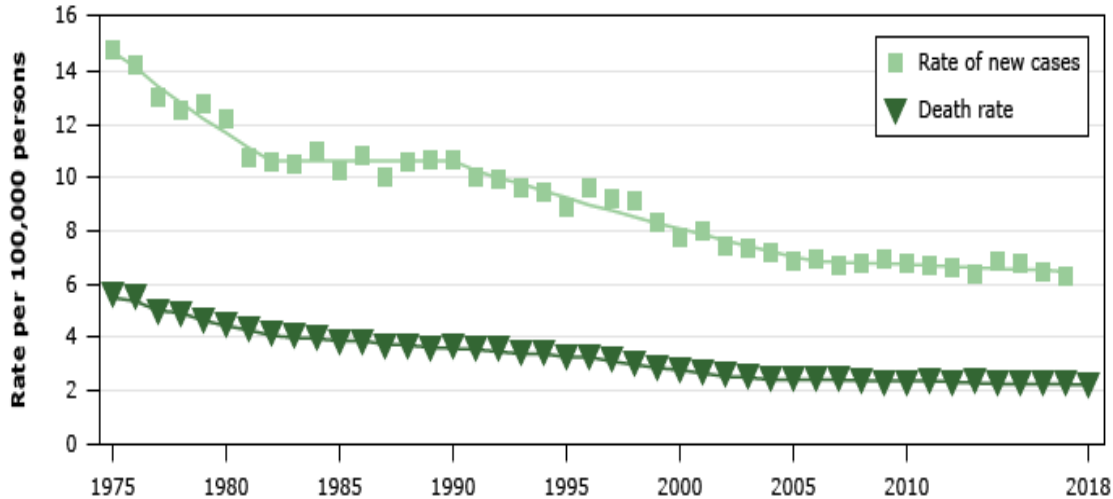


Cervical Cancer

The Age of Immunotherapy

Cervical Cancer Incidence and Mortality

- Worldwide: 604,127 new cases and 341,831 deaths
- US: 14,100 cases and 4,280 deaths



Rationale for Immunotherapy

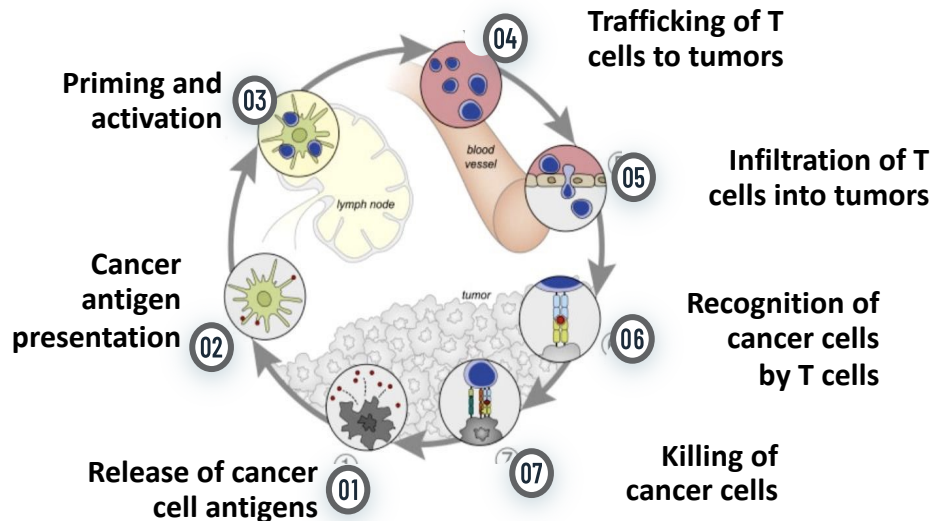
- TCGA data

- Amplifications in PD-L1 and PD-L2

- Correlates with key immune cytolytic effectors
 - Can limit protective immunity

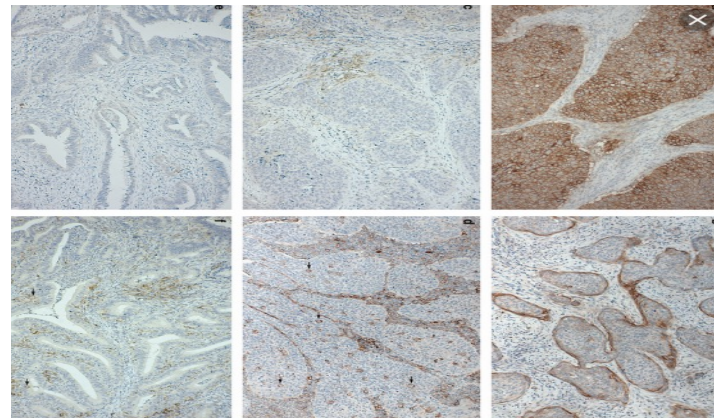
- PD-1/PD-L1 inhibition

- Promote T cell activation against tumor

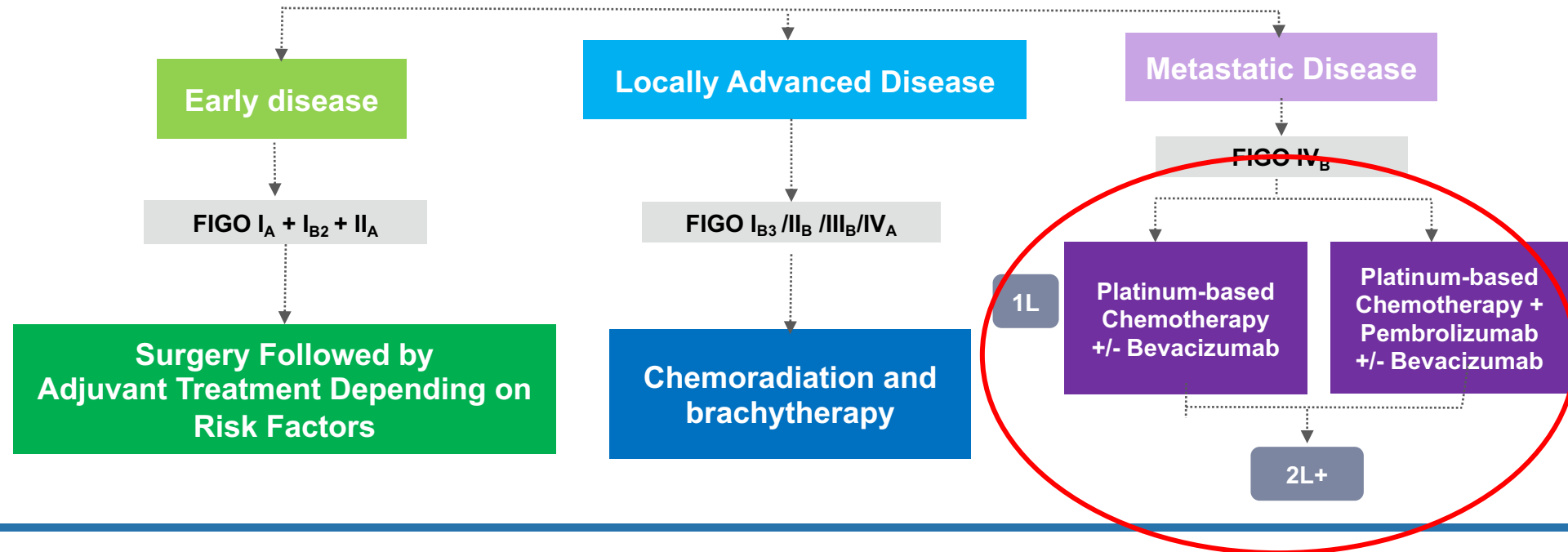


Biomarkers for Cervical Cancer

- PD-L1 expression: 60-90%
- Combined Positive Score (CPS) ≥ 1
 - Number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) to all tumor cells
- TMB-high: 6%
- MMRd/MSI status: 3-14%



Cervical Cancer: Treatment Overview

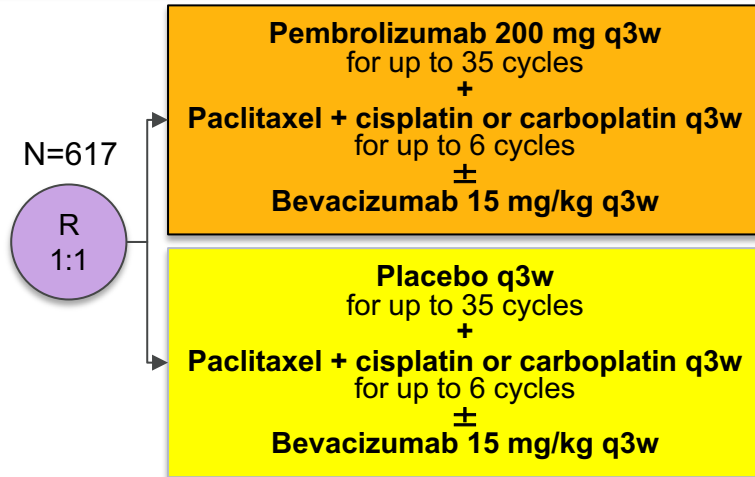


Recurrent Disease: Immunotherapy

	N	PD-L1 rate	RR in PDL1+	DoR	PFS (mo)	OS (mo)
Pembrolizumab	98	77%	17.1%	NR	3	11
Cemiplimab	304	-	21.1%	16.4	2.9	12
Balstilimab	138	61%	20%	18.4		
Nivolumab/Ipilimumab	45	58%	39%	25.6		20.9
Balstilimab/Zalifrelimab	143	51%	32.8%	NR	2.7	12.8

First-line treatment: KEYNOTE 826

- Persistent, recurrent, or metastatic cervical cancer
- No prior systemic chemotherapy
- ECOG PS 0-1



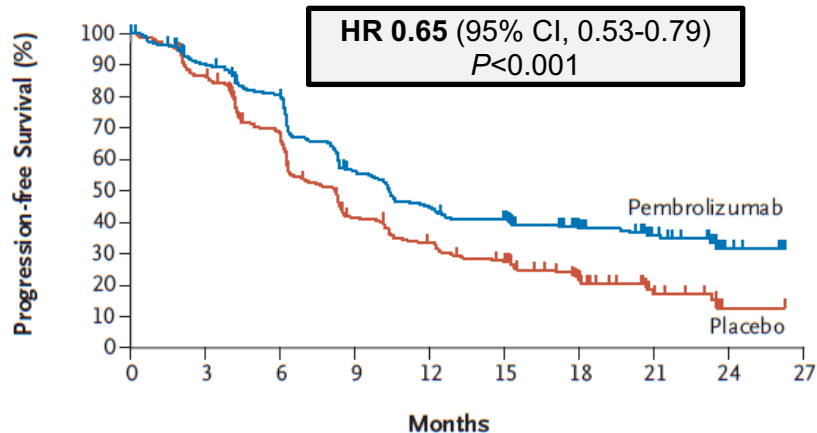
	Pembrolizumab group (n=308)	Placebo group (n=309)
Age, median (range), y	51 (25-82)	50 (22-79)
ECOG PS 1, No. (%)	128 (42)	139 (45)
SCC, No. (%)	235 (76)	211 (68)
PD-L1 CPS, No. (%)		
<1	35 (11)	34 (11)
1 to <10	115 (37)	116 (38)
≥10	158 (51)	159 (51)
Bevacizumab use during trial, No. (%)	196 (64)	193 (62)

Endpoints

- Dual primary: OS and PFS
- Secondary: ORR, DOR, 12-mo PFS, and safety

KEYNOTE 826: Progression Free Survival

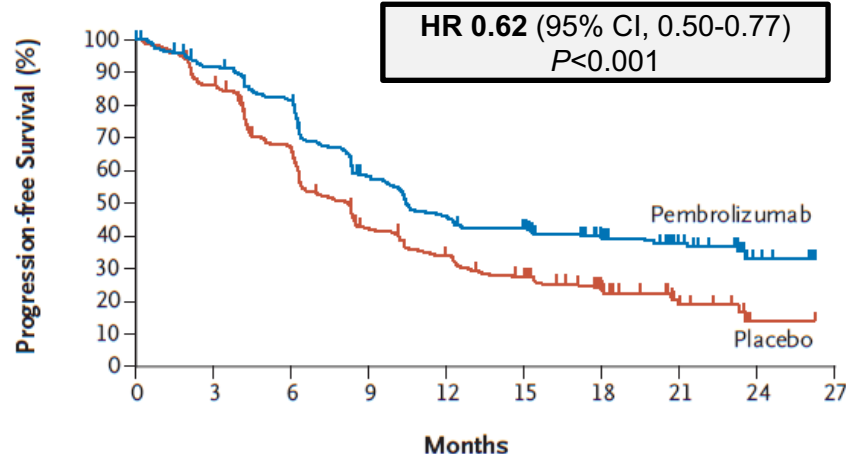
ITT Population



No. at Risk

Pembrolizumab	308	263	229	155	123	110	70	35	10	0
Placebo	309	259	195	113	89	71	39	13	1	0

PD-L1 CPS ≥ 1 Population



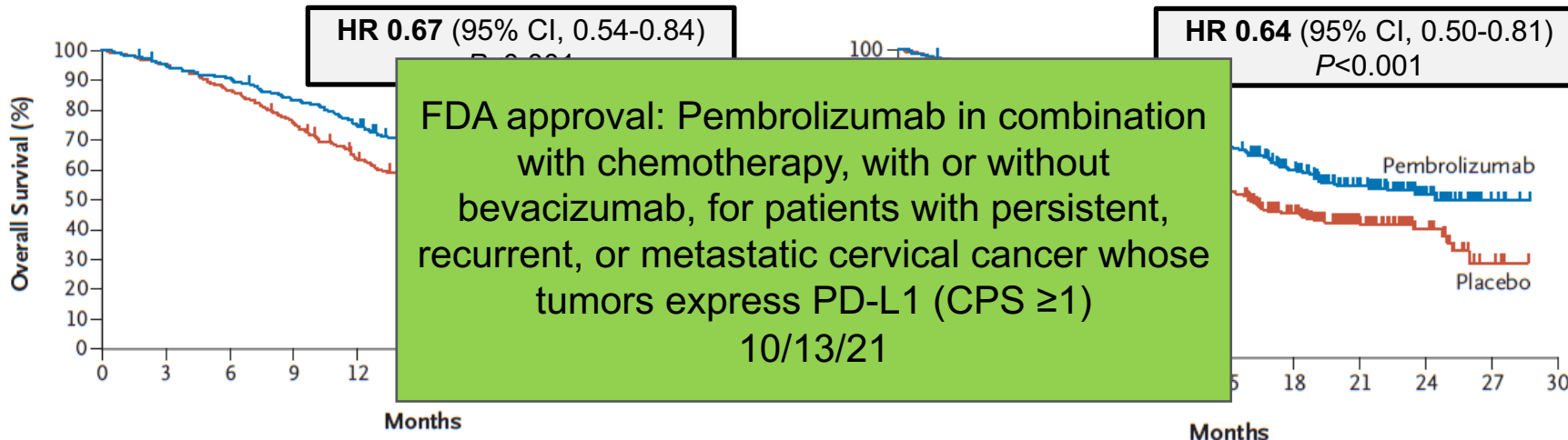
273	238	208	143	112	101	66	34	10	0
275	229	170	103	81	63	38	13	1	0

PD-L1 CPS ≥ 10
HR 0.58 (95% CI, 0.44-0.77); P<0.001

KEYNOTE 826: Overall Survival

ITT Population

PD-L1 CPS ≥ 1 Population



No. at Risk

Pembrolizumab	308	291	277	254	228	201	145	89	36	6	0	273	260	250	229	204	181	132	82	34	6	0
Placebo	309	295	268	234	191	160	116	60	28	4	0	275	261	235	206	168	140	100	55	25	4	0

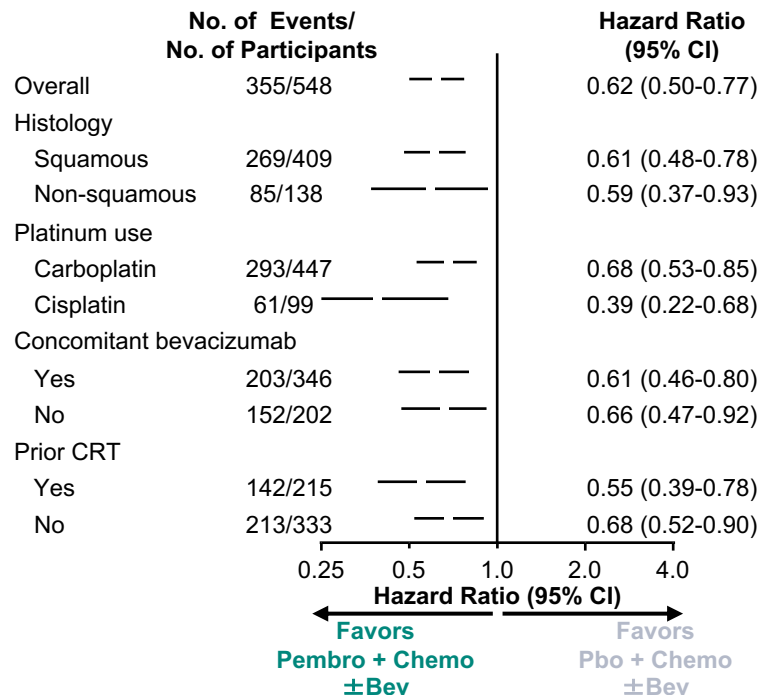
Pembrolizumab group mOS (ITT):
24.4 months

PD-L1 CPS ≥ 10
HR 0.61 (95% CI, 0.44-0.84); *P* < 0.001

Outcomes by subgroup

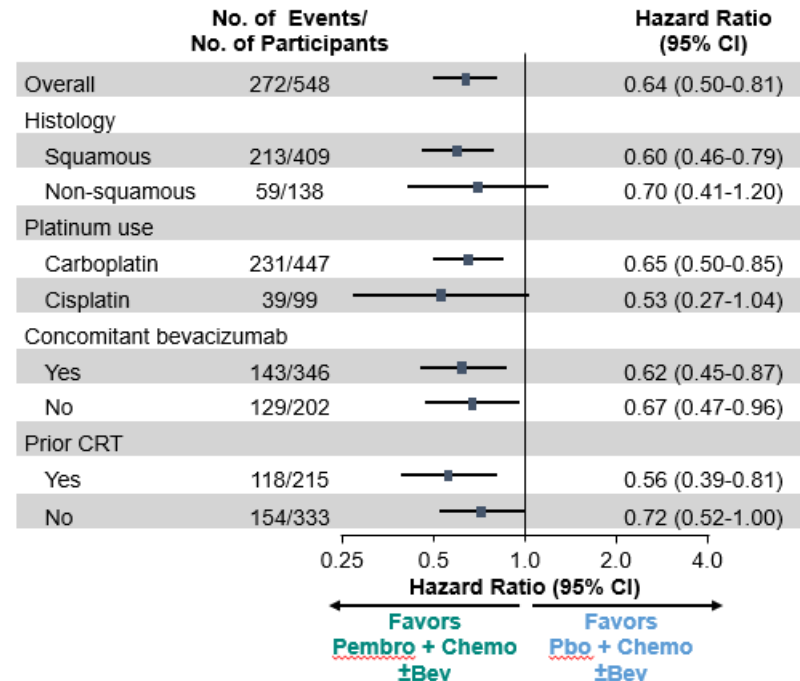
Progression Free Survival

CPS ≥1

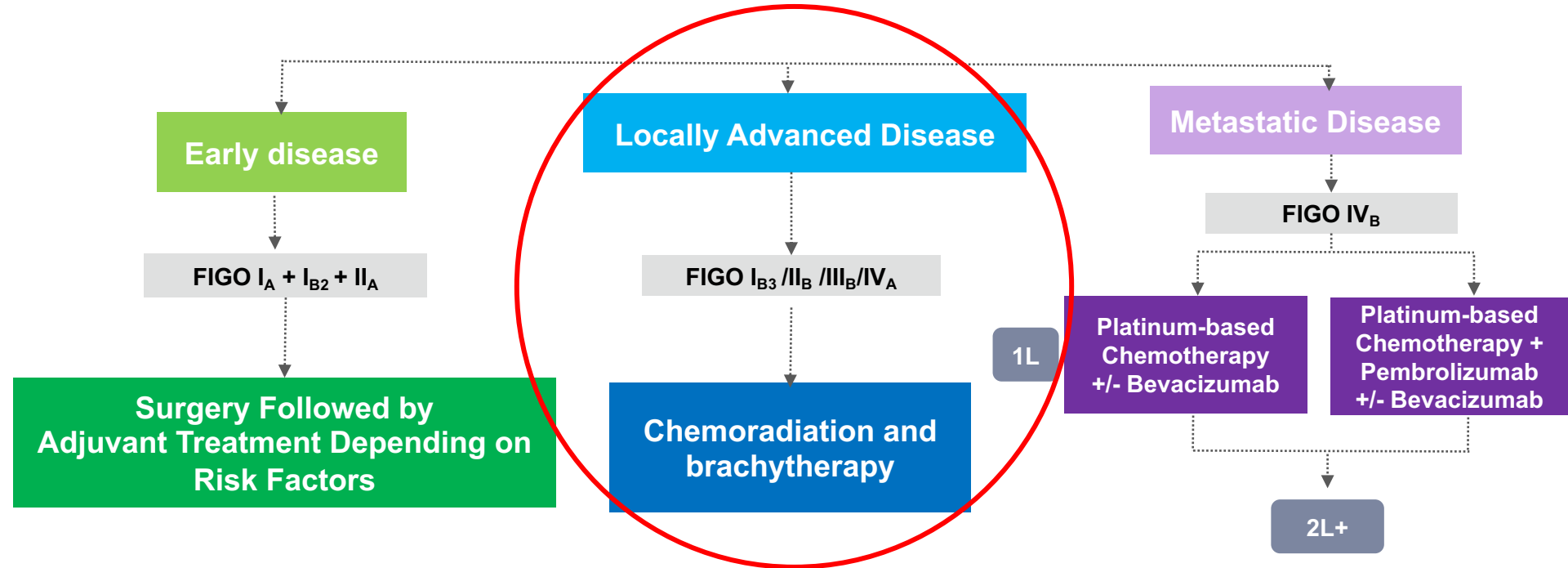


Overall Survival

CPS ≥1

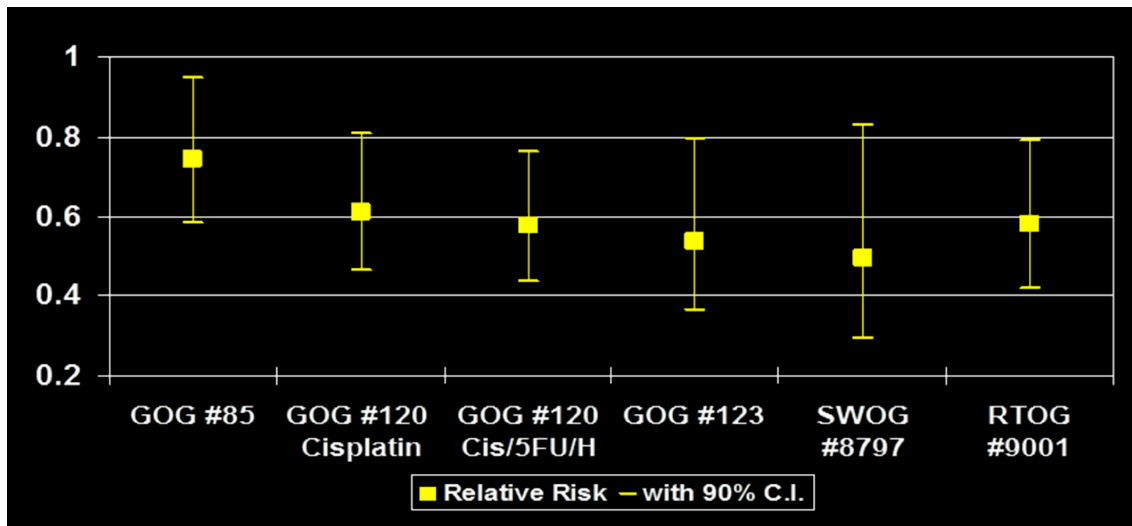


Cervical Cancer: Treatment Overview



Locally Advanced Cervical Cancer

- Chemoradiation and brachytherapy
 - PFS and OS ~60-70%



**New strategies
are needed!**

CALLA: Durvalumab and Chemoradiation

Study population

- FIGO 2009 Stages IB2 to IIB (N ≥1) OR IIIA to IVA (N ≥0)
- Nodal staging (pelvic and/or para-aortic) may be either surgical or by imaging (RECIST v1.1)
- No evidence of metastatic disease (M0)

(R)
1:1

Durvalumab 1500 mg Q4W (N=357)
EBRT + Brachy with platinum

Placebo Q4W (N=357)
EBRT + Brachy with platinum

Primary endpoint

PFS

Secondary endpoints

OS, ORR, CR rate, incidence of local progression, distant disease recurrence, secondary malignancy, HRQoL, PK, ADAs

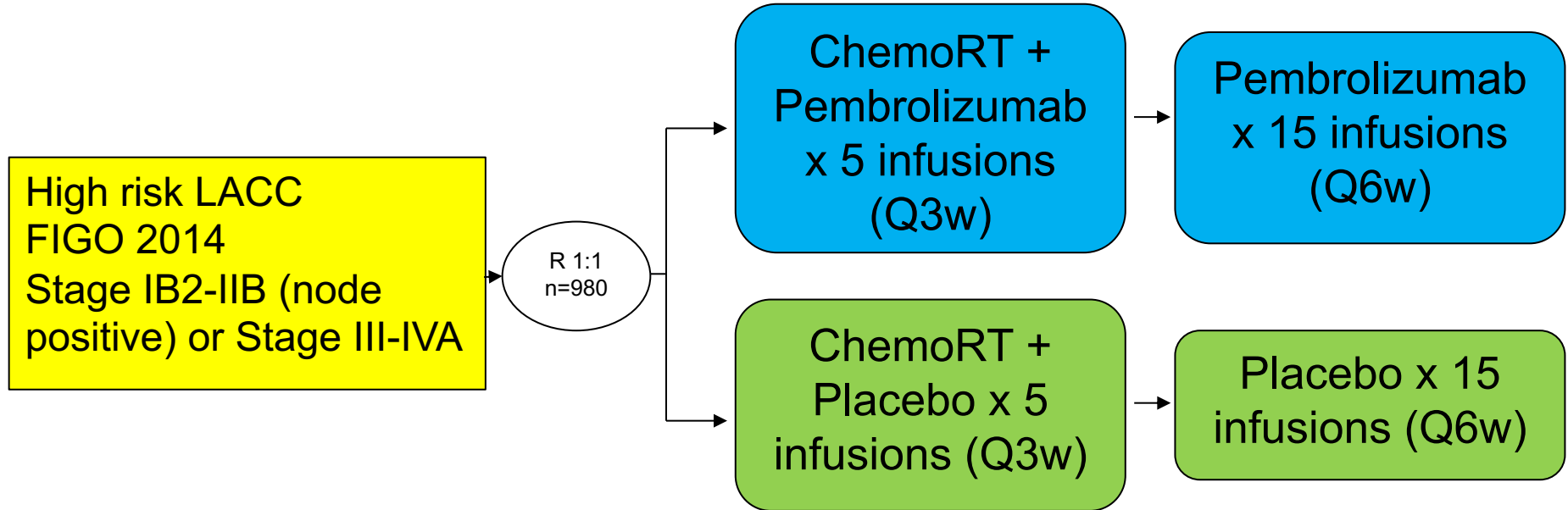
Stratification

- Stage: Stage <III and N positive, Stage ≥III and N negative, or Stage ≥III and N positive
- Region: United States, Canada, European Union, South Korea, and Japan versus rest of the world

March 24, 2022: Press release

The CALLA Phase III trial for [REDACTED] (durvalumab) given concurrently with chemoradiotherapy (CRT) did not achieve statistical significance for the primary endpoint of improving progression-free survival (PFS) versus CRT alone in the treatment of patients with locally advanced cervical cancer.

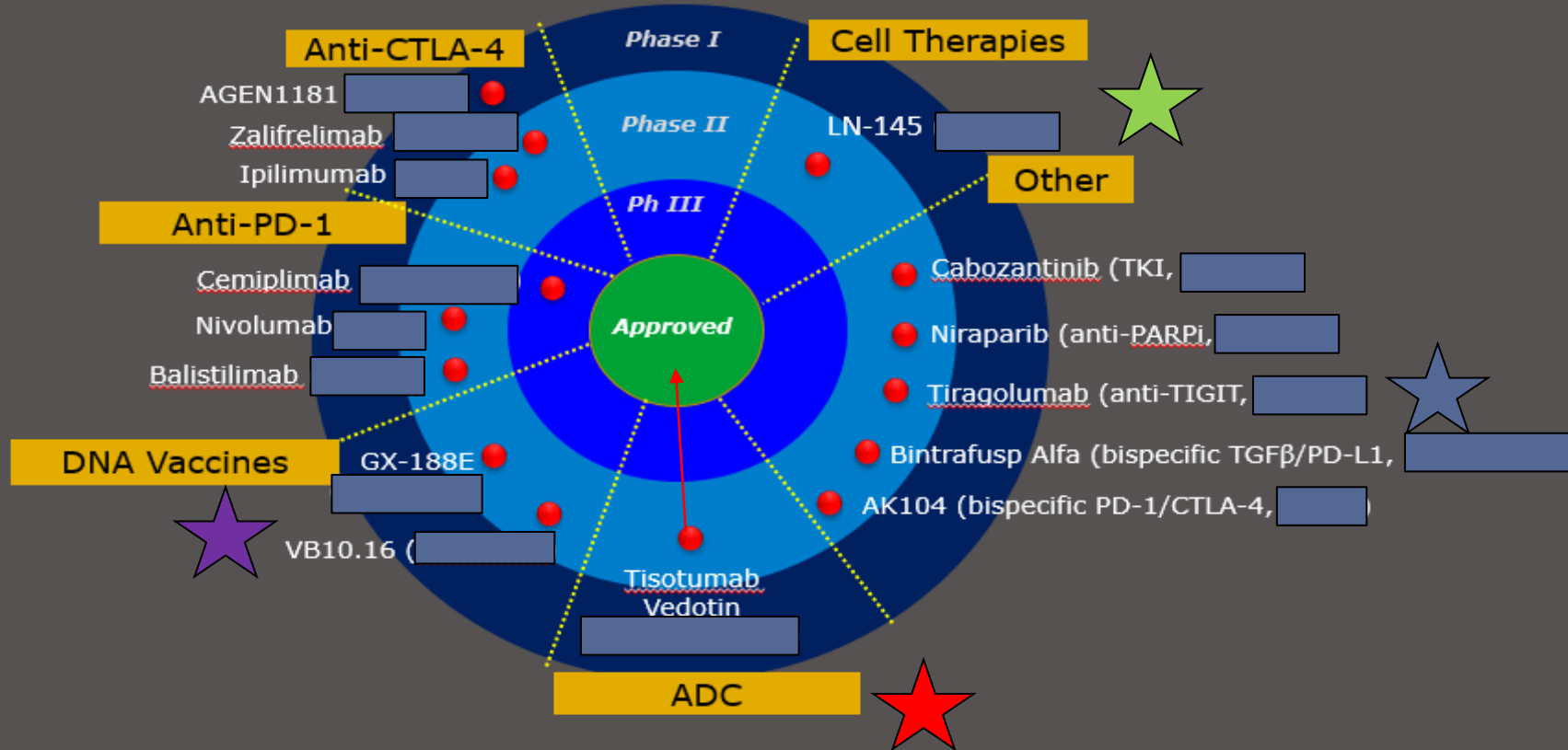
KEYNOTE A18/GOG 3047: Pembrolizumab and Chemoradiation



- Study closed, results pending

Cervical Cancer The Future

Recurrent Disease: Ongoing Studies



Recurrent Disease: Ongoing Studies

Immunotherapy Combinations	
Tisotumab + Pembrolizumab	38% ORR
TILs (LN-145)**	44% ORR
Cadonilimab (PD-1/CTLA4 bispecific)	33% ORR
Atezolizumab +/- Tiragolumab	Study closed
DNA Vaccines	
GX-188E + Pembrolizumab	32% ORR
VB10.16 + Checkpoint Inhibitor**	In Development

- **Prior checkpoint inhibitor therapy

Conclusions

- The immune system is critical in cervical cancer development and treatment
- Screening and prevention should be prioritized
 - HPV Vaccination can reduce the risk of cancer by ~80%
- Checkpoint inhibitor therapy is transforming treatment options
 - In frontline and be investigated in locally advanced cervical cancer
- Novel combinations are being further explored

Thank you

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“It’s always Sit, Stay, Heel - never
Think, Innovate, Be yourself.”