ESGO
European Society of Gynaecological Oncology

25th European Congress on Gynaecological Oncology
March 7-10, 2024 | Barcelona, Spain

Treatment innovations in cervical cancer

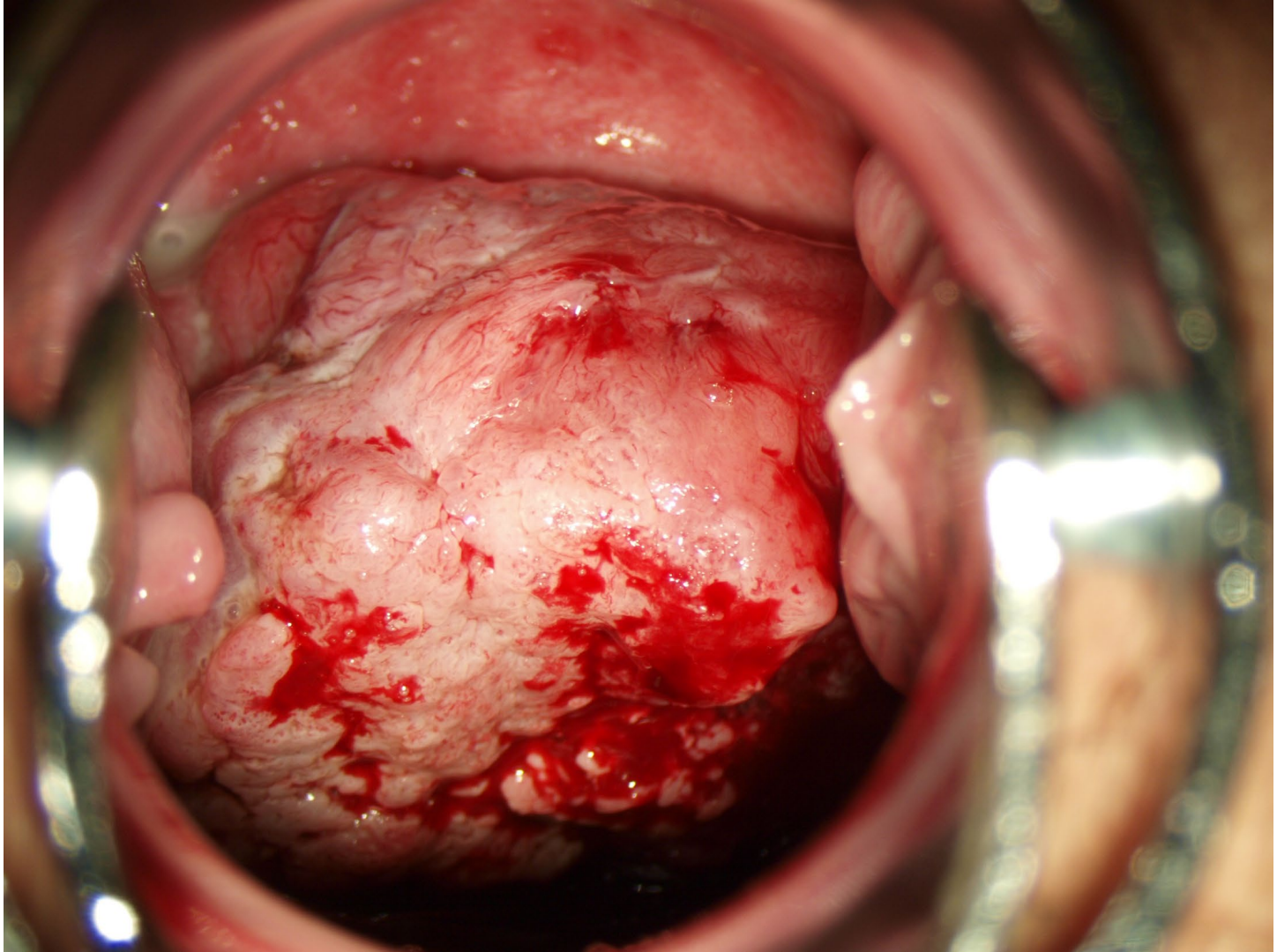
ENGAGE Patient Advocacy Seminar

Date: March 8, 2024
Name: David Cibula

congress.esgo.org

Declarations of interests

The authors declare no conflict of interest.



INNOVATIONS

- **De-escalation of radical surgical treatment in early stages**
- Fertility sparing treatment
- Improvement of radiotherapy
- Immunotherapy in advanced and recurrent tumors
- Future trends

Stage IA – IIA – (IIB)

RADICAL SURGERY

SLN instead of PLND

Abandoning LN staging

Abandoning parametrectomy

Cone instead of Radical trachelectomy

Stage IA – IIA – (IIB)

RADICAL SURGERY

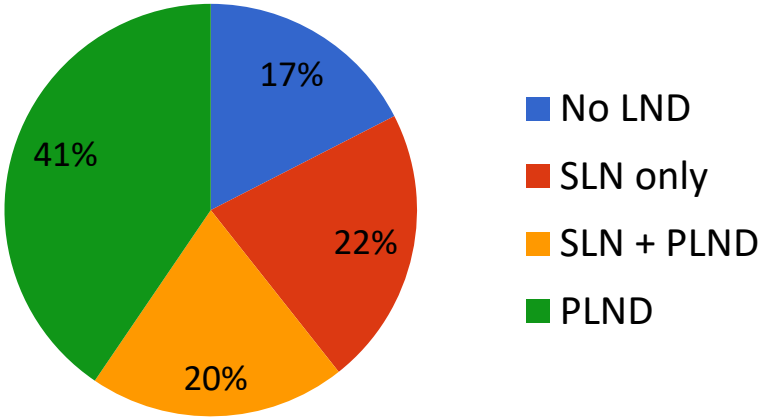
DE-ESCALATION TRENDS

- ✓Only conisation without lymphadenectomy or radical hysterectomy in very small tumors

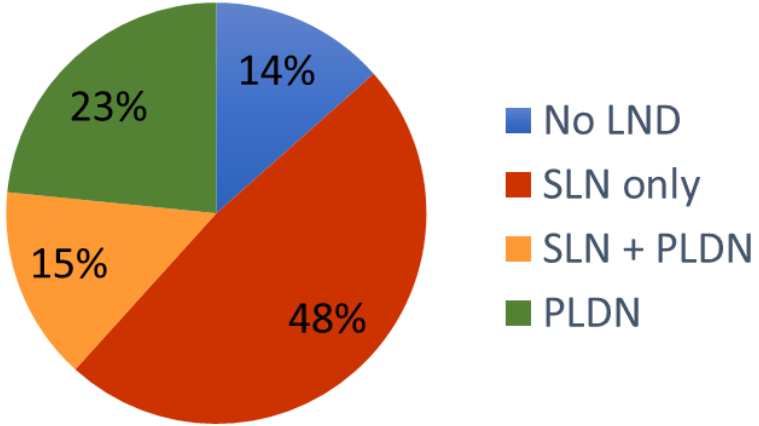
ESGO survey 2017 vs 2021

- **Management of stage IA2 / LVSI negative – <u>lymph node dissection</u>**

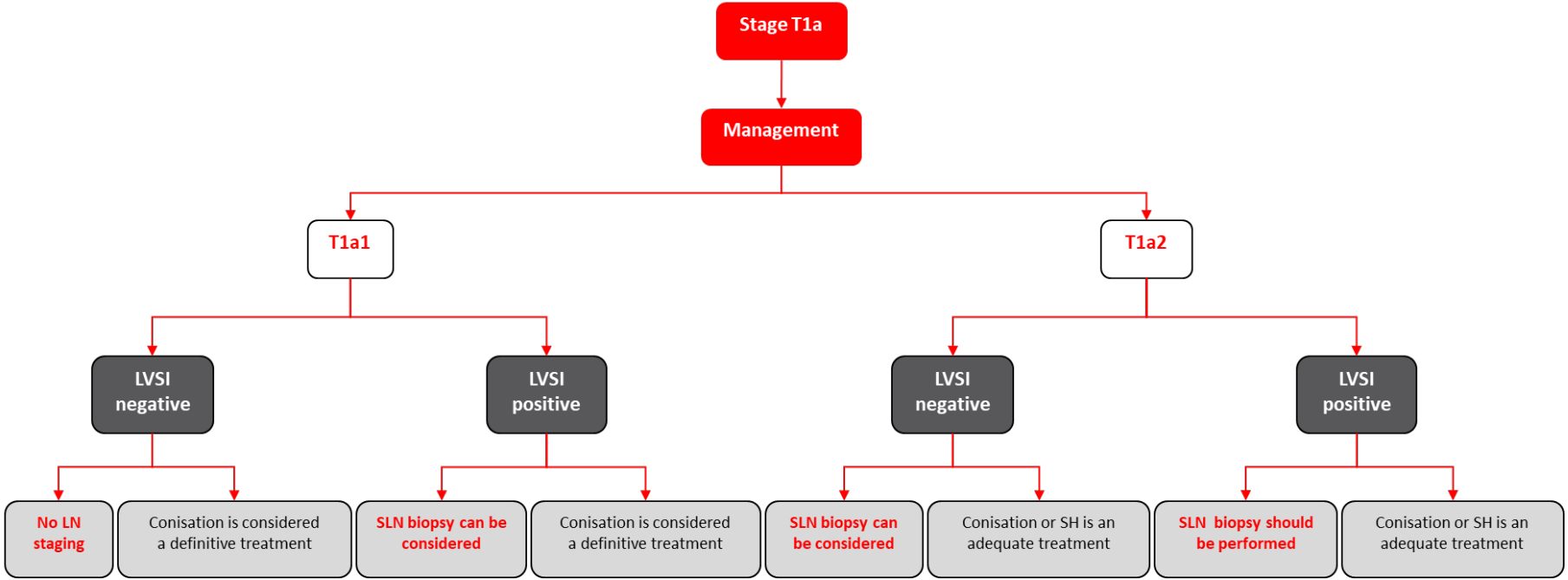
2017



2021



ESGO-ESTRO-ESP Cervical cancer Guidelines (2023)
LN staging

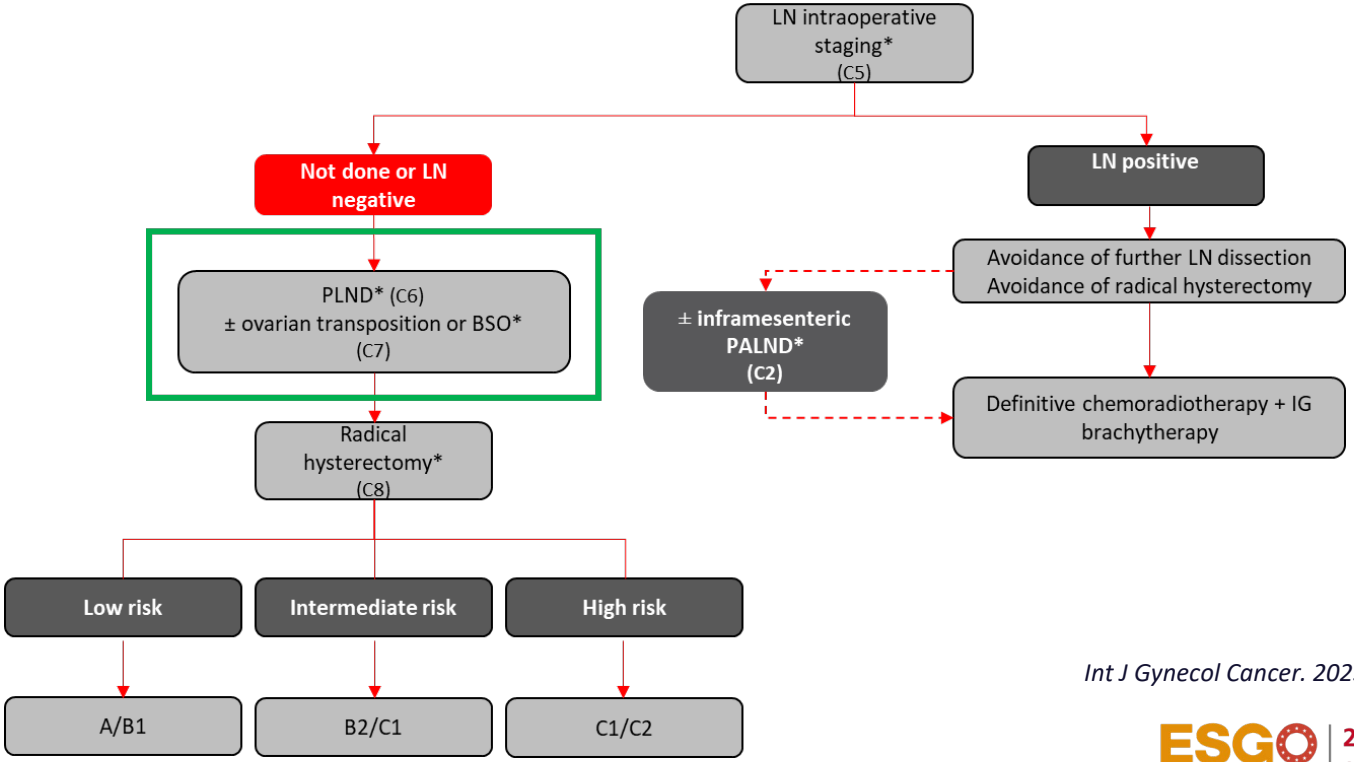


Int J Gynecol Cancer. 2023 May 1;33(5):649-666

DE-ESCALATION TRENDS

- ✓ Removal of a few „sentinel lymph nodes“ instead of pelvic lymphadenectomy

ESGO-ESTRO-ESP Cervical cancer Guidelines (2023)
LN staging



Int J Gynecol Cancer. 2023 May 1;33(5):649-666

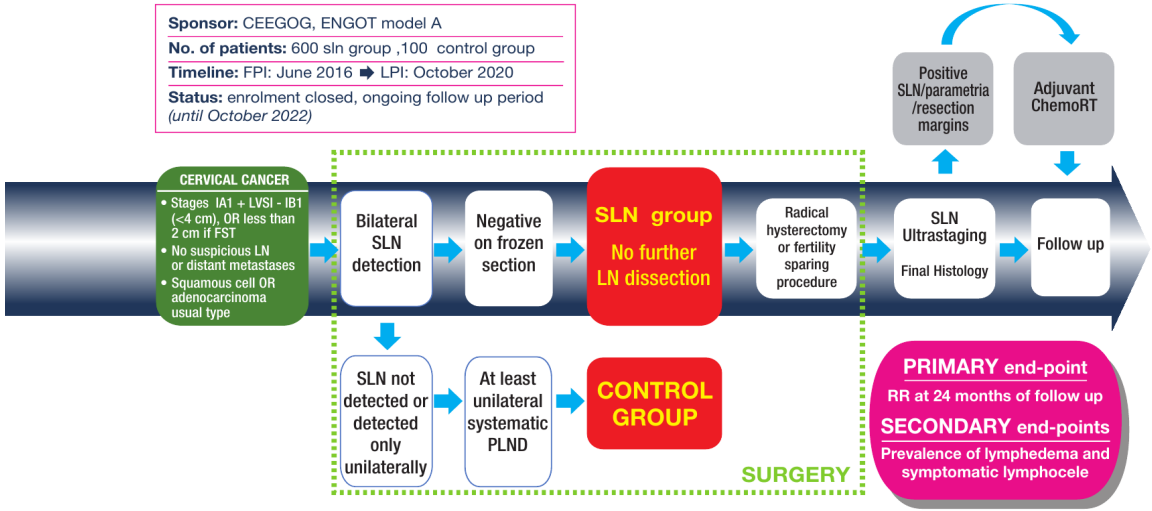
ESGO European Society of Gynaecological Oncology | 25th European Congress on Gynaecological Oncology | March 7-10, 2024 | Barcelona, Spain

SENTIX trial design

SLN biopsy in early cervical cancer

CEEGOG Central and Eastern European Gynecologic Oncology Group

SENTIX



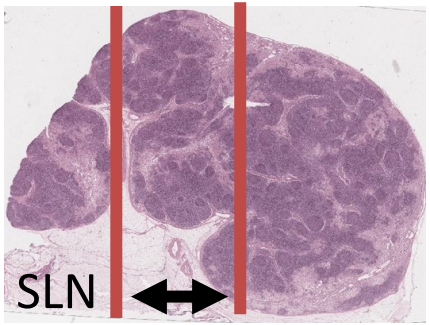
RESULTS

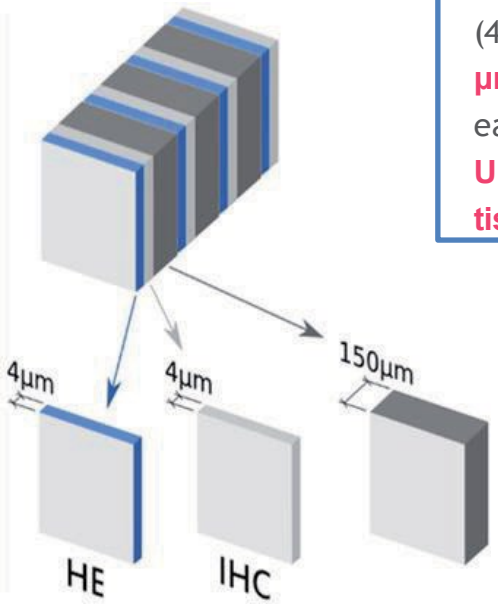
SENTIX

	SENTIX	LACC		ConCerv	SENTICOL II		SHAPE
Subgroup	All	Open	MIS	All	SLN	PLND	All
	N=594	**N=312**	**N=319**	**N=100**	**N=105**	**N=101**	**N=700**
2Y DFS	93.3%	97.1%	91.2%	~95.0%	92%	94.4%	
3Y DFS	92.3%	97.1%	91.2%		92%	94.4%	97.5%
3Y OS	96.9%	99.0%	93.8%				
3Y DSS	97.6%	0.6%	4.4%				99.3%
Main inclusion criteria	IA1 LVSI, IA2 – IB1 Max dimension ≤40 mm Sqamous cell, Adenocarcinoma	IA1 LVSI, IA2 – IB1 Max dimension ≤4 cm Sqamous cell, Adenocarcinoma, Adenosquamous		IA2–IB1 squamous cell (any grade) adenocarcinoma (grade 1-2) histology tumor size ≤2 cm	IA1 LVSI, IA2 – IIA1 Max dimension ≤40 mm All histologic types except neuroendocrine carcinoma		IA2 – IB1 <10mm/ <50% strom. Inv. Max dimension ≤20 mm Sq., adeno., adenosq.
Reference	This work.	Ramirez 2018. Doi: 10.1056/NEJMoa1806395		Schmeler 2021. doi:10.1136/ijgc-2021-002921	Mathevet 2021. doi: 10.1016/j.ejca.2021.02.009		Plante 2024. https://www.cancer.net/CX5-SHAPE

Intensive SLN ultrastaging

After fixation in 10% buffered formalin, all SLNs were sliced **at 2 mm intervals** and embedded in paraffin.





Two consecutive sections (4 µm-thick) obtained in regular **150 µm intervals**, which were cut from each paraffin block …
Until there was no lymph node tissue remaining.

The 1st section was stained with **H&E** and the 2nd was examined immunohistochemically with antibody against cytokeratins **(AE1 / AE3).**

RESULTS

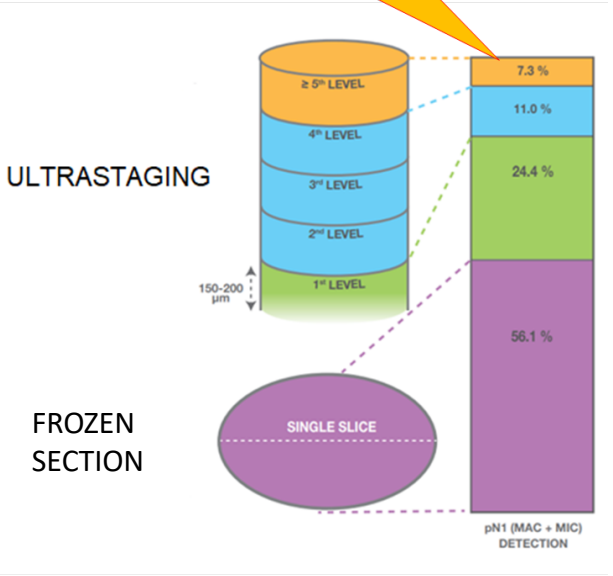
SENTIX

N = 647

	FROZEN SECTION	ULTRASTAGING			TOTAL % of all patients
		1st level	2nd - 4th level		
MAC	36 (83.7%)	6 (14.0%)	1 (2.3%)	0 (0%)	43 (6.6%)
MIC	10 (25.6%)	14 (35.9%)	8 (20.5%)	6 (15.4%)	39 (6.0%)
ITC	2 (9.1%)	6 (27.3%)	10 (45.4%)	4 (18.2%)	22 (3.4%)
pN1 (MAC + MIC)	46 (56.1%)	20 (24.4%)	9 (11.0%)	6 (7.3%)	82 (12.7%)

ITC: isolated tumour cells; MAC: [illegible]metastases; MIC: micrometastases

>90% of detected pN1 cases (MAC, MIC) in 4 levels!

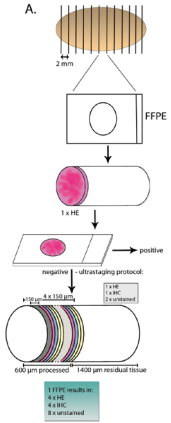


>56% of detected pN1 cases (MAC, MIC) by frozen section

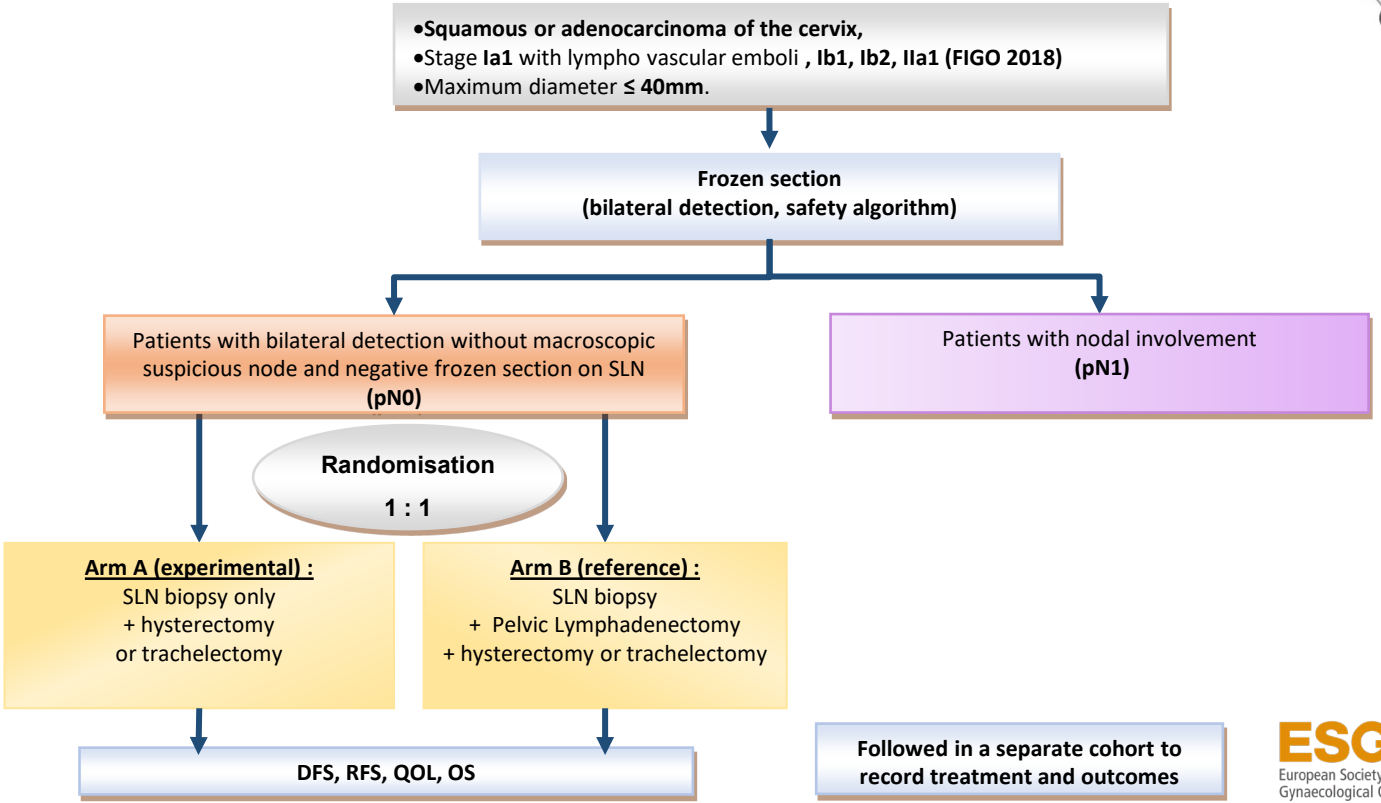
QI for LN staging

No of LN retrieved by surgeon

SLN biopsy and quality of ultrastaging

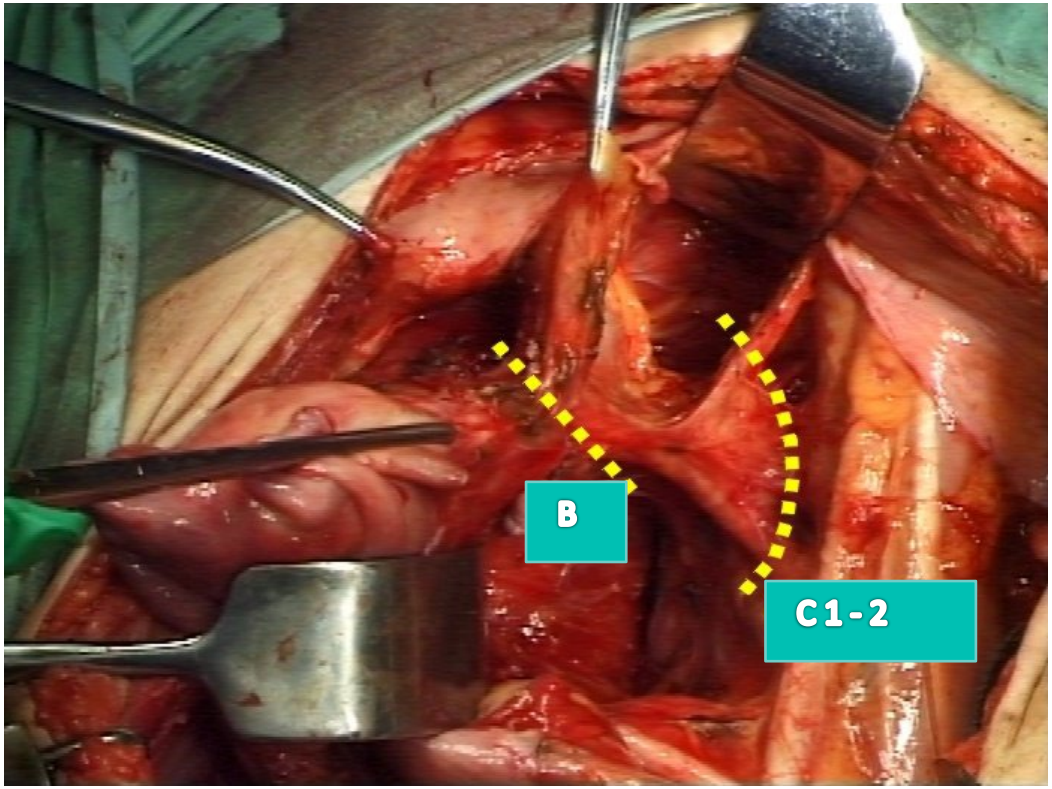


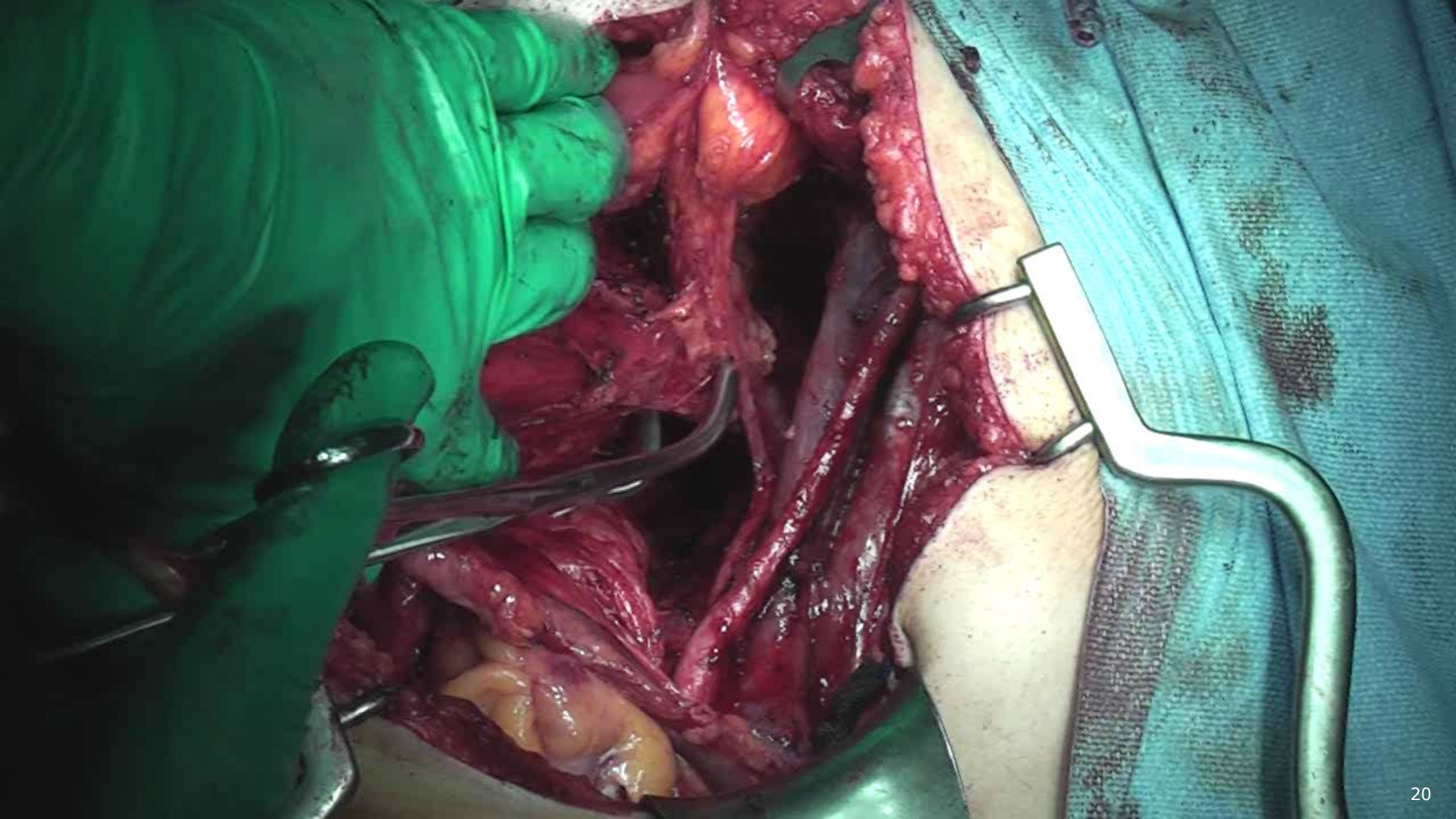
ENGOT-Cx24/SENTICOL III – study design
SLN biopsy in early cervical cancer



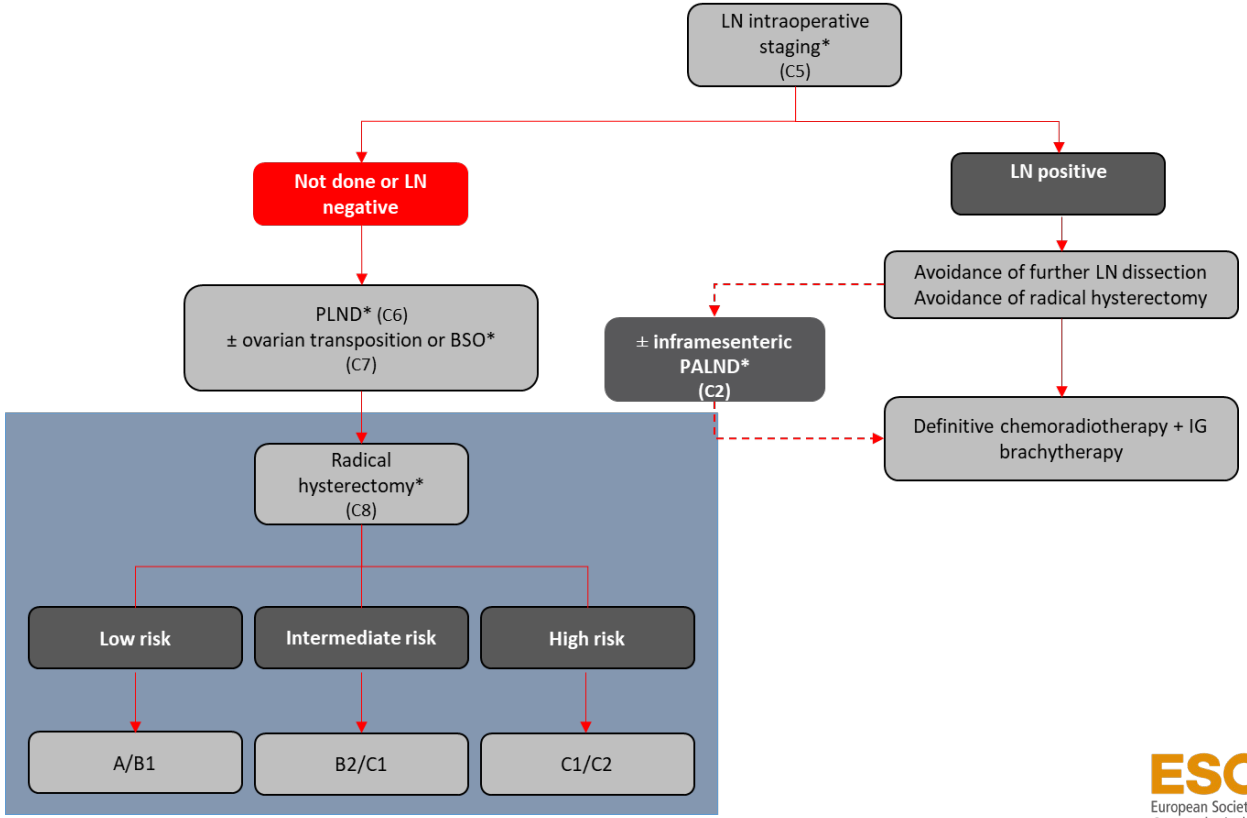
DE-ESCALATION TRENDS

✓Hysterectomy instead of radical hysterectomy in small tumors


B
C1-2



ESGO-ESTRO-ESP CERVICAL CANCER GUIDELINES (2023)



2023 ASCO ANNUAL MEETING

GCIG GYNECOLOGIC CANCER INTERGROUP

Canadian Cancer Trials Group | Groupe canadien des essais sur le cancer

An international randomized phase III trial comparing radical hysterectomy and pelvic node dissection vs simple hysterectomy and pelvic node dissection in patients with low-risk early-stage cervical cancer

A Gynecologic Cancer Intergroup study led by the Canadian Cancer Trials Group

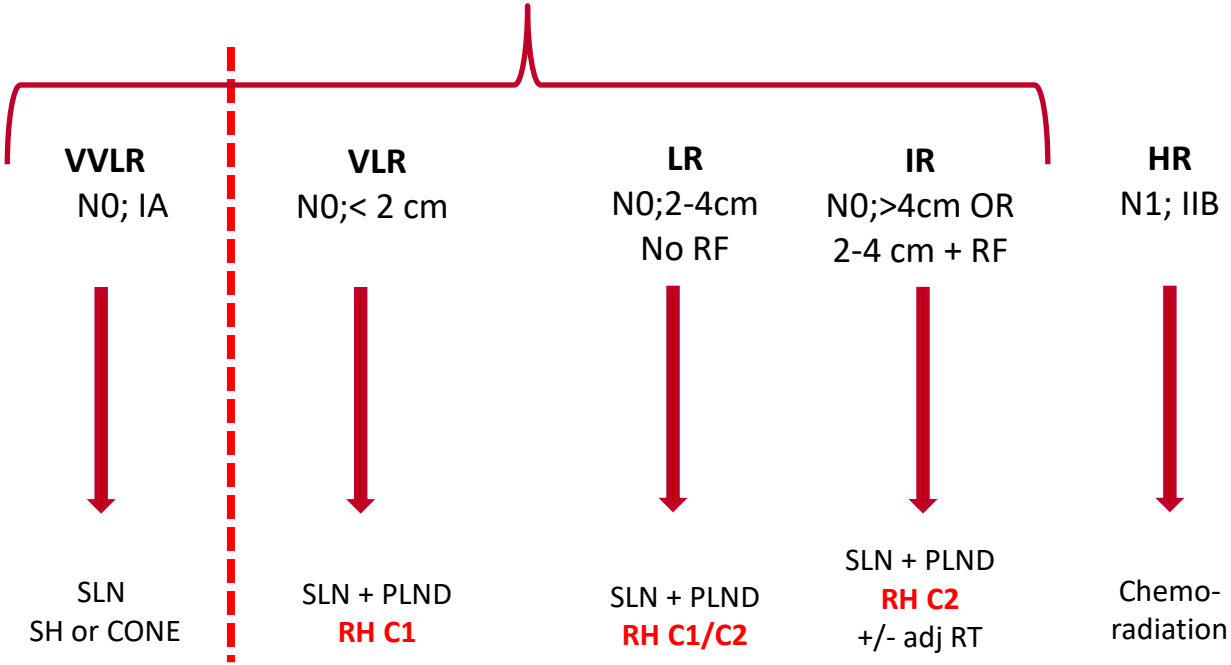
CCTG CX.5 - SHAPE

NCT01658930

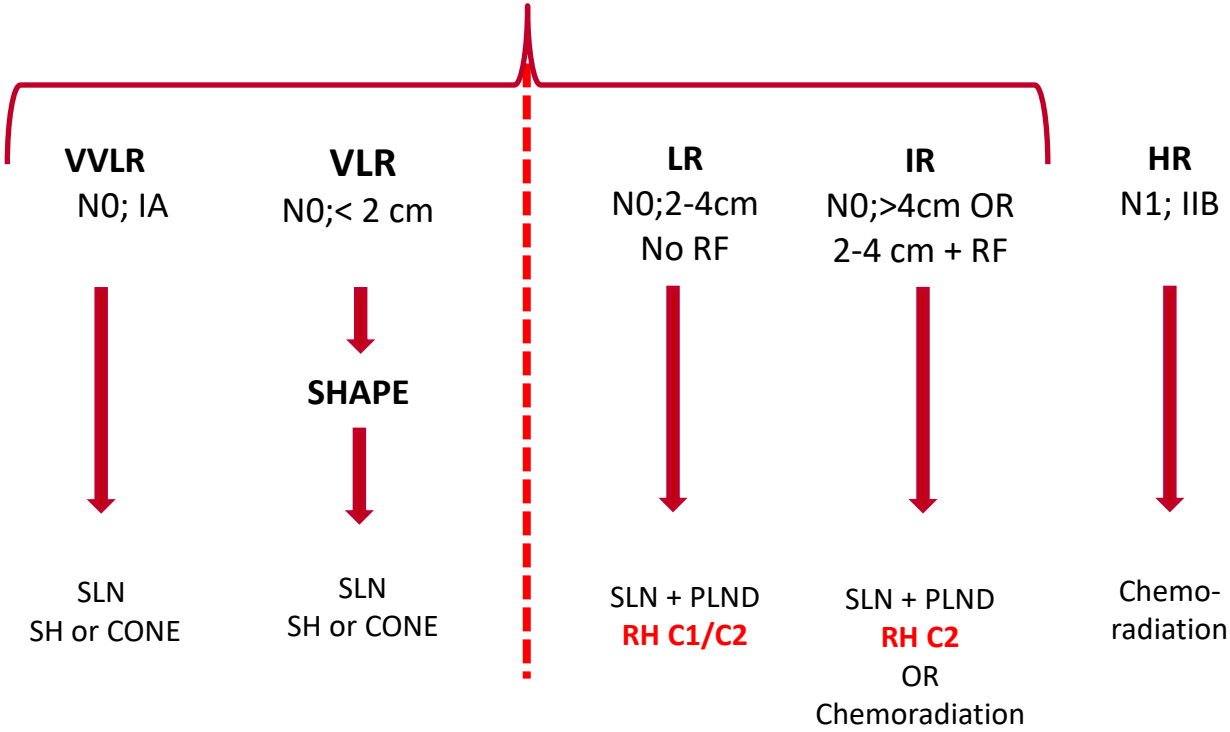
Marie Plante, Janice Kwon, Sarah Ferguson, Vanessa Samouelian, Gwenael Ferron, Amandine Maulard, Cor de Kroon, Willemien Van Driel, John Tidy, Sven Mahner, Stefan Kommoss, Frederic Goffin, Christian Marth, Karl Tamussino, Brynhildur Eyjolfsdottir, Jae-Weon Kim, Noreen Gleeson, Juliana Ubi, Lori Brotto, Dongsheng Tu, Lois Shepherd

On behalf of the SHAPE investigators

Surgical management of IB stage

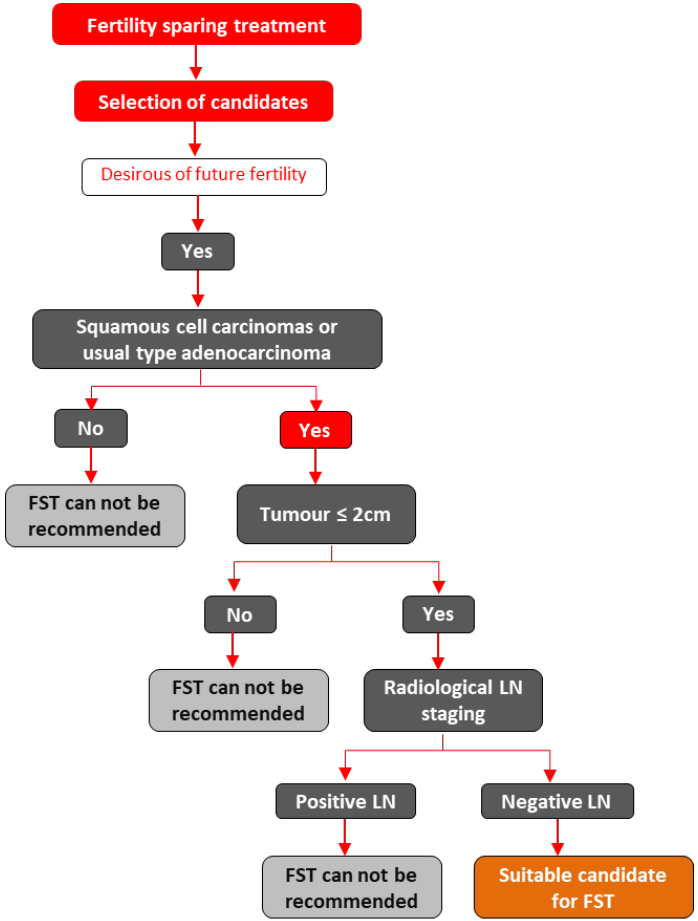


Surgical management of IB stage



INNOVATIONS

- De-escalation of radical surgical treatment in early stages
- **Fertility sparing treatment**
- Improvement of radiotherapy
- Immunotherapy in advanced and recurrent tumors
- Future trends

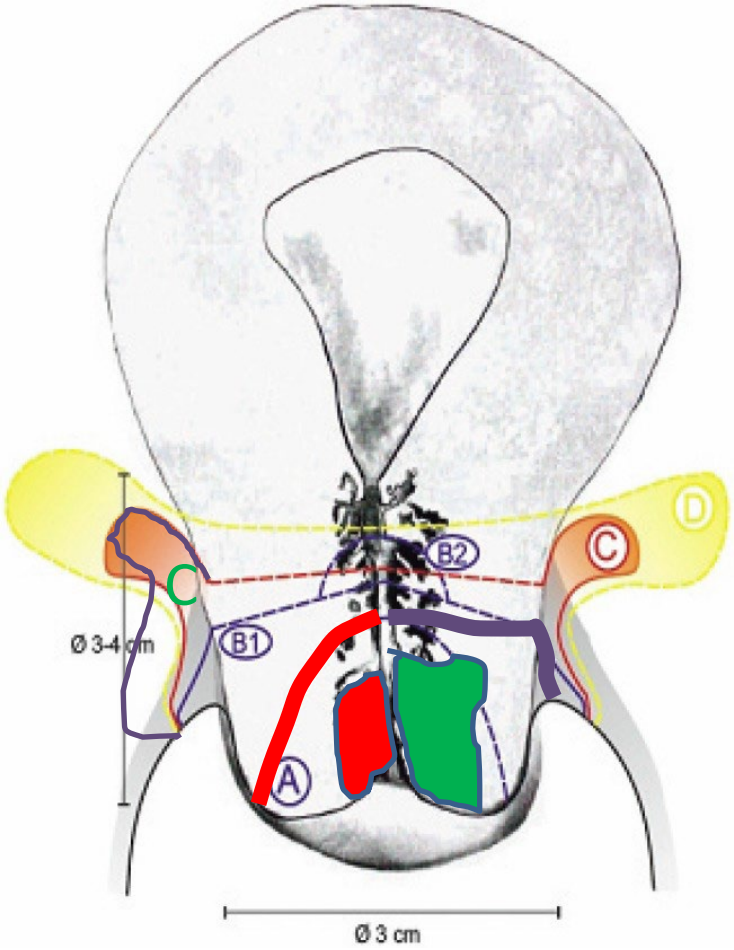

Fertility sparing treatment
Selection of candidates
Desirous of future fertility
Yes
Squamous cell carcinomas or usual type adenocarcinoma
No
Yes
FST can not be recommended
Tumour ≤ 2cm
No
Yes
FST can not be recommended
Radiological LN staging
Positive LN
Negative LN
FST can not be recommended
Suitable candidate for FST

A = conization

B = simple trachelectomy (ST)

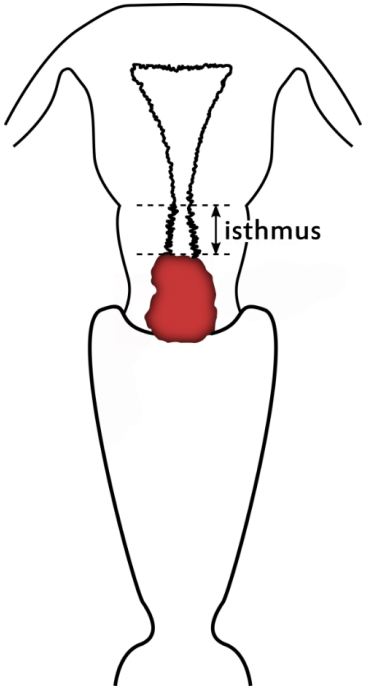
C = vaginal radical trachelectomy

D = abdominal radical trachelectomy

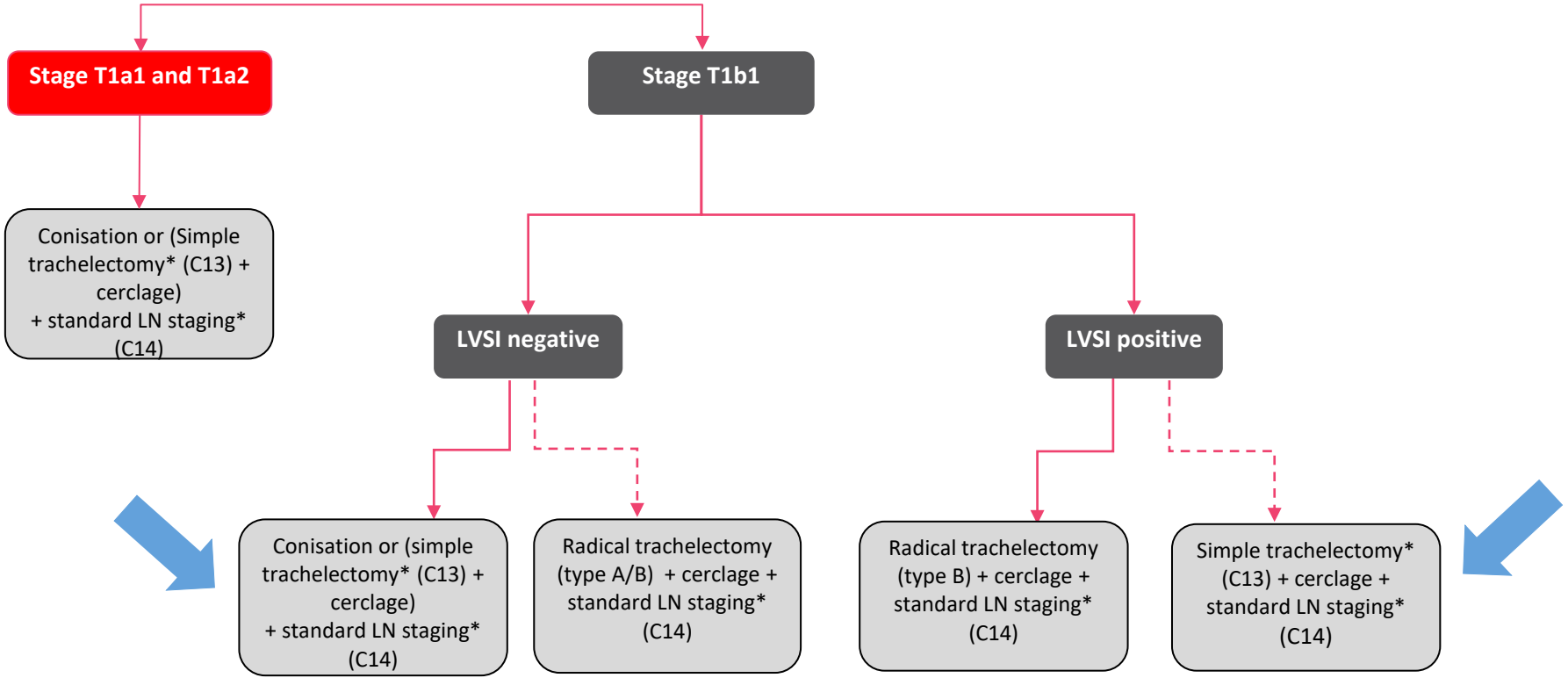


DE-ESCALATION TRENDS

The aim of FST must be the resection of invasive tumor with adequate free margins and preservation of the upper part of the cervix.



ESGO-ESTRO-ESP CLINICAL PRACTICE GUIDELINES (2023)



INNOVATIONS

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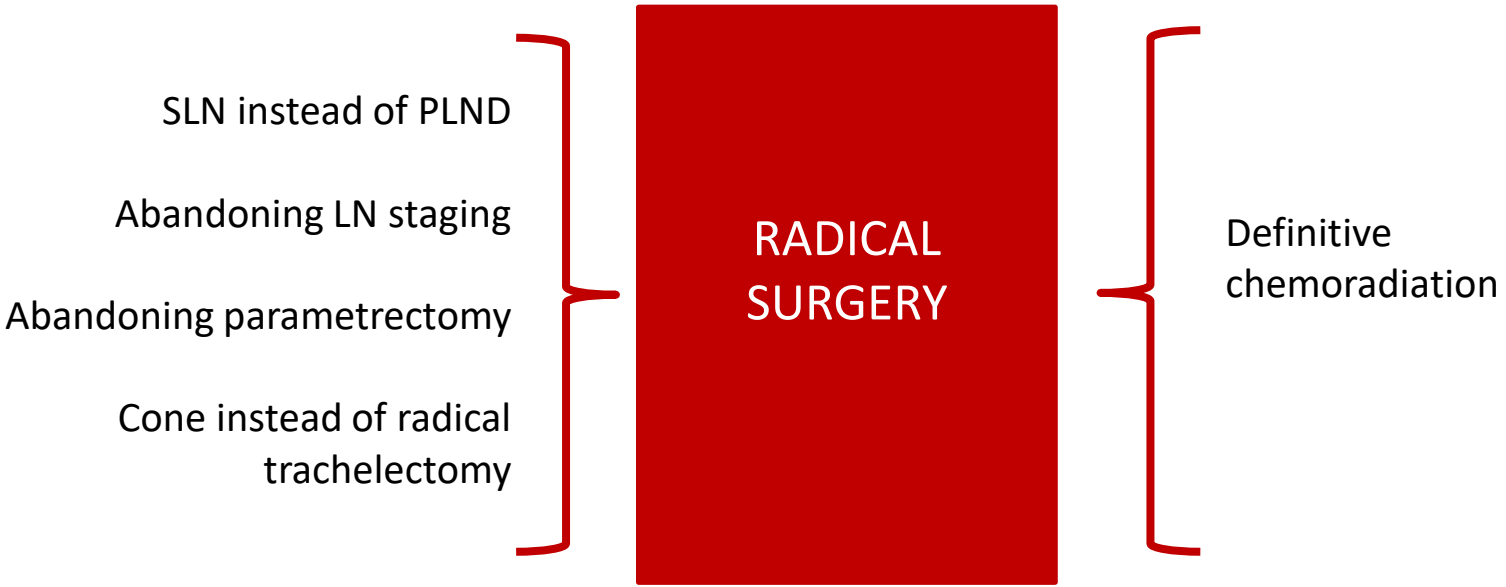
- Fertility sparing treatment
- **Improvement of radiotherapy**
- Immunotherapy in advanced and recurrent tumors
- Future trends


SLN instead of PLND
Abandoning LN staging
Abandoning parametrectomy
Cone instead of radical trachelectomy
RADICAL SURGERY
Definitive chemoradiation

Outcome of chemoradiation in LACC
EMBRACE 1 - prospective observational study

24 sites in Europe, Asia, North America

FIGO IB-IVA; 2008 - 2015

Standardized chemoradiation

- 45-50 Gy EBRT, 1.8-2Gy/f
- wkl Cisplatin 40 mg/m2, 5-6 cycles
- MRI-based IGABT

N=1341

- IB1 124 (9.2%)
- IB2 119 (8.9%)
- IIA1 38 (2.8%)
- IIA2 31 (2.3%)
- IIB 693 (51.7%)
- IIIA 13 (1.0%)
- IIIB 190 (14.2%)
- IVA 34 (2.5%)
- IVB 98 (7.3%)
- Missing 1 (0.1%)

	Number of patients	CTV_{HR} volume, cm³*	CTV_{HR} $D_{90\%}$ $EQD2_{10}$ Gy	Local failure (n)	Pelvic failure (n)	Any failure (n)	Patients dead (n)	5-year local control (95% CI)	5-year pelvic control (95% CI)	5-year disease-free survival (95% CI)	5-year overall survival (95% CI)
IB1	124	22 (17–27)	91 (87–95)	2	6	20	24	98% (94–100)	95% (87–98)	76% (67–83)	83% (75–89)
IB2	119	26 (20–38)	89 (84–93)	9	18	36	35	92% (84–96)	84% (75–90)	65% (56–73)	73% (64–81)
IIA1	38	23 (14–31)	91 (85–96)	3	4	6	7	91% (73–97)	88% (71–95)	75% (58–86)	80% (63–90)
IIA2	31	34 (24–42)	87 (80–91)	3	6	10	8	89% (68–96)	77% (55–89)	65% (44–79)	74% (53–87)
IIB	693	27 (19–36)	90 (86–95)	55	78	146	152	91% (88–93)	88% (85–90)	73% (69–76)	78% (75–82)
IIIA	13	30 (24–35)	84 (82–88)	0	0	2	3	100%	100%	76% (43–92)	76% (42–91)
IIIB	190	40 (30–56)	88 (83–91)	15	24	61	78	92% (86–95)	86% (79–90)	59% (52–66)	64% (57–71)
IVA	34	57 (39–89)	86 (78–89)	3	6	10	17	91% (75–97)	81% (62–91)	47% (28–63)	52% (33–68)
IVB	98	34 (22–47)	89 (85–92)	8	16	40	38	89% (79–95)	81% (70–88)	48% (37–58)	61% (49–70)
Total	1341†	28 (20–40)	90 (85–94)	98	158	331	363†	92% (90–93)	87% (85–89)	68% (65–70)	74% (72–77)

Data are n, median (IQR), or Kaplan-Meier estimates (95% CI). *Mean dose delivered over all fractions. †One patient with unknown FIGO stage. FIGO=The International Federation of Gynaecology and Obstetrics. CTV_{HR}= high-risk clinical target volume. $D_{90\%}$=minimal dose to 90% of the clinical target volume. $EQD2_{10}$=equi-effective dose in 2 Gy per fraction of 10 Gy.

Table 3: CTV_{HR} volume, and dose and clinical outcomes according to $FIGO_{2009}$ stage

Potter 2021; Lancet Oncology 22: 538-47

INNOVATIONS

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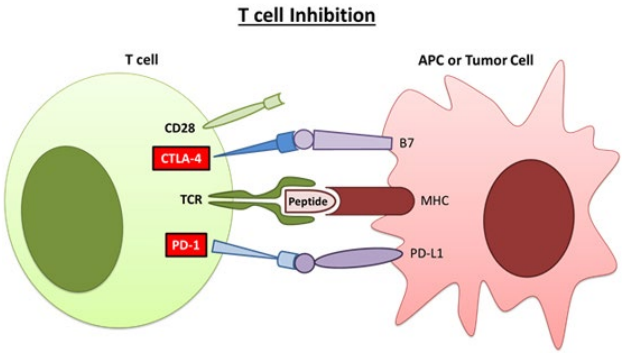
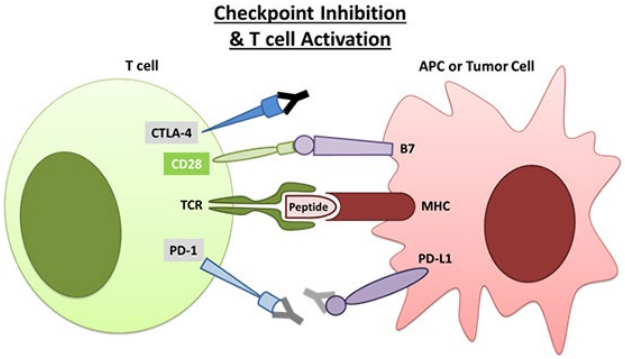
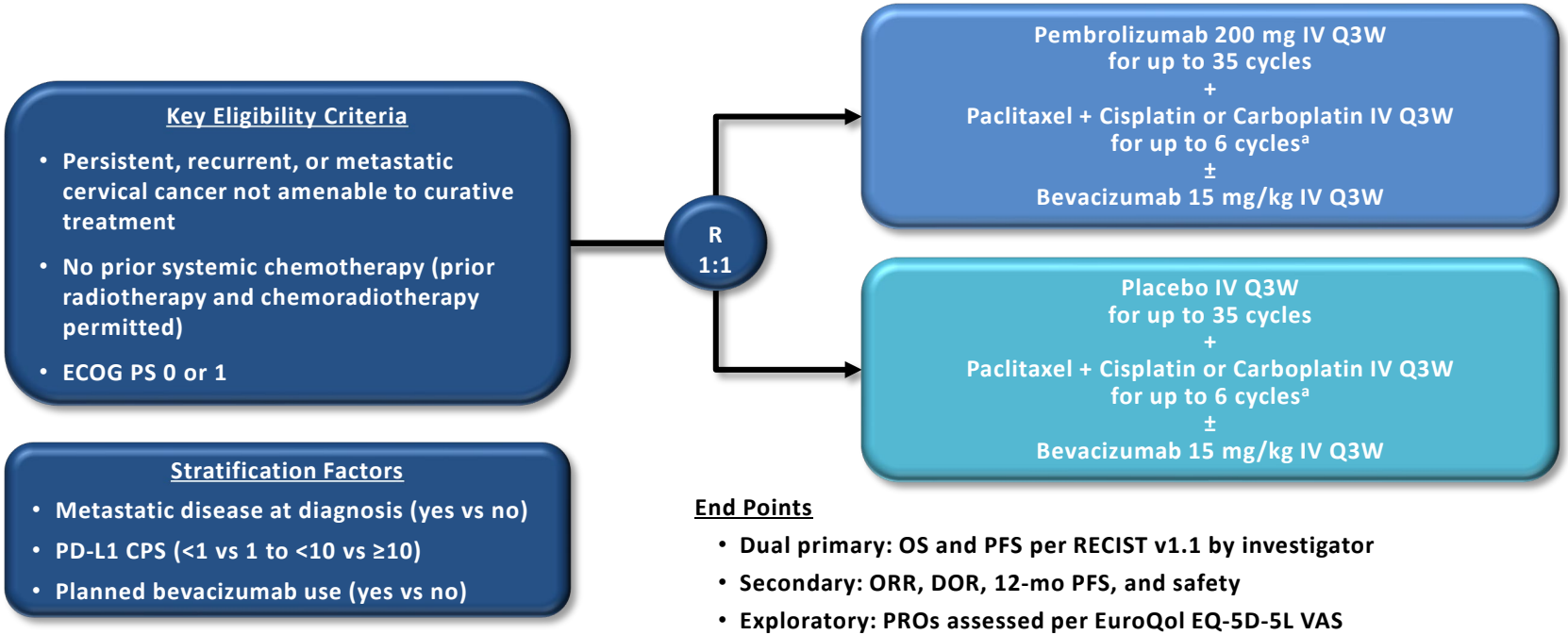

T cell Inhibition
T cell
APC or Tumor Cell
CD28
CTLA-4
TCR
PD-1
B7
Peptide
MHC
PD-L1


Checkpoint Inhibition
& T cell Activation
T cell
APC or Tumor Cell
CTLA-4
CD28
TCR
PD-1
B7
Peptide
MHC
PD-L1

KEYNOTE-826: Randomized, Double-Blind, Phase 3 Study



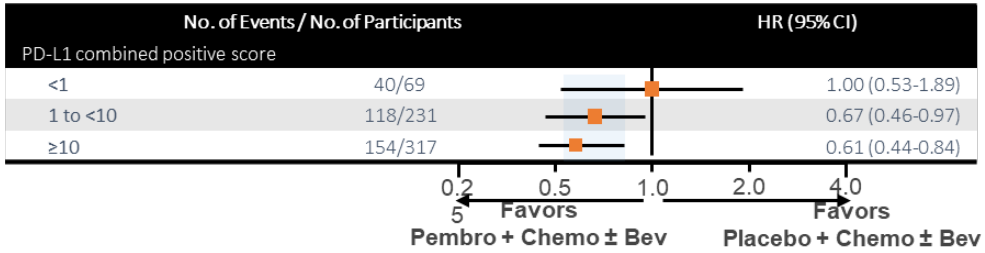
End Points

- **Dual primary: OS and PFS per RECIST v1.1 by investigator**
- **Secondary: ORR, DOR, 12-mo PFS, and safety**
- **Exploratory: PROs assessed per EuroQol EQ-5D-5L VAS**

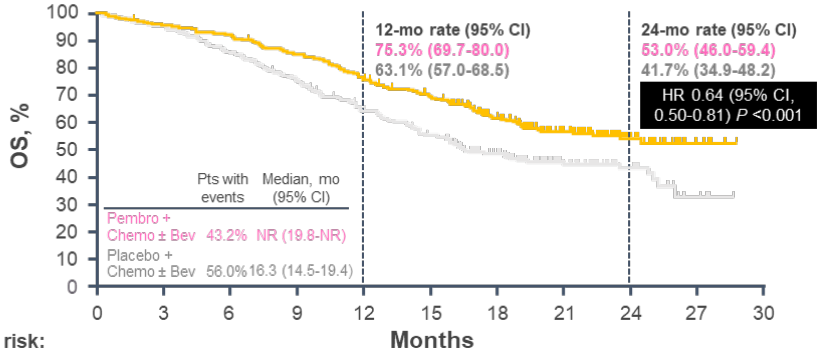
- [a]Paclitaxel: 175 mg/m^2. Cisplatin: cisplatin 50 mg/m^2. Carboplatin: AUC 5 mg/mL/min. The 6-cycle limit was introduced with protocol amendment 2, although participants with ongoing clinical benefit who were tolerating chemotherapy could continue beyond 6 cycles after sponsor consultation.
- CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100); PROs, patient-reported outcomes; VAS, visual analog scale. KEYNOTE-826 ClinicalTrials.gov identifier, NCT03635567.

KEYNOTE-826/MK-3475-826 Overall survival

Sub-group analysis



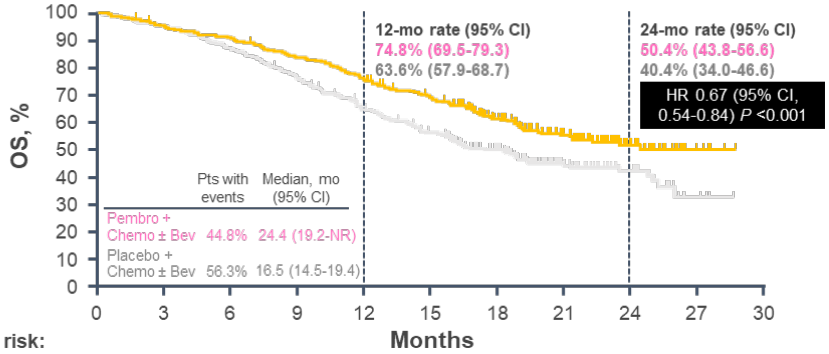
OS: PD-L1 CPS ≥1 population



No. at risk:

Pembro + Chemo ± Bev	273	260	250	229	204	181	132	82	34	6	0
Placebo + Chemo ± Bev	275	261	235	206	168	140	100	55	25	4	0

OS: All-comer population



No. at risk:

Pembro + Chemo ± Bev	308	291	277	254	228	201	145	89	36	6	0
Placebo + Chemo ± Bev	309	295	268	234	191	160	116	60	28	4	0

Data cutoff date: May 3, 2021.

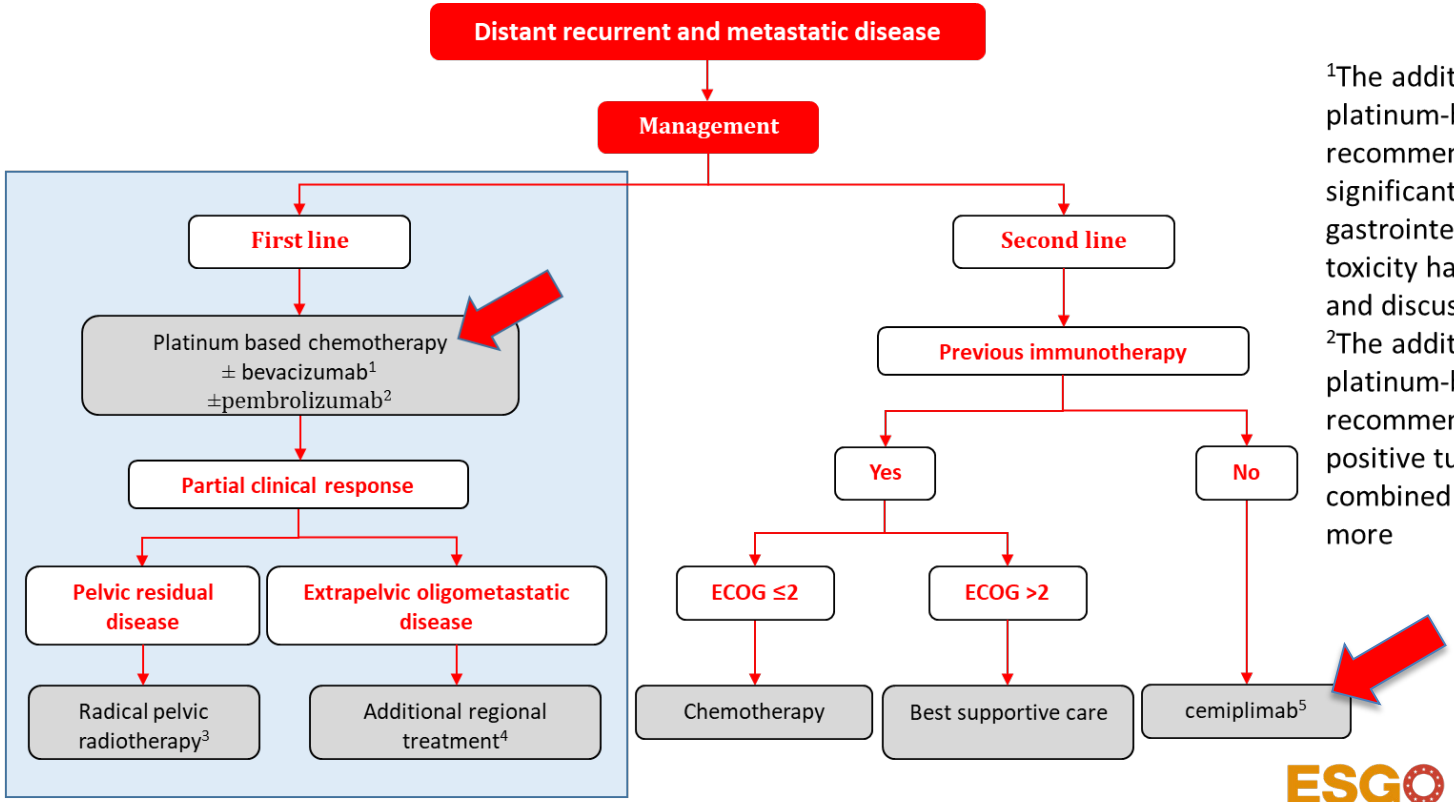
Bev, bevacizumab; Chemo, chemotherapy; CI, confidence interval; CPS, combined positive score; HR, hazard ratio; mo, months; NR, not reached; OS, overall survival; PD-L1, programmed death ligand 1; Pembro, pembrolizumab; pts, patients; RECIST v1.1, Response evaluation criteria in solid tumors.

Colombo et al. *N Engl J Med.* 2021.

Evolution of 1L treatments of LACC

Design	N	ORR (%)	PFS (months)	*P*-value	OS (months)	P-value	Landmark Study
Pembro+CT±Bev vs Placebo+CT±Bev	308 309	65.9 50.8	10.4 8.2	<0.001	24.4 16.5	+8mo <0.001	KEYNOTE-826
Pac/Cis or Top/Cis +/- Bev*	227 225	48 36	8.2 5.9	0.002	17.0 13.3	+4mo 0.004	GOG 240 Study
Pac/Cis vs Car/Pac	121 123	-- --	6.9 6.2	0.053	18.3 17.5	+1mo 0.032	JCOG 0505 Study
Pac/Cis Vin/Cis Gem/Cis Top/Cis	103 108 112 111	29.1 25.9 22.3 23.4	5.82 3.98 4.70 4.57	 0.06 0.04 0.19	12.87 9.99 10.28 10.25	 0.71 0.90 0.89	GOG 204 Study
Pac/Cis Cis	130 134	36 19	4.8 2.8	<0.001	9.7 8.8	NS	GOG 169 Study
Top/Cis Cis	147 146	27 13	4.6 2.9	0.014	9.4 6.5	0.017	GOG 179 Study

ESGO-ESTRO-ESP Cervical Cancer Guidelines 2023



[1]The addition of bevacizumab to platinum-based chemotherapy is recommended when the risk of significant gastrointestinal/genitourinary toxicity has been carefully assessed and discussed with the patient

[2]The addition of pembrolizumab to platinum-based chemotherapy is recommended in patients with PD-L1 positive tumours, assessed as combined positive score of 1 or more

ENGOT-cx11/GOG-3047/KEYNOTE-A18: Randomized, Double-Blind, Phase 3 Study

Key Eligibility Criteria

- FIGO 2014 stage IB2-IIB (node-positive disease) or FIGO 2014 stage III-IVA (either node-positive or node-negative disease)
- RECIST 1.1 measurable or non-measurable disease
- Treatment naïve

Stratification Factors

- Planned EBRT type (IMRT or VMAT vs non-IMRT or non-VMAT)
- Stage at screening (stage IB2-IIB vs III-IVA)
- Planned total radiotherapy dose (<70 Gy vs ≥70 Gy [EQ2D])

R
1:1
N = 1060

- Cisplatin 40 mg/m^2 QW for 5 cycles[a] + EBRT followed by brachytherapy + Pembrolizumab 200 mg Q3W for 5 cycles
- Pembrolizumab 400 mg Q6W for 15 cycles
- Cisplatin 40 mg/m^2 QW for 5 cycles[a] + EBRT followed by brachytherapy + Placebo Q3W for 5 cycles
- Placebo Q6W for 15 cycles

[a]A 6th cycle was allowed per investigator discretion. EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; Gy, grays; IMRT, intensity-modulated radiotherapy; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; VMAT, volumetric-modulated arc therapy. ENGOT-cx11/GOG-3047/KEYNOTE-A18 ClinicalTrials.gov identifier, NCT04221945.

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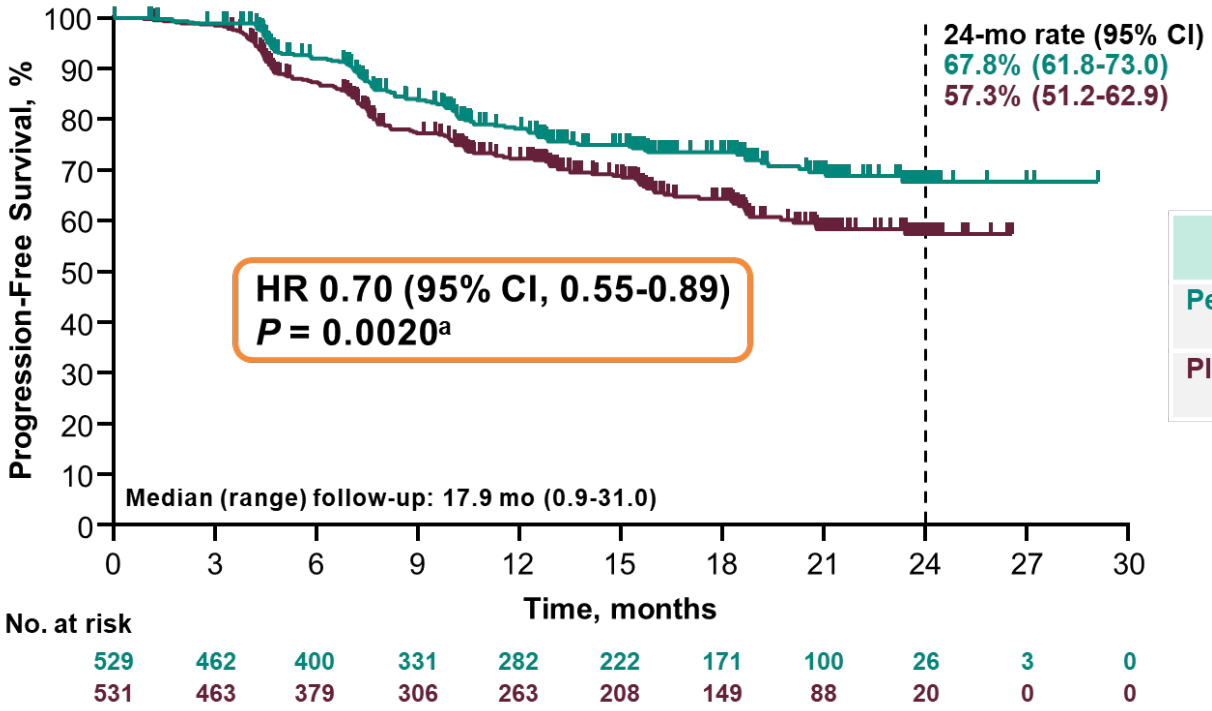
Primary Endpoint: Progression-Free Survival



	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	21.7%	NR (NR-NR)
Placebo Arm	29.0%	NR (NR-NR)

Response assessed per RECIST v1.1 by investigator review or histopathologic confirmation. [a]With 269 events (88.5% information fraction), the observed *P* = 0.0020 (1-sided) crossed the prespecified nominal boundary of 0.0172 (1-sided) at this planned first interim analysis. The success criterion of the PFS hypothesis was met, and thus no formal testing of PFS will be performed at a later analysis. Data cutoff date: January 9, 2023.

Presented by: Domenica Lorusso

INNOVATIONS

- De-escalation of radical surgical treatment in early stages
- Fertility sparing treatment
- Improvement of radiotherapy
- Immunotherapy in advanced and recurrent tumors
- **Future trends**

FUTURE TRENDS

Diagnostics

More accurate detection of metastases (IA)

New prognostic markers (radiomics; tumor microenvironment)

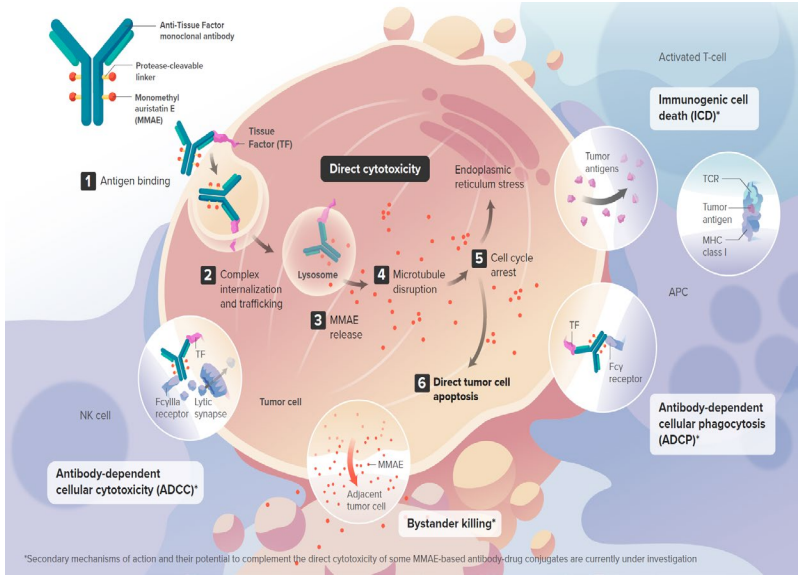
Treatment

Active immunotherapy (vaccines)

Antibody drug conjugates (TV)

Antibody-drug conjugates: Tisotumab Vedotin

- **Tisotumab vedotin** is an investigational antibody-drug conjugate **directed to tissue factor (TF)** and covalently linked to the microtubule-disrupting agent MMAE via a protease-cleavable linker[1,2]
- TF is highly prevalent in cervical cancer and other solid tumors and is associated with cancer pathophysiology and poor prognosis[3-5]
  - TF is co-opted by tumor cells to promote tumor growth, angiogenesis, and metastasis[6]
  - In normal physiology, TF's primary role is to initiate the coagulation cascade after vascular injury[6]
- Tisotumab vedotin has multiple anti-tumor effects[1,2,7]



Tisotumab vedotin is an investigational agent, and its safety and efficacy have not been established.

1. Breij EC et al. *Cancer Res.* 2014;74(4):1214-1226. 2. De Goeij BE et al. *Mol Cancer Ther.* 2015;14(5):1130-1140. 3. Pan L et al. *Mol Med Rep.* 2019;19:2077-2086. 4. Cocco E et al. *BMC Cancer.* 2011;11:263. 5. Zhao X et al. *Exp Ther Med.* 2018;16:4075-4081. 6. Forster Y et al. *Clin Chim Acta.* 2006;364:12-21 7. Alley SC et al. American Association for Cancer Research Annual Meeting; March 29 – April 3, 2019; Atlanta, GA, USA; Abstract #221.
ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; MMAE, monomethyl auristatin E; MOA, mechanism of action; TF, tissue factor.

Therapeutic HPV vaccines

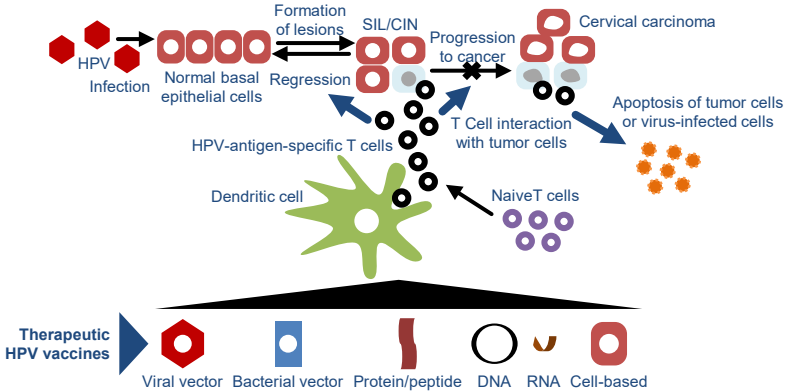
Background

- **HPV evades the immune system**
  - Low levels of viral protein
  - Replicates without cell death and resulting in pro-inflammatory mechanisms
  - HPV replication occurs in an immunologically isolated site
- **Little activation of adaptive immunity by natural infection**

Vaccines

- **Goal:**
  Elimination of HPV induced lesions via activation of T-cell immune response against HPV infected cells
- **Principle:**
  Induction of specific T-cell response against HPV E6/E7 epitopes presented by tumor/dysplastic cells
- **Various different approaches**
  (peptids/protein-based, DNA based, cellular approach)

Therapeutic HPV vaccines and HPV progression[2]



[1]Einstein et al. *Lancet Inf Dis* 2009. [2]Hung et al. *Expert Opin Biol Ther*. 2008.

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