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# Treatment of advanced or metatastic cervical cancer:

## VEGF Inhibitors, ADCs, and Immunotherapy

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# Systemic Therapy
# NCCN Guidelines, v1.2024

| Squamous Cell Carcinoma, Adenocarcinoma, or Adenosquamous Carcinoma | | |
|---|---|---|
| Chemoradiation[b] | Recurrent or Metastatic Disease | |
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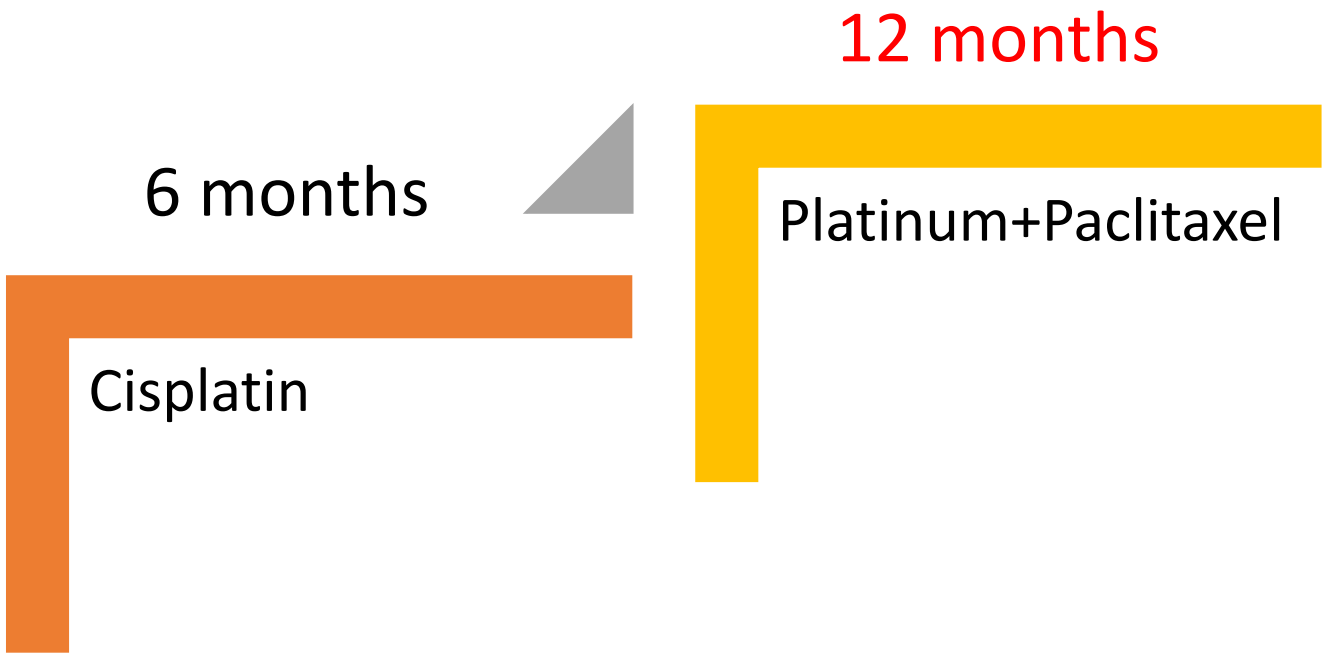
| **Preferred Regimens**<br>• Cisplatin<br>• Carboplatin if patient is cisplatin intolerant<br><br>**Other Recommended Regimens[c] (if cisplatin and carboplatin are unavailable)**<br>• Capecitabine/ mitomycin[1]<br>• Gemcitabine[2]<br>• Paclitaxel[3,4] | **Preferred Regimens**<br>• PD-L1–positive tumors<br>▸ Pembrolizumab + cisplatin/paclitaxel ± bevacizumab (category 1)[e,f,g,h,5]<br>▸ Pembrolizumab + carboplatin/paclitaxel ± bevacizumab (category 1)[e,f,g,h,5]<br>• Cisplatin/paclitaxel/bevacizumab[e,h,6] (category 1)<br>• Carboplatin/paclitaxel/bevacizumab[e,h]<br><br>**Other Recommended Regimens**<br>• Cisplatin/paclitaxel (category 1)[7,8]<br>• Carboplatin/paclitaxel[9,10] (category 1 for patients who have received prior cisplatin therapy)<br>• Topotecan/paclitaxel/bevacizumab[e,h,6,11] (category 1)<br>• Topotecan/paclitaxel[11]<br>• Cisplatin/topotecan[11]<br>• Cisplatin[8]<br>• Carboplatin[12,13] | **Preferred Regimens**<br>• Pembrolizumab for TMB-H tumors[f,j] or PD-L1–positive[g] or MSI-H/dMMR tumors[f,14]<br>• Tisotumab vedotin-tftv[15]<br>• Cemiplimab[f,16]<br><br>**Other Recommended Regimens**<br>• Bevacizumab[e]<br>• Paclitaxel[13,17]<br>• Albumin-bound paclitaxel<br>• Docetaxel<br>• Fluorouracil<br>• Gemcitabine<br>• Pemetrexed<br>• Topotecan<br>• Vinorelbine<br>• Irinotecan<br><br>**Useful in Certain Circumstances**<br>• PD-L1–positive tumors<br>▸ Nivolumab[f,g,18]<br>• HER2-positive tumors (IHC 3+ or 2+)<br>▸ Fam-trastuzumab deruxtecan-nxki[19]<br>• RET gene fusion-positive tumors<br>▸ Selpercatinib<br>• *NTRK* gene fusion-positive tumors<br>▸ Larotrectinib<br>▸ Entrectinib |

# Progress in cervical cancer



# Targeted treatments in cervical cancer management

VEGF Inhibitors: Bevacizumab

Immune checkpoint inhibitors: Pembrolizumab, Cemiplimab, Atezolizumab

ADCs: Tisotumab vedotin

# GOG 240

## Patients:

- Metastatic, persistent, or recurrent disease

## Interventions:

- Control + Bevacizumab (15 mg/kg D1);
- Topotecan (0.75 mg/m2 D1-3) + Paclitaxel (175 mg/m2 D1)
- Topotecan+Paclitaxel + Bevacizumab

## Control:

- Cisplatin (50 mg/m2 D1) + Paclitaxel (135 mg/m2 D1)

## Outcomes:

- Primary: Overall Survival

Tewari KS, Sill MW, Long HJ, et al. NEJM 2014; 370:734-43

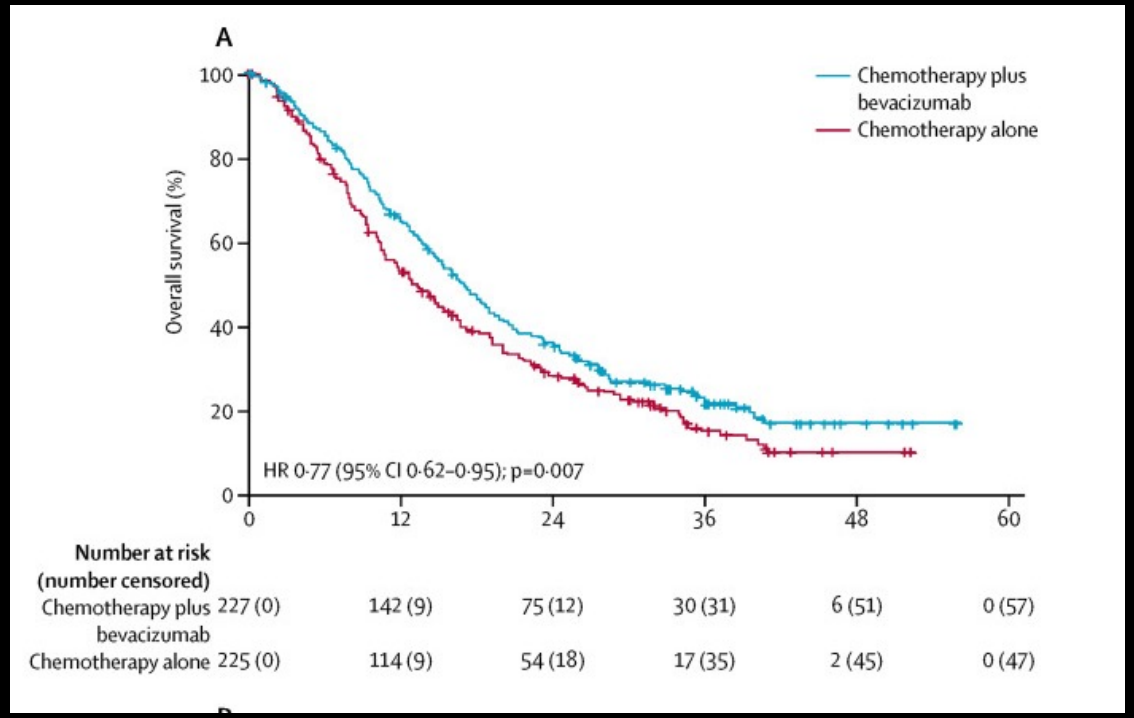
# GOG240: Overall Survival

Median OS:

- CT+B: 16.8m
- CT: 13.3m
- HR 0.77 (95%CI, 0.62-0.95)
- No difference by CT arm

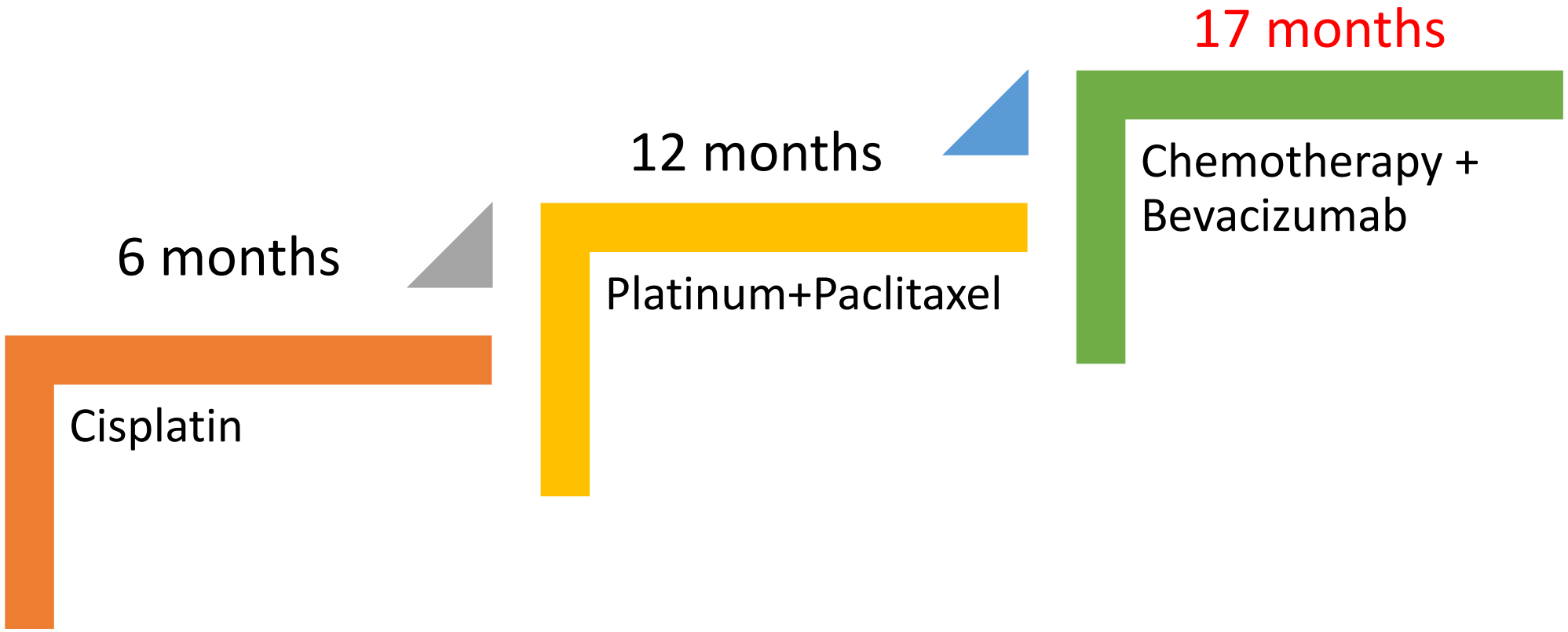
Postprogression OS was <12m

- CT+B: 8.4m
- CT: 7.1m




Tewari KS, et al. Lancet 2017; 390: 1654-1663

# Progress in cervical cancer



# GOG240: A cautionary note

- Analysis done by intention to treat
- *Maintenance* therapy was not tested

*Impact of DC chemotherapy and continuing on single-agent bevacizumab not studied!*

# Checkpoint Inhibitors: Second- or later line

| Trial | Volunteers | Intervention | Comparator | Outcomes |
|---|---|---|---|---|
| Keynote 158 | 98 | Pembrolizumab | NA | In PDL1+ setting:<br>mOS 11m (12mOS 47%)<br>mPFS 2.1m (6mPFS 25%) |
| GOG 3016<br>ENGOT En-Cx9 | 608 | Cemiplimab | Single-agent chemotherapy | **HR OS** 0.69, 95%CI 0.56-0.84 [median, 12 v 8.5m)<br>**HR PFS** 0.75, 95%CI 0.63-0.89 [median, 2.8 v 2.9m] |

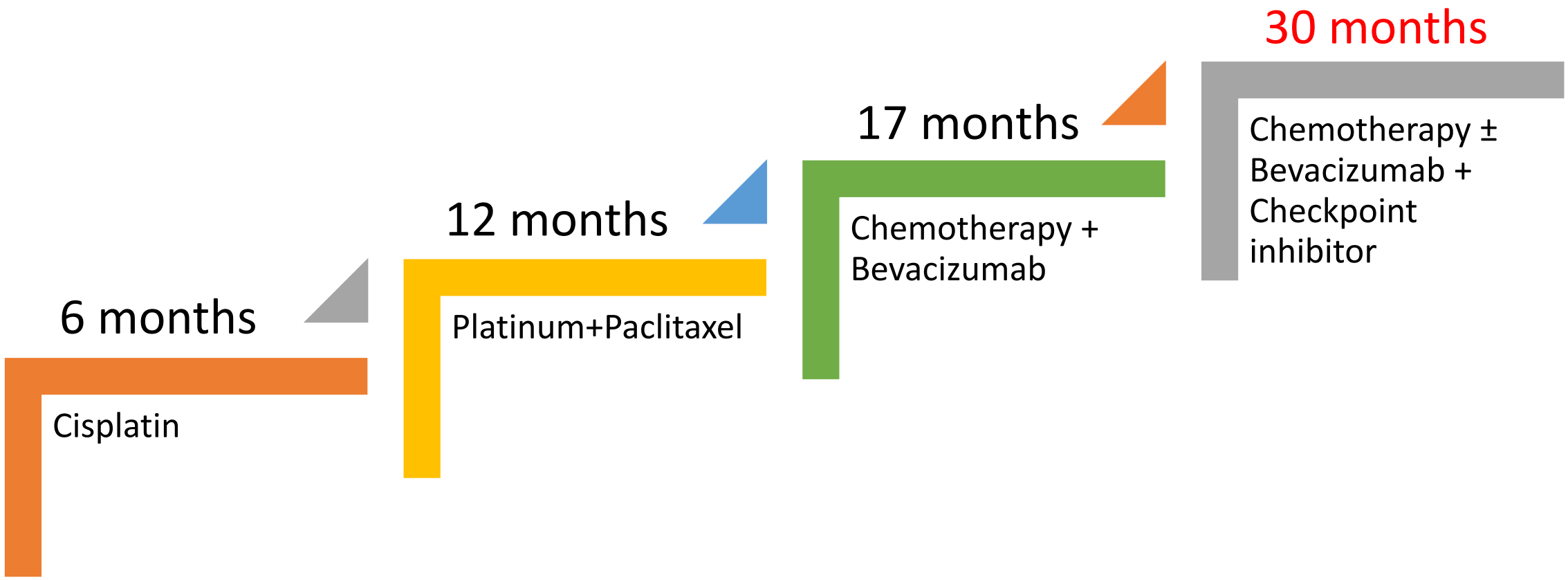
Chung HC, et al. J Clin Oncol 2019; 37:1470-78; Tewari K, et al. N Engl J Med 2022; 386:544-555

# Checkpoint inhibitors: 1st line

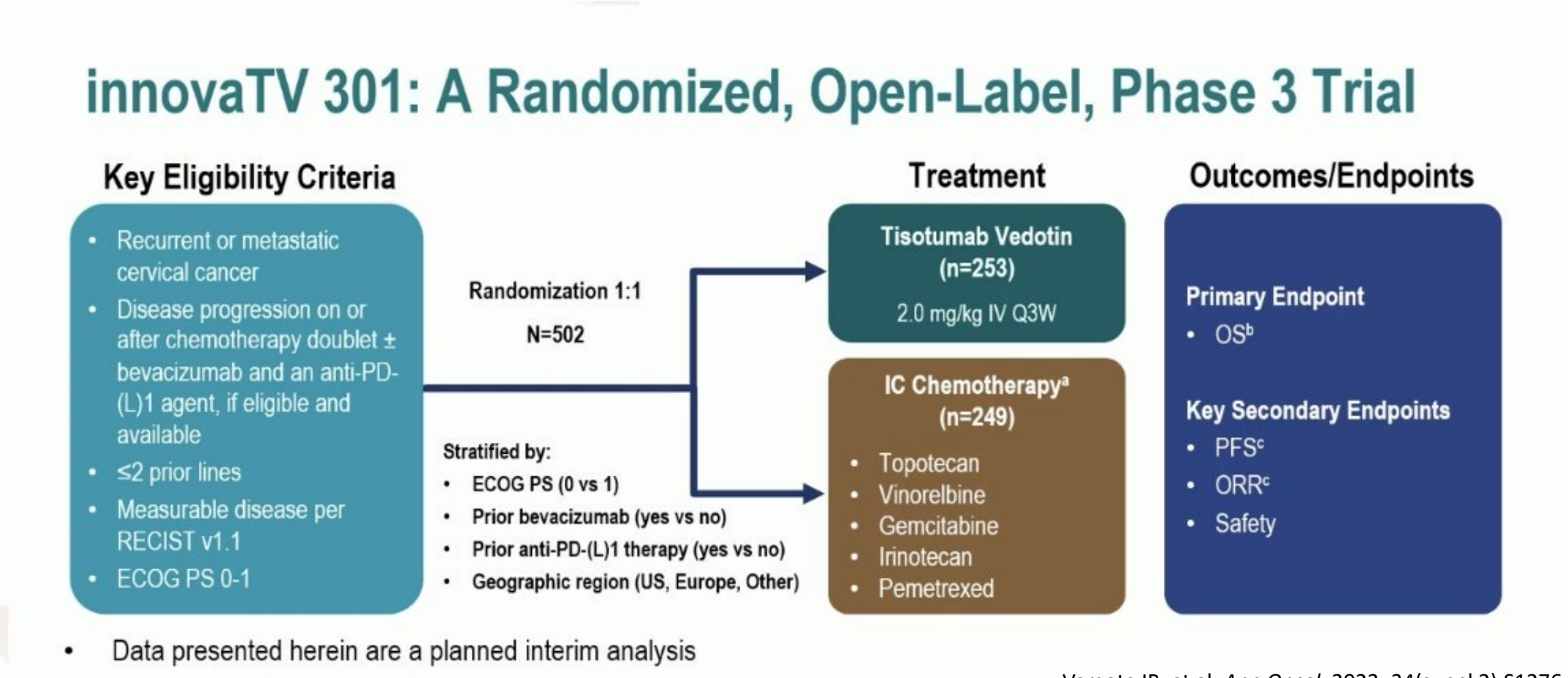
| Trial | Volunteers (n) | Intervention | Comparator | Outcomes |
|---|---|---|---|---|
| Keynote 826 | 617<br><br>CPS≥1 required | Carboplatin+ Paclitaxel ± Bevacizumab + **Pembrolizumab** → Pembrolizumab maintenance<br><br>*2/3rd received bevacizumab | Carboplatin+ Paclitaxel ± Bevacizumab → Placebo maintenance | **HR OS** 0.60, 95% CI 0.49-0.74) [median, 28.6 v 16.5m)<br>**HR PFS** 0.65 (95%CI 0.53-0.79) [median, 10.4 v 8.2m) |
| BEATcc | 519 | Carboplatin or cisplatin + Paclitaxel + Bevacizumab + Atezolizumab<br><br>*DC chemo allowed per investigator | Carboplatin or cisplatin + Paclitaxel + Bevacizumab | **HR OS** 0.68, 95%CI 0.52-0.88) [median, 32.1 v 22.8m]<br>**HR PFS** 0.62 (95%CI 0.49-0.78) [median, 13.7 v 10.4m] |

Colombo N, et al. N Engl J Med 2021; 385:1856-67; Monk B, et al. J Clin Oncol 2023; 41: 5505-5511; Oaknin A, et al. Lancet 2024; 403:31-43

# Progress in cervical cancer: OS gains



# Tisotumab vedotin for metastatic cervical cancer



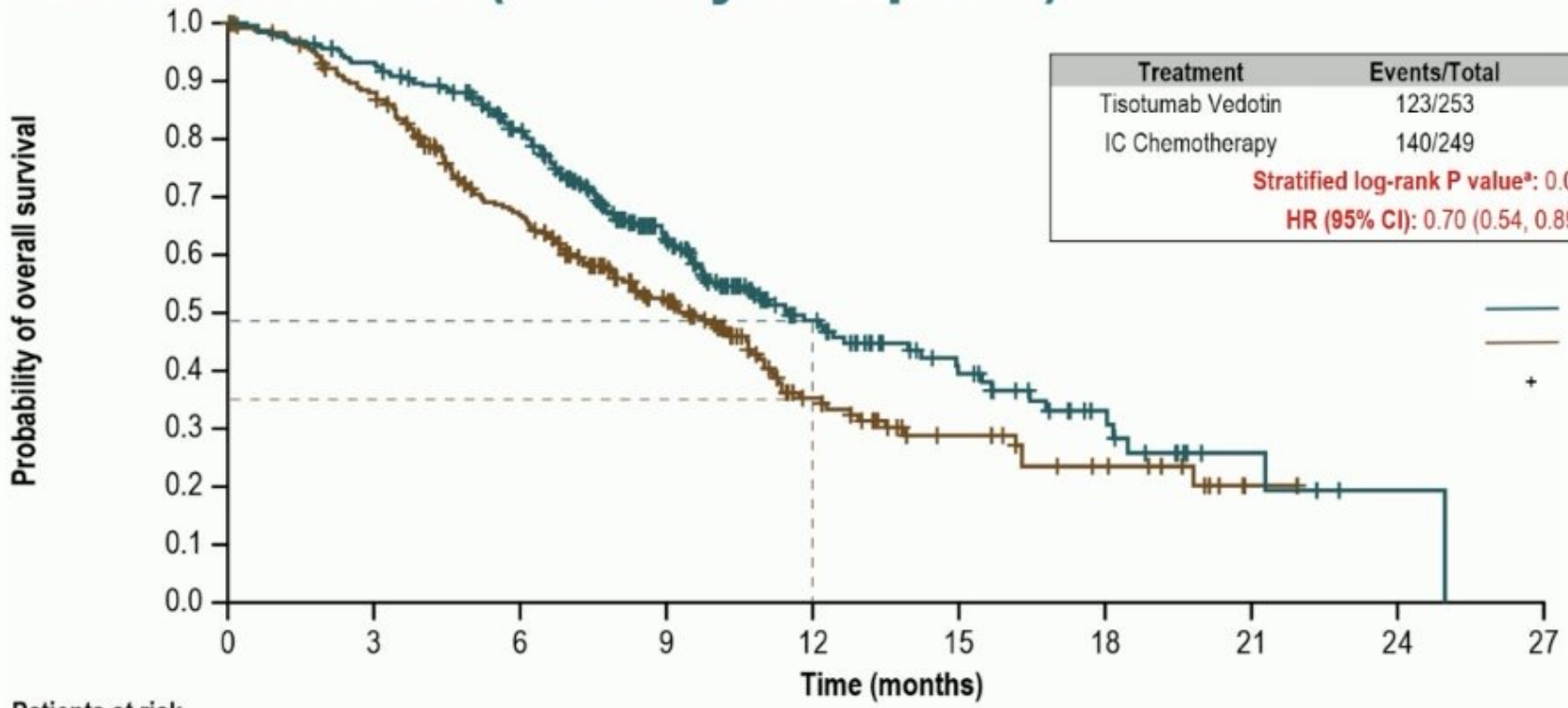

Vergote IB, et al. *Ann Oncol*. 2023; 34(suppl 2):S1276-S1277.

# InnovaTV 301

- N= 502 patients
- Median FU: 10.8m
- Prior treatment:
  - Prior Bevacizumab 64%
  - Prior Checkpoint inhibitors 27.5%
- ORR was higher with TV (17.8 vs 5.2% with chemotherapy)
- Unique toxicities with TV: ocular toxicities

Vergote IB, et al. *Ann Oncol*. 2023; 34(suppl 2):S1276-S1277.

# Overall Survival (Primary Endpoint)




| Treatment | Events/Total | Median (95% CI) |
|---|---|---|
| Tisotumab Vedotin | 123/253 | 11.5 (9.8, 14.9) |
| IC Chemotherapy | 140/249 | 9.5 (7.9, 10.7) |

**Stratified log-rank P value[a]:** 0.0038

**HR (95% CI):** 0.70 (0.54, 0.89)

**Patients at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Tisotumab vedotin | 253 | 234 | 191 | 109 | 52 | 29 | 14 | 4 | 1 | 0 |
| IC Chemotherapy | 249 | 212 | 150 | 87 | 37 | 19 | 11 | 1 | 0 | 0 |

[a]The threshold for statistical significance is 0.0226 (2-sided), based on the actual number of OS events at interim analysis.

MADRID 2023 ESMO congress

Vergote IB, et al. *Ann Oncol*. 2023; 34(suppl 2):S1276-S1277.

# Conclusions

Progress in cervical cancer is a good thing

Not easy to make a universal conclusion

Shared decision making is important in treatment

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