

Combine *and* Conquer

Minimizing the Impact of Toxicity Associated with Novel Immunotherapy-Angiogenesis Inhibitor Combinations



Endometrial Carcinoma Tweetorial

References

1/[#OncTwitter](#) [#TumorBoardTuesday](#) [#MedTweetorial](#)



CME Info

bit.ly/3VBGJEJ

[#EndometrialCancer](#) AE deep dive

Trial results

Tox for TKI-ICI

w [@DrMMurphy](#) [@MeganLeigh127](#) & us!

[#CME](#) [@BonumCE](#) bit.ly/3VBGJEJ

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[#gynscsm](#) [#gynonc](#) [#EndometrialCancer](#)

[#MedTweetorial](#)

CME > full info ref list & program archive

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[#CME](#) info

COMBINE *and* CONQUER

Minimizing the Impact of Toxicity Associated with Novel Immunotherapy-Angiogenesis Inhibitor Combinations

FACULTY INFO & DISCLOSURES

TWEETORIAL: Endometrial Carcinoma



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Disclosures

Nothing to disclose.



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Nothing to disclose.


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[#GynOnc](#) [#gyncsm](#) [#EndometrialCancer](#)

● Which I/O + tx combo is FDA approved for treatment of advanced or metastatic [#EndometrialCarcinoma](#)?

nivo = nivolumab
dostarlimab = dostarlimab-gxly
pembro = pembrolizumab




- nivo + bevacizumab
- nivo + larotrectinib
- dostarlimab + olaparib
- pembro + lenvatinib

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Ref #

1-4

If you picked pembro + lenva...
You're right! 🎉

Pembro (PD-1 mAb) + lenva (multi-TKI)
➡  accelerated approval adv EC in 2019

Ph3 confirmatory trial  ➡ [#KEYNOTE-775](#)
➡ full FDA approval 2021

5/[#TumorBoardTuesday](#) [#OncTwitter](#) [#GynCSM](#)
[#gynonc](#)


Ref #

5-9

[#EndometrialCancer](#) most common gyn cancer in 

Rates 

Est in 2022...

 New cases: 69,950

 Deaths: 12,550

Most pts dx early stage - gd prognosis 

Approx 9% dx met disease ➡ 5y survival <20% ➡ plat
chemo SOC 1st line tx

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Ref #
5, 9, 10

After progression on chemotx, tx for metastatic #EndometrialCancer is influenced by tumor molecular subtype

Cancer Genome Atlas ID'd **4** mol subclasses...

- 1** POLE ultramutated
- 2** dMMR/MSI-H
- 3** Copy # low
- 4** Copy # high

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#gynccsm #gynonc

Ref #
10-14

Faulty DNA repair (dMMR/MSI-H) high tumor mutation burden

- more tumor neoantigens
- sensitivity to ICI

Two FDA approved ICIs in dMMR/MSI-H

#EndometrialCancer:

- Pembro (PD-1 mAb)
- Dostarlimab (PD-1 mAb)

EC Molecular Subclasses

Openshaw MR, et al. Front Digit Health 2020;2:573010.

Not Highly Responsive	Highly Responsive
<p>MSS, CN Low</p> <p>TP43 variants common CCNE1 amplification common Higher relapse rate Poor overall survival</p>	<p>MSI-High</p> <p>Hypermutated Highly responsive to immunotherapy</p>
<p>CN High</p>	<p>POLE-Mutated</p> <p>POLE exonuclease domain variation Ultramutated Highly responsive to immunotherapy Excellent prognosis</p>
	<p> Not used for clinical decision-making</p>

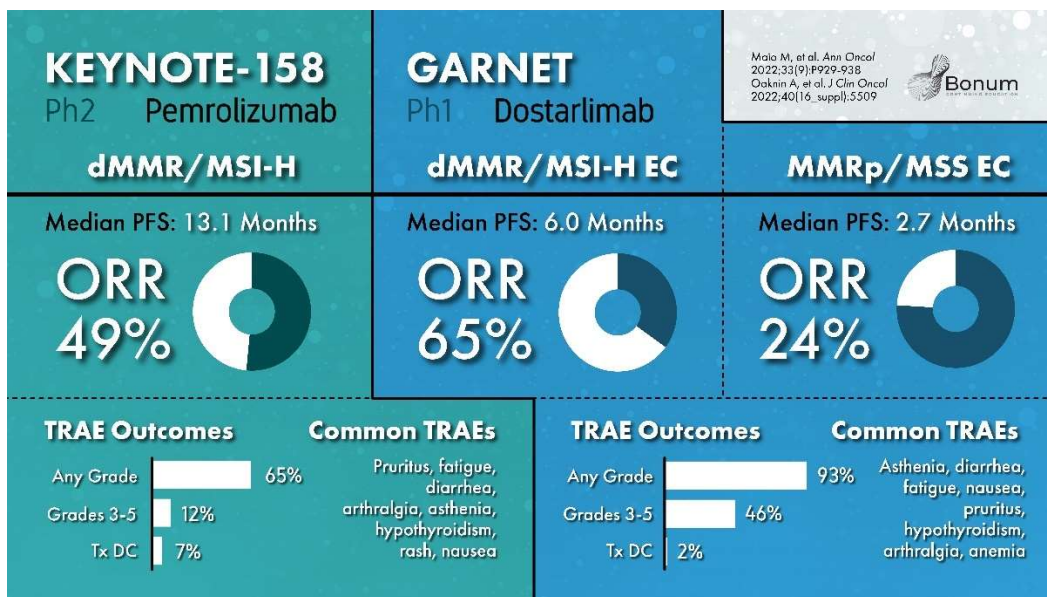
8/#TumorBoardTuesday #BonumCE #OncTwitter
#GynCSM #gynonc #EndometrialCancer

Ref #
15-16

Pivotal trials leading to FDA approval in 2L met MSI-H/dMMR #EndometrialCarcinoma

- ◆ Pembro: #KEYNOTE158 (phase 2)
- ◆ Dostarlimab: #GARNET (phase 1)

🔑 Efficacy & safety data 📷 📌



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Ref #
17-20

⚙️ Lenva=multi 🎯 TKI (incl VEGFR)
 🛑 Blocks angiogenic signaling
 VEGFR signals also have immunosuppressive role

⚙️ Pembro=ICI
 🛡️ Boosts anti-tumor immune response

🔑 Combo tx=synergistic anti-tumor activity

10/[#TumorBoardTuesday](#) [#GynCSM](#)

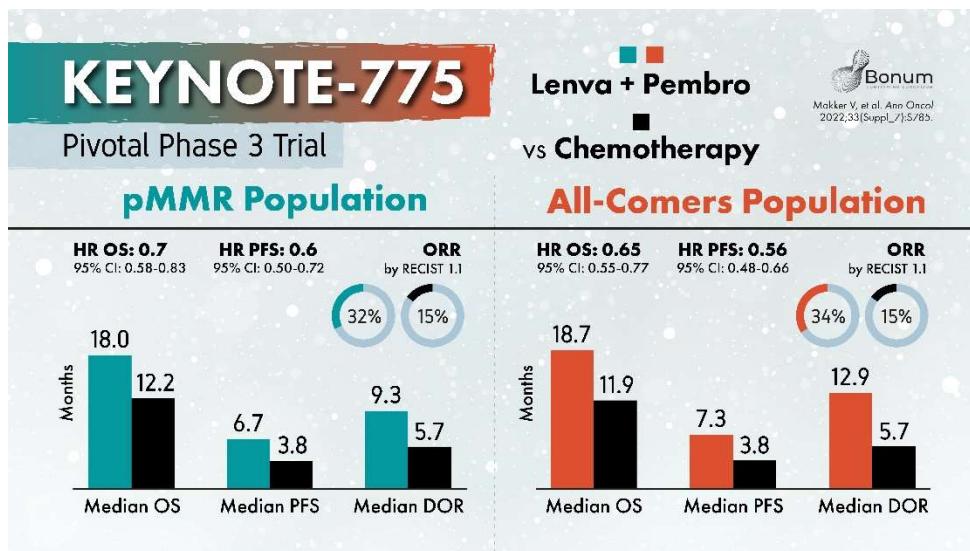
Ref #

1-5

Tx for adv MSS or pMMR [#EndometrialCancer](#) tumors was 🔑 unmet need until lenva-pembro approval

Pivotal P3 [#KEYNOTE775](#) trial confirmed ✅ OS, PFS, & ORR benefit vs chemo for adv/met EC

★ Benefit independent of dMMR/MSI status
 NEW Update @ [#ESMO2022](#)



11/[#TumorBoardTuesday](#) [#BonumCE](#) [#OncTwitter](#) [#GynCSM](#) [#gynonc](#)

● What is the most common grade 3 or higher toxicity associated w/ the combination of pembro & lenva in pts w/ [#EndometrialCancer](#)?

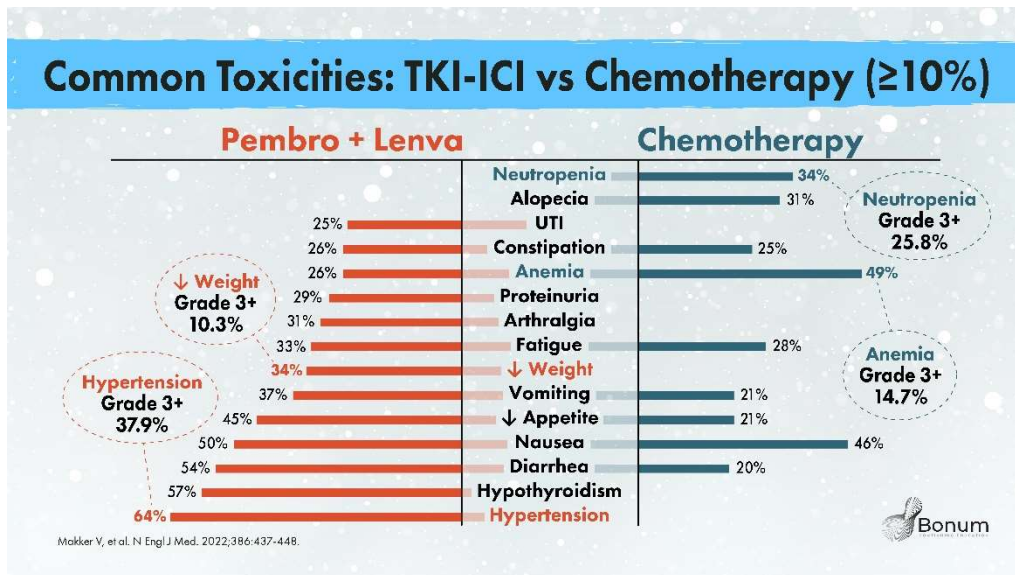
- Alopecia
- Fatigue
- Hypertension
- Proteinuria

12/[#TumorBoardTuesday](#) [#GynCSM](#) [#gynonc](#) [#EndometrialCancer](#)

Ref #

13,4,21

- 🖍 Lenva-pembro tox distinct from chemotx
- 🖍 Safety profile of combo tx consistent w those of individual agents
- 🖍 Most common any grade & grade 3+TRAE = HTN
- 🖍 Shortest ⌚ to onset: HTN
- 🖍 Later: hypothyroidism & weight loss ⬇️



13/#OncTwitter #TumorBoardTuesday

Ref #

17, 21, 30

🔑 s to tackling lenva-pembro tox:

- 📝 Comprehensive mgmt plan
- 👤 Pt/caregiver education
- ⚠️ Regular monitoring during tx (BP, thyroid & liver function, urine protein)
- 👩‍⚕️ MDTeam care
- ⚡ Watch out for comorbidities
- 💊 Supportive care
- 🔧 TKI dose mods

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Ref #

22-24

- 🚨 VEGFR TKI-related class tox e.g. HTN, proteinuria
- 📅 Typ occur 1st few wks tx
- 💊 Dose-dependent
- 👩‍⚕️ Managed w dose mods & supportive care (e.g. anti-hypertensive)

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🟢 During tx w/ pembro-lenva, a pt develops grade 3 HTN requiring reduction in lenva. Starting dose of lenva was 20mg.

Which dose is recommended for lenva now?

- 18 mg
- 14 mg
- 10 mg
- 8 mg

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#gynscm #gynonc #EndometrialCancer

Ref #

17

👉 Lenva dose mods = dose reduce ⬇️ or withhold 🛑
for more severe tox

Recommended lenva starting ▶️ dose adv EC: 20mg
QD

1 1st dose ⬇️ 14mg

2 2nd dose ⬇️ 10mg

3 3rd dose ⬇️ 8mg

17/#TumorBoardTuesday #BonumCE #OncTwitter
#GynCSM #gynonc #EndometrialCancer

Ref #

3, 32, 33

45.6% pts ≥ 2 ⬇️ lenva dose #KEYNOTE775

◆ Often need new 30d dose pack b4 finishing current
supply

bit.ly/3gYHvOd

NEW Eisai dose exchange program - cover all indicated
dose ⬇️ bit.ly/3gYHvOd

18/#TumorBoardTuesday #EndometrialCancer

Ref #

17, 31

😞 Pre-empt tox w reduced lenva starting ▶️ dose?

Retro analysis 70 pts: 20mg vs lower dose (mostly
14mg)

📈 # dose reductions & 📉 time to tox @ 20mg
ORR, PFS, & OS did NOT differ significantly w lower
dose

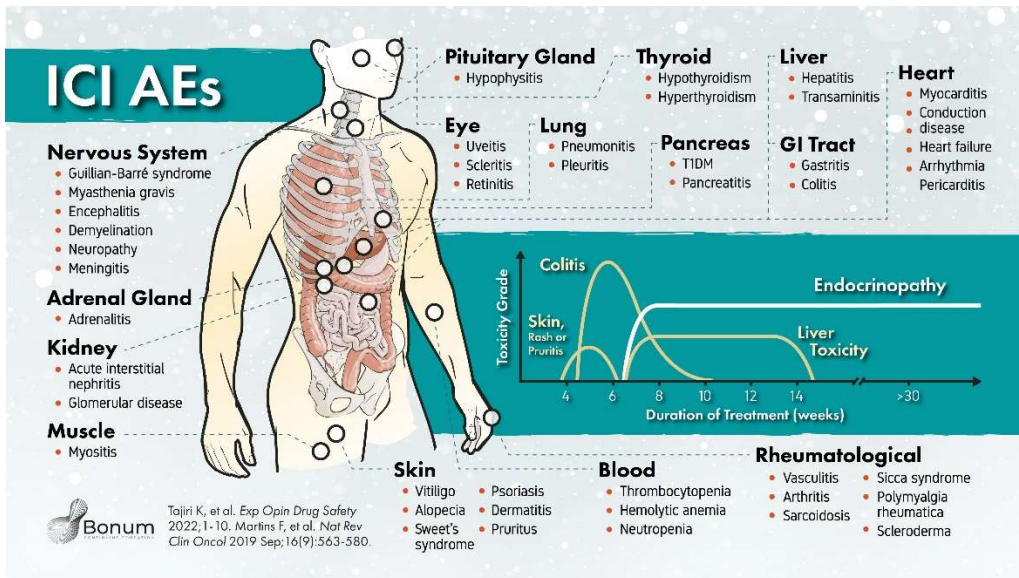
✳️ Need prospective data ✳️

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#EndometrialCancer

Ref #
25-27

🚩 Pembro-related immune tox 🚩

- ◆ Can affect any organ @ any time during/after tx
- ◆ Can become severe/fatal if not promptly dx & tx
- ◆ Typically reversible (excl. endocrine)
- ◆ Managed w immunosuppressive tx - mainly corticosteroids



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#GynCSM #gynonc #EndometrialCancer

● During treatment w pembro & lenva, pt develops frequent, loose, watery stools

How could you quickly determine which drug is causing the diarrhea?

- Administer corticosteroids
- Dose reduce pembro
- Withhold pembro
- Withhold lenva

21/#TumorBoardTuesday #GynCSM

Ref #
22, 28-29

Overlapping tox: some AEs attributable to either drug


✅ Need to ID etiology to choose correct mgmt strategy


🕒 TKI ½-life allows rapid drug washout ➡ w/hold lenva + see if tox resolves

Common overlapping tox: diarrhea, fatigue, rash, hypothyroidism

22/#TumorBoardTuesday

Points

- ◆ Lenva-pembro=impt tx option 4 adv/met EC w MSS or pMMR
- ◆  OS, PFS, & ORR vs chemotx
- ◆ Distinct tox profile vs chemotx
- ◆ Most common tox=lenva-associated HTN
- ◆ Potential 4 o'lapping tox complicates mgmt
- ◆ Mgmt: lenva dose mod & steroids 4 irAEs

Claim your CME credit by completing the post-survey and evaluation. Link provided 



bit.ly/3jCyVFJ

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