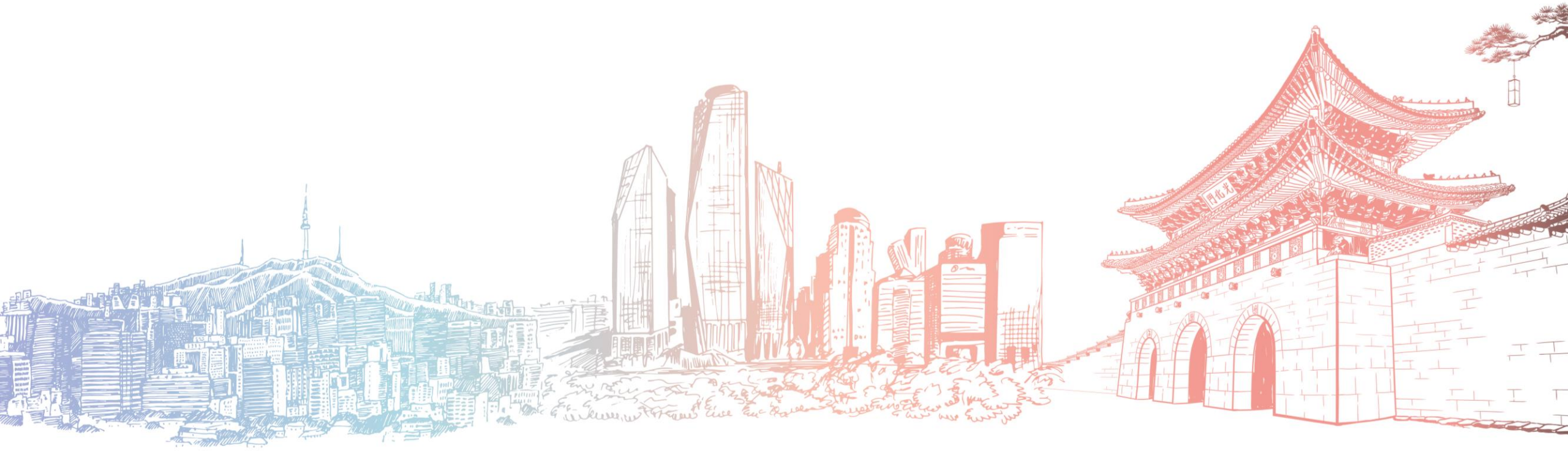
Emergence of ICI: monotherapy and TKI combination for treatment of advanced/recurrent EC

Dr. Jung-Yun Lee



Disclosures

- Advisory board positions: AstraZeneca (DP-02), GII (GI-101), OncoQuest (FLORA-5), Seagen (SGNTV-03), ImmunoGen (MIRASOL), Genmab (GEN1046-05), and MSD (MK4830-002)
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Chemotherapy/Targeted Therapy Does Not Work in Recurrent EC Patients Who Failed Prior Chemotherapy

Phase 2/3 studies involving 1887 patients

Type of Study and Number of EC Patients	Treatment	ORR	Durability of Response
Phase 2 N=42[1]	PLD	9.5%	Median # courses, 2.5; OS: 8.2 months
Phase 2 N=22[2]	Topotecan	9.0%	Median # courses, 4
Phase 2 N=44[3]	Paclitaxel	27.3%	DOR: 4.2 months; OS:10.3 months
Phase 2 N=52[4]	Oxaliplatin	13.5%	DOR: 10.9+ months
Phase 2 N=26[5]	Docetaxel	7.7%	PFS: 2.0 months; OS: 6.4 months
Phase 2 N=50[6]	Ixabepilone	12%	PFS: 2.9 months; OS: 8.7+ months
Group I N=586 for patients who received 2L in Phase 3 GOG trials Group II N=275 patients 2L chemo trials Phase 2[7]	Various		OS: <11months
Phase 2 (N=23)[8]	Gemcitabine	4.0%	PFS: 1.7 months
Phase 2 (N=28)[9]	Everolimus	0%	Median duration of SD: 4.5 months
Phase 2 (N=25 for patients previously treated with chemotherapy)[10]	Temsirolimus	4.0%	PFS: 3.25 months
Phase 2 (N=52)[11]	Bevacizumab	13.5%	PFS: 4.17 months; OS: 10.55 months
Phase 2 (N=45)[12]	Ridaforolimus	11%	6-month PFS: 18%
Phase 2 (N=35)[13]	Everolimus and letrozole	31.4%	PFS: 3.0 months; OS: 14 months
Phase 3 RCT (N=496)[14]	Ixabepilone vs paclitaxel or doxorubicin	15.2% vs 15.7%	Ixabepilone: PFS:3.4 months; OS:10.9 months Paclitaxel or Doxorubicin: PFS:4.0 months; OS, 12.3 months
Phase 2 trial (N=82)[15]	Anastrozole	7%	PFS 3.2 months

There are no completed direct head-to-head-trials of these products. There are inherent limitations in cross-study comparisons; caution should be exercised in comparing trials. This slide is for information purposes only and is not intended to imply or infer the noninferiority or superiority of any product, in terms of efficacy or safety.

2L, second-line; DOR, duration of response; EC, endometrial cancer, GOG, Gynecologic Oncology Group; ORR, objective response rate; OS, overall survival, PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; RCT, randomized controlled trial; SD. stable disease.

1. Muggia FM et al. *J Clin Oncol* 2002;20:2360-2364. 2. Miller DS et al. *Gynecol Oncol* 2002;87:247-251. 3. Lincoln S et al. *Gynecol Oncol* 2003;88:277-281. 4. Fracasso PM et al. *Gynecol Oncol* 2006;103:523-526. 5. Garcia AA et al. *Gynecol Oncol* 2008;111:22-26. 6. Dizon DS et al. *J Clin Oncol* 2009;27:3104-3108. 7. Moore KN et al. *Cancer* 2010;116:5407-5414. 8. Tait DL et al. *Gynecol Oncol* 2011;121:118-121. 9. Slomovitz BM et al. *Cancer* 2010;116:5415-5419. 10. Oza AM et al. *J Clin Oncol* 2011;29:3278-3285. 11. Aghajanian C et al. *J Clin Oncol* 2011;29:2259-2265. 12. Colombo N et al. *Br J Cancer* 2013;108:1021-1026. 13. Slomovitz BM et al. *J Clin Oncol* 2015;33:930-936. 14. McMeekin S et al. *Gynecol Oncol* 2015;138:18-23. 15. Mileshkin L et al. *Gynecol Oncol* 2019;154:29-37.

Recurrent EC case study #1

History and initial presentation

- 61-year-old woman after optimum surgery for Stage 1A Grade 2 endometrioid EC
- **Recurrence:** March 2016 with dMMR recurrent Grade 3 EC
- **Failed chemotherapy**
  - **1L:** 6 cycles C/P
  - **2L:** pegylated liposomal doxorubicin
- Continued extensive progression
- Bilateral ureteric blockage: double J stent required
- **Palliative radiation tried but failed**
- Severe pain with progression

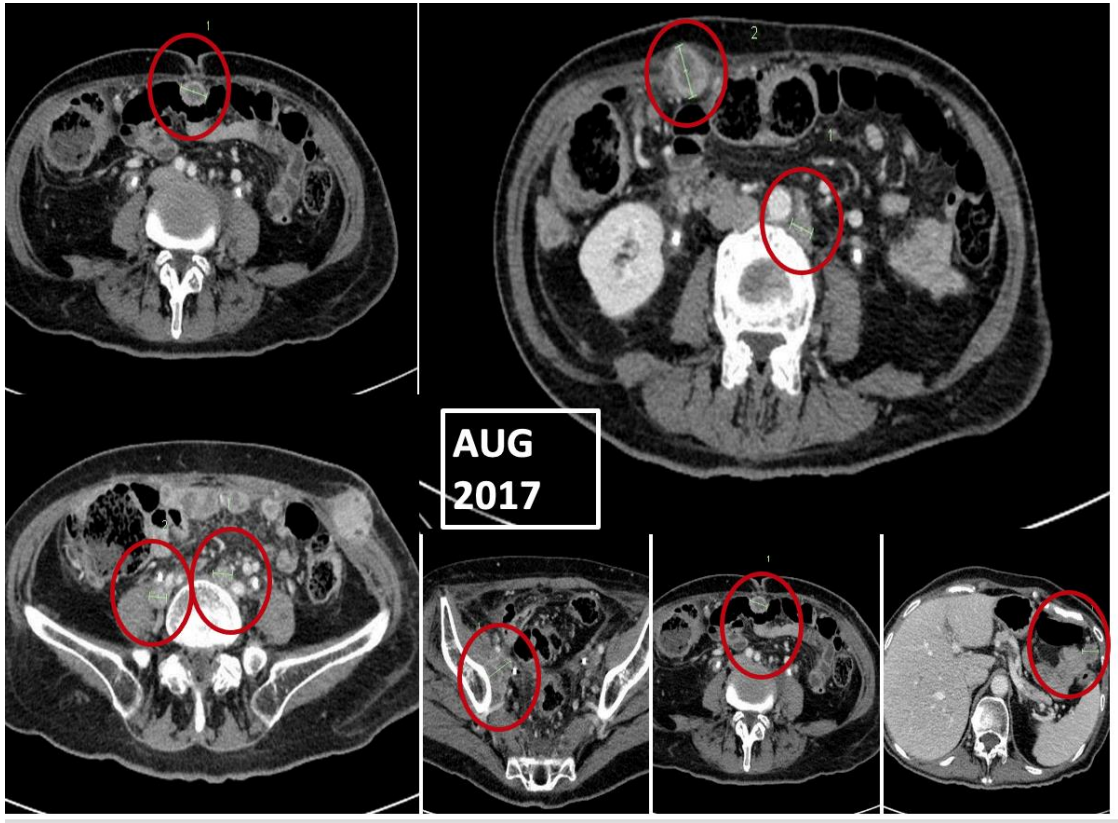
Courtesy of Dr. Lucy Gilbert, McGill University, Montreal, QC, Canada.

1L = first-line; 2L = second-line; C/P = carboplatin/paclitaxel; dMMR = mismatch repair deficient; EC = endometrial cancer; PLD = pegylated liposomal doxorubicin.

Recurrent EC case study #1

Treatment

- Patient enrolled in an anti-PD-1 clinical trial after repeated treatment failure with chemotherapy
- Initially received 500 mg IV for C1 – C4 Q3W
  - Then 1000 mg IV Q6W from C5



Courtesy of Dr. Lucy Gilbert, McGill University, Montreal, QC, Canada.

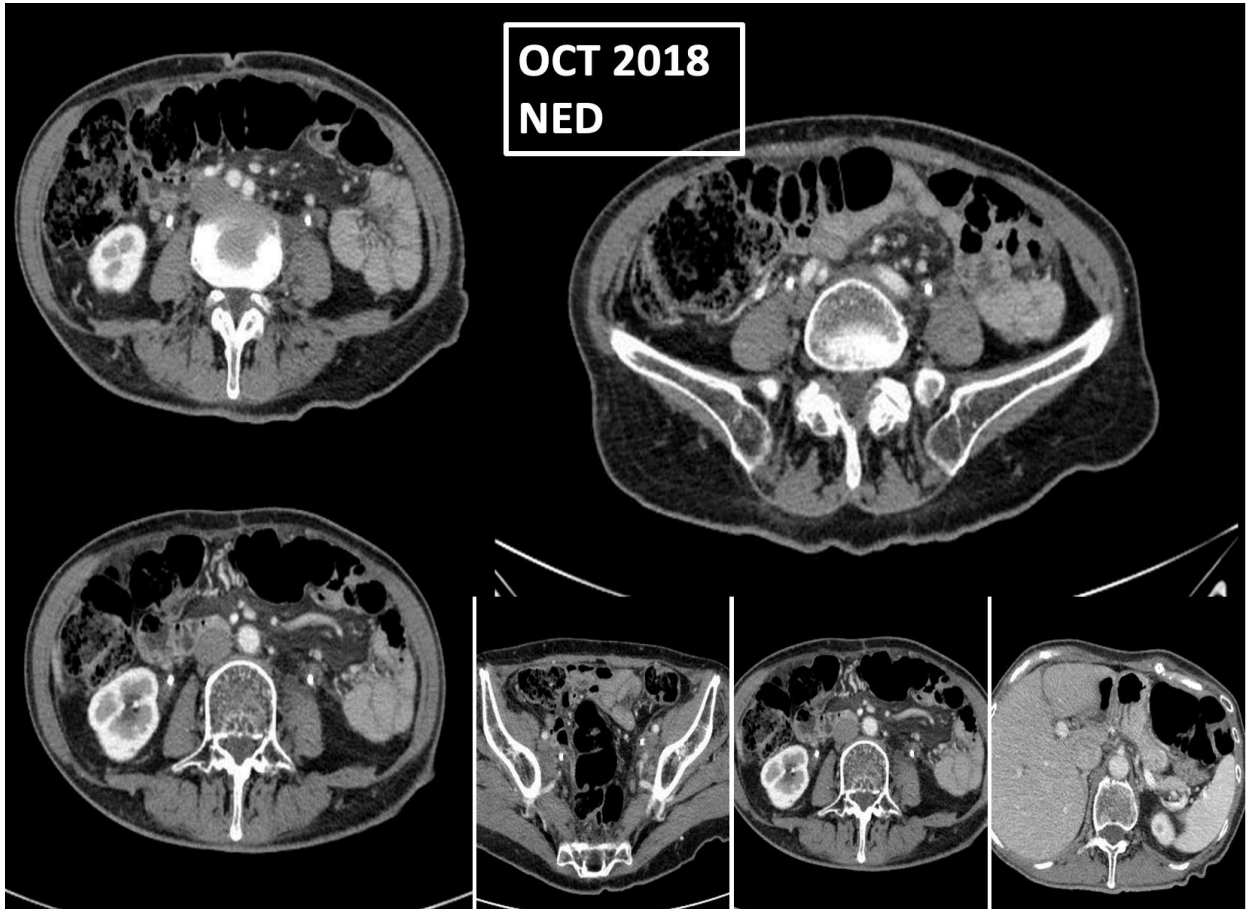
Aug = August; C# = cycle #; EC = endometrial cancer; IV = intravenous; PD-1 = programmed death protein-1; QXW = every X weeks.

Recurrent EC case study #1

Treatment response

- Patient showed CR within 1 year of anti-PD-1 therapy
- Patient remains in CR after treatment
- AEs were manageable

> 5 years later:
Remains disease free!



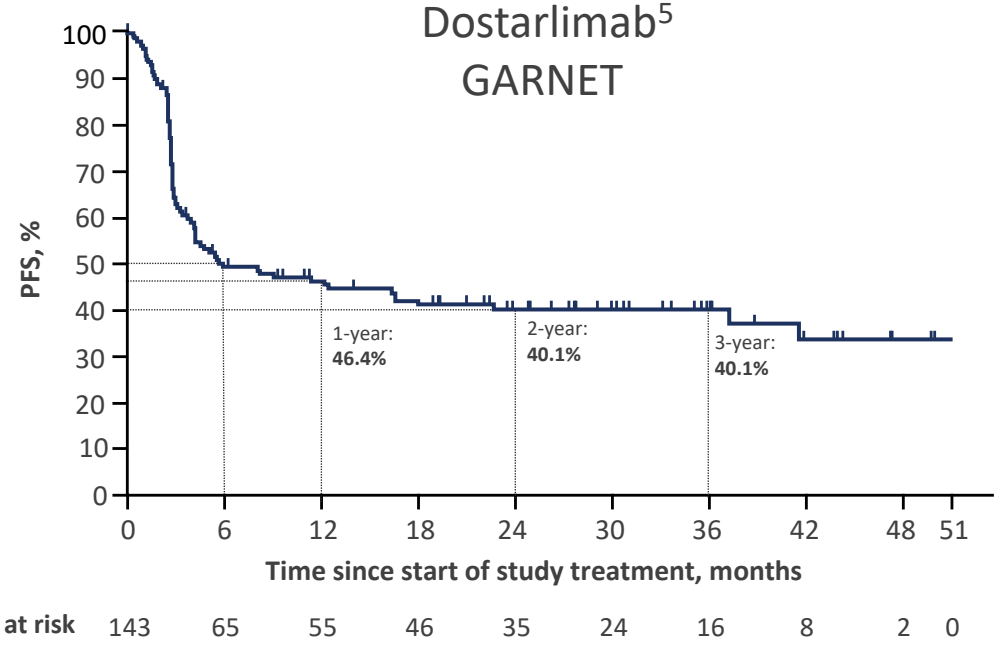
Courtesy of Dr. Lucy Gilbert, McGill University, Montreal, QC, Canada.

AE = adverse event; CR = complete response; EC = endometrial cancer; NED = no evidence of disease; Oct = October; PD-1 = programmed cell death protein 1.

Rationale for ICI monotherapy: PFS in dMMR/MSI-H EC

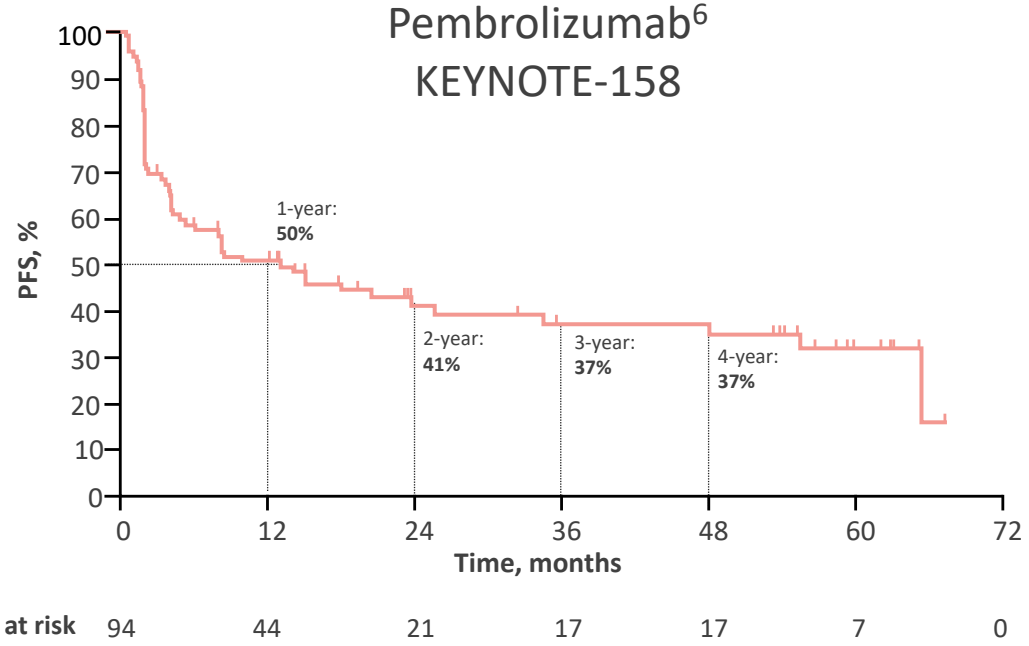
Dostarlimab and pembrolizumab are approved as monotherapy for dMMR (dostarlimab, US),[1] dMMR/MSI-H (pembrolizumab, US),[2] and dMMR/MSI-H (dostarlimab, pembrolizumab, EU)[3,4] advanced/recurrent EC with progression following platinum-based therapy

Dostarlimab[5]
GARNET



The most common TRAEs (>10% of dMMR/MSI-H patients) were diarrhea (16.3%) , asthenia (15.7%), fatigue (13.7%), and nausea (12.4%)

Pembrolizumab[6]
KEYNOTE-158



The most common TRAEs (>10% of patients) were pruritus (26%), fatigue (20%), diarrhea (17%), arthragia (16%), hypothyroidism (14%), nausea (14%), and rash (12%)

There are no completed direct head-to-head trials of these products in EC. There are inherent limitations in cross-study comparisons; caution should be exercised in comparing trials. This slide is for information purposes only and is not intended to imply or infer the noninferiority or superiority of any product, in terms of efficacy or safety.

CI, confidence interval; dMMR, mismatch repair deficient; EC, endometrial cancer; IO, immuno-oncology; mPFS, median progression-free survival; MSI-H, microsatellite instability-high; PFS, progression-free survival; TRAE, treatment-related adverse event.

1. Jemperli (dostarlimab-gxly) [prescribing information]. GlaxoSmithKline LLC, Research Triangle Park, NC, USA; 2023. 2. Keytruda (pembrolizumab) [prescribing information]. Merck & Co., Inc., Whitehouse Station, NJ, USA; 2023. 3. Jemperli (dostarlimab) [summary of product characteristics]. GlaxoSmithKline (Ireland) Ltd., Dublin, Ireland.; 2023. 4. Keytruda (pembrolizumab) [summary of product characteristics]. Merck Sharp & Dohme B.V., Haarlam, The Netherlands; 2023. 5. Oaknin A et al. *Clin Cancer Res*. 2023;doi:10.1158/1078-0432.CCR-22-3915. 6. O'Malley DM et al. *Ann Oncol* 2022;33(suppl_7):S796-S797.

Clinical trials in advanced/recurrent MMRp/MSS EC

	Single arm	RCT	
	GARNET[1] Dostarlimab MMRp/MSS	KEYNOTE-775[2] Pembrolizumab + Lenvatinib MMRp	KEYNOTE-775[2] Doxorubicin or paclitaxel[2] MMRp
Efficacy population, N	156	346	351
Median FU (range), months	33.0	18.7[a]	12.2[a]
ORR, % (n)	**15.4 (24) 95% CI, 10.1-22.0**	**32.4 (112) 95% CI, 27.5-37.6**	**15.1 (53) 95% CI, 11.5-19.3**
Median DOR, months	19.4 (8.2-NR)	9.3	5.7
KM probability of remaining in response, %	12 months – 60.3 24 months – 44.2		
Median survival, months	PFS 2.7 OS 16.9	PFS 6.7 OS 18.0	PFS 3.8 OS 12.2
Safety population, N	161	406[b]	388[b]
Grade ≥3 TRAE, %	**20.5**	**78.8**	**60.1**
Any TRAE leading to discontinuation, %	8.7	12.1[c]	NA[c]
TRAE leading to death, %	**0**	**1.5**	**2.3**

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2L = second-line; CI = confidence interval; DOR = duration of response; EC = endometrial cancer; FU = follow up; KM = Kaplan-Meier; MMRp = mismatch repair proficient; MSS = microsatellite stable; NR = not reached; ORR = objective response rate; PFS = progression-free survival; RCT = randomized clinical trial; TRAE = treatment-related adverse event.

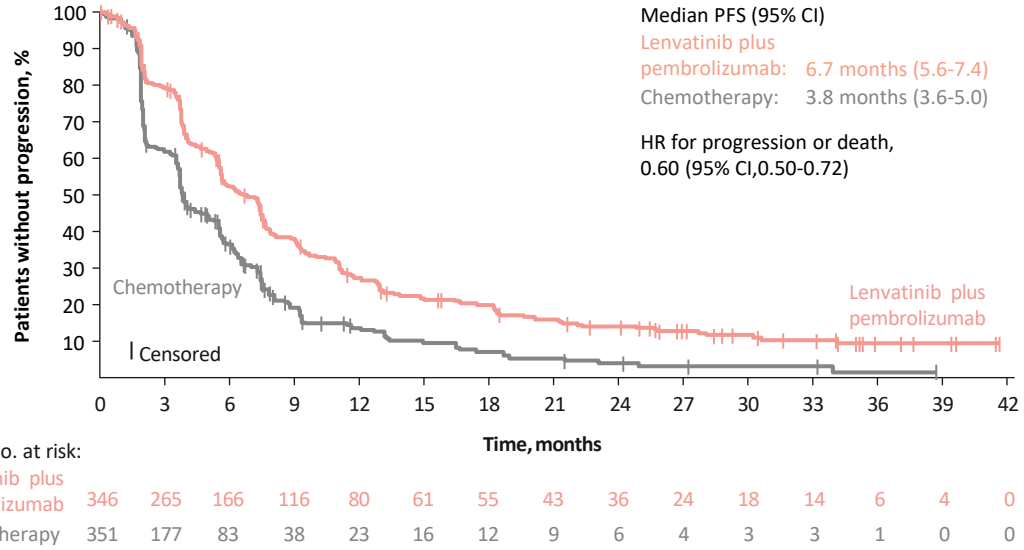
[a]Number of patients in the safety analysis population (all patients who were randomized and received ≥1 dose of pembrolizumab or chemotherapy). [b]Discontinuation of pembrolizumab.

1. Oaknin A et al. *Clin Cancer Res*. 2023;doi:10.1158/1078-0432.CCR-22-3915. 2. Makker V et al. *J Clin Oncol* 2023;41:2904-2910.

Rationale for other combinations: pembrolizumab + lenvatinib combination regimen in advanced/recurrent EC[1]

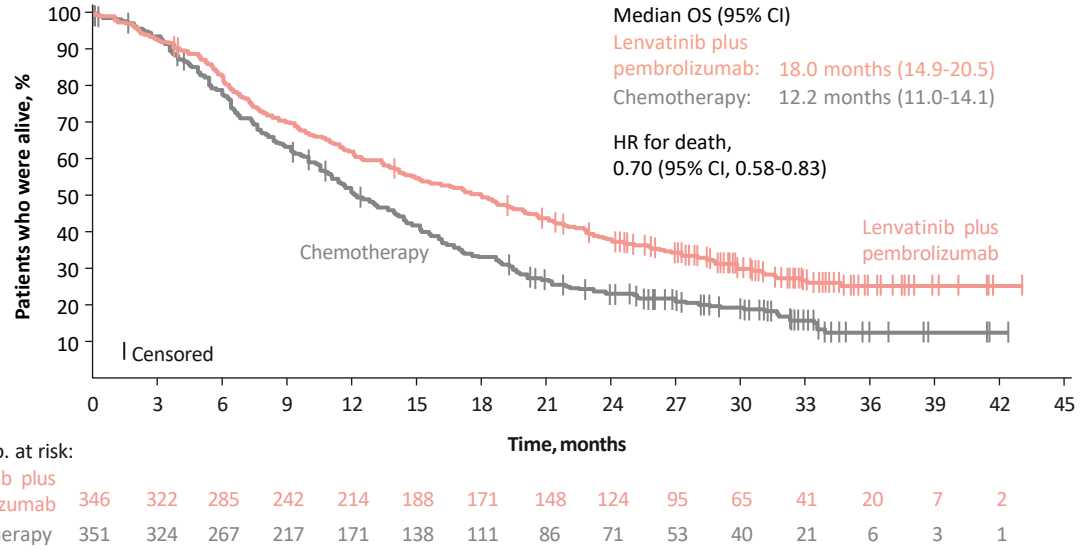
Pembrolizumab + lenvatinib is approved for advanced/recurrent EC (EU)[2] with progression following platinum-based therapy and for advanced MMRp EC (US)[3] with progression

KEYNOTE-775[1]



No. at risk:

Lenvatinib plus pembrolizumab	346	265	166	116	80	61	55	43	36	24	18	14	6	4	0
Chemotherapy	351	177	83	38	23	16	12	9	6	4	3	3	1	0	0



No. at risk:

Lenvatinib plus pembrolizumab	346	322	285	242	214	188	171	148	124	95	65	41	20	7	2
Chemotherapy	351	324	267	217	171	138	111	86	71	53	40	21	6	3	1

Adapted from Makker V, et al. *J Clin Oncol.* 2023;41(16):2904-2910.

The most common TEAEs (>20% of patients) in the pembrolizumab + lenvatinib arm were hypertension (61.8%), hypothyrodism (55.7%), diarrhea (43.1%), nausea (39.9%) and decreased appetite (37.9%), fatigue (28.6%), proteinuria (26.6%), vomiting (24.4%), weight decreased (22.7%), arthralgia (22.2%), and palmar-plantar erythrodysesthesia syndrome (20.7%)

CI = confidence interval; EC = endometrial cancer; HR = hazard ratio; ICI = immune checkpoint inhibitor; OS = overall survival; PFS = progression-free survival; TEAE = treatment-emergent adverse event.

1. Makker V et al. *J Clin Oncol* 2023;41(16):2904-2910. 2. Keytruda (pembrolizumab) [summary of product characteristics]. Merck Sharp & Dohme B.V., Haarlam, The Netherlands; 2023. 3. Keytruda (pembrolizumab) [prescribing information]. Merck & Co., Inc., Whitehouse Station, NJ, USA; 2023.

Anti-PD-1s in an Asian patient population

Recurrent EC case study #2

History and initial presentation

- 52-year-old
- Stage IIIC2 Grade 3 endometrioid EC
- Total hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection, paraaortic lymph node dissection (Approximately September 2019)
- 1L carboplatin/paclitaxel C6 (Approximately February 2020) followed by RT (WBRT + para-aoritc lymph nodes) (Approximately May 2020)
- **Recurrence: multiple liver metastases** (July 2020)
- Liver biopsy: metastatic adenocarcinoma, dMMR loss (MLH1 loss), p53abn, HER2 1+

Courtesy of Dr. Jung-Yun Lee.

1L = first-line; dMMR = mismatch repair deficient; EC = endometrial cancer; HER2 = human epidermal growth factor receptor 2; MLH1 = mutL homolog 1 protein; p53abn = p53 abnormal; RT = radiotherapy; WBRT = whole brain radiotherapy.

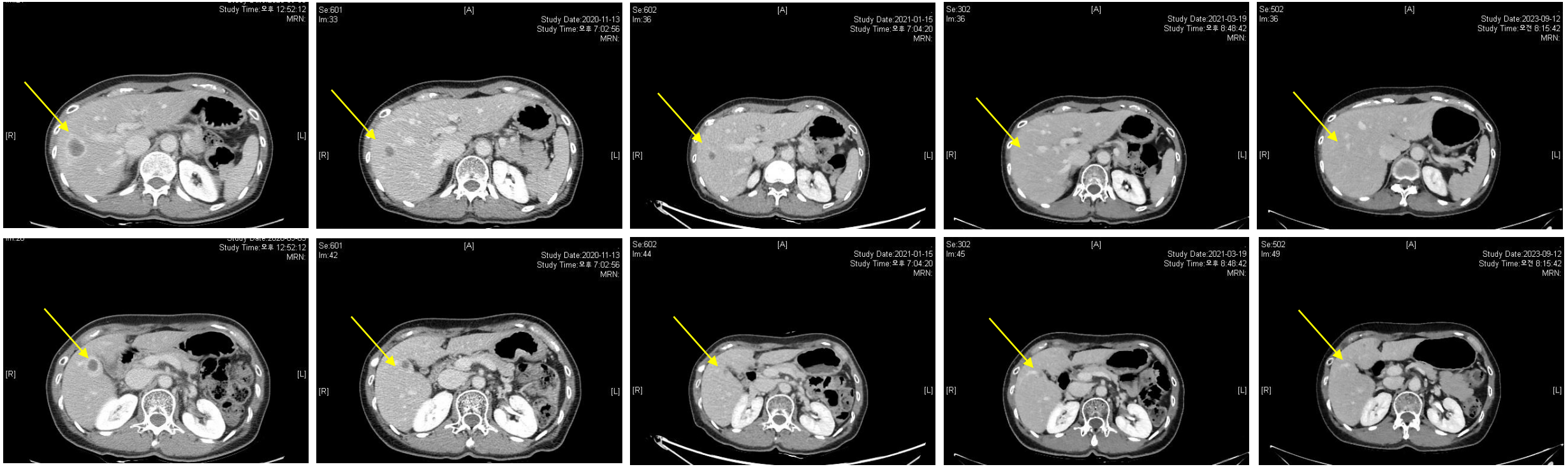
Recurrent EC case study #2

Treatment

- Patient treated anti-PD-1 after recurrence
- C19 (September 2020 ~ October 2021)

> 3 years later:
> **Remains disease free!**

[Sept 2020] [Nov 2020] : PR [Jan 2021] : PR [March 2021] : CR [Sept 2023] : CR

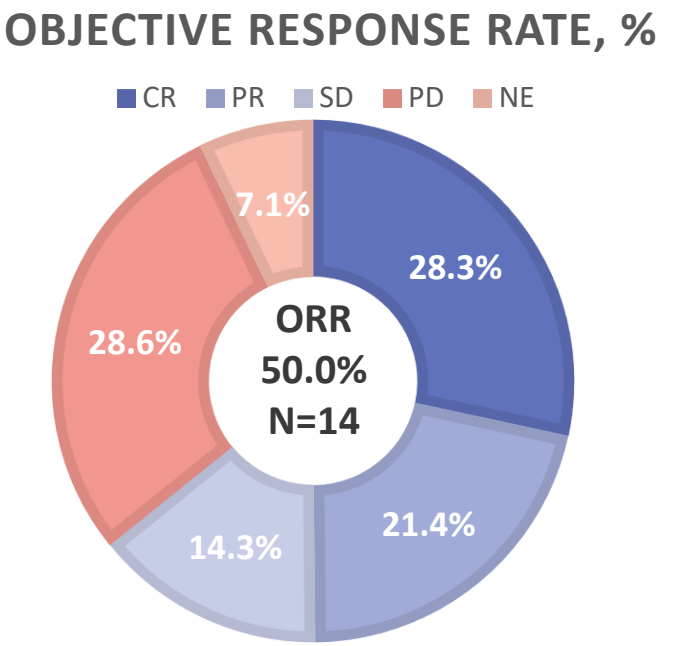


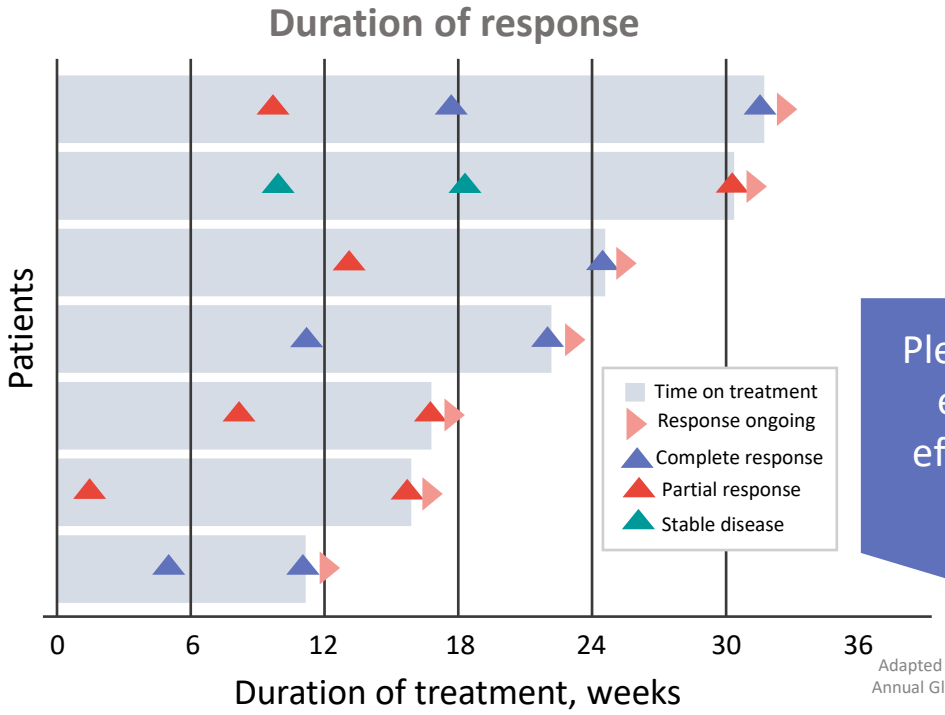
C# = cycle #; CR = complete response; EC = endometrial cancer; PD-1, programmed death protein-1; PR = partial response.

Courtesy of Dr. Jung-Yun Lee.

Dostarlimab demonstrated encouraging antitumor activity in Korean patients with dMMR/MSI-H EC

Dostarlimab monotherapy in dMMR/MSI-H advanced or recurrent EC in the Korean Expanded Access Program





Please refer to IGCS e-poster for full efficacy and safety data

Adapted from Park SJ et al. Presented at IGCS 2023 Annual Global Meeting. November 4-7, 2023; Seoul, Republic of Korea.

The safety profile was consistent with the registration trial of GARNET; grade 1-2 TEAEs included abdominal pain, constipation, hypothyroidism, and urticaria (n=1 each) and grade 3 TEAEs included anemia, brain abscess, diarrhea, and wound infection (n=1 each). There were no discontinuations or deaths

CR = complete response; dMMR = mismatch repair deficient; EC = endometrial cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; FIGO = Federation of Gynecology and Obstetrics; MSI-H = microsatellite instability-high; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.

1. Park SJ et al. Presented at IGCS 2023 Annual Global Meeting. November 4-7, 2023; Seoul, Republic of Korea.

Safety profile of anti-PD-1s

Safety update 1-year post-treatment with anti-PD-1 monotherapy

Recurrent EC case studies 1 & 2

Patients developed

- Polyarthralgia involving large and small joints
- Helped by **steroids**

- ✓ Anti-PD-1 treatment is capable of durable responses[1,2]
- ✓ Similar safety profile was observed in case studies 1 and 2
- ✓ Treat new symptoms arising during ICI treatment with suspicion and possibly related to treatment until proven otherwise[3]

ICPi arthritis

- **1%-7% of patients** on ICI therapy[4]
- Patients who receive ICI monotherapy are more likely to have **initial small joint involvement and have IA as their only irAE[5]**
- Presentations include[4]
  - **Rheumatoid arthritis**
  - **Reactive arthritis**
  - **Seronegative spondylarthritis**
  - Oligoarthritis and polyarthritis[5]
- Important to assess patients for **pre-existing auto-immune conditions[5]**

Courtesy of Dr. Lucy Gilbert, McGill University, Montreal, QC, Canada.

EC = endometrial cancer; IA = inflammatory arthritis; ICI = immune checkpoint inhibitor; ICPi = immune checkpoint inhibitor-induced; irAE = immune-related adverse event; PD-1 = programmed cell death-1.

3. Oaknin A et al. *Clin Cancer Res* 2023; doi: 10.1158/1078-0432.CCR-22-3915. 4. O'Malley DM et al. *J Clin Oncol* 2022;40:752-761. 5. Brahmer JR et al. *J Clin Oncol.* 2018; 36:1714-1768. 4. Cappelli LC et al. *Arth Care Res* 2017;69:1751-1763. 5. Connolly C et al. *Front Oncol* 2019;9:530.

Learnings from recurrent EC case studies[1,2]

Early recognition of ICI arthritis

Prompt treatment

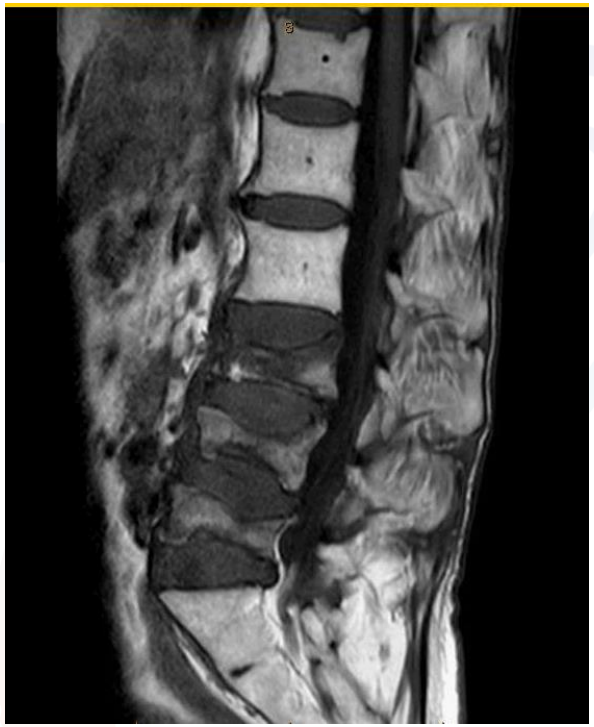
Multidisciplinary approach

Given durable response and significant prolongation of life from ICI therapy:

- **Be proactive**
- Early recognition of ICI AE and **AEs from steroids**

Keep in mind steroid-related complications:

- Osteoporosis
- Diabetes
- GI toxicity
- Opportunistic infections



L3, L4, L5 compression fractures

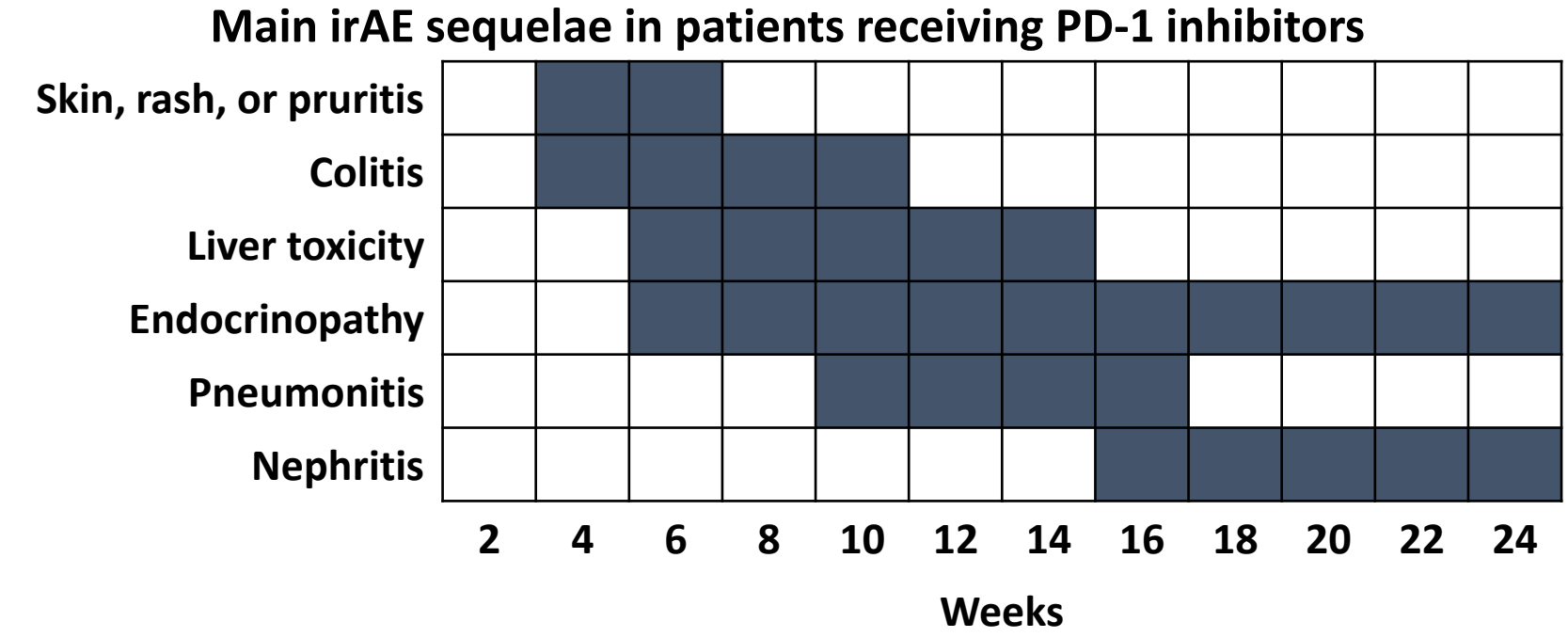
Courtesy of Dr. Lucy Gilbert, McGill University, Montreal, QC, Canada.

AE = adverse event; EC = endometrial cancer; ICI = immune checkpoint inhibitor; L# = lumbar vertebrate #.

1. Brahmer JR et al. *J Clin Oncol* 2018; 36:1714-1768. 2. Haanen JBAG et al. *Ann Oncol* 2017;28:i119-i142.

Panel discussion

How do you manage irAEs in your patients?



ICPi = immune checkpoint inhibitor-induced; PD-1 = programmed cell death protein-1.
Martins F, et al. *Nat Rev* 2019;16:563-580.

irAE –management CTCAE Grades 1 – 5[1,2]

Grade 1

Minimal or no symptoms; diagnostic changes only

- In general, checkpoint inhibitor therapy should be continued with close monitoring, with the exception of some neurologic, hematologic, and cardiac toxicities

Grade 2

Mild to moderate symptoms

- Hold checkpoint inhibitor therapy for most grade 2 toxicities
- Consider resuming immunotherapy when symptoms and/or laboratory values revert to grade 1 or lower
- Corticosteroids (initial dose of 0.5-1 mg/kg/d of prednisone or equivalent) may be administered

Grades 3/4

Severe or life-threatening symptoms

Grade 3 toxicities:

- Hold checkpoint inhibitor therapy for most grade 3/4 toxicities
- Initiate high dose corticosteroids (prednisone 1-2 mg/kg/d or methylprednisone IV 1-2 mg/kg/d)
- If symptoms do not improve within 48-72 hours of high dose corticosteroids, infliximab may be offered for some toxicities
- Taper corticosteroids over the course of at least 4-6 weeks
- When symptoms and/or laboratory values revert to grade 1 or lower, rechallenging with immunotherapy may be offered; however, caution is advised, especially in those patients with early-onset irAEs. Dose adjustments are not recommended

Grade 4 toxicities:

- In general, permanent discontinuation of checkpoint inhibitor therapy is warranted, with the exception of endocrinopathies that have been controlled by hormone replacement

irAE = immune-related adverse event; CTCAE = Common Terminology Criteria for Adverse Events.

1. Brahmer JR et al. *J Clin Oncol*. 2018;36:1714-1768. 2. NCCN® Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities, version 1.2023. (Accessed 05/01/2023).

Conclusions

- The incidence and mortality of EC have continued to rise worldwide
- ICI, as a monotherapy or in combination with TKI, emerged as a treatment option for patients with previously-treated advanced/recurrent EC
- Guidelines now recommend ICI as the preferred treatment in previously treated dMMR/MSI-H EC, based upon
  - Deep and durable responses
  - Low toxicity and manageable safety profile
- ICI + TKI combination has shown significant improvements in efficacy outcomes compared with single-agent chemotherapy
  - ICI + TKI is recommended as an option in previously treated advanced/recurrent MMRp EC

dMMR = mismatch repair deficient; EC = endometrial cancer; ICI = immune checkpoint inhibitor; MMR = mismatch repair; MMRp = mismatch repair proficient; MSI-H = microsatellite instability-high; TKI = tyrosine kinase inhibitor.