

XXIV

# SIMPOSIO DE REVISIONES EN CÁNCER

*“Tratamiento médico del cáncer en el año 2022”*

## **Nuevo estándar de tratamiento en el cáncer de endometrio avanzado con dMMR/MSI-H**

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# Disclosures

**M<sup>a</sup> Jesús Rubio Pérez**

Consulting and Advisory role: Pharmamar, Astra Zeneca, GSK, Clovis, Roche, MSD

Speaking: Pharmamar, Astra Zeneca, GSK, Clovis, Roche, MSD

Travel expenses: Pharmamar, Astra Zeneca, GSK, Roche

## Introducción: *epidemiología de cáncer de endometrio en España*

1<sup>st</sup>

Es la neoplasia Ginecológica más frecuente

63

La edad media al diagnóstico

6.804

Casos nuevos en 2020

75-80%

% de casos diagnosticados en estadio inicial

1.583

Nº muertes en año 2018

25-30%

dMMR/MSI-H

dMMR, deficient mismatch repair; MSI-H, microsatellite instability-high

1. SEOM. Sánchez Lorenzo, L. Cáncer de endometrio-útero 2020. <https://seom.org/info-sobre-el-cancer/endometrio> [Accessed January, 2021]. 2. Colombo N et al. Ann Oncol. 2016;27(1):16-41. 3. SEOM. Las cifras del cáncer en España 2020. [https://seom.org/seomcms/images/stories/recursos/Cifras\\_del\\_cancer\\_2020.pdf](https://seom.org/seomcms/images/stories/recursos/Cifras_del_cancer_2020.pdf). [Accessed January, 2021]. 4. Hause R et al. Nat Med. 2016;22:1342-1350.



## ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Nicole Concin <sup>1,2</sup>, Xavier Matias-Guiu, <sup>3,4</sup> Ignace Vergote, <sup>5</sup> David Cibula, <sup>6</sup> Mansoor Raza Mirza, <sup>7</sup> Simone Marnitz, <sup>8</sup> Jonathan Ledermann, <sup>9</sup> Tjalling Bosse, <sup>10</sup> Cyrus Chhagari, <sup>11</sup> Anna Fagotti, <sup>12</sup> Christina Fotopoulou, <sup>13</sup> Antonio Gonzalez Martin, <sup>14</sup> Sigurd Lax, <sup>15,16</sup> Domenica Lorusso, <sup>12</sup> Christian Marth, <sup>17</sup> Philippe Morice, <sup>18</sup> Remi A Nout, <sup>19</sup> Dearbhla O'Donnell, <sup>20</sup> Denis Querleu, <sup>12,21</sup> Maria Rosaria Raspollini, <sup>22</sup> Jalid Sehouli, <sup>23</sup> Alina Sturdza, <sup>24</sup> Alexandra Taylor, <sup>25</sup> Anneke Westermann, <sup>26</sup> Pauline Wimberger, <sup>27</sup> Nicoletta Colombo, <sup>28</sup> François Planchamp, <sup>29</sup> Carlen L Creutzberg <sup>30</sup>

2021

The combination of carboplatin and paclitaxel is the standard chemotherapy treatment of advanced/recurrent endometrial carcinoma based on a randomized phase 3 trial comparing carboplatin-paclitaxel versus carboplatin-paclitaxel-anthracyclines that reported overlapping progression-free survival and overall survival between the two arms but an increased toxicity for the triple combination.<sup>398</sup> No standard treatment has been identified as second-line therapy; a response rate of about 10–15% has been seen among all the available treatment options. Thus, enrollment of patients in

## Introducción: recomendación de guías para la 2ªL en CE

|                         | ESGO/ESTRO/ESP (2021) <sup>1</sup>                                                                                       | ESMO-ESGO-ESTRO (2016) <sup>2</sup>                                                                             | SEOM 2017 <sup>3</sup>                                                                                                                                                      |
|-------------------------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>1L</b>               | Carboplatin + paclitaxel (I,A)                                                                                           | Carboplatin + paclitaxel                                                                                        | Carboplatin + paclitaxel (I,A)                                                                                                                                              |
| <b>2L</b>               | <b>There is no standard</b><br>The most effective treatments are considered to be doxorubicin and paclitaxel (IV,C).     | <b>There is no standard</b>                                                                                     | <b>There is no standard</b>                                                                                                                                                 |
| <b>Terapia hormonal</b> | First-line systemic treatment of choice for patients with low-grade carcinomas without rapid disease progression (II, A) | Indicated in patients with endometrioid histology, grade 1 and 2 (IV, B) and hormone receptor positive (III, B) | Grade 1/2 tumours, hormone receptor positive and without rapid disease progression (IV, A)<br>Megestrol acetate 160mg/day or medroxyprogesterone acetate 200mg/day (III, A) |

**Existe la necesidad de terapias efectivas, con un buen perfil de tolerabilidad y sin afectar negativamente la calidad de vida, en las que las pacientes con cáncer de endometrio avanzado o recurrente que progresan después de un tratamiento previo basado en platino puedan identificarse con un biomarcador**

1. Concin N, Matias-Guiu X, Vergote I, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer 2021;31:12–39. 2. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO CONSENSUS CONFERENCE ON ENDOMETRIAL CANCER. Ann Oncol 2016;27:16–41. 3. Santaballa A, Matías-Guiu X, Redondo A, et al. SEOM clinical guidelines for endometrial cancer (2017). Clin Transl Oncol 2018;20:29–37. 4. Makker V, Green AK, Wenham RM, Mutch D, Davidson B, Miller DS. New therapies for advanced, recurrent, and metastatic endometrial cancers. Gynecol Oncol Res Pract 2017;4(1):1–12.

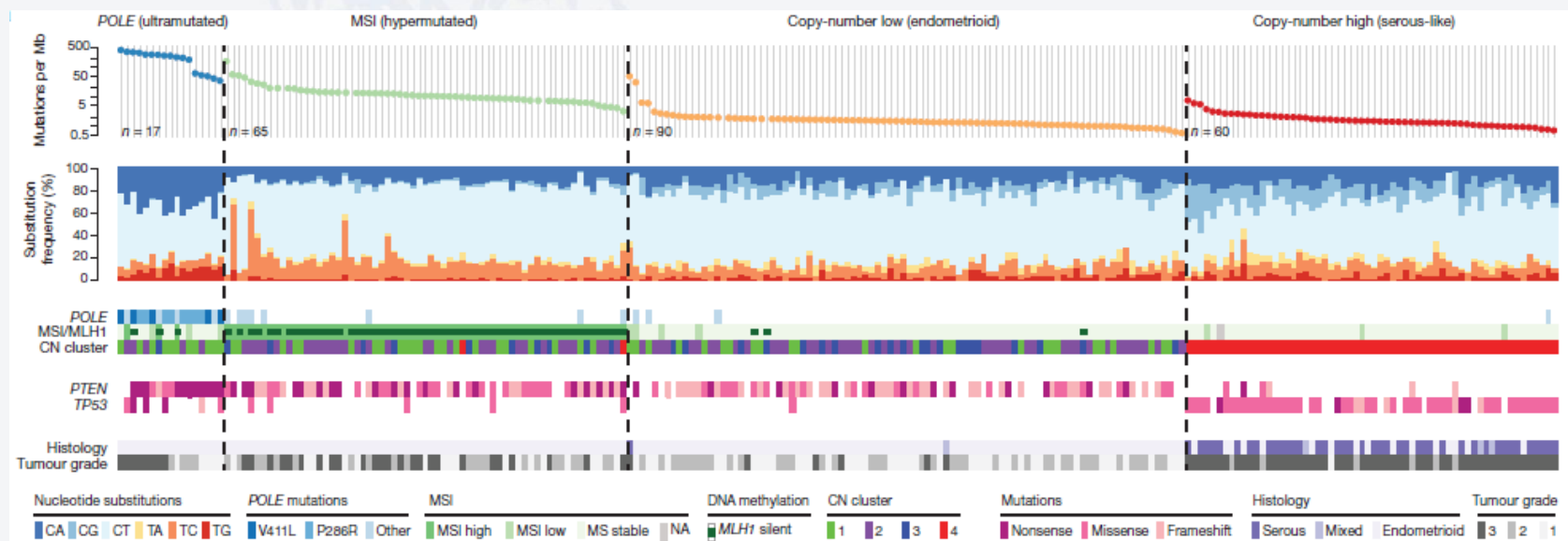
## Cambio de paradigma en CE. Integración de la clasificación molecular,

**Cuatro subtipos moleculares principales de cáncer de endometrio han sido caracterizados por TCGA1**

Dos de estos subtipos (POLE y MSI-alto) tienen una alta carga mutacional tumoral

Estos tumores a menudo se caracterizan por altos TIL y una alta expresión de moléculas de puntos de control inmunitarios

TCGA → MSI



PROMISE → MMRd

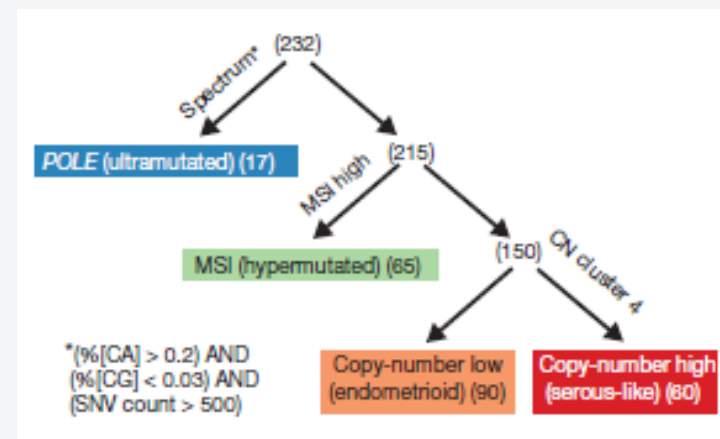


Image adapted from: Cancer Genome Atlas Research Network, et al. *Nature*. 2013;497(7447):67-73.

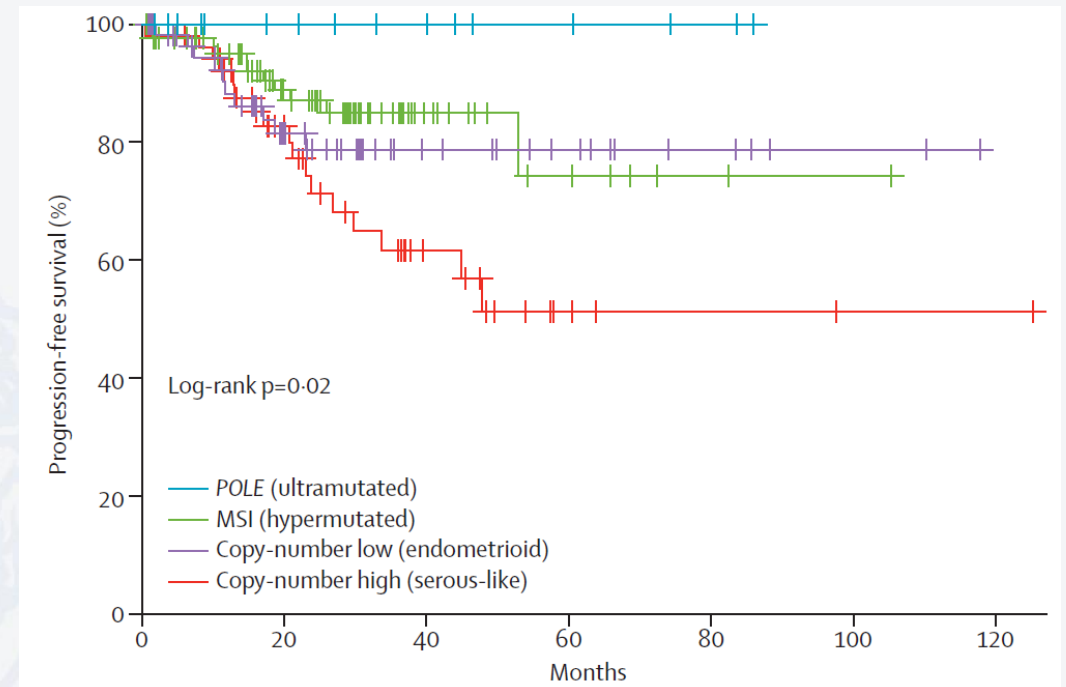
## Cambio de paradigma en CE. Integración de la clasificación molecular, correlación con el pronóstico de la enfermedad

La mayoría de los CE (97%) se pueden incluir dentro de uno de los 4 subgrupos moleculares que se correlaciona estrechamente con el pronóstico de la enfermedad

### Molecular Subgroups<sup>2</sup>

|                                      | <i>POLE</i><br>ultramutated | MSI<br>hypermuted | Copy-number<br>low, MSS | Copy-number<br>high, serous-like |
|--------------------------------------|-----------------------------|-------------------|-------------------------|----------------------------------|
| Mutation load                        |                             |                   |                         |                                  |
| Somatic copy number alterations load |                             |                   |                         |                                  |
| Histology                            | Endometrioid                | Endometrioid      | Endometrioid            | Serous and endometrioid          |
| Grade                                |                             |                   |                         |                                  |
| <i>PI3K</i> alterations              |                             |                   |                         |                                  |
| <i>KRAS</i> mutation                 |                             |                   |                         |                                  |
| <i>TP53</i> mutation                 | 35%                         | 5%                | 1%                      | >90%                             |
| Prognosis                            | Excellent                   | Intermediate      | Intermediate            | Poor                             |

### PFS According to Molecular Subgroup<sup>2</sup>



Images adapted from Morice P et al. *Lancet*. 2016;387(10023):1094-1108.

MSI, microsatellite instability; MSS, microsatellite stable; PFS, progression-free survival; *POLE*, polymerase epsilon.

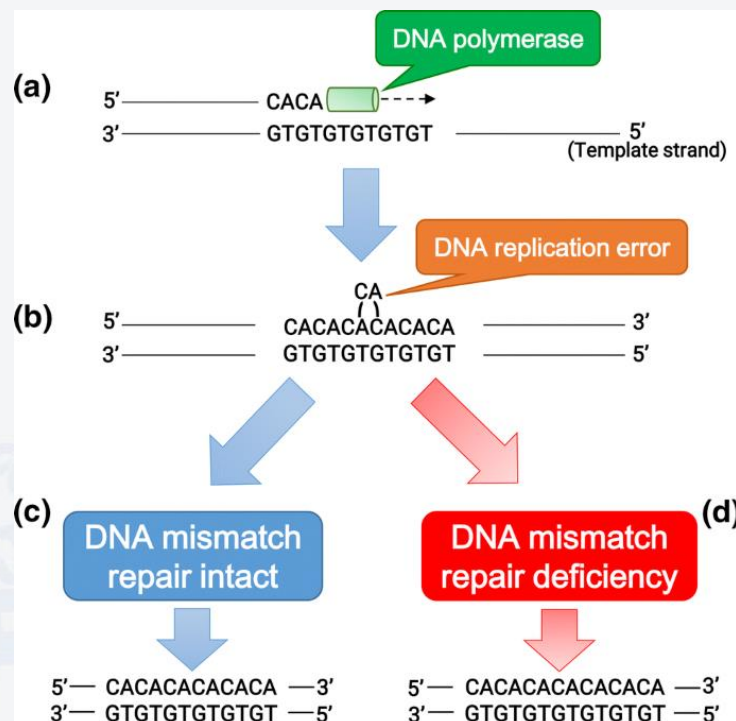
1. Lee YC et al. *Curr Opin Obstet Gynecol*. 2017;29:47-58. 2. Morice P et al. *Lancet*. 2016;387:1094-1108. 3. Soslow RA et al. *Int J Gynecol Pathol*. 2019;38(Suppl 1):S64-S74. 1

## ¿MMRd=IMS?

✓ Los **microsatélites** son *secuencias cortas de ADN repetidas* en tándem a lo largo del genoma muy sensibles a errores de reapareamiento del DNA.

Mecanismo de reparación de apareamientos erróneos cometidos por el ADN polimerasa (**Mismatch Repair –MMR–**)

MLH1  
MSH2,  
MSH6,  
y PMS2



Cuando el sistema **MMR** es DEFICIENTE (mutación vs causa epigenética)

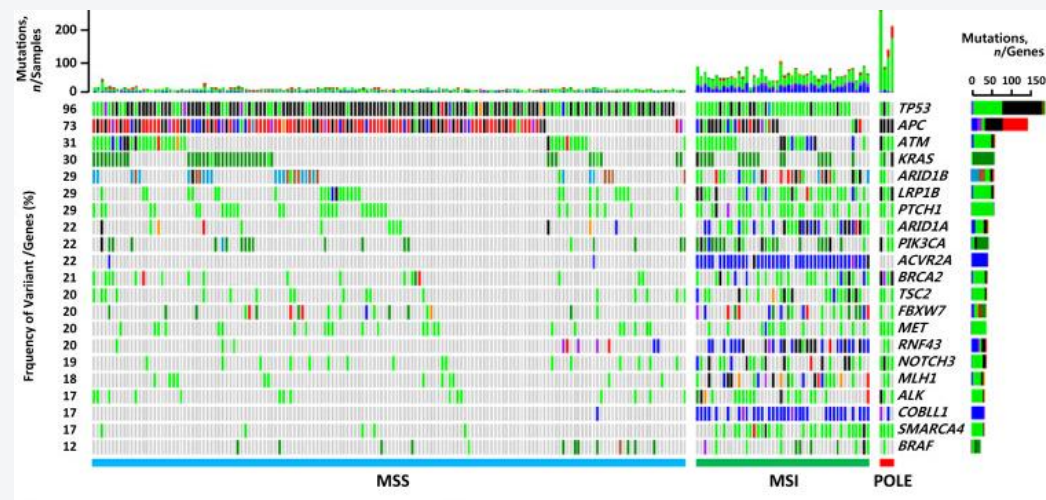
Los errores de replicación cometidos por el ADN polimerasa **NO** son reparados....

Se genera una alteración en la longitud de los microsatélites del ADN tumoral 2º a inserciones o deleciones de bases de forma errónea

## ¿MMRd=IMS?

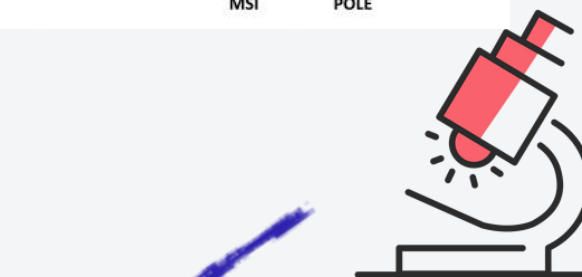
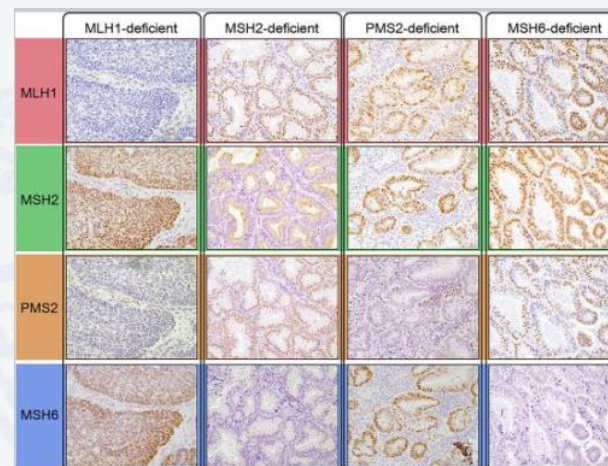
### IMS → NGS

Se valora la falta de **funcionalidad correcta** de las **proteínas reparadoras**.



### dMMR → IHQ

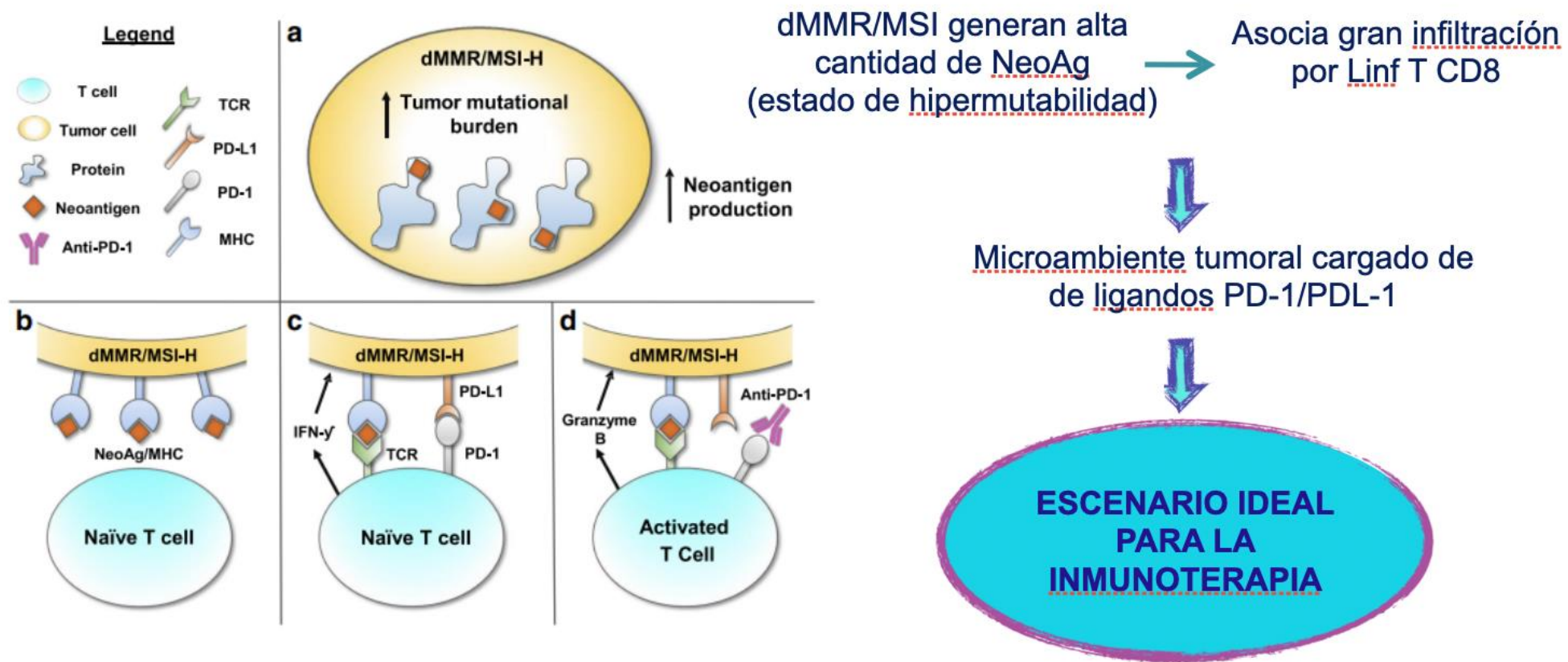
Se valora la **expresión de las proteínas reparadoras** MLH1, MSH2, MSH6 Y PMS2. Funcionan en heterodímeros: MLH1 y PMS2; MSH2 y MSH6.



Ausencia de expresión nuclear = proteína dañada (mutación del gen)

**En Resumen:** **MMRd**(pérdida de expresión de proteínas reparadoras) Es la Causa de MSI.....  
.....y **MSI** es el Reflejo, el genotipo, de MMRd

## Racional para el uso de Inmunoterapia



Boyadzis et al. Journal for ImmunoTherapy of Cancer (2018)0

El 30% de las cánceres de Endometrio presentan MSI y de estos, del 13 al 30% van a recurrir....

## SINGLE-AGENT IMMUNOTHERAPY EFFICACY

### Biomarker-selected endometrial cancer

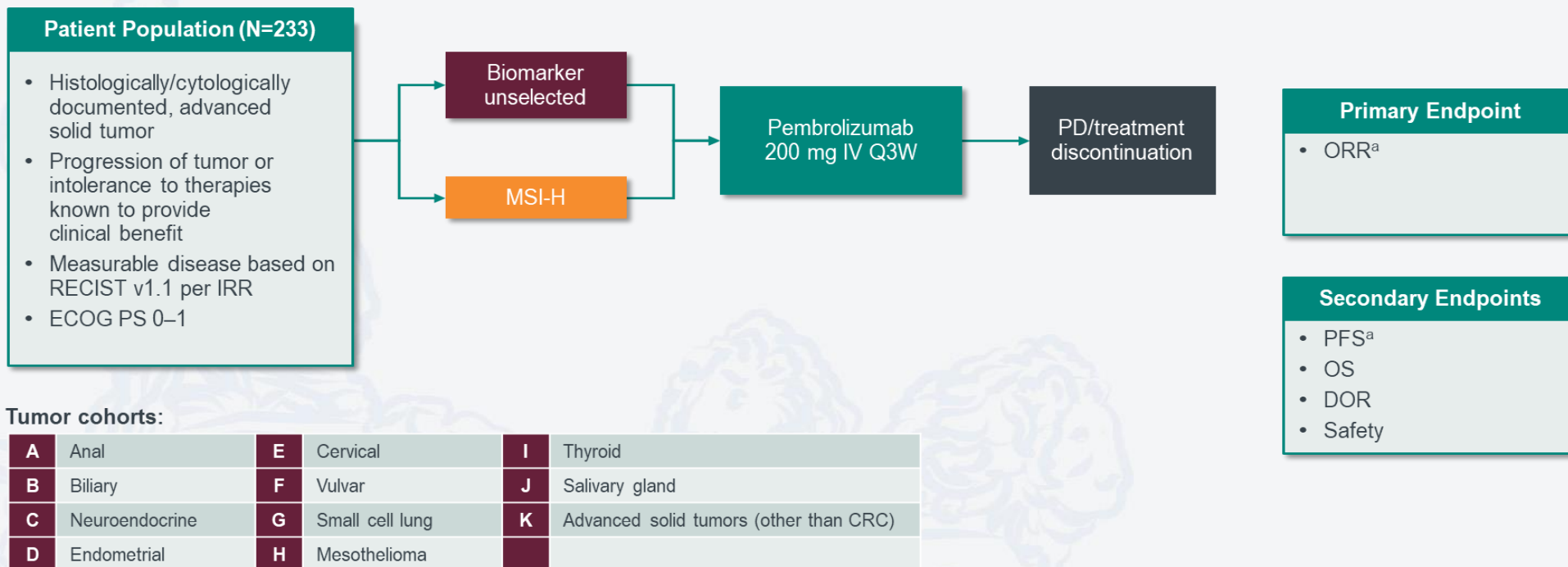
| Study                    | Drug          | N   | Patient Selection                          | ORR (%) |
|--------------------------|---------------|-----|--------------------------------------------|---------|
| KEYNOTE-158 <sup>1</sup> | Pembrolizumab | 49  | Advanced/metastatic dMMR                   | 57%     |
| GARNET <sup>2</sup>      | Dostarlimab   | 103 | Previously treated Recurrent/advanced dMMR | 45%     |
| PHAEDRA <sup>3</sup>     | Durvalumab    | 35  | Advanced/metastatic dMMR                   | 43%     |
| NCT02912572 <sup>4</sup> | Avelumab      | 15  | Advanced/persistent dMMR                   | 27%     |

dMMR, mismatch repair-deficient; IO, immuno-oncology; MMRp, mismatch repair-proficient; ORR, overall response rate

1. Marabelle A, et al. *J Clin Oncol.* 2020;38(1):1-10. 2. Oaknin A, et al. Presented at European Society for Medical Oncology Virtual Congress 2020. 3. Antill YC, et al. *J Clin Oncol.* 2019;37(15\_suppl):5501. 4. Konstantinopoulos PA, et al. *J Clin Oncol.* 2019;37(30):2786-2794; Bonneville R, et al. *JCO Precis Oncol.* 2017;1:1-15.

## KEYNOTE 158: Pembrolizumab en MSI-H

### KEYNOTE-158: Study Design<sup>1,2</sup>



<sup>a</sup>By IRR using RECIST v1.1.

1. Marabelle A et al. *J Clin Oncol*. 2020;38(1):1–10. 2. [clinicaltrials.gov/ct2/show/NCT02628067](https://clinicaltrials.gov/ct2/show/NCT02628067). Accessed 26 January 2021.

## KEYNOTE 158: Pembrolizumab en MSI-H. *Resultados*

| Parameter                                 | Endometrial Cancer <sup>1</sup>              |                                           | All Patients With MSI-H Cancers <sup>2</sup><br>(N=233) |
|-------------------------------------------|----------------------------------------------|-------------------------------------------|---------------------------------------------------------|
|                                           | MSI-H (Cohorts D + K) <sup>a</sup><br>(n=49) | Cohort D: Biomarker Unselected<br>(n=107) |                                                         |
| ORR, % (95% CI)                           | 57.1 (42.2–71.2) <sup>b</sup>                | 11.2 (5.9–18.8)                           | 34.3 (28.3–40.8)                                        |
| BOR, n (%)                                |                                              |                                           |                                                         |
| CR                                        | 8 (16.3)                                     | 0                                         | 23 (9.9)                                                |
| PR                                        | 20 (40.8)                                    | 12 (11.2)                                 | 57 (24.5)                                               |
| SD                                        | 8 (16.3)                                     | 26 (24.3)                                 | 42 (18.0)                                               |
| PD                                        | 11 (22.4)                                    | 56 (52.3)                                 | 92 (39.5)                                               |
| Not evaluable <sup>c</sup>                | 1 (2.0)                                      | 2 (1.9)                                   | 2 (0.9)                                                 |
| Not assessed <sup>d</sup>                 | 1 (2.0)                                      | 11 (10.3)                                 | 17 (7.3)                                                |
| Median follow-up duration, months (range) | 24.4 (0.5–34.2)                              | 11.1 (0.5–34.6)                           | 13.4 (0.4–34.2)                                         |

|                                                |                       |                       |
|------------------------------------------------|-----------------------|-----------------------|
| <b>Median PFS, months (95% CI)</b>             | <b>25.7 (4.9–NR)</b>  | <b>4.1 (2.4–4.9)</b>  |
| 12-month PFS rate, %                           | 58.4                  | 33.9                  |
| <b>Median OS, months (95% CI)</b>              | <b>NR (27.2–NR)</b>   | <b>23.5 (13.5–NR)</b> |
| 12-month OS rate, %                            | 73.5                  | 60.7                  |
| <b>Median DOR, months (95% CI)<sup>a</sup></b> | <b>NR (2.9–27.0+)</b> | <b>NR (2.9–31.3+)</b> |
| 12-month DOR rate, %                           | 89.0                  | 86.9                  |

1. O'Malley D et al. Presented at ESMO 2019; abstract 3394.

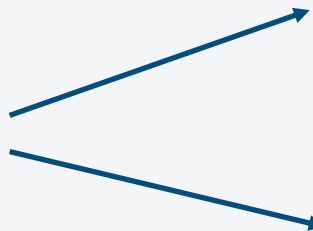
2. Marabelle A et al. *J Clin Oncol*. 2020;38(1):1–10.

## GARNET: Dostarlimab(TSR-042) monoterapia en CE

- Key inclusion/exclusion criteria for cohorts A1 and A2:

- Patients must have progression on or after platinum doublet therapy
- Patients must have received  $\leq 2$  prior lines of treatment for recurrent or advanced disease
- Patients must have measurable disease at baseline
- Patients must be anti-PD-(L)1 naive

- Patients could be screened based on local MMR/MSI testing results using IHC, PCR, or NGS performed in a certified local laboratory, but patient cohort assignment was by MMR IHC results



### Part 2B Expansion Cohorts

#### Cohort A1<sup>†</sup>: dMMR EC

Dostarlimab 500 mg IV Q3W for 4 cycles, then 1000 mg IV Q6W  
(n = 129)

#### Cohort A2<sup>‡</sup>: pMMR EC

Dostarlimab 500 mg IV Q3W for 4 cycles, then 1000 mg IV Q6W  
(n = 161)

→ Until PD

- Primary endpoint: ORR
- Secondary endpoints: DoR, DCR

\*Tumor MMR/MSI screening based on local MMR/MSI testing results using IHC, PCR, or NGS performed in a certified local laboratory, but patient eligibility needs to be confirmed by MMR IHC results.

<sup>†</sup>Includes 3 patients with MMRunk/MSI-H disease.

<sup>‡</sup>Includes 16 patients with MMRunk/MSS disease.

## Primary Endpoint Analysis

ORR was 44.7% in patients with dMMR EC, and 13.4% in patients with MMRp EC

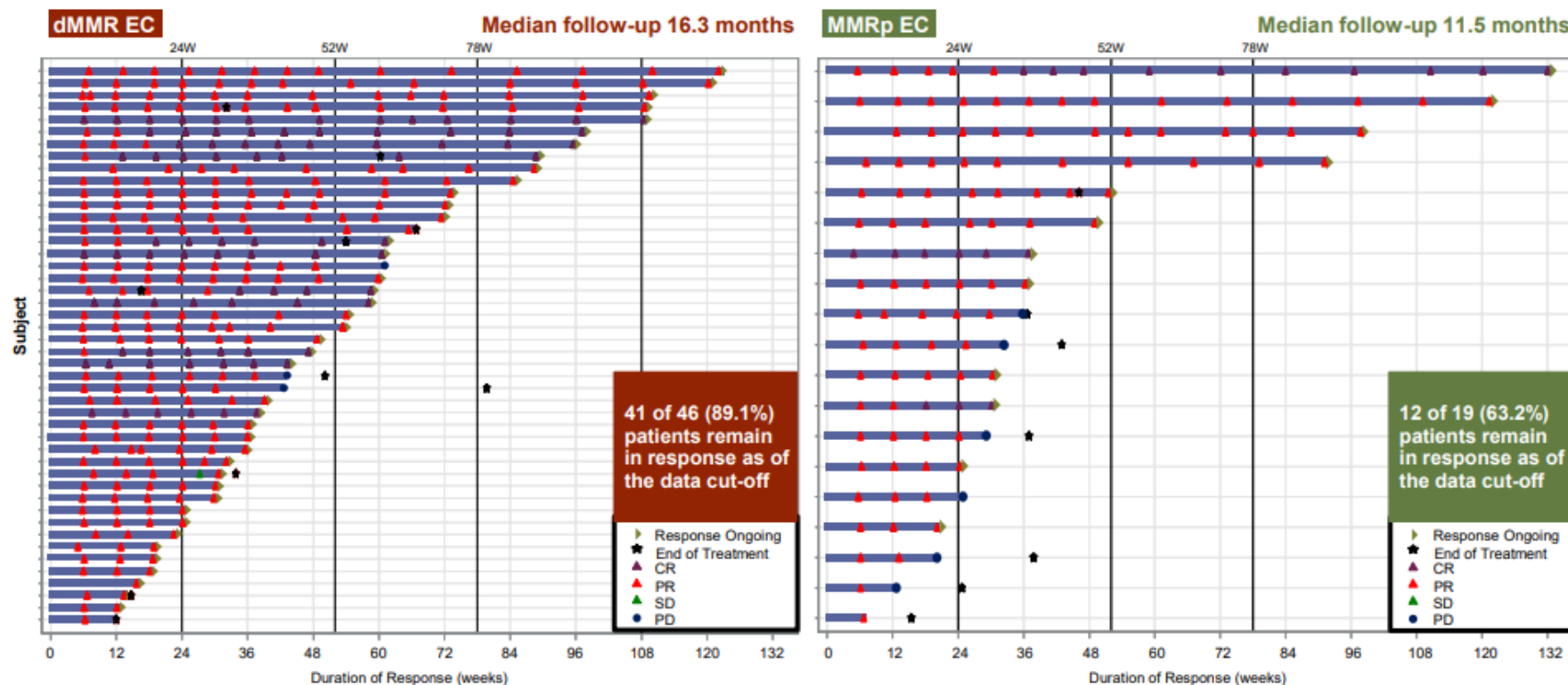
| Variable                                                           | dMMR EC, n=103                   | MMRp EC, n=142                    |
|--------------------------------------------------------------------|----------------------------------|-----------------------------------|
| Median follow-up time, mo                                          | 16.3                             | 11.5                              |
| <b>Objective response rate*, n (%; 95% CI)</b>                     | <b>46 (44.7%, 34.9–54.8)</b>     | <b>19 (13.4%, 8.3–20.1)</b>       |
| Complete response, n (%)                                           | 11 (10.7)                        | 3 (2.1)                           |
| Partial response, n (%)                                            | 35 (34.0)                        | 16 (11.3)                         |
| Stable disease, n (%)                                              | 13 (12.6)                        | 31 (21.8)                         |
| Progressive disease, n (%)                                         | 39 (37.9)                        | 77 (54.2)                         |
| Not evaluable, n (%)                                               | 3 (2.9)                          | 0                                 |
| Not done, n (%)                                                    | 2 (1.9)                          | 15 (10.6)                         |
| <b>Disease control rate†, n (%; 95% CI)</b>                        | <b>59 (57.3%, 47.2–67.0)</b>     | <b>50 (35.2%, 27.4–43.7)</b>      |
| <b>Response ongoing, n (%)</b>                                     | <b>41 (89.1)</b>                 | <b>12 (63.2)</b>                  |
| <b>Median duration of response, (range) mo</b>                     | <b>Not reached (2.63–28.09+)</b> | <b>Not reached (1.54+–30.36+)</b> |
| <b>Kaplan–Meier estimated probability of remaining in response</b> |                                  |                                   |
| at 6 mo, %                                                         | 97.8                             | 83.0                              |
| at 12 mo, %                                                        | 90.6                             | 61.3                              |
| at 18 mo, %                                                        | 79.2                             | 61.3                              |

\*Responses required confirmation at a subsequent scan; SD had to be observed at ≥12 weeks on study to qualify as SD; †Includes confirmed CR, PR or SD at ≥12 weeks.  
CR, complete response; dMMR, mismatch mutation repair deficient; EC, endometrial cancer; MMRp, mismatch mutation repair proficient; ORR, objective response rate; PR, partial response; SD, stable disease.

## GARNET: Dostarlimab(TSR-042) monoterapia en CE. Resultados

### GARNET primary endpoint: DoR

Con una mediana de seguimiento de 11.2 meses, el **83%** de las pacientes que habían respondido, **continuaban en respuesta**.



Data cut-off date March 1, 2020. CR, complete response; dMMR, mismatch mutation repair deficient; EC, endometrial cancer; MMRp, mismatch mutation repair proficient; PD, progressive disease; PR, partial response; SD, stable disease.  
Oaknin A, et al. Presented at European Society for Medical Oncology Virtual Congress 2020.

## GARNET: Dostarlimab(TSR-042) monoterapia en CE. Seguridad

TRAES with dostarlimab were generally low grade and characteristic of anti-PD-1 therapy

1.9

%

of patients discontinued treatment owing to TRAES, and no treatment-related deaths were reported

Perfil de seguridad aceptable con un % de interrupciones debido a TEAEs <2% y sin muertes relacionadas con el tratamiento.

| Outcome, n (%)                          | Cohort A1 dMMR EC <sup>1</sup><br>Safety population<br>(n=104) |
|-----------------------------------------|----------------------------------------------------------------|
|                                         | Any grade                                                      |
| <b>Most common TRAES*</b>               |                                                                |
| Asthenia                                | 16 (15.4)                                                      |
| Diarrhea                                | 16 (15.4)                                                      |
| Fatigue                                 | 15 (14.4)                                                      |
| Nausea                                  | 13 (12.5)                                                      |
| Pruritus                                | 10 (9.6)                                                       |
| Hypothyroidism                          | 9 (8.7)                                                        |
| Arthralgia                              | 8 (7.7)                                                        |
| Anemia                                  | 7 (6.7)                                                        |
| <b>Discontinuations due to TRAES</b>    | 2 (1.9)                                                        |
| <b>Deaths attributed to dostarlimab</b> | 0                                                              |

\*In ≥5% of patients.

dMMR, mismatch repair deficient; EC, endometrial cancer; PD-1, programmed cell death protein 1; TRAE, treatment-related adverse event.

1. Oaknin A et al. *JAMA Oncol* 2020;6(11):1766-1772.

## GARNET: Dostarlimab(TSR-042) monoterapia en CE. Seguridad.

### Grade $\geq 3$ Immune-Related TRAEs in Cohort A1

Grade  $\geq 3$  immune-related TRAEs were reported in a small number of patients

The most common immune-related TRAEs were diarrhea, colitis, and increased lipase and transaminases

| Outcome, n (%)                      | Cohort A1 dMMR EC <sup>1</sup><br>Safety population<br>(n=104) |
|-------------------------------------|----------------------------------------------------------------|
| Grade $\geq 3$ immune-related TRAEs | 12 (11.6)                                                      |
| Most common TRAEs                   |                                                                |
| Diarrhea                            | 3 (2.9)                                                        |
| Colitis                             | 2 (1.9)                                                        |
| Lipase increased                    | 2 (1.9)                                                        |
| Transaminases increased             | 2 (1.9)                                                        |
| Amylase increased                   | 1 (1.0)                                                        |
| ALT increased                       | 1 (1.0)                                                        |
| Acute pancreatitis                  | 1 (1.0)                                                        |



FDA grants accelerated approval for GSK's JEMPERLI (dostarlimab-gxly) for women with recurrent or advanced dMMR endometrial cancer

***DOSTARLIMAB (monoT<sup>a</sup>)***  
***CE enfermedad avanzada /***  
***recurrente con***  
***dMMR/MSI tras QT basada en***  
***platino***

23 April 2021



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

European Commission approves GSK's JEMPERLI (dostarlimab), the first anti-PD-1 therapy approved for recurrent or advanced endometrial cancer

Mayo de 2021

Dostarlimab NO está comercializado en España



**EAP Core Entry Criteria**

**Inclusion**



**Inclusion  
Criteria**

- Patients must be female, ≥18 years old (and able to understand the program)
- Histologically diagnosed endometrial cancer (note: all histologies are permitted except endometrial sarcoma [including carcinosarcoma])
- Evidence of tumor DNA damage repair dysfunction (dMMR/MSI-H) via locally available, validated methodology
- Patient has progressed on or after platinum-containing chemotherapy (and has received no more than 2 lines of anticancer therapy for recurrent or advanced [Stage ≥IIIB] disease [1L or 2L]); prior treatment with hormone therapies is acceptable and does not count toward the number of lines of therapy
- ECOG performance status ≤2
- Cannot be satisfactorily treated with commercially available alternative treatments, in accordance with treatment guidelines

**¡Abierto hasta abril de 2022!**

## 2º Análisis intermedio de las cohortes A1 y A2 de GARNET

Oaknin A, et al. J Immunother Cancer 2022;10:e003777. doi:10.1136/jitc-2021-003777

**Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: interim results from GARNET – a phase I, single-arm study**

Ana Oaknin <sup>1</sup>, Lucy Gilbert,<sup>2</sup> Anna V Tinker,<sup>3</sup> Jubilee Brown,<sup>4</sup> Cara Mathews,<sup>5</sup> Joshua Press,<sup>6</sup> Renaud Sabatier,<sup>7</sup> David M O'Malley,<sup>8</sup> Vanessa Samuelian,<sup>9</sup> Valentina Boni,<sup>10</sup> Linda Duska,<sup>11</sup> Sharad Ghamande,<sup>12</sup> Prafull Ghatage,<sup>13</sup> Rebecca Kristeleit,<sup>14</sup> Charles Leath III,<sup>15</sup> Wei Guo,<sup>16</sup> Ellie Im,<sup>16</sup> Sybil Zildjian,<sup>16</sup> Xinwei Han,<sup>16</sup> Tao Duan,<sup>16</sup> Jennifer Veneris,<sup>16</sup> Bhavana Pothuri<sup>17</sup>

### ***Con una mediana de Seguimiento de 16,3 meses:***

En esta nueva publicación del segundo análisis, en las pacientes con cáncer de endometrio dMMR/MSI-H (Cohorte A1):

- Población de eficacia **108 pacientes**.

- **ORR** según RECIST v1.1 fue del **43,5%** (IC del 95%: 34,0% a 53,4%), con 11 (**10,2%**) **respuestas completas** y 36 (**33,3%**) **respuestas parciales**.

- **La mediana de duración de la respuesta (DOR) no se había alcanzado** y 42 (**89,4%** de las **respondedoras**) **seguían en respuesta** en el momento del corte de datos( marzo 2020).

- Los **datos de PFS eran inmaduros**, con un 47,2% de los datos censurados. No obstante, para el subconjunto de 72 pacientes con dMMR/MSI-H que tenían un mínimo de ≥13,5 meses de seguimiento (mediana de seguimiento de 19,2 meses), la **mediana de PFS fue de 12,2 meses**.

En cuanto al perfil de seguridad de dostarlimab, se presentan los datos combinados de las cohortes A1+A2 (N=290), siendo la mayoría de los TRAE (Treatment-related adverse events) de grado 1 o 2. Para la población combinada, los TRAE más comunes de cualquier grado fueron fatiga (17,6%), diarrea (13,8%) y náuseas (13,8%). Los TRAEs de Grado ≥3 ocurrieron en el 16,6% de las pacientes. Sólo el 5,5% de las pacientes discontinuó dostarlimab debido a un TRAE, y no se notificaron muertes relacionadas con el tratamiento.

INFORME SEOM DE EVALUACIÓN DE FÁRMACOS

Dostarlimab (Jemperli®) indicado en monoterapia para el tratamiento de pacientes adultas con cáncer de endometrio (CE) en recaída o avanzado con pérdida del mecanismo de reparación de apareamiento de bases (dMMR) / inestabilidad de microsatélites alta (MSI-H) que han progresado durante o después de un tratamiento previo basado en platino

6. CONCLUSIONES

- Dostarlimab es un anticuerpo monoclonal humanizado del isotipo IgG4 que se une a receptores de PD-1 y bloquea las interacciones de unión con sus ligandos PD-L1 y PD-L2.
- Ha demostrado una elevada tasa de respuestas parciales (43.5% de las pacientes adultas con carcinoma epitelial de endometrio (no carcinosarcoma) metastásico o localmente avanzado en progresión a una primera línea de tratamiento con quimioterapia basada en platino y estado general conservado (ECOG PS 0-2). Estas respuestas alcanzadas son duraderas y el 90% de pacientes mantienen la respuesta al cabo de un año.
- Se recomienda mantener el tratamiento hasta progresión, toxicidad inaceptable o un máximo de dos años, si bien se podría continuar el tratamiento si la paciente mantiene beneficio clínico.
- La tasa de respuesta es independiente de los tratamientos sistémicos previos.
- No se ha demostrado un mayor beneficio en subgrupos de pacientes por expresión de PD-L1 o por CPS.
- Su perfil de efectos secundarios es el esperado para anticuerpos anti-PD1, sin nuevos datos de toxicidad respecto a fármacos de su clase terapéutica.
- Los datos de calidad de vida reportados por las pacientes presentan una mejoría del estado global de salud comparado con la situación basal. La pauta de administración con una fase de inducción de tratamiento cada 3 semanas y posteriormente cada 6 semanas permite mayor autonomía de la paciente, y menor número de visitas al hospital.
- Ha sido aprobado para esta indicación por la FDA y la EMA de forma condicional a falta de resultados maduros del estudio GARNET y del estudio RUBY en primera línea combinado con quimioterapia.

En las pacientes que progresan a la primera línea no existía hasta la aprobación de dostarlimab ningún tratamiento específico recomendado por las guías de consenso. Las opciones de terapia sistémica utilizadas en segunda línea, tras exposición previa a la terapia que contiene platino, en el CE recurrente o avanzado incluyen doxorubicina convencional y liposomal, oxaliplatino, docetaxel, topotecán y bevacizumab (18-22), que proporcionan tasas de respuesta objetiva (TRO) del 7% al 14% y una mediana de supervivencia global (SG) de entre 6 a 11 meses (18-22), pero ninguna está aprobada en Europa. Por tanto, hasta la aprobación de dostarlimab no se disponía de una segunda línea de tratamiento estándar.

## Phase III Keynote 775: Second line Pembrolizumab + Lenvatinib vs Chemotherapy in advanced EC

### Study Design

#### Key eligibility criteria

- Advanced, metastatic, or recurrent endometrial cancer
- Measurable disease by BICR
- 1 Prior platinum-based CT<sup>a</sup>
- ECOG PS 0-1
- Tissue available for MMR testing

#### Stratification factors

**MMR status** (pMMR vs dMMR) and further stratification within pMMR by:

- Region (R1: Europe, USA, Canada, Australia, New Zealand, and Israel, vs R2: rest of the world)
- ECOG PS (0 vs 1)
- Prior history of pelvic radiation (Y vs N)

R  
(1:1)

**Lenvatinib**  
20 mg PO QD  
+  
**Pembrolizumab<sup>b</sup>**  
200 mg IV Q3W

Treat until progression or  
unacceptable toxicity

**Doxorubicin**  
60 mg/m<sup>2</sup> IV Q3W<sup>c</sup>  
or  
**Paclitaxel**  
80 mg/m<sup>2</sup> IV QW  
(3 weeks on/1 week off)

#### Primary endpoints

- PFS by BICR
- Overall survival

#### Secondary endpoints

- ORR
- HRQoL
- Pharmacokinetics
- Safety

#### Key exploratory endpoint

- Duration of response

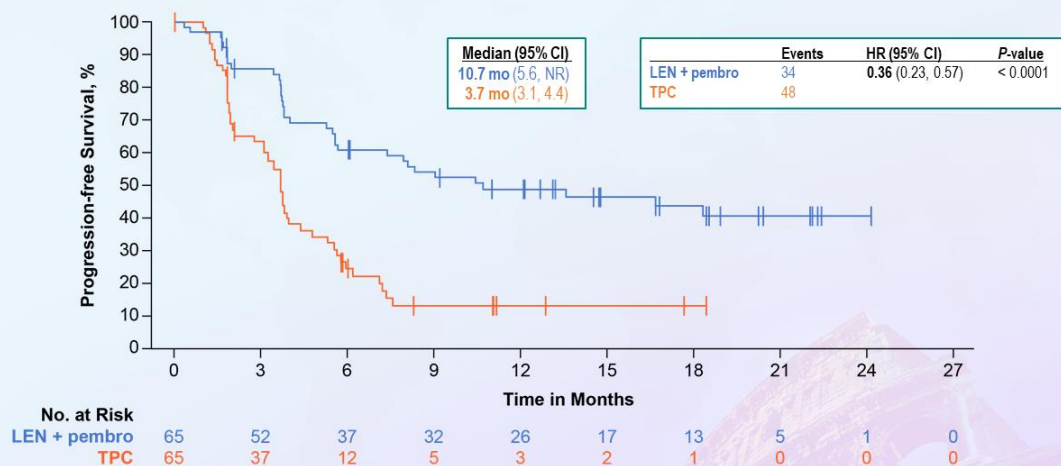
<sup>a</sup>Patients may have received up to 2 prior platinum-based CT regimens if 1 is given in the neoadjuvant or adjuvant treatment setting. <sup>b</sup>Maximum of 35 doses. <sup>c</sup>Maximum cumulative dose of 500 mg/m<sup>2</sup>.

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IV, intravenous; ORR, objective response rate; PFS, progression-free survival; pMMR, mismatch repair-proficient; PO, per os (by mouth); QD, once daily; Q3W, every 3 weeks; QW, once weekly.

# Phase III Keynote 775: Second line Pembrolizumab + Lenvatinib vs Chemotherapy in advanced EC. Resultados

## Progression-free Survival<sup>a</sup> of the dMMR Population

Makker\_KN775\_dMMR\_IGCS\_2021\_Oral



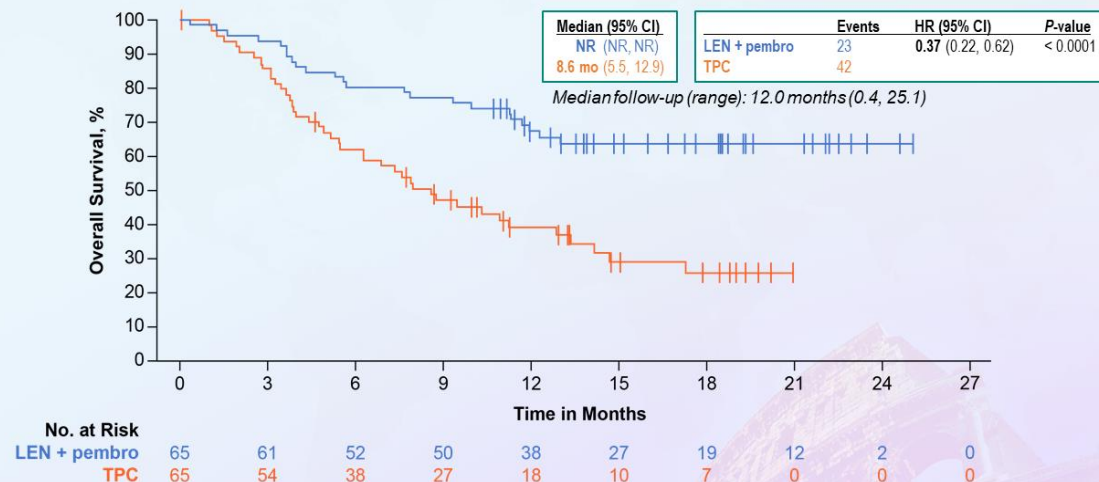
<sup>a</sup>By blinded independent central review per RECIST version 1.1.

dMMR, DNA mismatch repair-deficient; LEN + pembro, lenvatinib plus pembrolizumab; NR, not reached; TPC, treatment of physician's choice.

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## Overall Survival of the dMMR Population

Makker\_KN775\_dMMR\_IGCS\_2021\_Oral



dMMR, DNA mismatch repair-deficient; LEN + pembro, lenvatinib plus pembrolizumab; NR, not reached; TPC, treatment of physician's choice.

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## Phase III Keynote 775: Second line Pembrolizumab + Lenvatinib vs Chemotherapy in advanced EC. Resultados

Makker\_KN775\_dMMR\_IGCS\_2021\_Oral

### Objective Responses<sup>a</sup> of the dMMR Population

|                                                    | LEN + pembro<br>(n = 65)                  | TPC<br>(n = 65)                            |
|----------------------------------------------------|-------------------------------------------|--------------------------------------------|
| Objective response, % (95% CI)                     | 40.0 (28.0–52.9)                          | 12.3 (5.5–22.8)                            |
| Difference vs TPC, %; P-value                      | 27.7; 0.0002                              | --                                         |
| <b>Best overall response, %</b>                    |                                           |                                            |
| Complete response                                  | 13.8                                      | 3.1                                        |
| Partial response                                   | 26.2                                      | 9.2                                        |
| Stable disease                                     | 38.5                                      | 43.1                                       |
| Progressive disease                                | 10.8                                      | 23.1                                       |
| Not evaluable / assessed                           | 4.6 / 6.2                                 | 1.5 / 20.0                                 |
| <b>Median duration of response, months (range)</b> | NR (2.1 <sup>b</sup> –20.4 <sup>b</sup> ) | 4.1 (1.9 <sup>b</sup> –15.6 <sup>b</sup> ) |
| <b>Median time to response, months (range)</b>     | 2.9 (1.7–16.3)                            | 1.9 (1.8–3.7)                              |
| <b>Disease control rate<sup>c</sup>, %</b>         | 73.8                                      | 47.7                                       |

<sup>a</sup>By blinded independent central review per RECIST version 1.1; <sup>b</sup>No progressive disease reported by the time of the last disease assessment. <sup>c</sup>The proportion of participants who have best overall response of complete response, partial response, or stable disease achieved at ≥ 7 weeks after randomization.

dMMR, DNA mismatch repair-deficient; LEN + pembro, lenvatinib plus pembrolizumab; NR, not reached; TPC, treatment of physician's choice.

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# Phase III Keynote 775: Second line Pembrolizumab + Lenvatinib vs Chemotherapy in advanced EC. Resultados

Makker\_KN775\_dMMR\_IGCS\_2021\_Oral

## Safety Summary of the dMMR Population

|                                                                          | LEN + pembro<br>(n = 64) | TPC<br>(n = 63)  |
|--------------------------------------------------------------------------|--------------------------|------------------|
| Median duration of treatment, days (range)                               | 335.5 (2.0–762.0)        | 86.0 (1.0–331.0) |
| Patients with any TEAEs, %                                               | 100                      | 98.4             |
| Grade ≥ 3                                                                | 95.3                     | 73.0             |
| Patients with any TEAEs leading to dose reductions, % <sup>a</sup>       | 64.1                     | 12.7             |
| Patients with any-grade TEAEs leading to interruption, % <sup>b</sup>    | 71.9                     | 22.2             |
| LEN <sup>c</sup>                                                         | 60.9                     | -                |
| Pembro <sup>c</sup>                                                      | 59.4                     | -                |
| LEN + pembro                                                             | 39.1                     | -                |
| Patients with any-grade TEAEs leading to discontinuation, % <sup>b</sup> | 43.8                     | 6.3              |
| LEN <sup>c</sup>                                                         | 43.8                     | -                |
| Pembro <sup>c</sup>                                                      | 25.0                     | -                |
| LEN + pembro                                                             | 21.9                     | -                |

<sup>a</sup>Includes LEN only or TPC. <sup>b</sup>Includes LEN or pembro or LEN + pembro or TPC. <sup>c</sup>Regardless of action taken with the other drug in the combination arm.

dMMR, DNA mismatch repair-deficient; LEN, lenvatinib; pembro, pembrolizumab; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.



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## TEAEs With Frequency of ≥ 25% in Either Treatment Group

|                            | LEN + pembro (n = 64) | TPC (n = 63) |
|----------------------------|-----------------------|--------------|
| Patients with any TEAEs, % | 100                   | 98.4         |
| Hypothyroidism             | 68.8                  | 0            |
| Hypertension               | 56.3                  | 4.8          |
| Diarrhea                   | 51.6                  | 22.2         |
| Nausea                     | 50.0                  | 39.7         |
| Decreased appetite         | 48.4                  | 23.8         |
| Vomiting                   | 37.5                  | 22.2         |
| Anemia                     | 35.9                  | 47.6         |
| Fatigue                    | 32.8                  | 23.8         |
| Weight decreased           | 32.8                  | 6.3          |
| Dysphonia                  | 29.7                  | 0            |
| Proteinuria                | 28.1                  | 1.6          |
| Asthenia                   | 26.6                  | 27.0         |
| Arthralgia                 | 25.0                  | 4.8          |
| Neutropenia                | 10.9                  | 31.7         |

LEN + pembro, lenvatinib plus pembrolizumab; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.

# Conclusiones

- La clasificación TCGA ayuda a comprender la biología del cáncer de endometrio y las opciones terapéuticas más adecuadas en cada subtipo.
- Existe un biomarcador(dMMR/MSI-H) que es pronóstico y predictivo de respuesta a Inmunoterapia. La identificación en el tumor dMMR es clave para decidir la mejor estrategia terapéutica.
- El Estudio GARNET es el estudio en el que se han evaluado mas población de pacientes con dMMR/MSI-H
- Hasta la aprobación de Dostarlimab en 2ª línea de CE, no había SoC. Por tanto, teníamos una gran necesidad por cubrir.
- La inmunoterapia de agente único tiene altas tasas de respuesta en CE MMRd: Dostarlimab esta aprobado en Europa. Elevado porcentaje de respuestas y duración de las mismas con un perfil de toxicidad favorable

XXIV

# SIMPOSIO DE REVISIONES EN CÁNCER

*“Tratamiento médico del cáncer en el año 2022”*

## Gracias

