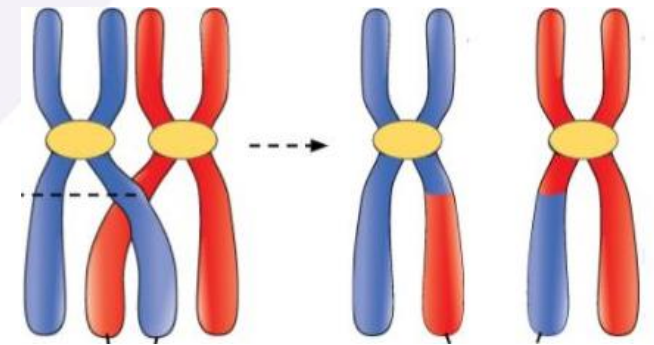




# Case series: use of olaparib in uncommon locations in patients with impaired homologous recombination.

- Héctor Carlos García-Díaz, María Larrosa-García<sup>1</sup>, Anna Farriols-Danés<sup>1</sup>, María Guerra-González<sup>1</sup>, Berta Renedo-Miró<sup>1</sup>, Carolina Valdivia-Vadell<sup>1</sup>, Lucas Rivera-Sánchez<sup>1</sup>, Carla Alonso-Martínez<sup>1</sup>, Maria J Carreras-Soler<sup>1</sup>, Maria Q Gorgas-Torner<sup>1</sup>

1. Department of Pharmacy. Vall d'Hebron Hospital Universitari. Barcelona, Spain.





Our DNA is constantly damaged,  
potentially leading to cancer.



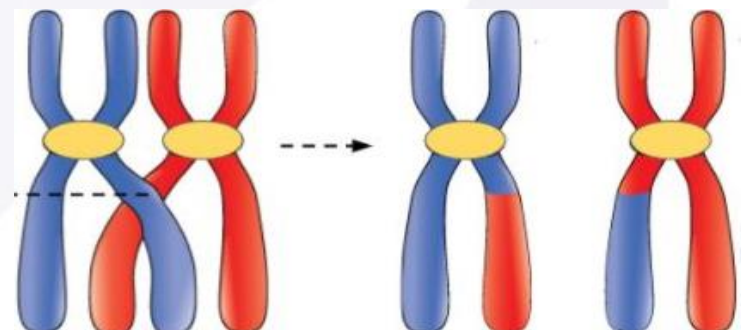
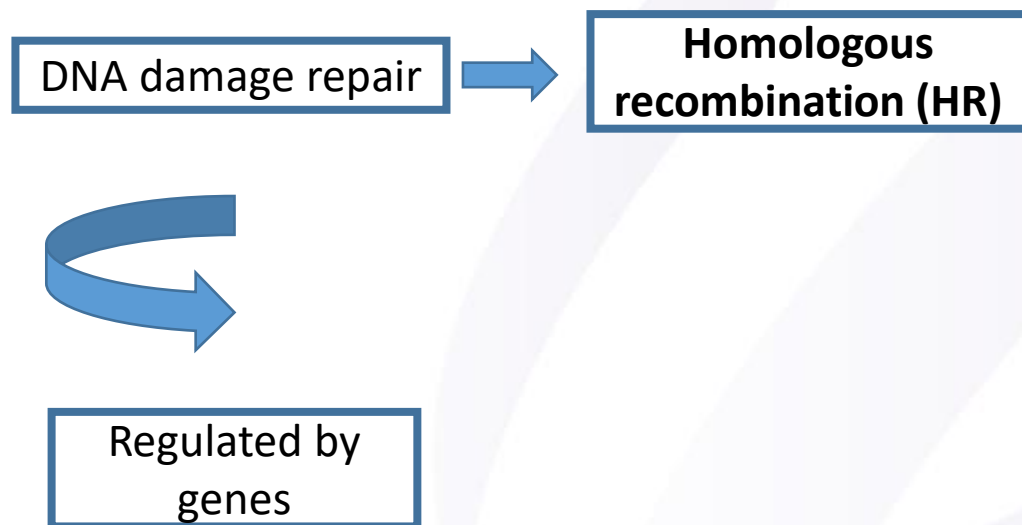


Our DNA is constantly damaged,  
potentially leading to cancer.



However, there are  
**mechanisms** that prevent  
this to happen...

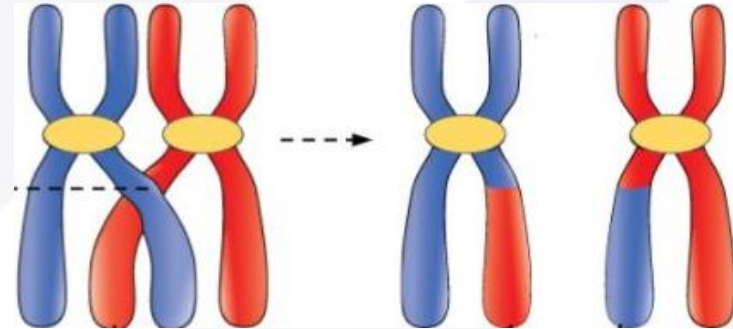






DNA damage repair

**Homologous  
recombination (HR)**



Regulated by  
genes

Category	Name
Homologous recombination repair	<b>ATM</b>
	BARD1
	<b>BRCA1</b>
	<b>BRCA2</b>
	BRIP1
	CHEK2
	NBN
	<b>PALB2</b>
	RAD51C
	RAD51D

HR deficiency (HRD) can be  
used as a predictor of  
response to certain therapies  
like **PARP inhibitors**...

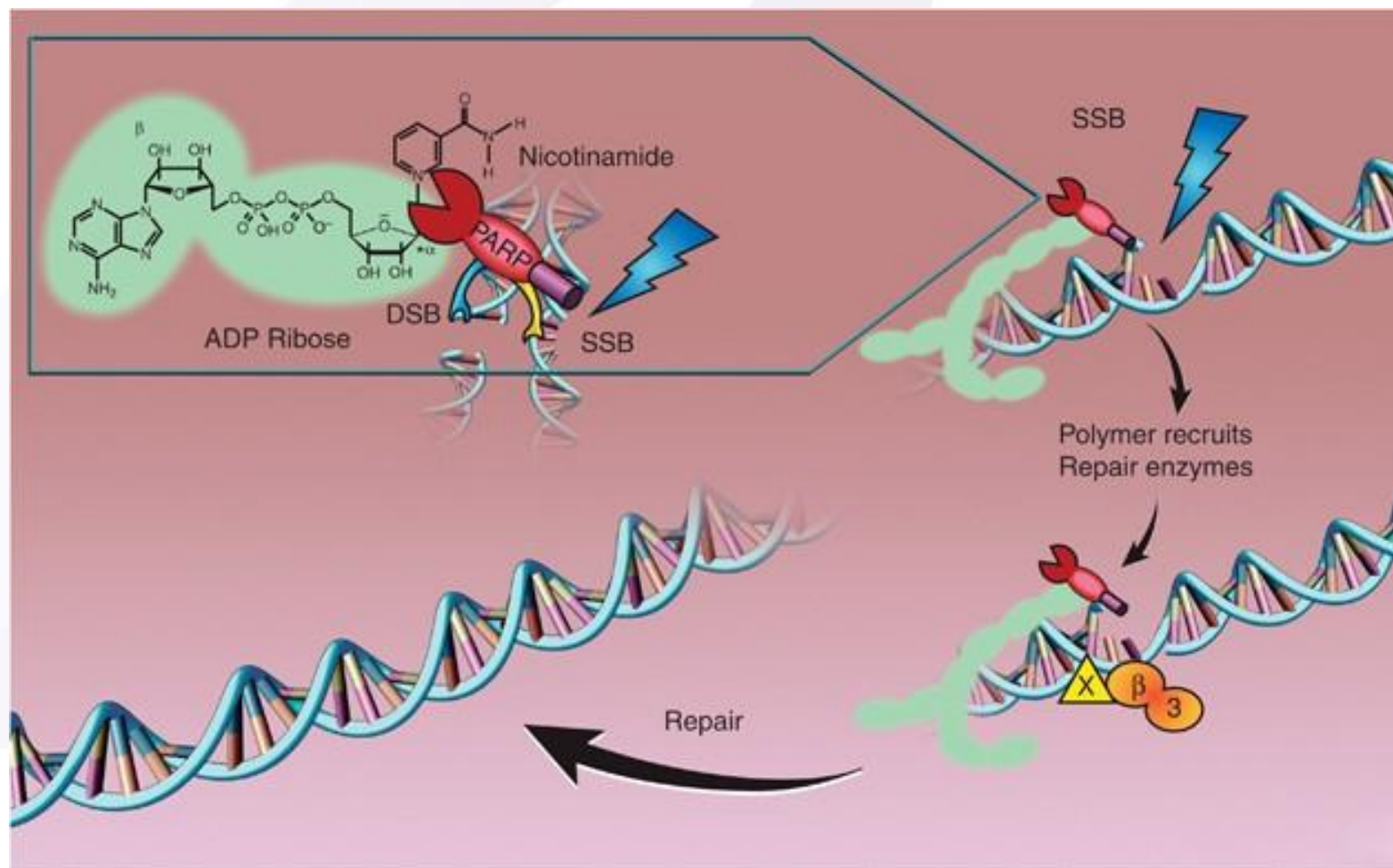


Modified from: H Kimura *et al.* 2022. Prognostic significance of pathogenic variants in *BRCA1*, *BRCA2*, *ATM* and *PALB2* genes in men undergoing hormonal therapy for advanced prostate cancer. *Br J Cancer*



# INTRODUCTION

PARP acts as an alternative repair mechanism when HR is impaired.



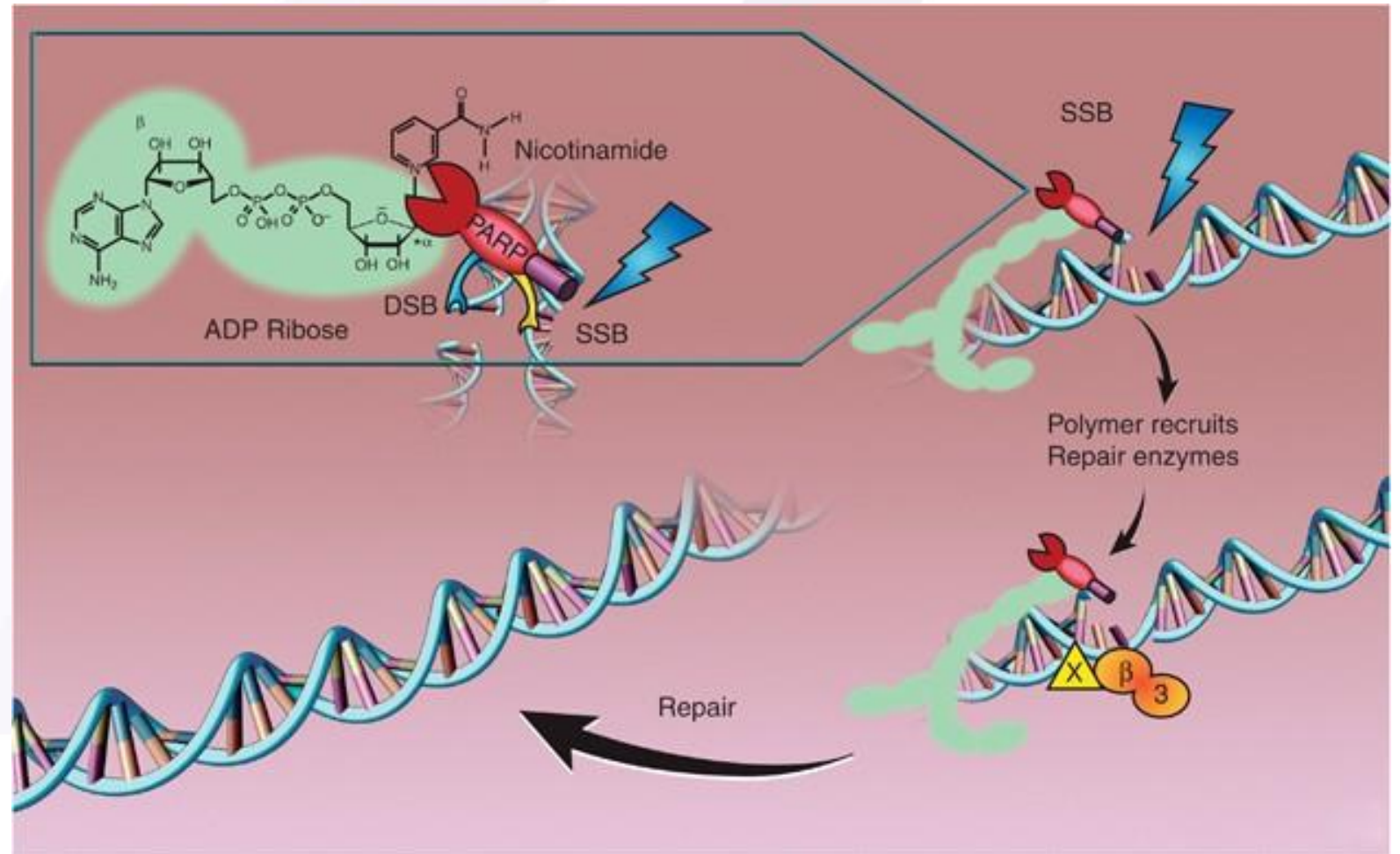
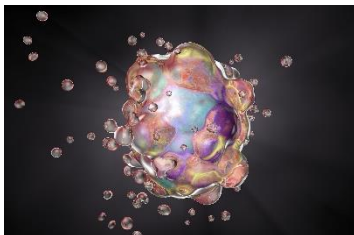


# INTRODUCTION

PARP acts as an alternative repair mechanism when HR is impaired.

So... if PARP is inhibited in  
cells with HRD...

**APOPTOSIS**





# INTRODUCTION

**Olaparib** is the first approved PARPi and currently has indication in: Ovarian, Breast, Pancreatic and Prostate cancer (FDA/EMA).



# INTRODUCTION

**Olaparib** is the first approved PARPi and currently has indication in:  
Ovarian, Breast, Pancreatic and Prostate cancer (FDA/EMA).

But **off-label indications** have been explored since 2015 in:

Primary endpoint  
Response Rate

Different locations (Phase II basket CT *Kaufman et al.*)

Other HR mutations than BRCA (Phase II CT *Mateo et al.*)

ORIGINAL REPORTS | Rapid Communications

**Olaparib Monotherapy in Patients With Advanced  
Cancer and a Germline *BRCA1/2* Mutation**



[Bella Kaufman](#), [Ronnie Shapira-Frommer](#), [Rita K. Schmutzler](#), [M. William Audeh](#),  
[Michael Friedlander](#), [Judith Balmaña](#)...

B Kaufmann *et al.* 2015. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol.*

Clinical Trial > [N Engl J Med.](#) 2015 Oct 29;373(18):1697-708. doi: 10.1056/NEJMoa1506859.

**DNA-Repair Defects and Olaparib in Metastatic  
Prostate Cancer**

[Joaquin Mateo](#) <sup>1</sup>, [Suzanne Carreira](#), [Shahneen Sandhu](#), [Susana Miranda](#), [Helen Mossop](#),

*J Mateo et al.* 2015. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. *N Engl J Med.*



# INTRODUCTION

[Journal of Clinical Oncology](#) > [List of Issues](#) > [Volume 33, Issue 3](#) >

**ORIGINAL REPORTS** | Rapid Communications

**Olaparib Monotherapy in Patients With Advanced Cancer and a Germline *BRCA1/2* Mutation**

Check for updates

[Bella Kaufman](#), [Ronnie Shapira-Frommer](#), [Rita K. Schmutzler](#), [M. William Audeh](#),  
[Michael Friedlander](#), [Judith Balmaña](#)...

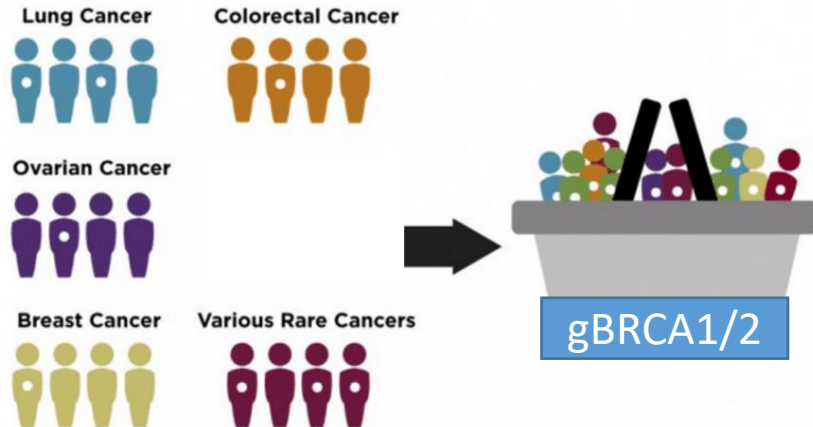
Response rate as the  
primary endpoint.

Ovarian: 193 patients  
Breast: 62 patients  
Pancreatic: 23 patients  
Prostate: 8 patients

“Others group” (n=12)

**Biliary tract: 4 patients**  
**Bladder: 2 patients**  
**Lung: 3 patients**  
**Colorectum: 1 patient**  
**Esophagus: 1 patient**  
**Uterus: 1 patient**

Stable disease in 58.3% of  
patients that persisted >8weeks





# INTRODUCTION

Clinical Trial > N Engl J Med. 2015 Oct 29;373(18):1697-708. doi: 10.1056/NEJMoa1506859.

## DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

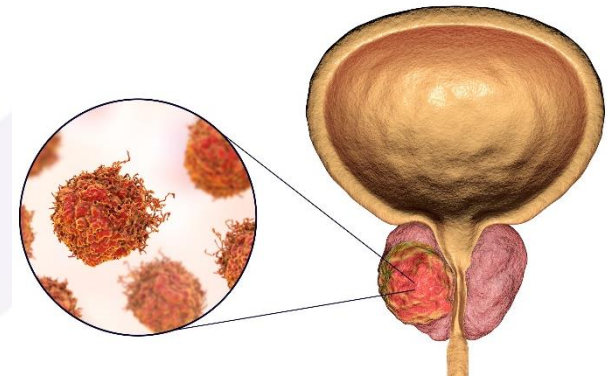
Joaquin Mateo<sup>1</sup>, Suzanne Carreira, Shahneen Sandhu, Susana Miranda, Helen Mossop,

Response rate as the  
primary endpoint.

→ 49 patients evaluated → 16 (33%) had a response.

14/16 (88%) = HRD

BRCA (7)  
ATM (4)  
BRCA/FANCA (1)  
PALB2 (1)  
HDAC2 (1)





# OBJECTIVE

**Describe the effectiveness and safety of olaparib  
off-label indications...**





# OBJECTIVE



**Describe the effectiveness and safety of olaparib  
off-label indications...**

**→ In patients with HRD and different solid  
tumors than those authorized.**



# METHODS

## **Design and patients:**

-Single-center, observational, retrospective study.

-Patients with tumor sites other than those authorized who initiated olaparib between June 2019 and April 2022 were included.

**Variables:** Age, sex, Eastern Cooperative Oncology Group performance status (ECOG), mutation, initial dosing, type (maintenance or not) and line of treatment, dose reductions, adverse events (AEs), best overall response (BOR), progression-free survival (PFS) and overall survival (OS).

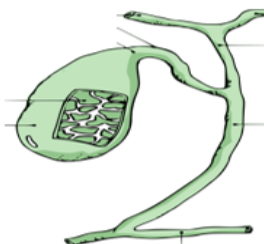
**Data:** Obtained from the clinical history and the outpatient dispensing program





## RESULTS

Four patients with metastatic disease were included, with a baseline ECOG of 1. No dose reductions were required.

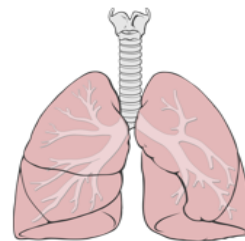
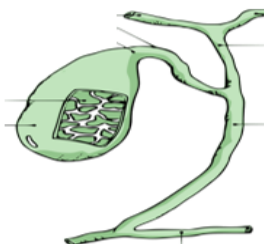


Type and tumor localization	Intrahepatic cholangiocarcinoma
Age/sex	66 years / Female
Mutated HR gene	<i>PALB2</i>
Posology	Capsules 400mg/12h
Type of treatment	Maintenance (3 <sup>rd</sup> line)
BOR	Stability
PFS	3.4 months
OS	4.1 months
AEs	Anemia G2



## RESULTS

Four patients with metastatic disease were included, with a baseline ECOG of 1. No dose reductions were required.

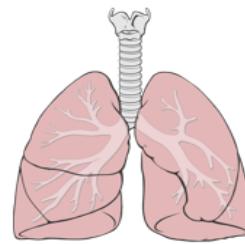
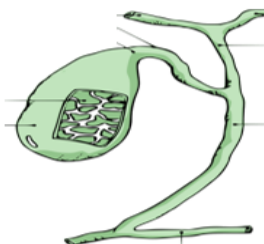


Type and tumor localization	Intrahepatic cholangiocarcinoma	Non-small cell lung cancer
Age/sex	66 years / Female	71 years / Female
Mutated HR gene	<i>PALB2</i>	<i>ATM</i>
Posology	Capsules 400mg/12h	Tablets 300mg/12h
Type of treatment	Maintenance (3 <sup>rd</sup> line)	Treatment (5 <sup>th</sup> line)
BOR	Stability	Stability
PFS	3.4 months	5.6 months
OS	4.1 months	10.2 months
AEs	Anemia G2	Asthenia G2



## RESULTS

Four patients with metastatic disease were included, with a baseline ECOG of 1. No dose reductions were required.

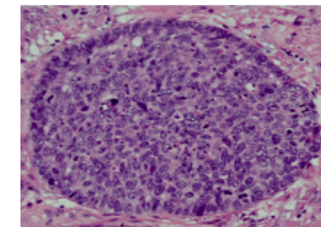
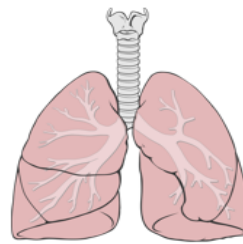
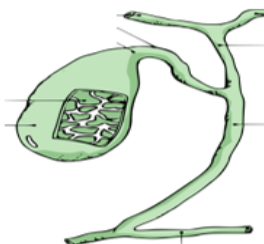


Type and tumor localization	Intrahepatic cholangiocarcinoma	Non-small cell lung cancer	<i>BRAF/EGFR</i> wt colorectal cancer
Age/sex	66 years / Female	71 years / Female	29 years / Male
Mutated HR gene	<i>PALB2</i>	<i>ATM</i>	<i>gBRCA2</i>
Posology	Capsules 400mg/12h	Tablets 300mg/12h	Tablets 300mg/12h
Type of treatment	Maintenance (3 <sup>rd</sup> line)	Treatment (5 <sup>th</sup> line)	Treatment (3 <sup>rd</sup> line)
BOR	Stability	Stability	Progression
PFS	3.4 months	5.6 months	1.4 months
OS	4.1 months	10.2 months	1.8 months
AEs	Anemia G2	Asthenia G2	None



## RESULTS

Four patients with metastatic disease were included, with a baseline ECOG of 1. No dose reductions were required.



Type and tumor localization	Intrahepatic cholangiocarcinoma	Non-small cell lung cancer	<i>BRAF/EGFR</i> wt colorectal cancer	Breast neuroendocrine tumor
Age/sex	66 years / Female	71 years / Female	29 years / Male	44 years / Female
Mutated HR gene	<i>PALB2</i>	<i>ATM</i>	<i>gBRCA2</i>	<i>gBRCA2</i>
Posology	Capsules 400mg/12h	Tablets 300mg/12h	Tablets 300mg/12h	Tablets 300mg/12h
Type of treatment	Maintenance (3 <sup>rd</sup> line)	Treatment (5 <sup>th</sup> line)	Treatment (3 <sup>rd</sup> line)	Maintenance (2 <sup>nd</sup> line)
BOR	Stability	Stability	Progression	Progression
PFS	3.4 months	5.6 months	1.4 months	1.3 months
OS	4.1 months	10.2 months	1.8 months	5.4 months
AEs	Anemia G2	Asthenia G2	None	Vomiting G2



# CONCLUSION

- We have described the off-label use of olaparib in 4 patients with HRD in uncommon tumor locations.
- Safety was adequate and similar to previous studies.
- **Further studies are needed to assess the efficacy and safety of olaparib in patients with HRD in new tumor sites.**
- **Currently, there are CT ongoing analyzing olaparib combination with antiangiogenics/ICIs.**