



THIRD ANNUAL
ISSPP
Congress 2022

*International Society
for the Study of Pleura
and Peritoneum*



PLENARY ABSTRACT | COLORECTAL CANCERS SESSION

Combination of Oxaliplatin+ATRi+Anti-PD1+for Treatment of Peritoneal Metastasis of Colorectal Origin is Highly Effective

Céline Gongora, PhD

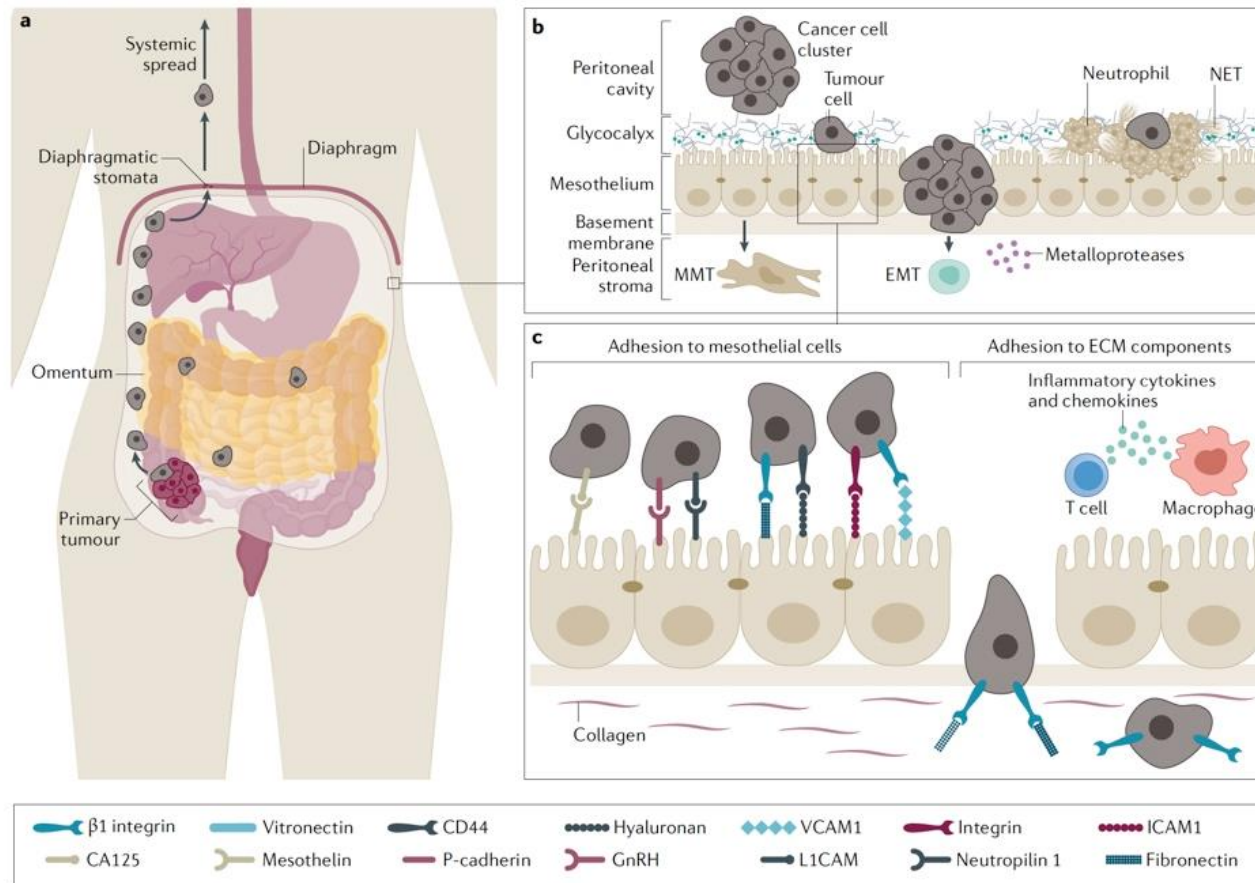
PI Drug Resistance and New Cancer Therapies
IRCM, INSERM, Montpellier, France

Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Peritoneal carcinomatosis of colorectal origin



Cortes Guiral D., ... , Sgarbura O, Turaga K et al. Nature Primers Rev, 2022

- ➔ 3rd most common site of metastasis from colorectal cancer
- ➔ 5-year overall survival : 40%

Three clinical situations

Resectable

- Cytoreduction (CSR) +/- HIPEC
- Perioperative chemotherapy

Borderline

- Induction chemotherapy
- CSR +/- HIPEC

Non resectable

- Chemotherapy
- PIPAC +/- sCT

Taibi A, Sgarbura O. ASO, 2022

Unicancer Prodiges 7 trial design

Peritoneal carcinomatosis of colorectal origin

Surgery: complete surgical resection ≤ 1 mm

RANDOMIZE

Stratification :

- Centre
- Residual tumor status (R0/R1 vs R2 ≤ 1 mm)
- Prior regimens of systemic chemotherapy
- Neoadjuvant Chemotherapy

with HIPEC

without HIPEC

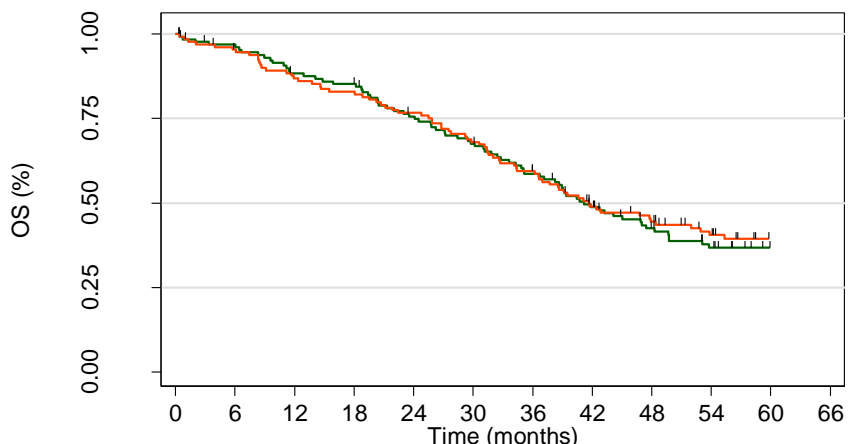
1:1

For both arms:

Patients received systemic chemotherapy for 6 months, either pre-operative, post-operative, or both

No PCI stratification

Quénet F et al, Lancet Oncol, 2022



| Number at risk | | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 | 66 |
|----------------|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|
| Non HIPEC | 132 | 124 | 113 | 109 | 94 | 83 | 72 | 56 | 45 | 36 | 27 | 22 | |
| HIPEC | 133 | 123 | 111 | 106 | 98 | 87 | 74 | 58 | 49 | 37 | 30 | 22 | |

— Non HIPEC — HIPEC

Median Follow Up: 64 months [95% CI:58.9-69.8]

| | HIPEC | Non-HIPEC | P-value |
|-----------------------------------|------------------|------------------|---------|
| Median Survival (months) [95% CI] | 41.7 [36.2-52.8] | 41.2 [35.1-49.7] | 0.995 |
| 1-year Survival | 86.9% | 88.3% | |
| 5-year Survival | 39.4% | 36.7% | |

HR=1.00: 95%CI [0.73 - 1.37] p=0.995

Oxaliplatin Resistance?

Identification of new therapeutic targets to overcome oxaliplatin resistance

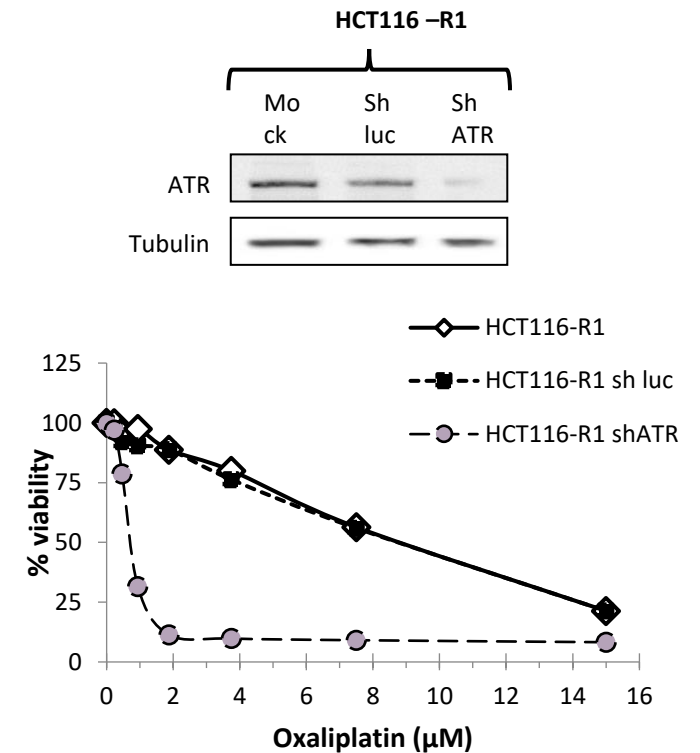
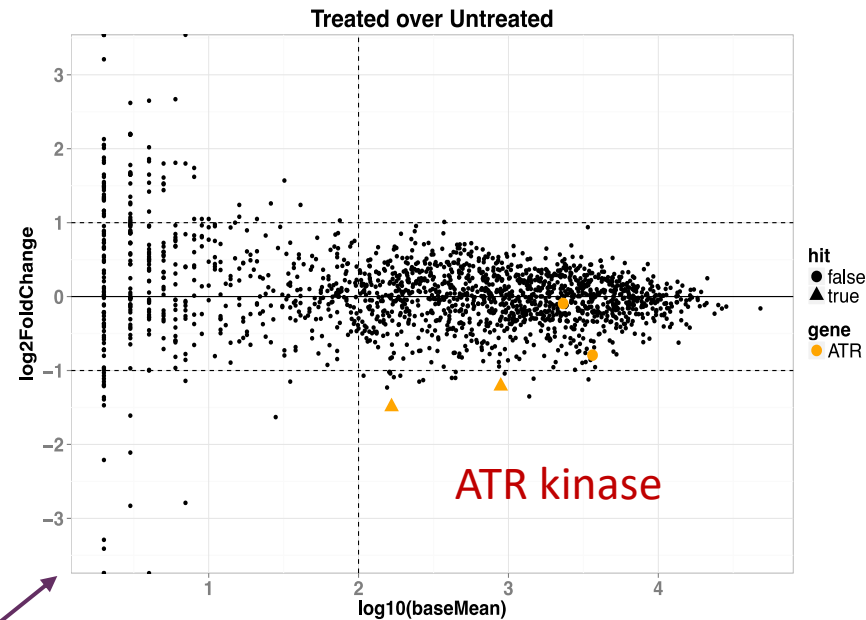
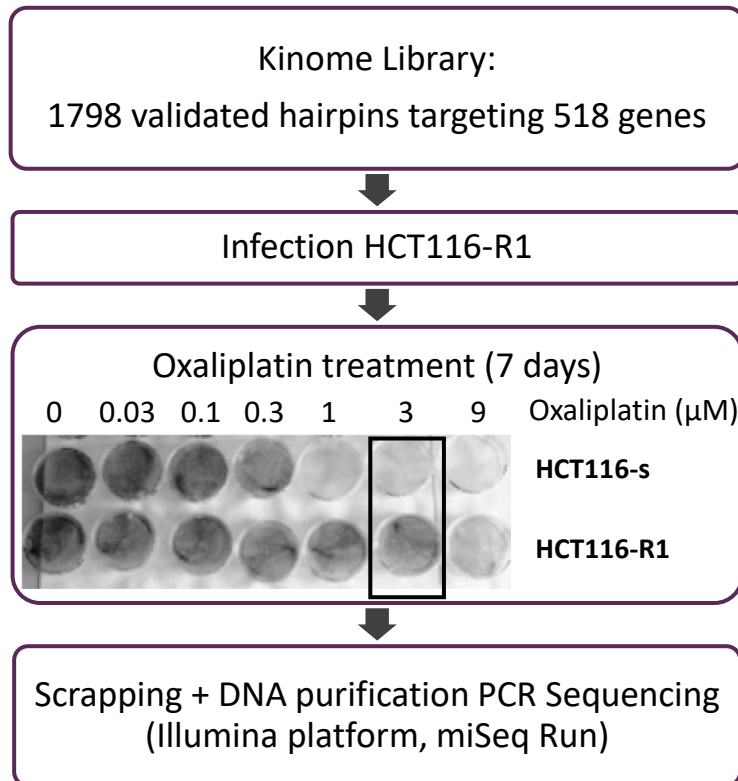
RNAi-based loss of function genetic screening
(Synthetic Lethality screening) →

| Sensitive Cells | Oxaliplatin resistant cells |
|----------------------------|------------------------------|
| HCT116 (IC50: 0.3 μ M) | HCT116-R1 (IC50: 10 μ M) |

Coll. R. Beijersbergen, NKI, Netherland

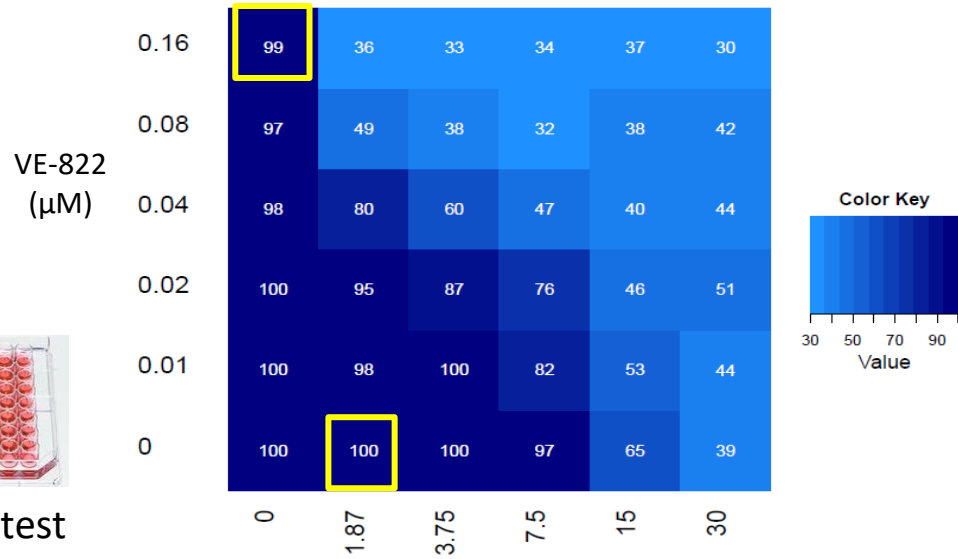
Gourdier et al, FEBS letter, 2002

Identify genes whose inhibition confers sensitivity

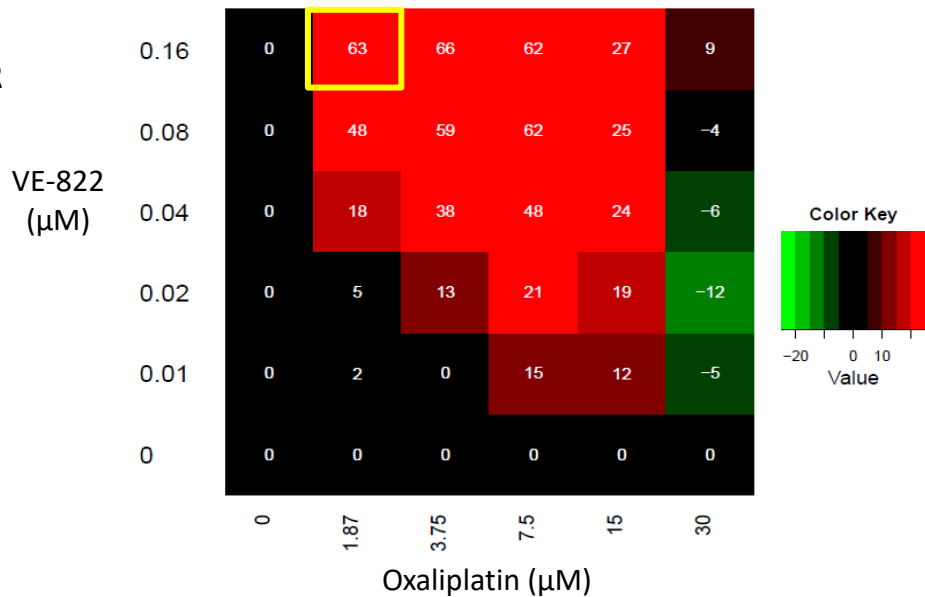


ATR pharmacologic inhibition is synergistic with oxaliplatin

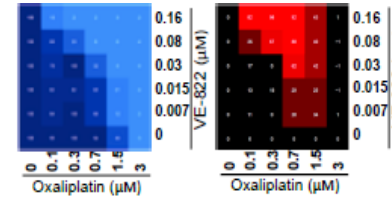
VIABILITY MATRIX



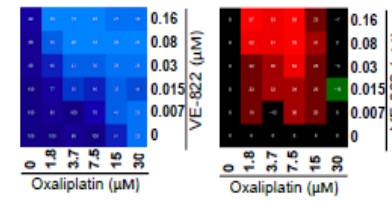
SYNERGY MATRIX



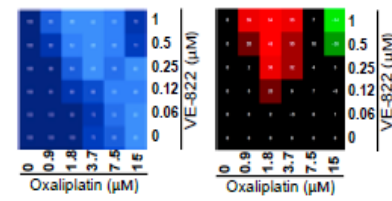
HCT116



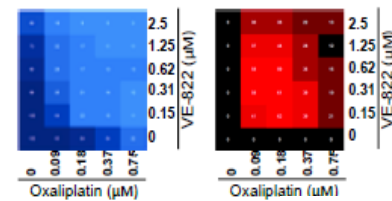
HCT116-R1



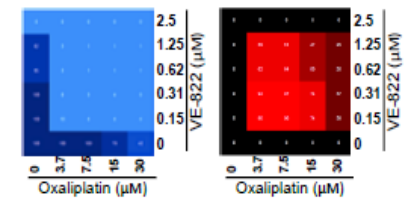
HCT116-R2



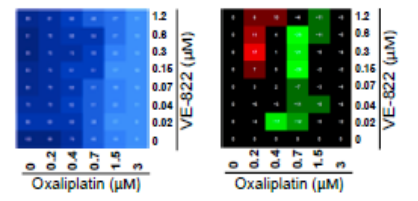
SW48



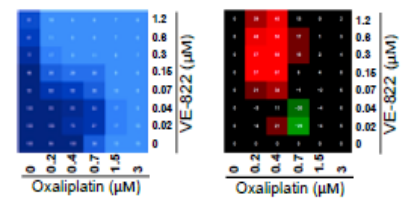
SW48-R



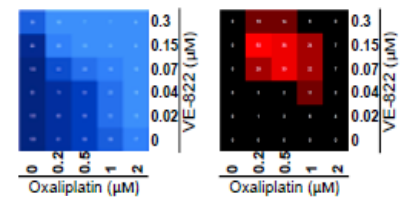
SW480



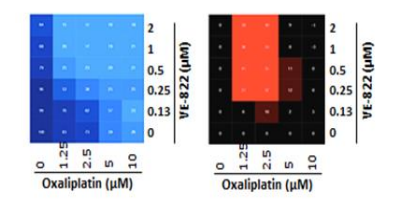
SW620



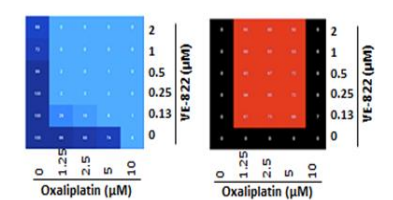
HT29



CT 26



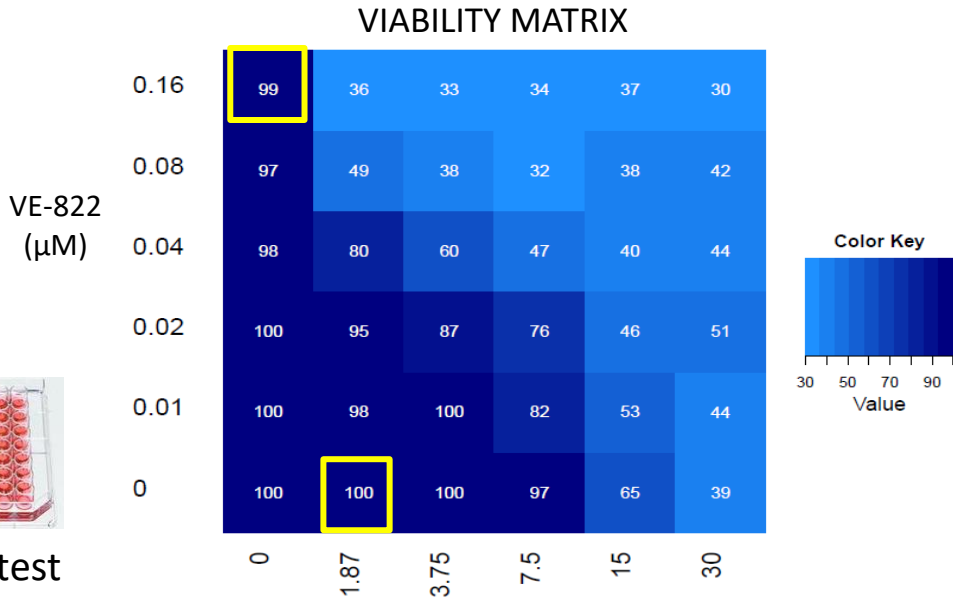
MC 38



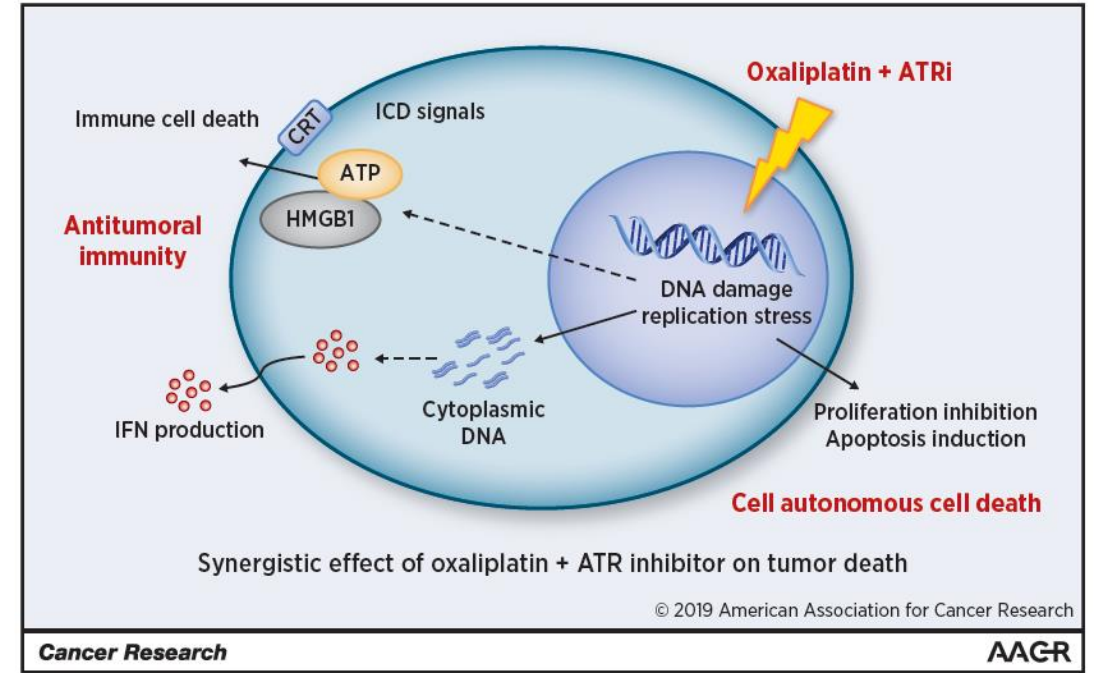
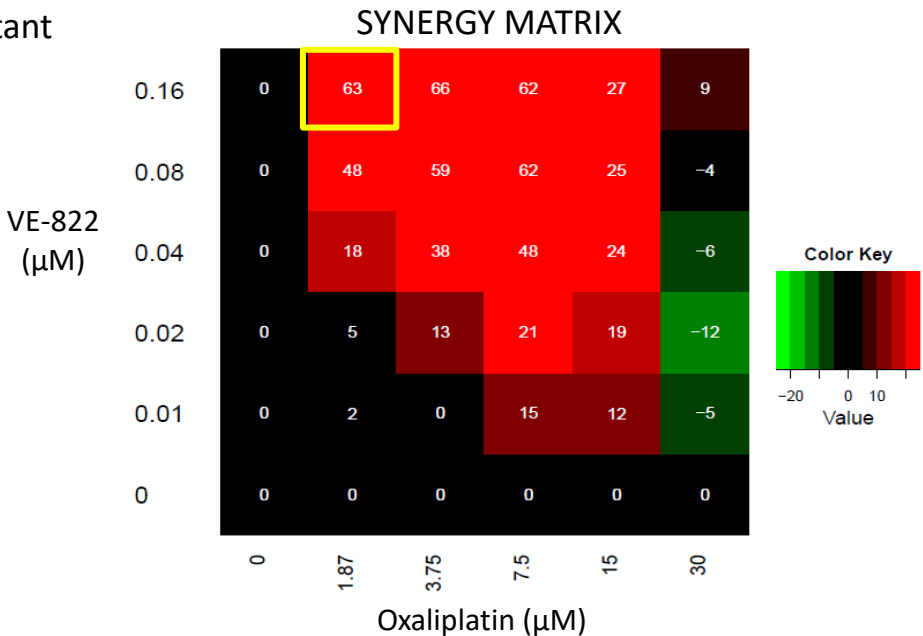
SRB cytotoxic test

HCT116-R1:
oxaliplatin resistant
cells
VE-822: ATR
inhibitor

ATR pharmacologic inhibition is synergistic with oxaliplatin



SRB cytotoxic test
HCT116-R1:
oxaliplatin resistant
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VE-822: ATR
inhibitor



Combes et al, Cancer Research, 2019

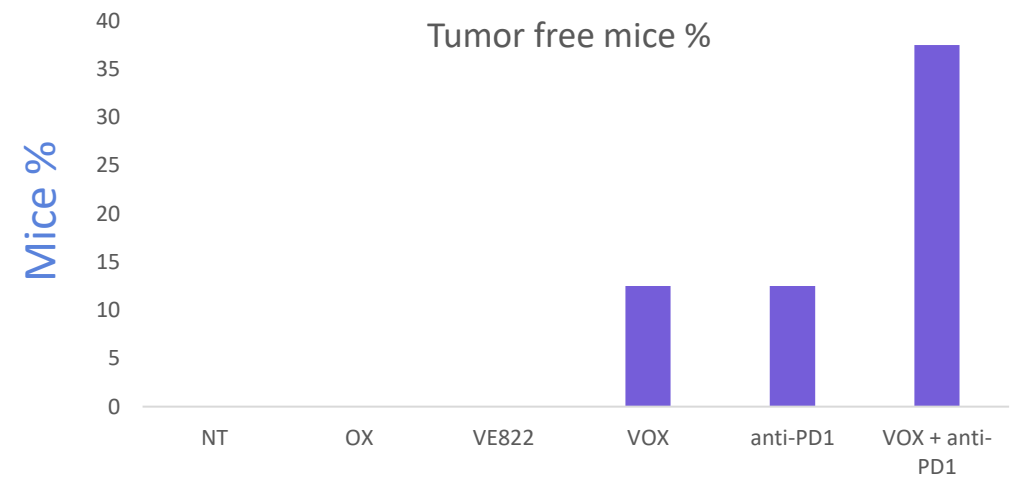
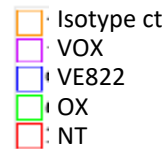
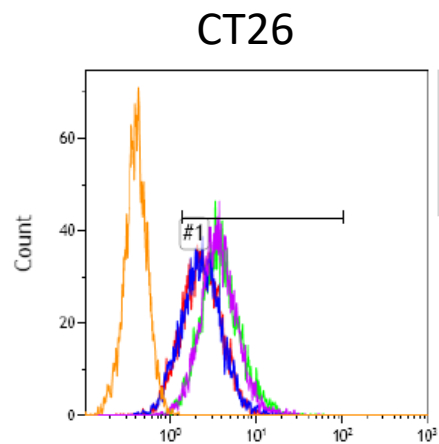
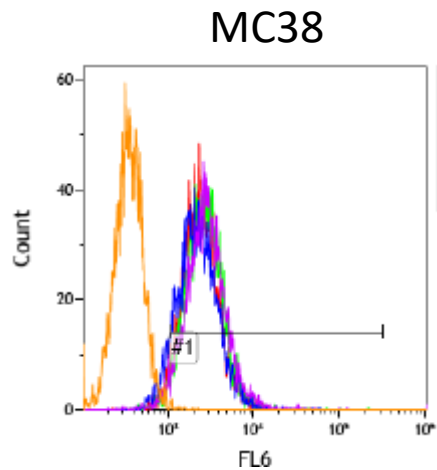
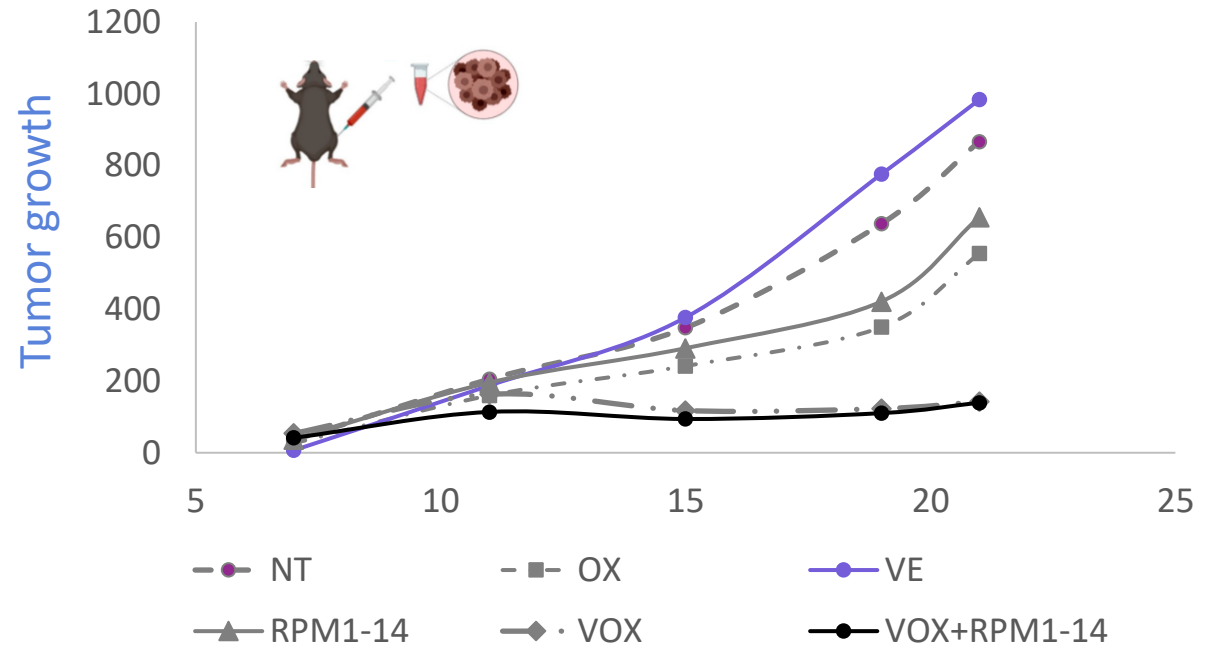
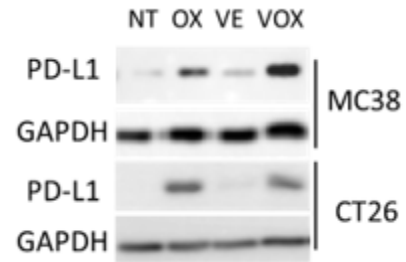
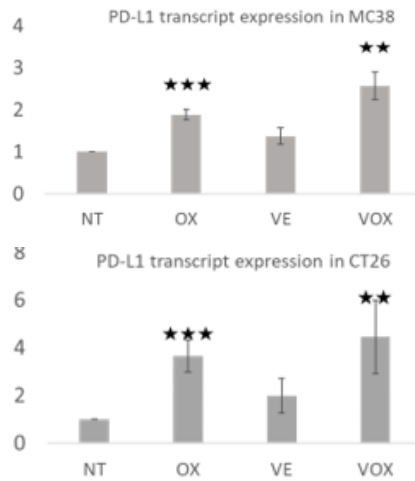
Anti-PD1 addition?

Improve patients treatments with a new therapeutic combination :

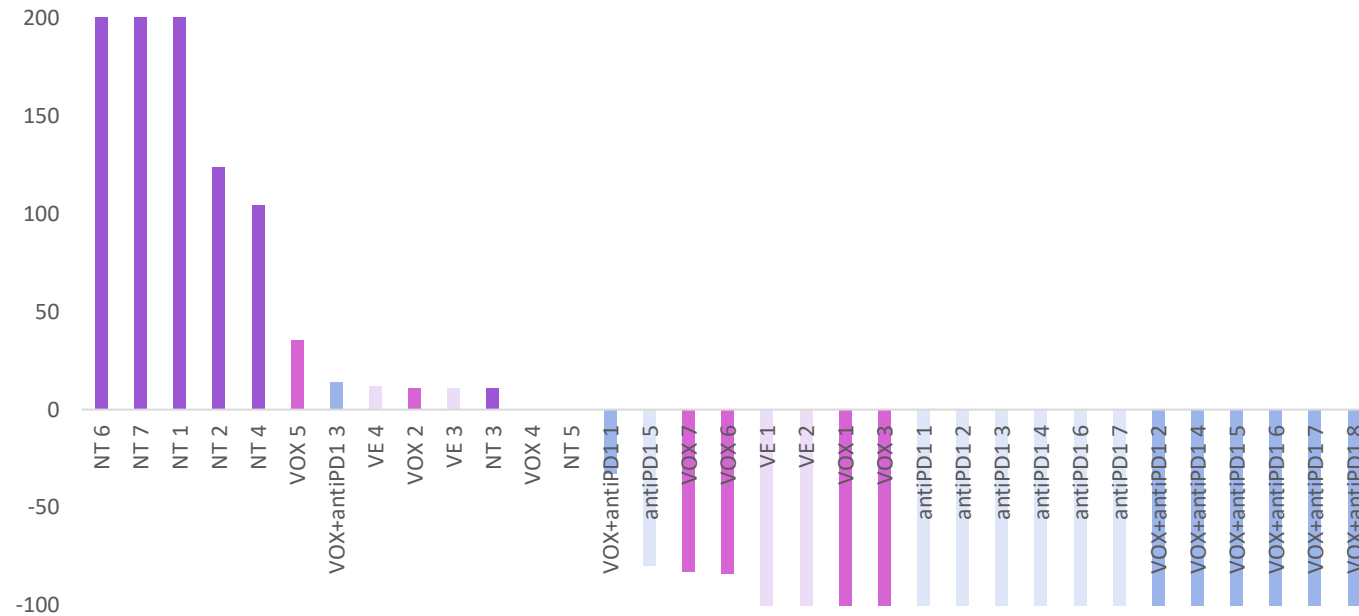
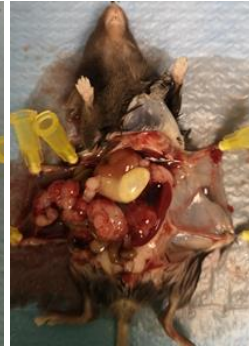
- Ve-822 : ATR inhibitor to limit oxaliplatin resistance
- Oxaliplatin : Standard chemotherapy
- Anti-PD1 : Approved for metastatic colorectal cancer MSI-H

Combinaison VOX+anti-PD1 in vivo: syngenic model, subcutaneous

PDL1 regulation

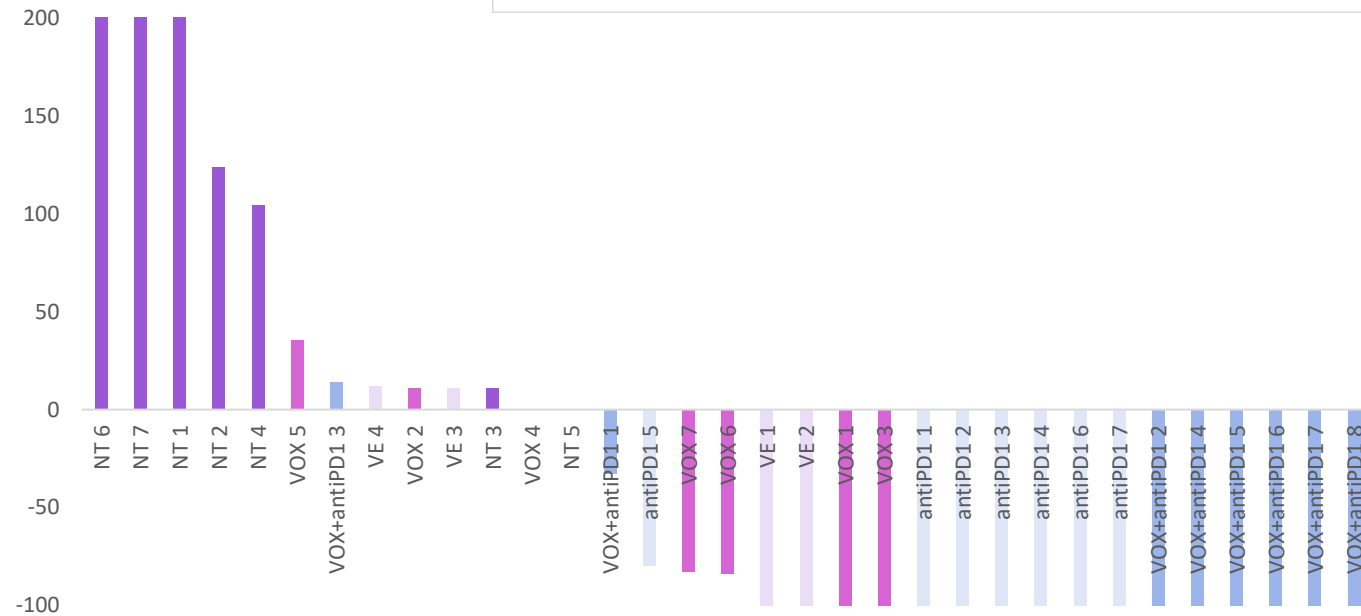
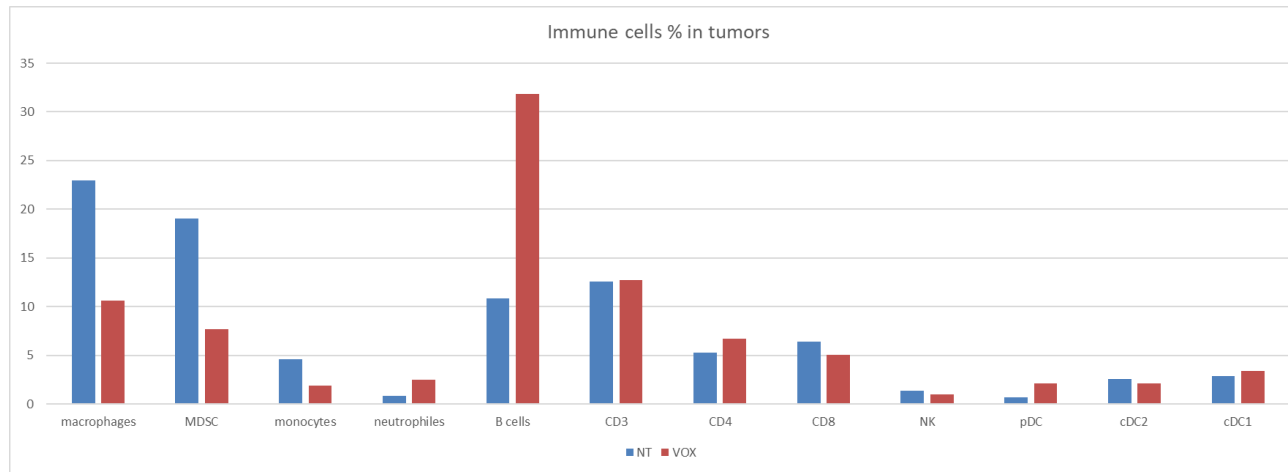


Combinaison VOX+anti-PD1 in vivo: orthotopic syngenic model PERITONEAL CARCINOMATOSIS



| | Tumor free mice % | Protected mice % |
|----------------|-------------------|------------------|
| VOX | 44 | 50 |
| anti-PD1 | 66 | 50 |
| VOX + anti-PD1 | 66 | 100 |

Combinaison VOX+anti-PD1 in vivo: orthotopic syngenic model PERITONEAL CARCINOMATOSIS

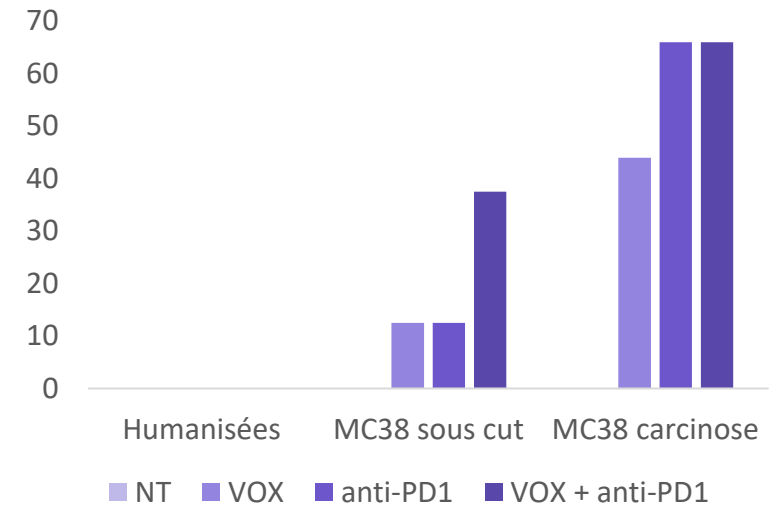


| | Tumor free mice % | Protected mice % |
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CONCLUSION

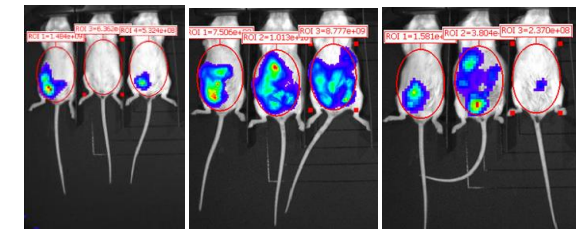
| | Cells | origine of the cells | Graft | Mice model |
|---|----------|----------------------|-----------------|----------------|
| 1 | HCT116-R | Human | subcutaneous | Humanized Nude |
| 3 | MC-38 | Murin | subcutaneous | C57BL/6 |
| 4 | MC-38 | Murin | intraperitoneal | C57BL/6 |

tumor free mice % depending on mice model

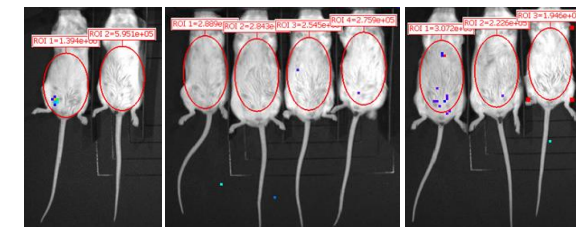


- Oxaliplatine + ATRi +anti-PD1 is efficient in peritoneal carcinomatosis (dMMR cells)
- Induce complete regression of the tumor + protection
- Favor tumor infiltration of neutrophils and B cells, and prevent macrophages, MDSCs and monocytes
- Current experiment on pMMR cells →

NT



VOX + anti-PD1



GONGORA'S TEAM

Véronique Garambois
Ileana Corbeau
Margot Vianney-Laud
Alexandra Fauvre
Laura Jeanson
Nadia Vie
Diego Tosi
Olivia Sgarburra
Céline Gongora

ICRM

Julien Faget
HA Michaud
Julie Constanzo
Salima Atis
Marion Larroque



ICM

Lakhdar Khellaf
Diego Tosi
Olivia Sgarburra,