2020 ASCO®

Gynécologie

Dr Anne Floquet (oncologue médicale, Institut Bergonié)

Points Forts

- Tumeurs de l'ovaire en rechute:
  - Place de la chirurgie : essai randomisé phase III **DESKTOP III (A du Bois)**
    - Résultats finaux sur la survie globale
  - Olaparib en maintenance: essai randomisé phase III **SOLO 2 (A Poveda)**
    - Résultats finaux sur la survie globale

- Tumeurs trophoblastiques gestationnelles (TTG)
  - Apport de l'immunothérapie: essai phase II **TROPHIMMUN (B You)**

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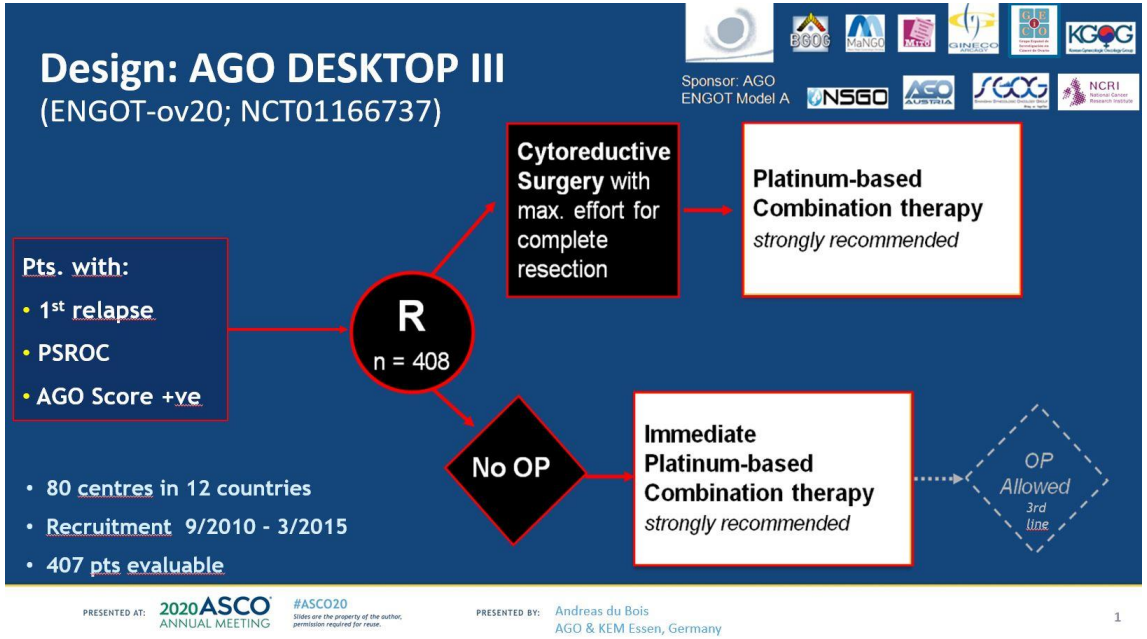
Essai DESKTOP III

Design



Rationnel

- Validation de la place d'une chirurgie complète à la rechute
- En situation de 1 ère rechute platine sensible
- Score AGO + :
  - ECOG 0
  - Aucun résidu à la chirurgie initiale
  - Volume ascite < 500 ml

Validation essais DESKTOP I et II

Harter P, du Bois A, Hahmann M, et al. Ann Surg Oncol 2006
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Objectif principal: survie globale

Objectifs secondaires:

SSP, taux de résection complète, morbi-mortalité

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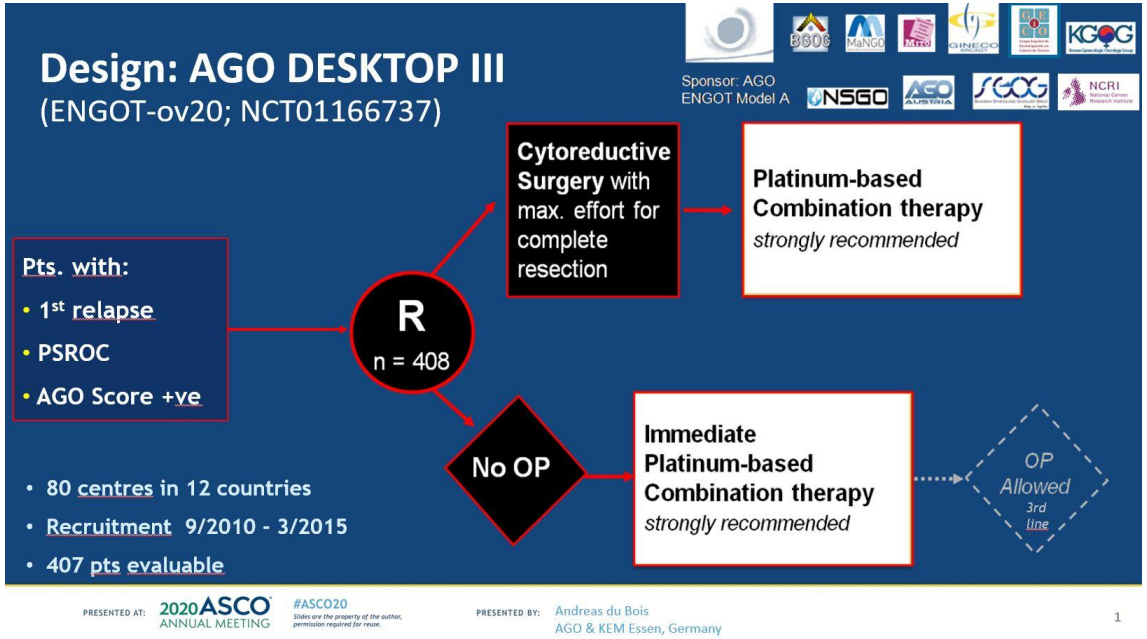

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Analyse intermédiaire prévue à 122 Evts
ASCO 2017: présentation bénéfice en SSP

Essai DESKTOP III

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Essai DESKTOP III

AGO DESKTOP III: Surgery arm

(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

Duration of surgery (minutes; median / quartiles)	222 (150 - 300)
GI-tract resection	35.8%
Stoma diversion temporary / permanent	3.7% / 4.2%
Blood loss (ml; median / quartiles)	250 (50 - 500)
RBC transfusion	17.6%
post-OP fever > 38°C	4.8%
Antibiotics (mainly for urinary tract infections)	19.7%
Re-laparotomy rate	3.7%
30-/90- days mortality	0 / 1 pat. (0.5%)
Macroscopic complete resection rate	**74.2%**

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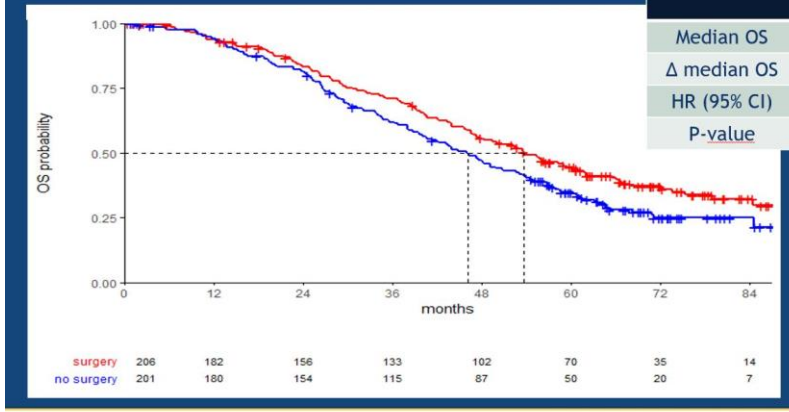

	surgery	no surgery
Median OS	53.7 mos	46.0 mos
Δ median OS	7.7 mos	
HR (95% CI)	0.75 (0.58 - 0.96)	
P-value	0.02	

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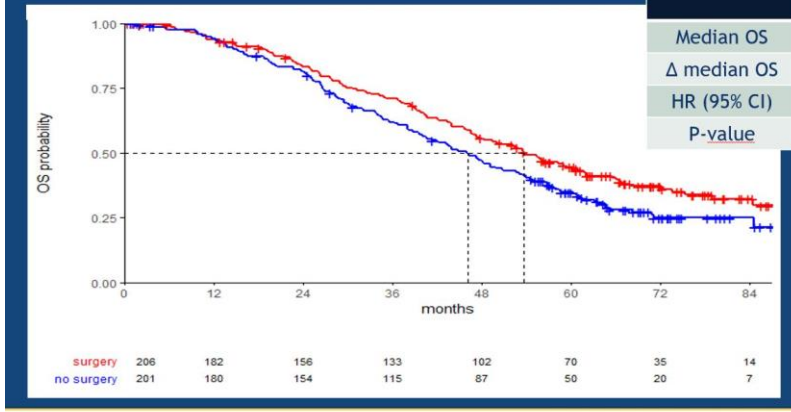

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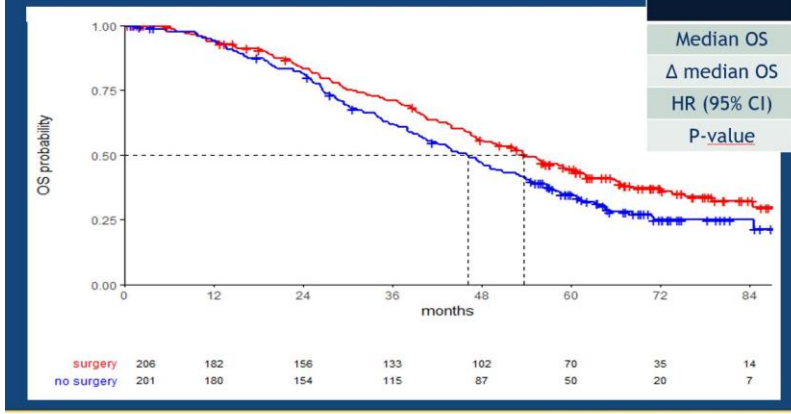

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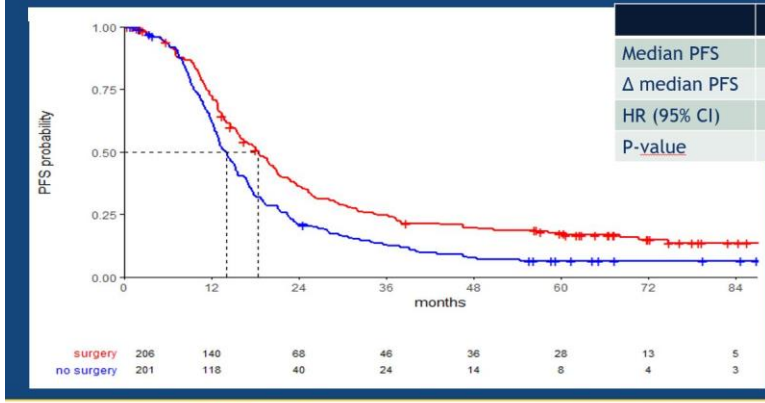
AGO DESKTOP III: Outcome 2 (PFS, ITT population, after DB closure Jan 17th 2020)
(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)



	surgery	no surgery
Median PFS	18.4 mos	14.0 mos
Δ median PFS	4.4 mos	
HR (95% CI)	0.66 (0.54 - 0.82)	
P-value	< 0.001	

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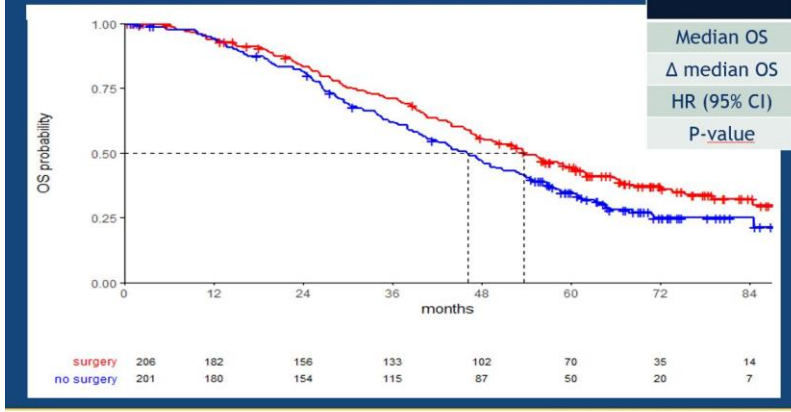

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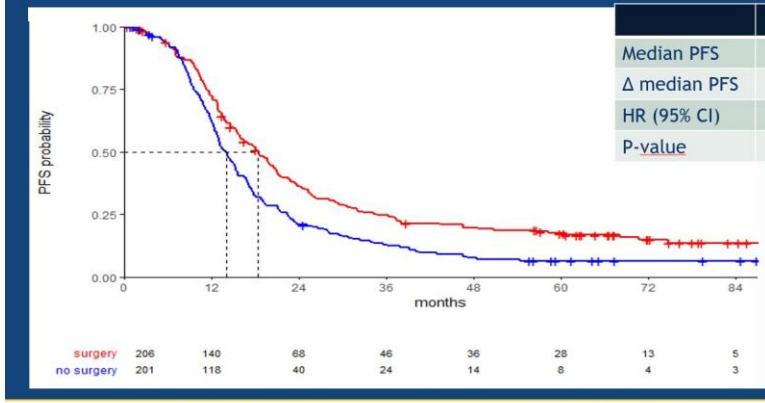

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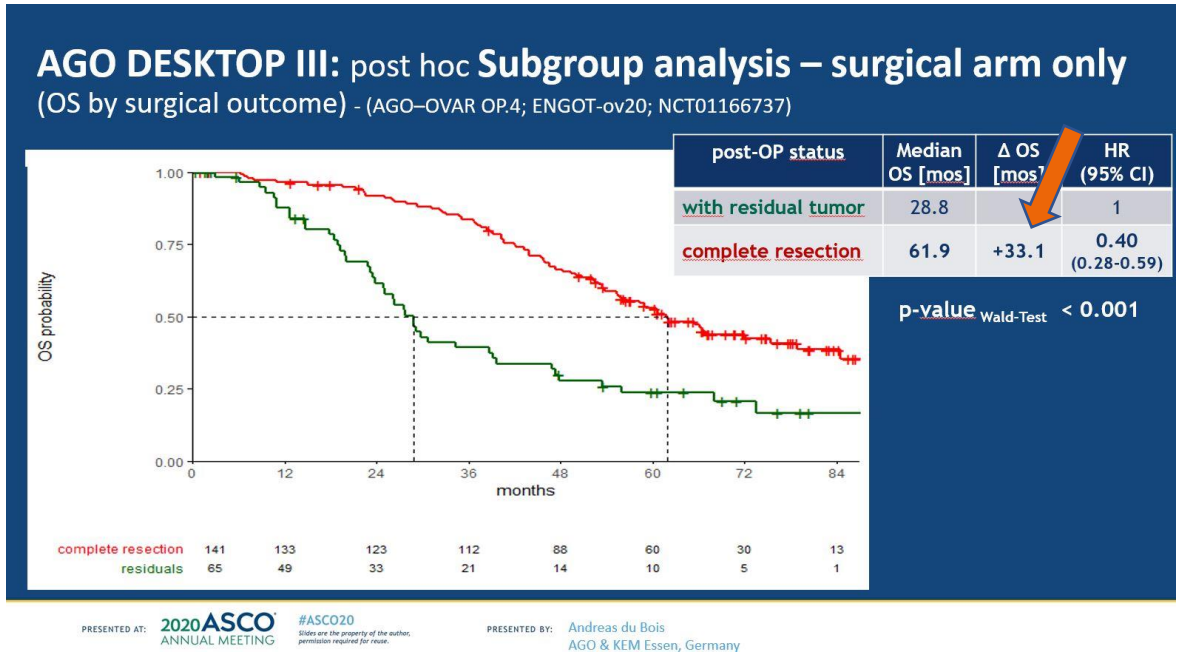
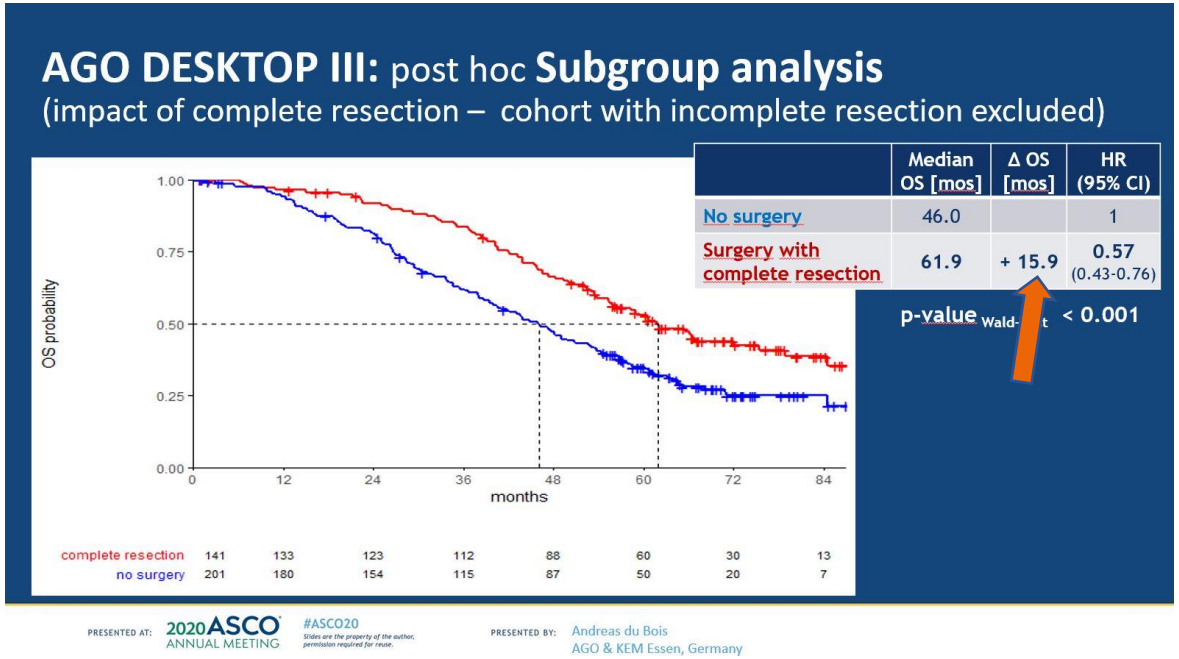


Patientes opérées: **impact de la chirurgie complète**

Impact d'une chirurgie complète / chimio seule



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- **DESKTOP III is the 1st prospectively randomised trial showing an OS benefit of debulking surgery in recurrent ovarian cancer.**
- **Cytoreductive surgery for pts with a Pt-free interval > 6 months *and* selected by the AGO Score significantly prolonged both overall and progression-free survival.**
- **The OS benefit was highest and exclusively seen in the cohort with complete resection indicating the importance of thorough selection process of both the right patient and centre.**

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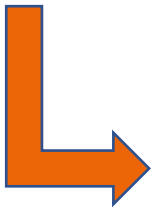

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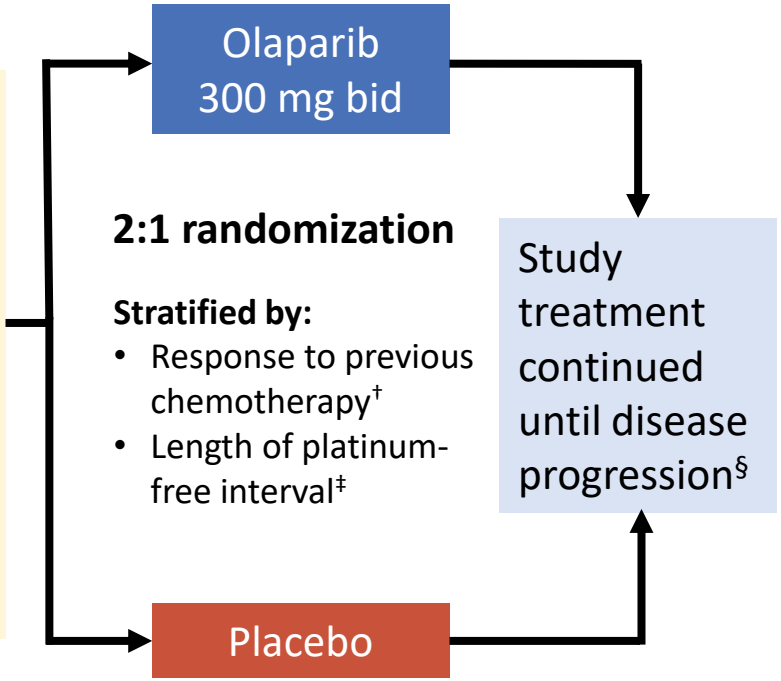
AGO DESKTOP III: translation into daily routine
(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

- **Patients with recurrent ovarian cancer and a platinum-free interval > 6 months should be evaluated regarding their eligibility for cytoreductive surgery:**
  - AGO Score, imaging, patient & tumor characteristics
- **and should be counseled for the options of secondary surgery (in specialized and experienced centres):**
  - 50% AGO Score positive in pts with platinum-free interval > 6 mos
  - 75% complete resection in AGO Score positive pts
  - median survival gain > 12 mos ***if complete resection*** is achieved

SOLO2: study design

Eligible patients had:
- Relapsed, high-grade serous or endometrioid ovarian cancer*
- BRCAm
- Received ≥2 previous lines of platinum-based chemotherapy
- Responded to most recent platinum regimen



Primary endpoint
- Investigator-assessed PFS

Time-dependent secondary endpoints
- **Overall survival**
- PFS2
- TFST
- TSST
- TDT
- HRQoL¶

Final analysis

DCO: Feb 3, 2020

- Planned for **60% data maturity** (~177 events)
- **Prespecified adjusted OS analysis (RPSFT model, re-censored):** to adjust for subsequent PARP inhibitor therapy in placebo group
- ***Post hoc* OS sensitivity analysis (eCRF)**: to correct for patients mis-stratified at randomization
- **Prespecified OS sensitivity analysis**: Myriad gBRCAm subgroup

*Includes primary peritoneal of fallopian tube cancer; †Complete or partial response; ‡>6–12 or >12 months; §Or until discontinuation criteria were met, and treatment could continue beyond progression if the investigator deemed the patient be experiencing benefit; ¶Assessed by the TOI of the FACT-O

eCRF, electronic case report form; gBRCAm, germline BRCA mutation; FACT-O, Functional Assessment of Cancer Therapy – Ovarian; HRQoL, health-related quality of life; PFS2, time to second progression; RPSFT, rank preserving structural failure time model; TDT, time to study treatment discontinuation or death; TFST, time to first subsequent therapy or death; TOI, trial outcome index; TSST, time to second subsequent therapy or death

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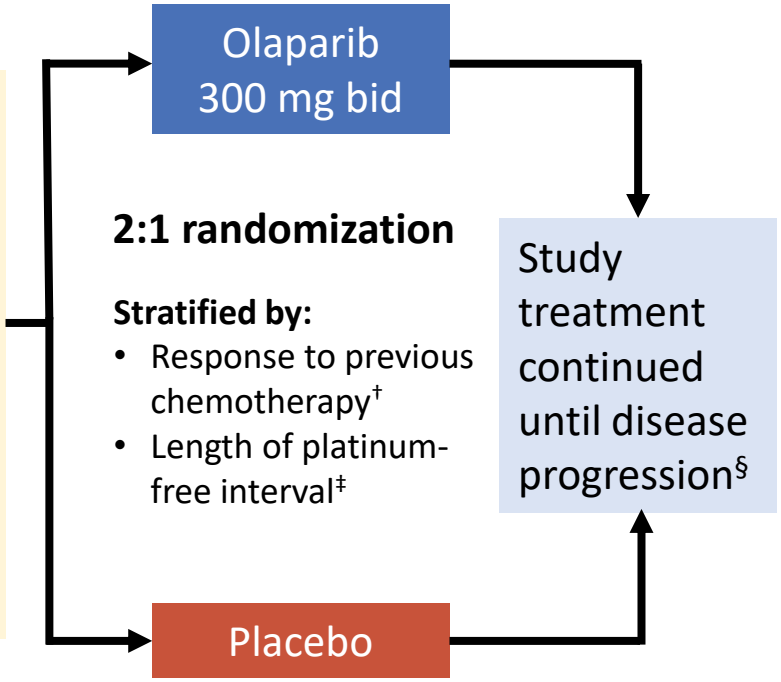

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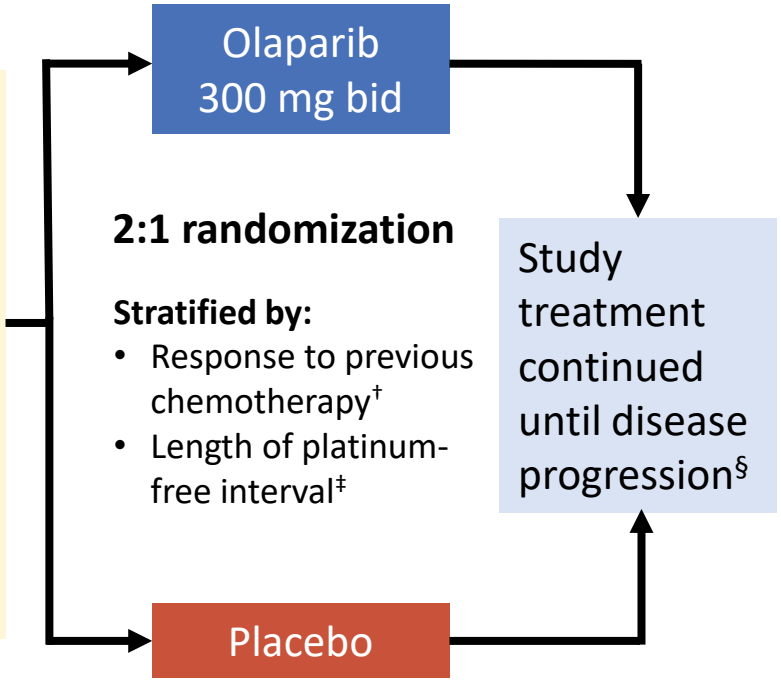

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Essai SOLO 2

Median duration of Follow up: **5,5 ans (olaparib) et 5,4 ans (placebo)**

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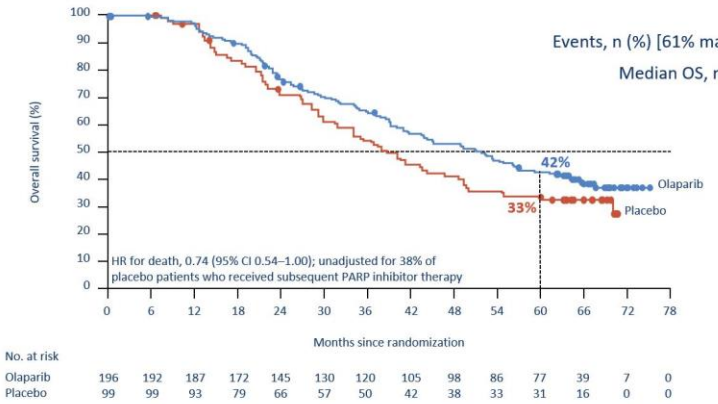
Median duration of Follow up: **5,5 ans (olaparib) et 5,4 ans (placebo)**

SOLO2: final analysis of OS

Median OS improved by 12.9 months with maintenance olaparib over placebo, despite 38% of placebo patients receiving subsequent PARP inhibitor therapy



	Olaparib (N=196)	Placebo (N=99)
Events, n (%) [61% maturity]	116 (59)	65 (66)
Median OS, months	51.7	38.8
HR 0.74		
95% CI 0.54–1.00; *P*=0.0537		

38% of placebo patients and 10% of olaparib patients received subsequent PARP inhibitor therapy*

OS analysis per eCRF in the full analysis set†
HR 0.70 (95% CI 0.52–0.96)

OS analysis in the Myriad gBRCAm subgroup†
HR 0.71 (95% CI 0.52–0.97)

*According to medical review of PARP inhibitor use
CI, confidence interval

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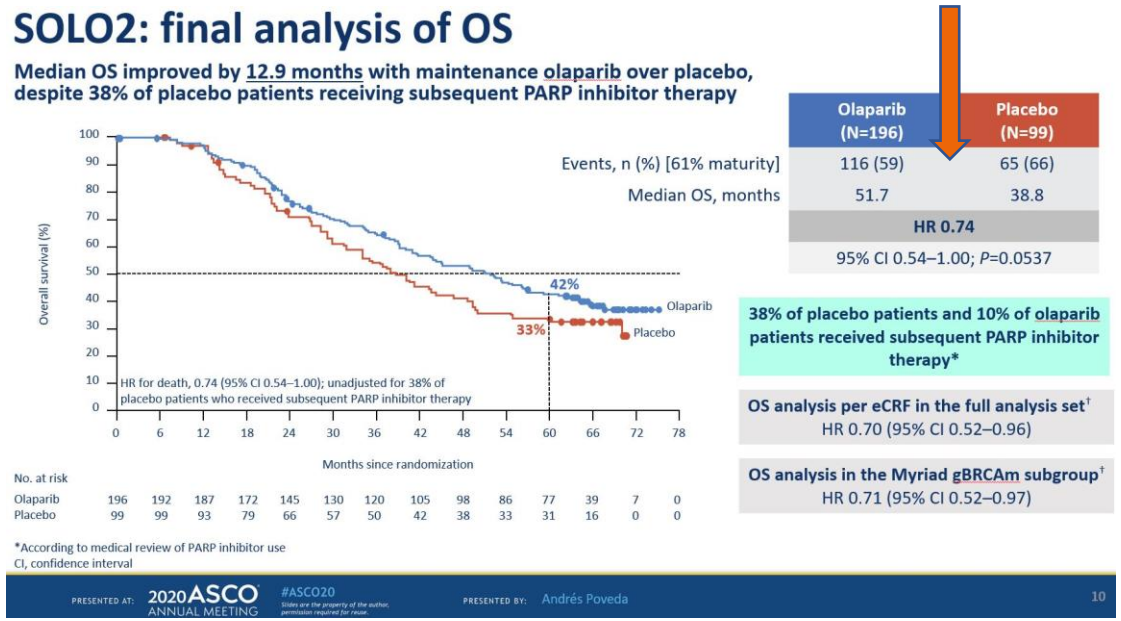

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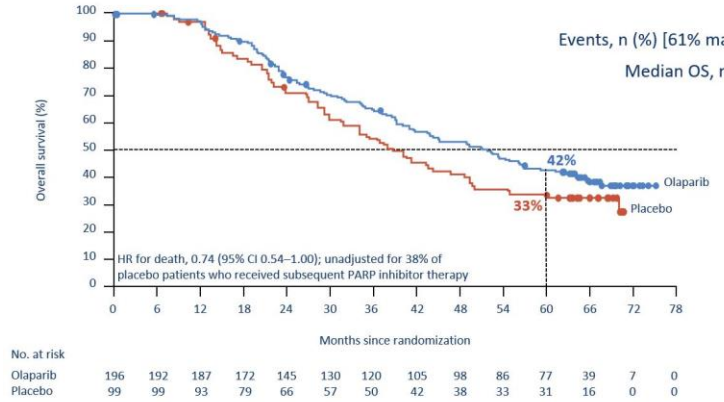

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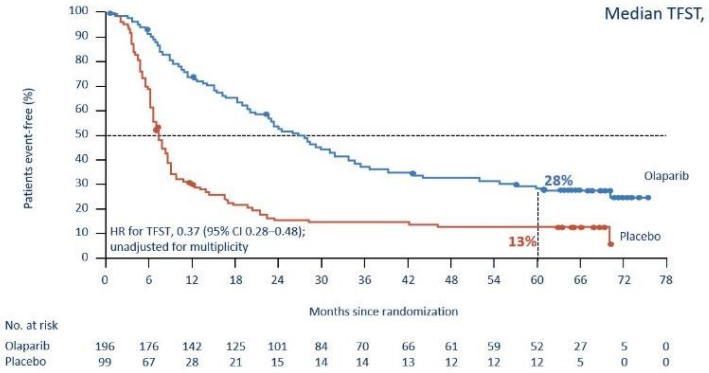
SOLO2: time to first subsequent therapy

At 5 years, 28% of olaparib patients vs 13% of placebo patients were alive and had not received subsequent therapy



	Olaparib (N=196)	Placebo (N=99)
Events, n (%) [76% maturity]	139 (71)	86 (87)
Median TFST, months	27.4	7.2
HR 0.37		
95% CI 0.28–0.48; *P*<0.0001		

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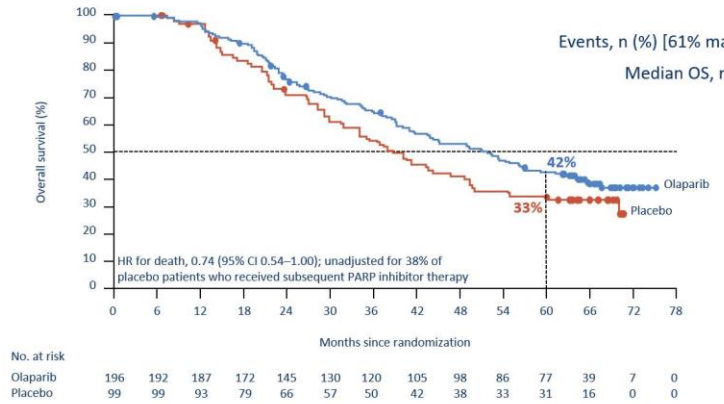
SOLO2: final analysis of OS

Median OS improved by 12.9 months with maintenance olaparib over placebo, despite 38% of placebo patients receiving subsequent PARP inhibitor therapy



	Olaparib (N=196)	Placebo (N=99)
Events, n (%) [61% maturity]	116 (59)	65 (66)
Median OS, months	51.7	38.8
HR 0.74		
95% CI 0.54–1.00; *P*=0.0537		

38% of placebo patients and 10% of olaparib patients received subsequent PARP inhibitor therapy*

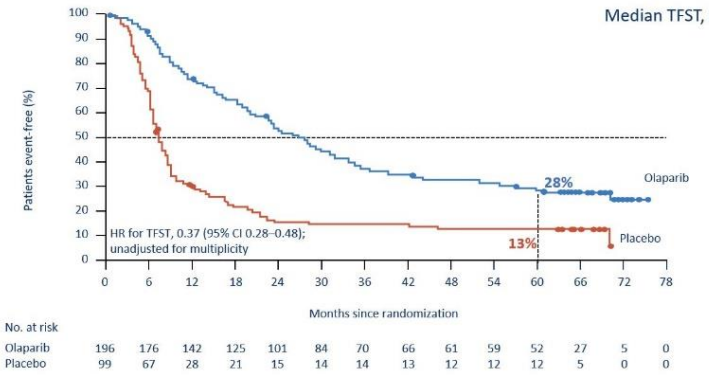
OS analysis per eCRF in the full analysis set†
HR 0.70 (95% CI 0.52–0.96)

OS analysis in the Myriad gBRCAm subgroup†
HR 0.71 (95% CI 0.52–0.97)

*According to medical review of PARP inhibitor use
CI, confidence interval

SOLO2: time to first subsequent therapy

At 5 years, 28% of olaparib patients vs 13% of placebo patients were alive and had not received subsequent therapy



	Olaparib (N=196)	Placebo (N=99)
Events, n (%) [76% maturity]	139 (71)	86 (87)
Median TFST, months	27.4	7.2
HR 0.37		
95% CI 0.28–0.48; *P*<0.0001		

Essai SOLO 2

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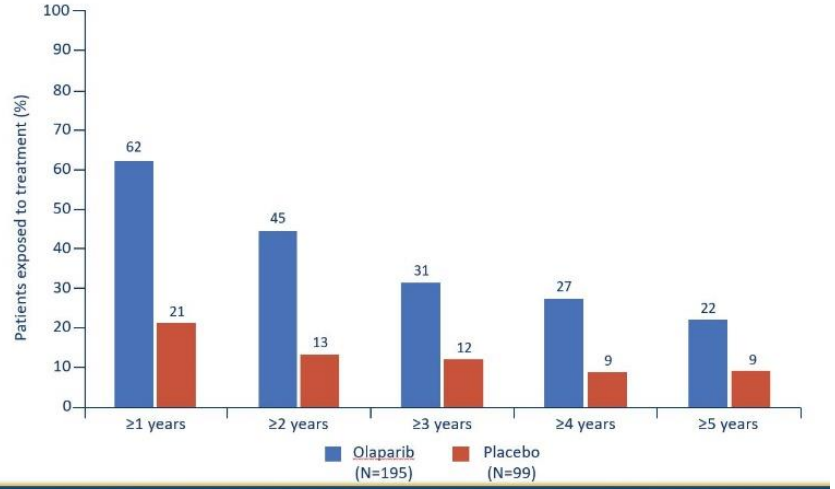
Essai SOLO 2

SOLO2: duration of treatment exposure

22% of patients received maintenance olaparib for ≥5 years, reflecting the therapeutic benefit and manageable tolerability of olaparib



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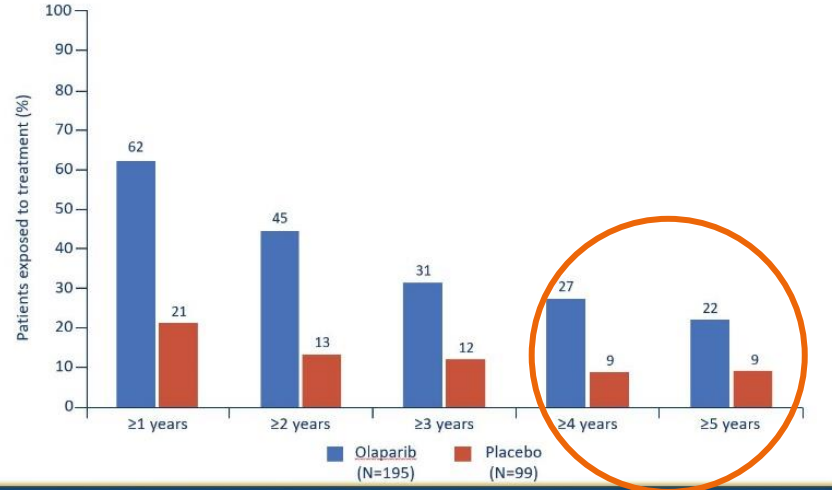

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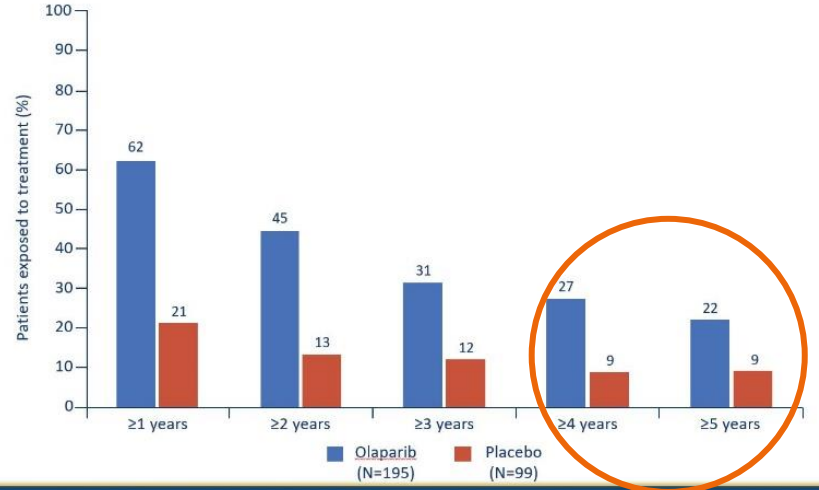

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SOLO2: safety overview – primary and final analyses*

Small increase in TEAEs, dose modifications and treatment discontinuations in the olaparib group compared with the primary analysis, despite longer treatment duration

	Olaparib (N=195)		Placebo (N=99)	
	Primary	Final	Primary	Final
Mean total treatment duration (SD), months	17.4 (9.8)	**29.1 (24.7)**	9.0 (8.1)	**13.1 (18.6)**
All-grade TEAEs, n (%)	192 (98)	**194 (99)**	94 (95)	**94 (95)**
Grade ≥3 TEAEs, n (%)	72 (37)	**90 (46)**	18 (18)	**19 (19)**
Serious TEAEs, n (%)	35 (18)	**50 (26)**	8 (8)	**8 (8)**
TEAEs leading to dose interruption, n (%)	88 (45)	**97 (50)**	18 (18)	**19 (19)**
TEAEs leading to dose reduction, n (%)	49 (25)	**54 (28)**	3 (3)	**3 (3)**
TEAEs leading to treatment discontinuation, n (%)	21 (11)	**33 (17)**	2 (2)	**3 (3)**

*Primary DCO: Sep 19, 2016; final DCO: Feb 3, 2020
SD, standard deviation; TEAE, treatment-emergent adverse event

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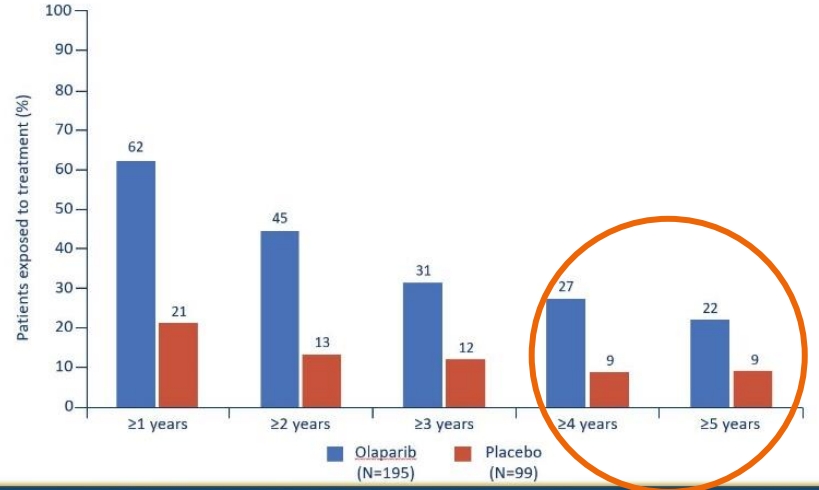

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SOLO2: AEs of special interest – primary and final analyses*†

	Olaparib (N=195)		Placebo (N=99)	
	Primary	Final	Primary	Final
Mean total treatment duration (SD), months	17.4 (9.8)	**29.1 (24.7)**	9.0 (8.1)	**13.1 (18.6)**
MDS/AML, n (%)	4 (2)	**16 (8)**	4 (4)	**4 (4)**
During the safety follow-up period (TEAE)		**7 (4)**		**0**
After the safety follow-up period (non-TEAE)		**9 (5)**		**4 (4)**
Pneumonitis, n (%)	3 (2)	**3 (2)**	0	**0**

MDS/AML

- **Actively solicited throughout study treatment and follow-up**
- **Incidences should be interpreted in the context of their late onset‡ and the longer OS observed with olaparib vs placebo**
- **Association with the number of prior platinum regimens, olaparib treatment and other potential risk factors is being explored**

In patients with newly diagnosed ovarian cancer and a BRCAm, at median follow-up of 65 months, MDS/AML occurred in 1% of olaparib patients and no placebo patients[1]

*Includes AEs that occurred outside safety follow-up period (during treatment and up to 30 days after discontinuation); †New primary malignancies (excluding hematologic malignancies) occurred in 1 olaparib patient (1%) and 1 placebo patient (1%) in the primary analysis, and in 8 olaparib patients (4%) and 2 placebo patients (2%) in the final analysis; ‡After the safety follow-up period
AML, acute myeloid leukemia; MDS, myelodysplastic syndrome
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Essai SOLO 2

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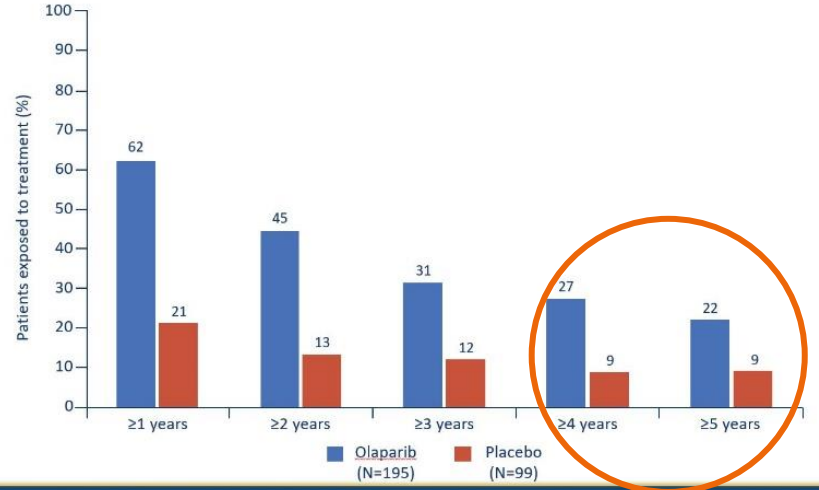

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Essai SOLO 2

Conclusions

- **SOLO2 is the first Phase III trial of maintenance PARP inhibitor therapy to report OS data for women with PSROC and a BRCAm since the introduction of platinum-based chemotherapy**
  - Maintenance olaparib provided a clinically meaningful prolongation of median OS by 12.9 months over placebo
- **At 5 years, 42% of patients treated with olaparib were alive**
  - 22% of patients remained on maintenance olaparib for ≥5 years
  - Time to first subsequent therapy was improved with olaparib vs placebo
- **Few additional AEs, and dose modifications or discontinuations due to AEs, occurred in olaparib patients with longer-term treatment**
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Essai TROPHIMMUN

- Rappel:
  - TTG : maladies rares ≈ 1 grossesse/10 000
  - FIGO score ≤ 6: dite à « bas risque »
  - Traitement: MTX IM
  - Si échec:
    - Actinomycine ou poly-chimiothérapie (EMA-CO, EA-EP, BEP)
- Rationnel pour avélumab:
  - 100% PDL1 exprimé
  - Case reports d'efficacité du pembrolizumab
  - Profil de tolérance

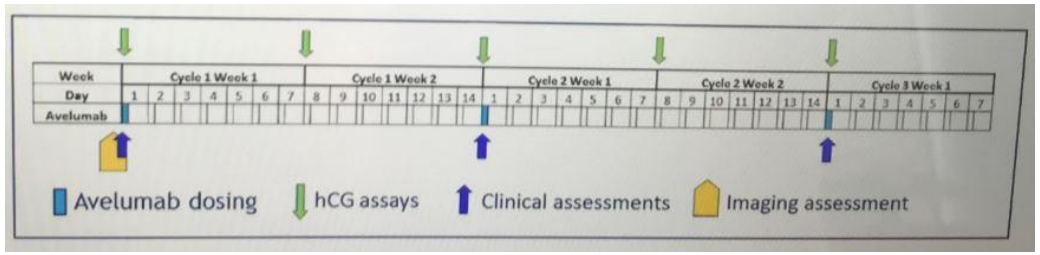
Essai TROPHIMMUN

2 cohortes dans l'essai

- Cohorte A: résistance à la mono-chimiothérapie (MTX+/- ActinoD)
- Cohorte B: résistance à la poly-chimiothérapie

- Principal objectif: normalisation hCG
- Objectifs secondaires: tolérance, délai à rechute, SG

1 schéma de traitement



Avélumab: 10 mg/kg IV toutes les 2 semaines
jusqu'à normalisation hCG en maintenance 3 cycles
Monitorage biologique hebdomadaire

Plan Simon en 2 étapes: 6 patientes et si ≥ 3 réponses, 15 patientes

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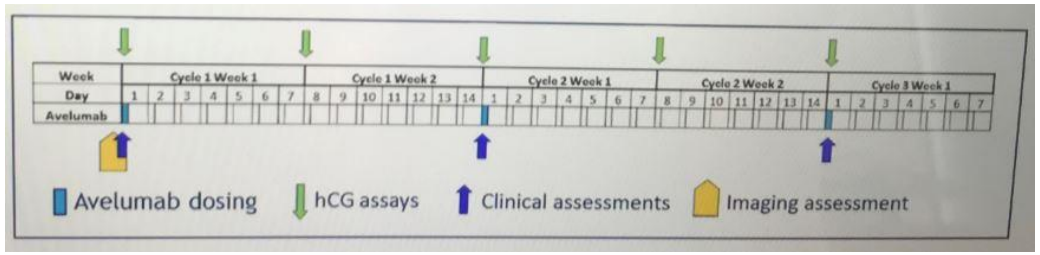

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Essai TROPHIMMUN

Caractéristiques patientes

N= 15 patientes (Déc 2016- Sept 2019)
Age médian: 34 ans
Score FIGO
0-2:0
3-4:5 (33%)
5-6:7 (46,7%)
≥ 7: 3 (20%)

Stade III avec atteinte pulmonaire: 47 %

100% pré traitées par MTX, 7 % avec ActinoD
Baseline hCG > 1000 UI/L: 27%
Nbre médian cycles: 8 (2-11)

Suivi médian: 30 mois

Résultats

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    - Aucune rechute
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  - Tolérance excellente: aucun gr 3
  - 93% gr ½ (Fatigue, NV, réaction injection, dysthyroidie, œil sec, diarrhées)

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POUR LA PRATIQUE

- Importance du travail en réseau pour les tumeurs rares
- 1er essai d'immunothérapie dans TTG
- L'avélumab est efficace après échec d'1 ou 2 mono-chimiothérapies
- La réponse est indépendante du stade et du score FIGO
- Profil de tolérance favorable
- L' avélumab représente une nouvelle option thérapeutique
- L'essai se poursuit dans la cohorte B
- Un nouvel essai est mis en place TROPHAMET

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Des questions ?

Merci de votre écoute