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Relacorilant, A Selective Glucocorticoid Receptor Modulator, In Combination With Nab-Paclitaxel Improves Progression-Free Survival In Patients With Recurrent Platinum-Resistant Ovarian Cancer: A 3-Arm, Randomized, Open-Label, Phase 2 Study

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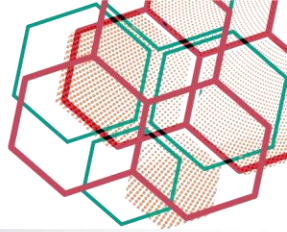
Declaration of Interests



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- Investigator/Researcher: GSK, CLOVIS, MSD, Astra Zeneca, Immonogen, Genmab, Corcept
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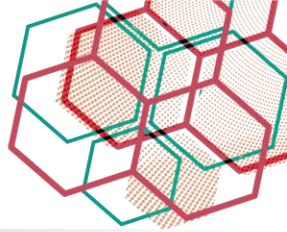
Platinum-resistant Ovarian Cancer: A Great Unmet Medical Need



Platinum resistance occurs in virtually all patients with recurrent ovarian cancer[1]

- Therapy options are limited to sequential chemotherapy not previously administered and molecular targeted agents
- Outcomes are generally poor
- Weekly paclitaxel is a standard regimen and nab-paclitaxel has also shown single-agent activity in a phase 2 study of patients with platinum-resistant ovarian cancer (objective response: 23%)[2]

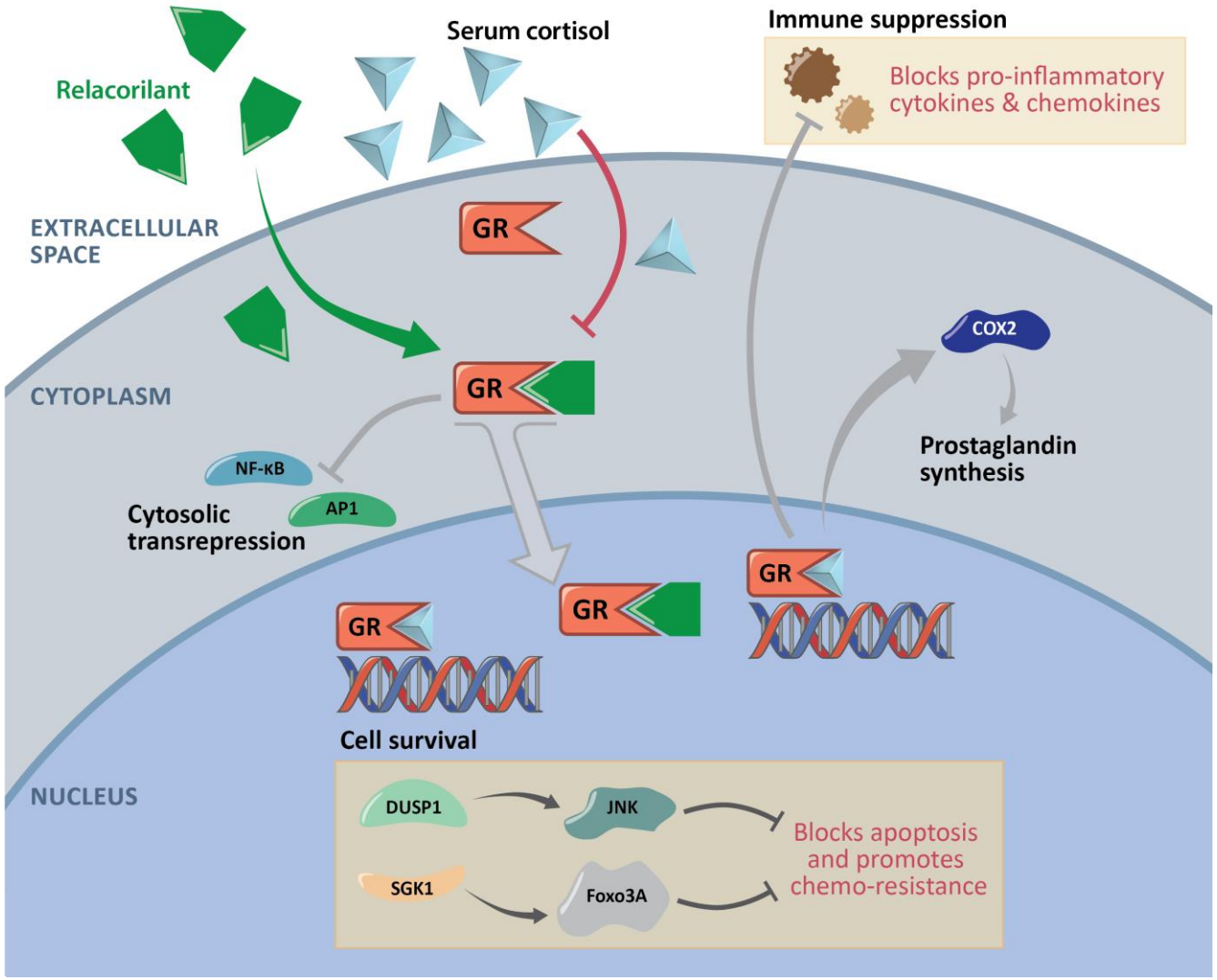
10-15%
Response rate to chemotherapy[1]

3-4 months
Progression-free survival[1]

<12 months
Overall survival[1]

[1] Luvero et al. 2014; [2] Coleman et al. 2011

Relacorilant May Enhance and/or Restore Chemotherapy Sensitivity



- Physiological cortisol levels can suppress immune activation and tumor cell apoptosis by activating the glucocorticoid receptor (GR)[1,2]
- Upon GR activation, tumor progression is obtained via activation of proliferative pathways (epithelial mesenchymal transition, TGF-β) and by inducing chemotherapy resistance[1]
- High GR expression has been reported in several solid tumors, including ovarian cancer,[2,3] where it has been correlated with reduced progression-free survival[3]
- Relacorilant, an investigational selective GR modulator, has demonstrated its potential to restore chemosensitivity[5] and enhance platinum and taxane efficacy in preclinical and early-phase clinical trials[4,5]

[1] Block et al. 2017; [2] Skor et al. 2013; [3] Veneris et al. 2018, [4] Greenstein & Hunt 2021; [5] Munster et al, 2019; GR, glucocorticoid receptor; TGF-β, Transforming growth factor beta

Preclinical and Phase 1 Results Suggest a Synergy Between Relacorilant and Nab-paclitaxel

Preclinical findings:

- *In vitro*, relacorilant restored paclitaxel-induced tumor cell apoptosis, which was reduced by cortisol[1]
- In xenograft models, under normal physiological glucocorticoid levels, GR antagonism promoted paclitaxel-induced tumor cell apoptosis[1,2]

Nab-paclitaxel does not require pretreatment with steroids and is thus well-suited for combination with relacorilant.

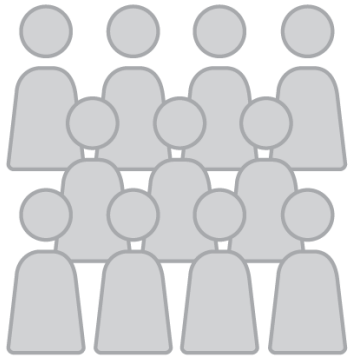
Phase 1 study of relacorilant + nab-paclitaxel in patients with solid tumors[3,4]

- 38% durable (≥16 wks) disease control in patients with ovarian, fallopian tube, and primary peritoneal cancer
- 28% with longer duration of benefit than on prior taxane

[1] Greenstein & Hunt 2021; [2] Skor et al. 2013; [3] Munster et al. 2019; [4] Greenstein et al. 2020

Phase 2 Study Design

178 patients with platinum-resistant/refractory ovarian, primary peritoneal, or fallopian tube cancer

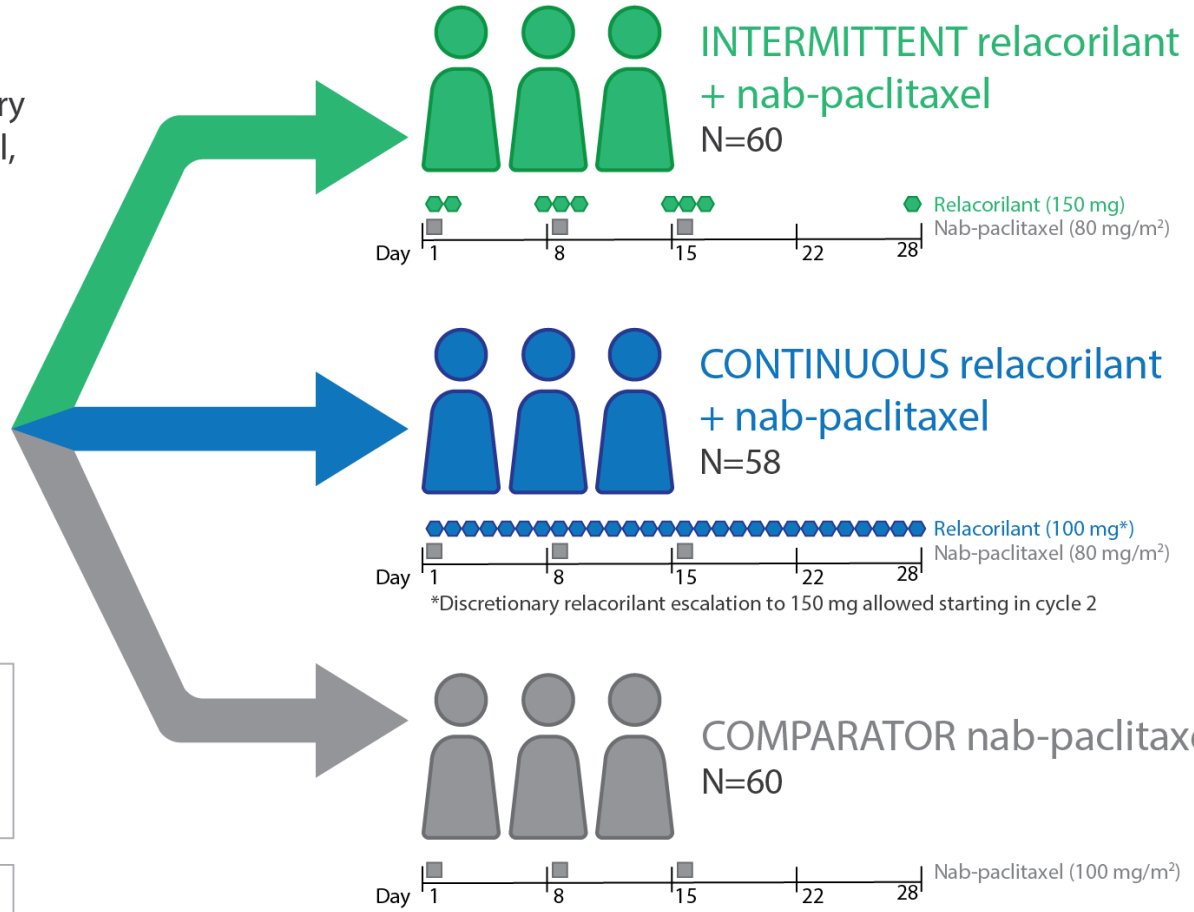


Randomized 1:1:1

- Measurable or non-measurable disease by RECIST v1.1
- Up to 4 prior chemotherapeutic regimens

Stratification factors:

- Relapse within 6 months of most recent taxane
- Presence of ascites



Primary endpoints:

- Progression-free survival (PFS) by RECIST v1.1

Secondary endpoints:

- Objective response rate (ORR)
- Duration of response (DoR)
- Overall survival (OS)
- Safety of the relacorilant + nab-paclitaxel combination

Statistical assumptions

- **CONTINUOUS vs COMPARATOR**: 91 PFS events to detect a HR=0.56 (median PFS increase from 3.8 to 6.8 mo)
- **INTERMITTENT vs COMPARATOR**: 92 PFS events to detect a HR=0.7 (median PFS increase from 3.8 to 5.4 mo)

Baseline Characteristics

	INTERMITTENT (N=60)	CONTINUOUS (N=58)	COMPARATOR (N=60)	Overall (N=178)
Age, median (range), years	60 (38, 81)	60 (45, 75)	61.5 (41, 81)	61 (38, 81)
Refractory**, no. (%)	23 (38.3%)	20 (34.5%)	22 (36.7%)	65 (36.5%)
Primary refractory, no (%)	7 (11.7%)	3 (5.2%)	1 (1.7%)	11 (6.2%)
Number of prior therapies, median (range)	2.5 (1, 4)	3 (1, 5)	3 (1, 4)	3 (1, 5)
Lines of prior chemotherapy, median (range)	2 (1, 4)	2 (1, 5)*	2 (1, 4)	2 (1, 5)
Prior cancer therapy, no. (%)				
Bevacizumab	31 (51.7%)	37 (63.8%)	37 (61.7%)	105 (59.0%)
PARP	18 (30.0%)	27 (46.6%)	20 (33.3%)	65 (36.5%)
Molecular profiling (available in a subset of the study population only)				
BRCA1(+), n/N (%)	5/43 (11.6%)	4/43 (9.3%)	7/49 (14.3%)	16/135 (11.9%)
BRCA2(+), n/N (%)	1/37 (2.7%)	3/39 (7.7%)	3/39 (7.7%)	7/115 (6.1%)

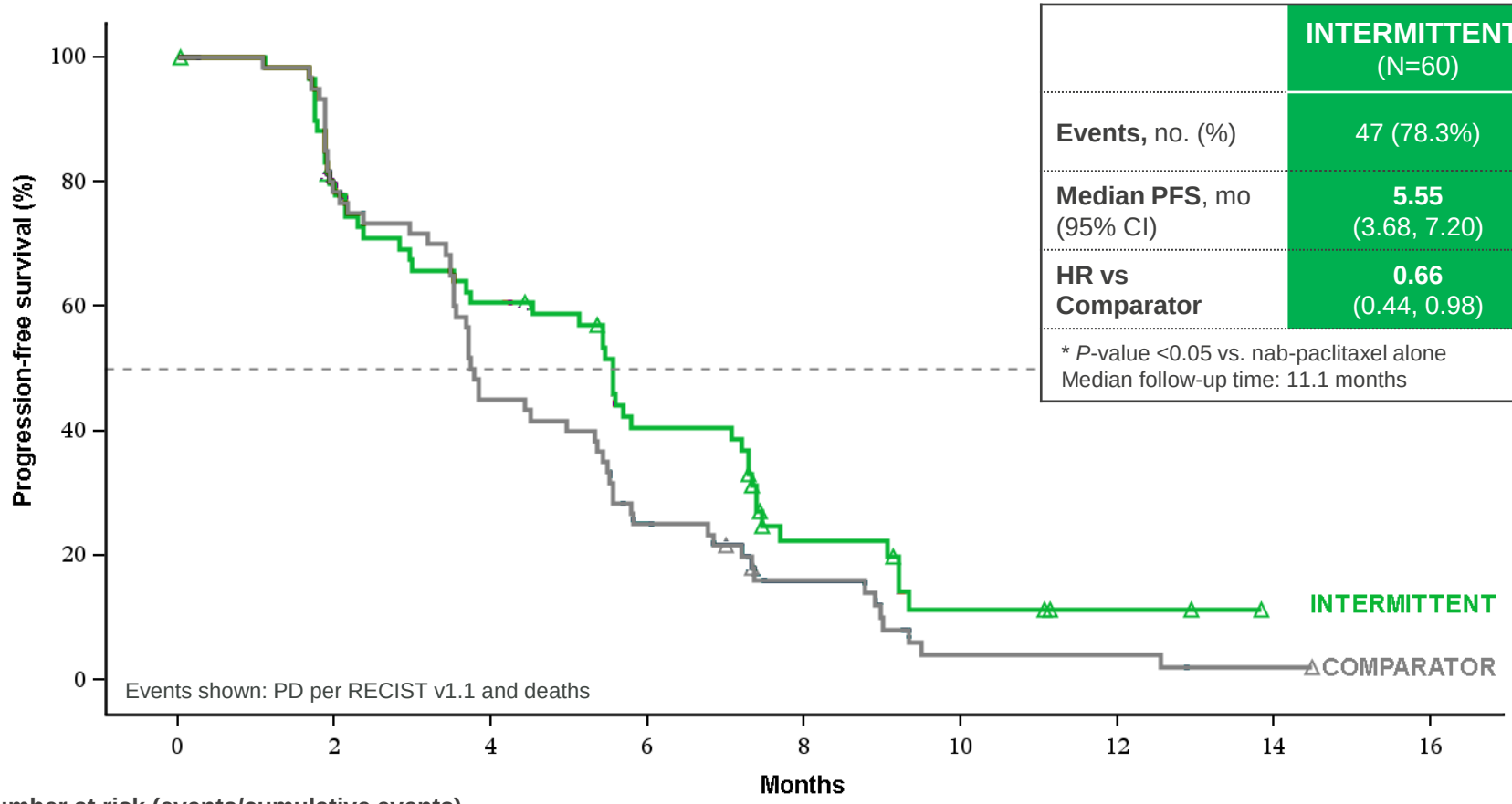
* 1 patient with bevacizumab counted as a separate line
** progressing during or within 1 month from last platinum treatment
CONTINUOUS, once-daily relacorilant + nab-paclitaxel; INTERMITTENT, intermittent relacorilant + nab-paclitaxel; COMPARATOR, nab-paclitaxel monotherapy

Patient Disposition

	INTERMITTENT (N=60)	CONTINUOUS (N=58)	COMPARATOR (N=60)	Overall (N=178)
Safety population	60	57	60	177
Discontinuation of study drug[a], no. (%)	53 (88.3%)	54 (93.1%)	56 (93.3%)	163 (91.6%)
Disease progression	40 (66.7%)	40 (69.0%)	47 (78.3%)	127 (71.3%)
Adverse event	7 (11.7%)	9 (13.8%)	4 (6.7%)	20 (11.2%)
Death	1 (1.7%)	2 (3.4%)	2 (3.3%)	5 (2.8%)
Other	5 (8.3%)[b]	3 (5.2%)	3 (5.0%)	11 (6.2%)

[a] Discontinuation of either relacorilant or nab-paclitaxel
[b] 1 patient discontinued relacorilant and nab-paclitaxel for different reasons (clinical progression and adverse event, respectively)
CONTINUOUS, once-daily relacorilant + nab-paclitaxel; INTERMITTENT, intermittent relacorilant + nab-paclitaxel; COMPARATOR, nab-paclitaxel monotherapy

INTERMITTENT Relacorilant + Nab-paclitaxel Improved Progression-Free Survival



	INTERMITTENT* (N=60)	COMPARATOR (N=60)
Events, no. (%)	47 (78.3%)	57 (95.0%)
Median PFS, mo (95% CI)	**5.55** (3.68, 7.20)	3.76 (3.52, 5.36)
HR vs Comparator	**0.66** (0.44, 0.98)	N/A

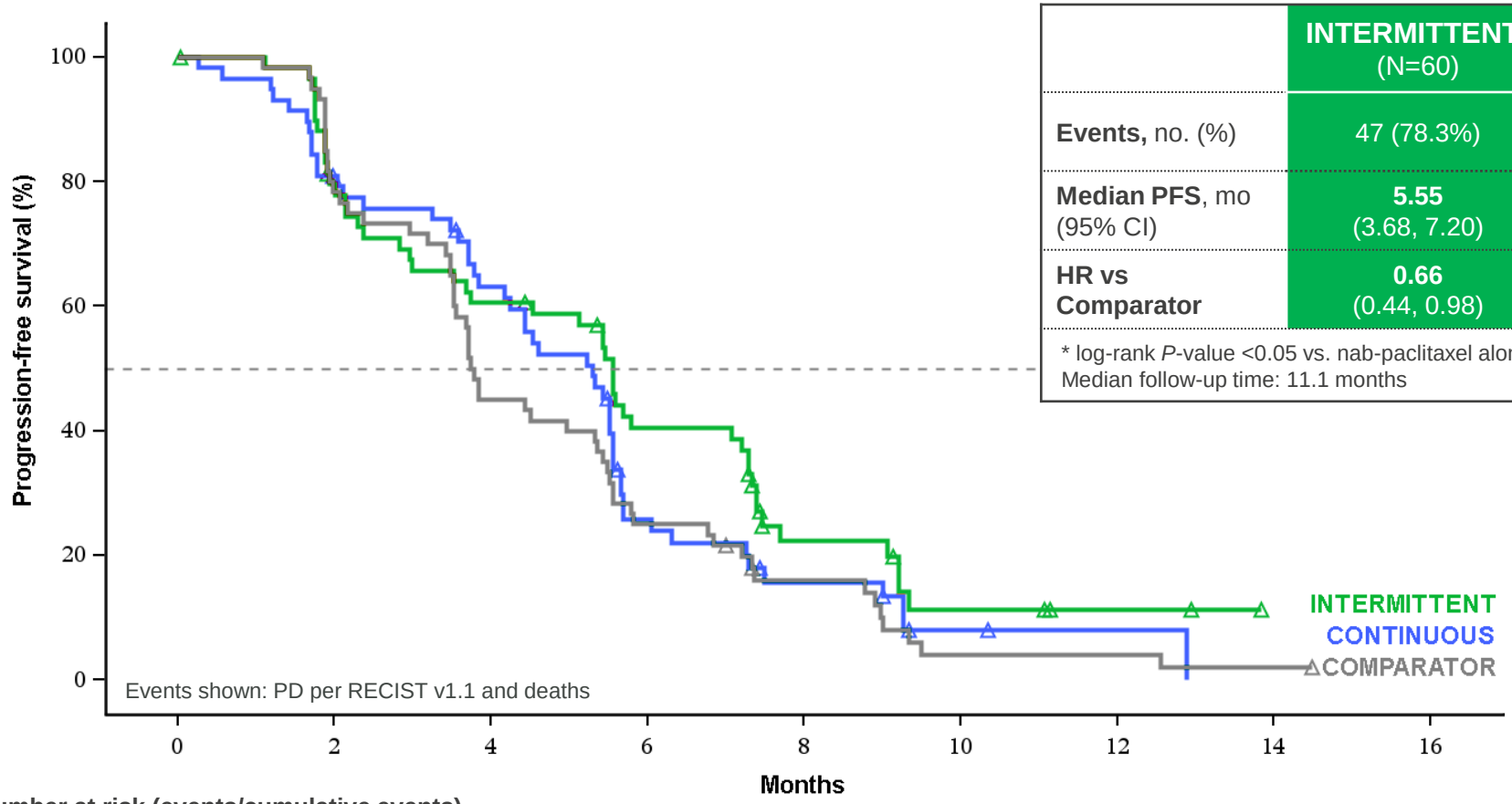
* *P*-value <0.05 vs. nab-paclitaxel alone
Median follow-up time: 11.1 months

Number at risk (events/cumulative events)

INTERMITTENT	60 (0/0)	46 (12/12)	35 (11/23)	22 (11/34)	9 (9/43)	4 (4/47)	2 (0/47)	0 (0/47)
COMPARATOR	60 (0/0)	47 (13/13)	27 (20/33)	15 (12/45)	8 (5/50)	2 (6/56)	2 (0/56)	1 (1/57)	0 (0/57)

CONTINUOUS, once-daily relacorilant + nab-paclitaxel; INTERMITTENT, intermittent relacorilant + nab-paclitaxel; COMPARATOR, nab-paclitaxel monotherapy; PFS, progression-free survival; HR, hazard ratio

INTERMITTENT Relacorilant + Nab-paclitaxel Improved Progression-Free Survival



	INTERMITTENT* (N=60)	CONTINUOUS (N=58)	COMPARATOR (N=60)
Events, no. (%)	47 (78.3%)	50 (86.2%)	57 (95.0%)
Median PFS, mo (95% CI)	**5.55** (3.68, 7.20)	5.29 (3.84, 5.55)	3.76 (3.52, 5.36)
HR vs Comparator	**0.66** (0.44, 0.98)	0.83 (0.56, 1.22)	N/A

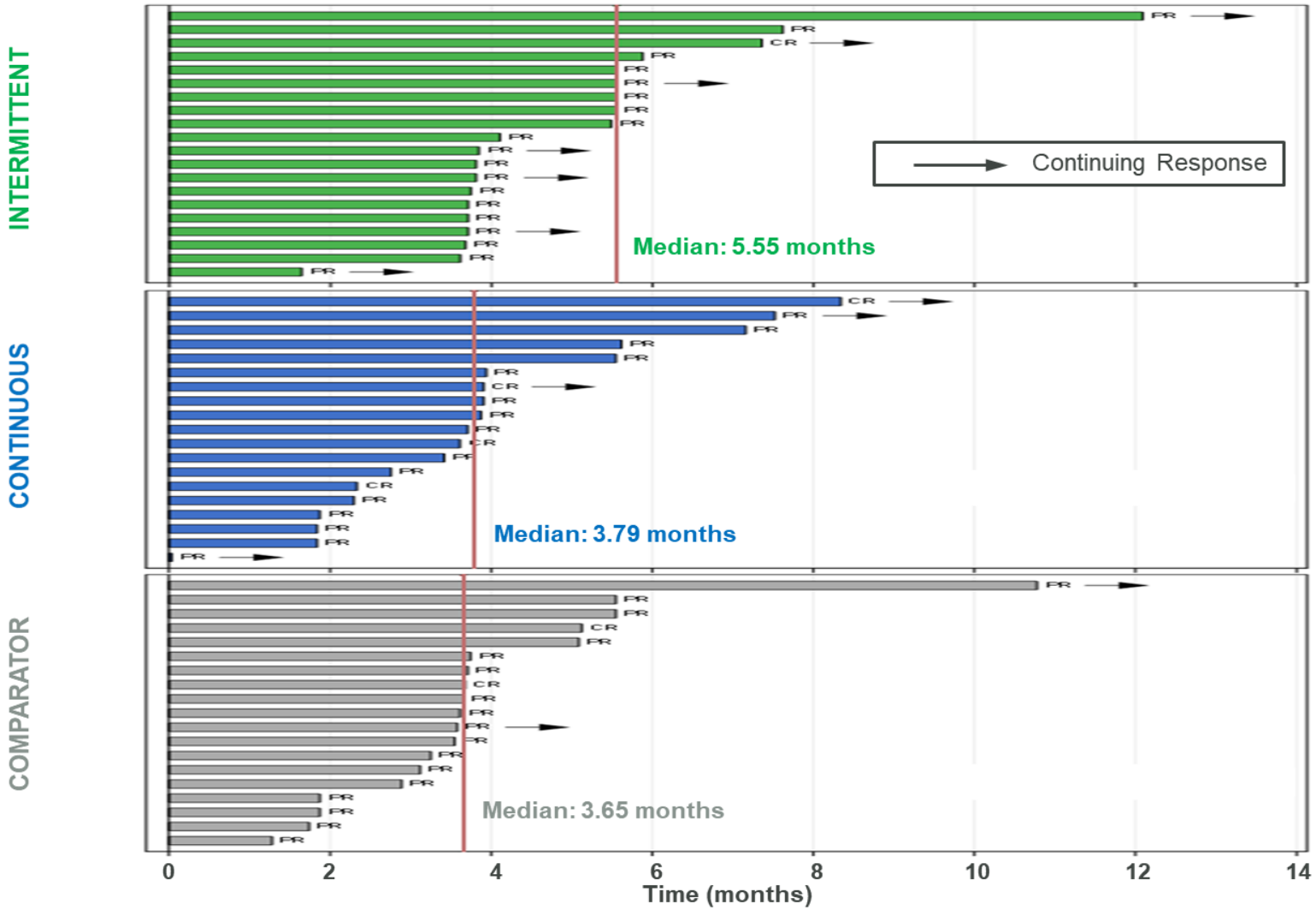
* log-rank *P*-value <0.05 vs. nab-paclitaxel alone
Median follow-up time: 11.1 months

Number at risk (events/cumulative events)

CONTINUOUS	58 (0/0)	46 (11/11)	35 (10/21)	13 (20/41)	7 (5/46)	2 (3/49)	1 (0/49)	0 (1/50)	
INTERMITTENT	60 (0/0)	46 (12/12)	35 (11/23)	22 (11/34)	9 (9/43)	4 (4/47)	2 (0/47)	0 (0/47)	
COMPARATOR	60 (0/0)	47 (13/13)	27 (20/33)	15 (12/45)	8 (5/50)	2 (6/56)	2 (0/56)	1 (1/57)	0 (0/57)

CONTINUOUS, once-daily relacorilant + nab-paclitaxel; INTERMITTENT, intermittent relacorilant + nab-paclitaxel; COMPARATOR, nab-paclitaxel monotherapy; PFS, progression-free survival; HR, hazard ratio

INTERMITTENT Relacorilant + Nab-paclitaxel Improved Duration of Response

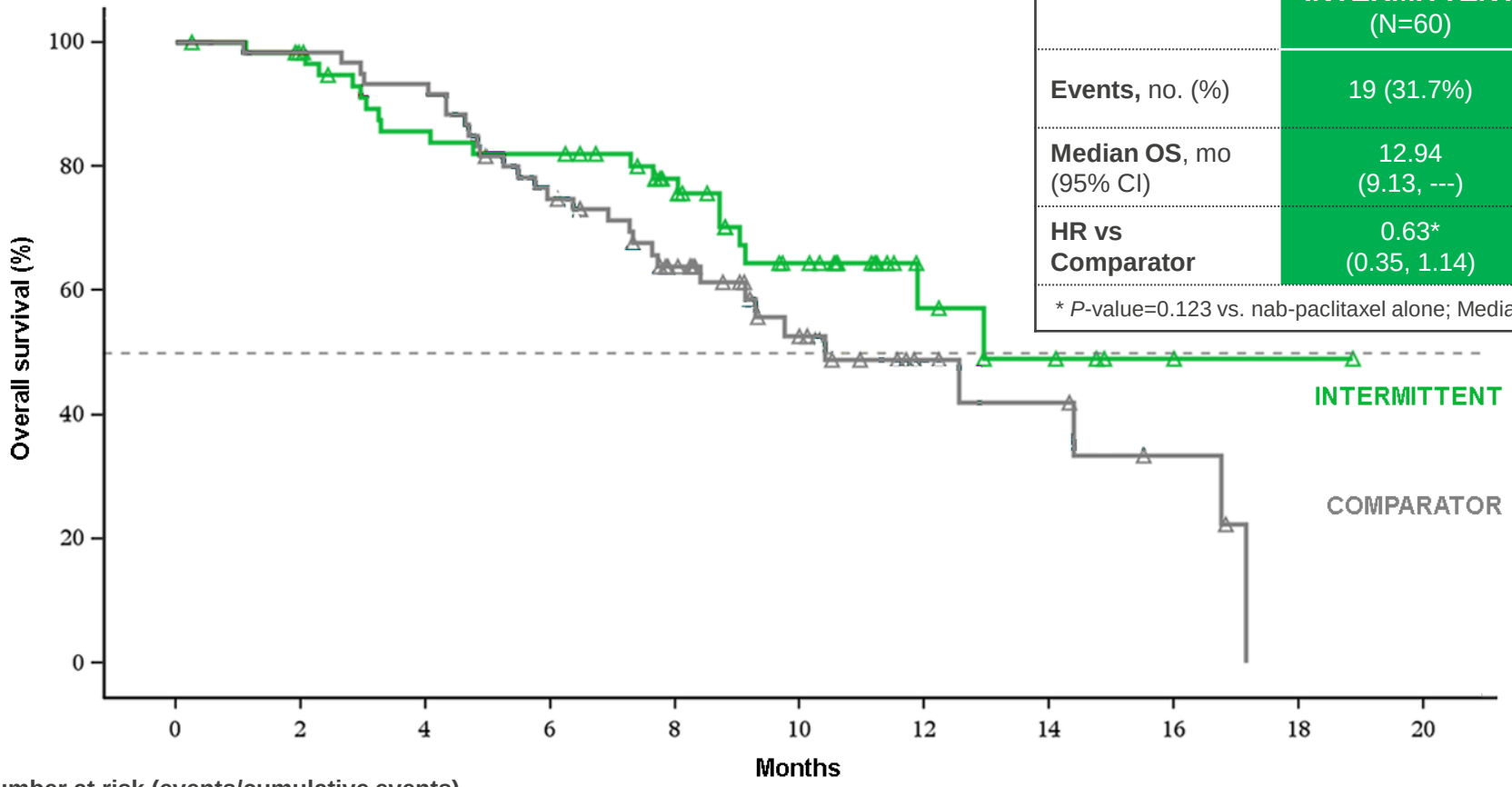


	ORR	
	n (%)	95% CI
INTERMITTENT	20 (35.7%)	(23.4, 49.6)
CONTINUOUS	19 (35.2%)	(22.7, 49.4)
COMPARATOR	19 (35.8%)	(23.1, 50.2)

While ORR was similar, DoR was **significantly improved** in the INTERMITTENT regimen.
HR 0.36, 95% CI (0.16-0.77), *P*=0.006

CONTINUOUS, once-daily relacorilant + nab-paclitaxel; INTERMITTENT, intermittent relacorilant + nab-paclitaxel; COMPARATOR, nab-paclitaxel monotherapy; ORR, objective response rate; DoR, duration of response

Trend Toward Improved Overall Survival Observed in the INTERMITTENT Arm in Interim Analysis (63% Maturity)



	INTERMITTENT (N=60)	COMPARATOR (N=60)
Events, no. (%)	19 (31.7%)	30 (50.0%)
Median OS, mo (95% CI)	12.94 (9.13, ---)	10.41 (8.41, 16.76)
HR vs Comparator	0.63* (0.35, 1.14)	N/A

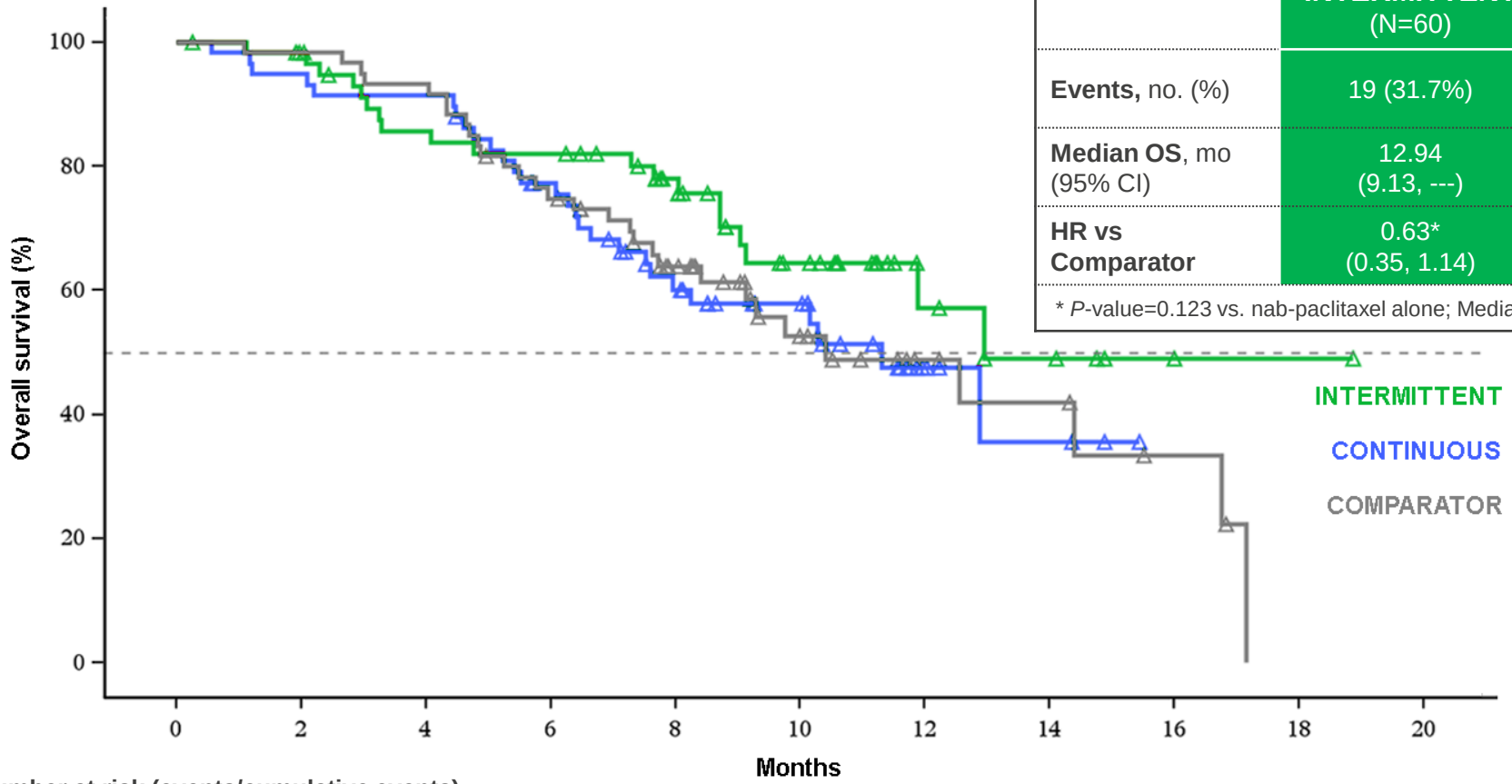
* *P*-value=0.123 vs. nab-paclitaxel alone; Median follow-up time: 10.3 months

Number at risk (events/cumulative events)

INTERMITTENT	60 (0/0)	56 (1/1)	47 (7/8)	45 (2/10)	33 (2/12)	20 (5/17)	8 (1/18)	5 (1/19)	2 (0/19)	1 (0/19)	0 (0/19)
COMPARATOR	60 (0/0)	59 (1/1)	56 (3/4)	44 (11/15)	31 (6/21)	16 (4/25)	8 (1/26)	6 (1/27)	3 (1/28)	0 (2/30)	

Interim analysis performed at the time of the primary analysis (March 2021, 154 PFS events, 76 OS events). Final OS analysis will be performed after at least 120 OS events.
CONTINUOUS, once-daily relacorilant + nab-paclitaxel; INTERMITTENT, intermittent relacorilant + nab-paclitaxel; COMPARATOR, nab-paclitaxel monotherapy; OS, overall survival

Trend Toward Improved Overall Survival Observed in the INTERMITTENT Arm in Interim Analysis (63% Maturity)



	INTERMITTENT (N=60)	CONTINUOUS (N=58)	COMPARATOR (N=60)
Events, no. (%)	19 (31.7%)	27 (46.6%)	30 (50.0%)
Median OS, mo (95% CI)	12.94 (9.13, ---)	11.30 (7.59, ---)	10.41 (8.41, 16.76)
HR vs Comparator	0.63* (0.35, 1.14)	1.07 (0.62, 1.85)	N/A

* *P*-value=0.123 vs. nab-paclitaxel alone; Median follow-up time: 10.3 months

Number at risk (events/cumulative events)

CONTINUOUS	58 (0/0)	55 (3/3)	53 (2/5)	42 (8/13)	29 (9/22)	21 (1/23)	6 (3/26)	3 (1/27)	0 (0/27)	
INTERMITTENT	60 (0/0)	56 (1/1)	47 (7/8)	45 (2/10)	33 (2/12)	20 (5/17)	8 (1/18)	5 (1/19)	2 (0/19)	1 (0/19)	0 (0/19)
COMPARATOR	60 (0/0)	59 (1/1)	56 (3/4)	44 (11/15)	31 (6/21)	16 (4/25)	8 (1/26)	6 (1/27)	3 (1/28)	0 (2/30)	

Interim analysis performed at the time of the primary analysis (March 2021, 154 PFS events, 76 OS events). Final OS analysis will be performed after at least 120 OS events.
CONTINUOUS, once-daily relacorilant + nab-paclitaxel; INTERMITTENT, intermittent relacorilant + nab-paclitaxel; COMPARATOR, nab-paclitaxel monotherapy; OS, overall survival

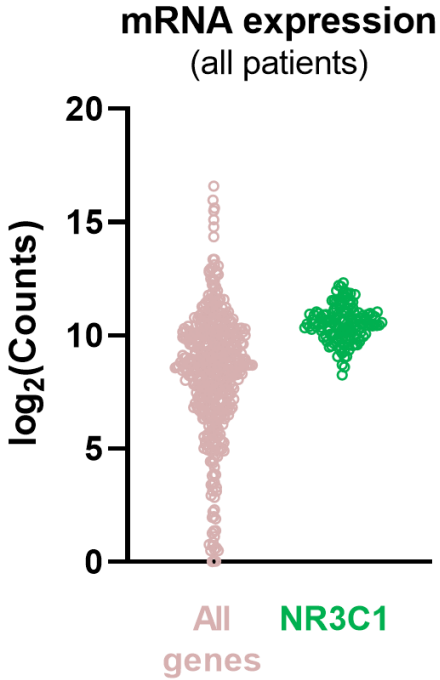
Safety and Tolerability: Most Frequently Reported Toxicity (>10%)

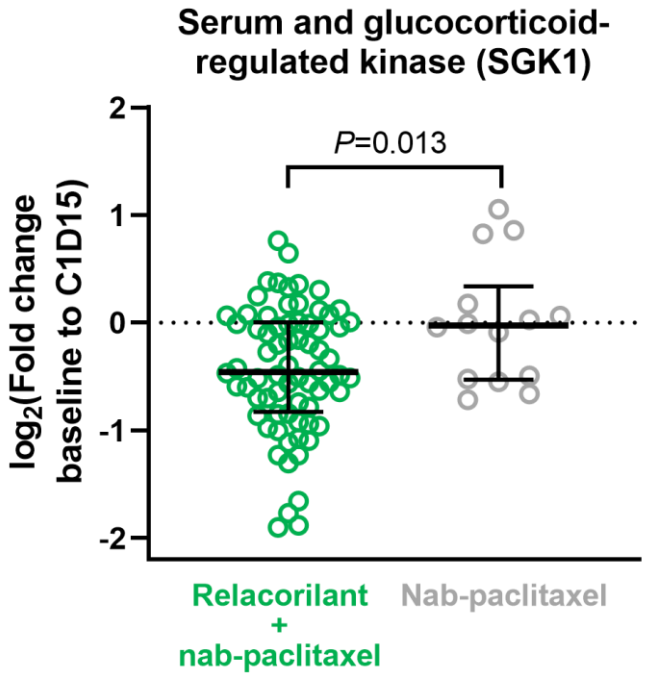
n, %	INTERMITTENT (N=60)	CONTINUOUS (N=57)	COMPARATOR (N=60)
Neutropenia[a]	12 (20.0%)	22 (38.6%)	22 (36.7%)
Grade ≥3	4 (6.7%)	15 (26.3%)	9 (15.0%)
Febrile neutropenia (Grade 3)[b]	0 (0.0%)	0 (0.0%)	1 (1.7%)
Anemia[c]	29 (48.3%)	37 (64.9%)	34 (56.7%)
Grade ≥3	8 (13.3%)	11 (19.3%)	7 (11.7%)
Peripheral neuropathy[d]	21 (35.0%)	27 (47.4%)	18 (30.0%)
Grade ≥3	0 (0.0%)	9 (15.8%)	3 (5.0%)
Fatigue or asthenia	33 (55.0%)	41 (71.9%)	39 (65.0%)
Grade ≥3	6 (10.0%)	5 (8.8%)	1 (1.7%)

[a] Neutropenia, neutrophil count decreased; [b] Secondary to E.coli urinary sepsis in this patient; [c] Anemia, hemoglobin decreased; [d] Neuropathy peripheral, neurotoxicity, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy
CONTINUOUS, once-daily relacorilant + nab-paclitaxel; INTERMITTENT, intermittent relacorilant + nab-paclitaxel; COMPARATOR, nab-paclitaxel monotherapy; G-CSF, granulocyte-colony stimulating factor

- All relacorilant-treated patients received prophylactic G-CSF per protocol to reduce the risk of neutropenia
- 46.7% of patients in the comparator arm received G-CSF per the investigator's standard practice

Baseline and Pharmacodynamic Biomarkers





- mRNA expression was measured in 137 pre-treatment tumor specimens across all three arms of the study
- All tested ovarian tumors showed **high mRNA expression of NR3C1,** the gene that encodes for the glucocorticoid receptor
- Evaluation of **GR expression by IHC** is ongoing

- Fold change in expression for a panel of 239 GR-agonist-inducible genes was assessed in whole blood from baseline to C1D15 (pre-dose)
- The pharmacodynamic analysis confirmed that relacorilant + nab-paclitaxel can suppress 221/239 glucocorticoid receptor target genes such as serum and glucocorticoid-regulated kinase (SGK1)

Median for GR in the 83rd percentile of median expression for all genes; IHC, immunohistochemistry

Error bars are median and interquartile ranges

Conclusions

- This study is the first randomized, controlled, phase 2 trial of relacorilant + nab-paclitaxel in patients with platinum-resistant/refractory ovarian, primary peritoneal, or fallopian tube cancer.
- In this heavily pretreated population (up to 5 lines of prior chemotherapy), substantial benefit was observed.
  - INTERMITTENT relacorilant + nab-paclitaxel significantly improved PFS and DoR compared to nab-paclitaxel alone.
  - Although OS data are not yet mature, a trend toward improved OS was observed with INTERMITTENT relacorilant + nab-paclitaxel.
- No additional toxicity was observed with the addition of INTERMITTENT relacorilant compared to nab-paclitaxel alone.
- A phase 3 trial evaluating the INTERMITTENT relacorilant + nab-paclitaxel schedule vs chemotherapy is being planned.

Thanks to all those who contributed to this study!

The study patients and their families.

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