



# Update on randomised phase II study of DMXAA (ASA404) combined with carboplatin and paclitaxel in recurrent ovarian cancer

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## Background

- Tumour vascular disrupting agents (VDAs) attack existing tumour blood vessels selectively, causing rapid shutdown of tumour blood flow<sup>1</sup>
- DMXAA (5,6-dimethylxanthenone-4-acetic acid, ASA404) is a small-molecule VDA with a unique mode of action<sup>2</sup>
- In animal models, DMXAA shows additive or supra-additive anti-tumour effects with cytotoxics, including taxanes<sup>3</sup>. Phase II trials have combined DMXAA with taxane or taxane plus platinum regimens in ovarian, lung and prostate cancers
- A phase II randomised trial in non-small cell lung cancer (NSCLC) compared patients receiving DMXAA plus carboplatin and paclitaxel with patients receiving only carboplatin and paclitaxel. Results showed increased response rates and time to tumour progression and a substantial survival advantage (median of 14.0 vs 8.8 months) in patients receiving DMXAA<sup>4</sup>. These findings were supported by a single arm study using a higher dose of DMXAA, recently presented at the 12th World Conference on Lung Cancer. A phase III study in NSCLC is planned
- The ICON4/AGO-OVAR-2.2 trial of 802 patients with platinum-sensitive ovarian cancer relapsing after 6 months showed treatment with paclitaxel plus platinum-based chemotherapy to give a 1-year progression-free survival rate of 50%, median progression-free survival of 13 months and 12-month survival of around 82%<sup>5</sup>

## Objectives

- To compare the efficacy of DMXAA in combination with carboplatin and paclitaxel (DMXAA arm) with that of carboplatin and paclitaxel alone (standard arm) in patients with recurrent, platinum-sensitive ovarian cancer
- To assess the safety and tolerability of DMXAA in combination with carboplatin and paclitaxel

## Methods

### Study design

- Randomised, multicentre, open-label, parallel, phase II study
- Women aged ≥18 years with:
  - histologically-confirmed ovarian epithelial cancer (including primary peritoneal serous carcinoma)
  - recurrent disease confirmed by imaging
  - FIGO stage Ic-IV at first diagnosis
  - ECOG performance status 0–2
  - adequate haematologic, renal and hepatic functions
  - life expectancy ≥3 months
  - progression-free interval >6 months after response to first-line platinum-based chemotherapy
  - ≥1 unidimensionally measurable lesion according to Response Evaluation Criteria In Solid Tumors (RECIST)<sup>6</sup>
- Patients received carboplatin AUC 6 mg/ml × min and paclitaxel 175 mg/m<sup>2</sup> plus DMXAA 1200 mg/m<sup>2</sup> (20-minute infusion) if allocated; treatment was given every 21 days for up to 6 cycles
- Follow-up:
  - imaging assessment 6-weekly until disease progression
  - 3-monthly after progression, for survival

### Safety assessments

- Adverse events, laboratory abnormalities, effect on QTc interval (from 12-lead electrocardiograms) and ophthalmic toxicity

### Efficacy assessments

- Tumour response evaluated by RECIST and categorised as complete (CR), partial (PR), stable disease (SD), or progressive disease (PD)
- Response rate (RR) defined as % of patients who achieved CR or PR
- Time to tumour progression (TTP) and survival

## Results

### Patient characteristics

- 77 patients were randomised; 75 received treatment (DMXAA arm, n=37; standard therapy arm, n=38)

Table 1: Analysis populations

Population	DMXAA 1200	Standard therapy
Safety (= treated)	37	38
Eligible (investigator assessment; also the population for survival)	36	38
Eligible (independent assessment)	37*	37

\*One patient had no response data, therefore n=36 in the DMXAA arm for the response analysis

- The two arms were well balanced for pre-treatment characteristics (Table 2)
- Patients in both groups received a median of 6 cycles of treatment

Table 2: Baseline characteristics of patients

	DMXAA 1200 (n=37)	Standard therapy (n=38)
Mean age (years)	58.7	61.2
ECOG performance status		
0	22	23
1	13	12
2	2	3
FIGO stage at first diagnosis*		
Ic	1	2
IIa	1	0
IIb	1	1
IIc	1	3
III	24	24
IV	8	7
Unclassified	1	1

\*2 patients in the DMXAA arm and 5 patients in the standard therapy arm had a diagnosis of primary peritoneal serous carcinoma

### Safety

- Addition of DMXAA to standard chemotherapy was generally well tolerated
- 16 (43.2%) patients in the DMXAA arm experienced one or more treatment-emergent serious adverse event (SAE), compared with 6 patients (15.8%) in the standard arm (Table 3)
- 22 (59.5%) patients in the DMXAA arm and 21 patients (55.3%) in the standard arm experienced treatment-emergent adverse events of CTC grade 3 and above
- The most commonly reported (≥10% of patients) adverse events of CTC grade 3 or above were neutropenia, thrombocytopenia and fatigue in the DMXAA arm, and neutropenia in the standard arm
- According to investigator assessment, there were two grade 5 events in the DMXAA arm; one of which was due to respiratory failure and was considered possibly related to DMXAA, the other was decompensation due to diabetes mellitus and dehydration and was considered unrelated to DMXAA
- The addition of DMXAA was not associated with clinically significant ophthalmic abnormalities
- No cardiac SAEs were observed and no patients showed clinically significant prolongation of QTc interval

Table 3: Treatment-emergent serious adverse events by number of patients

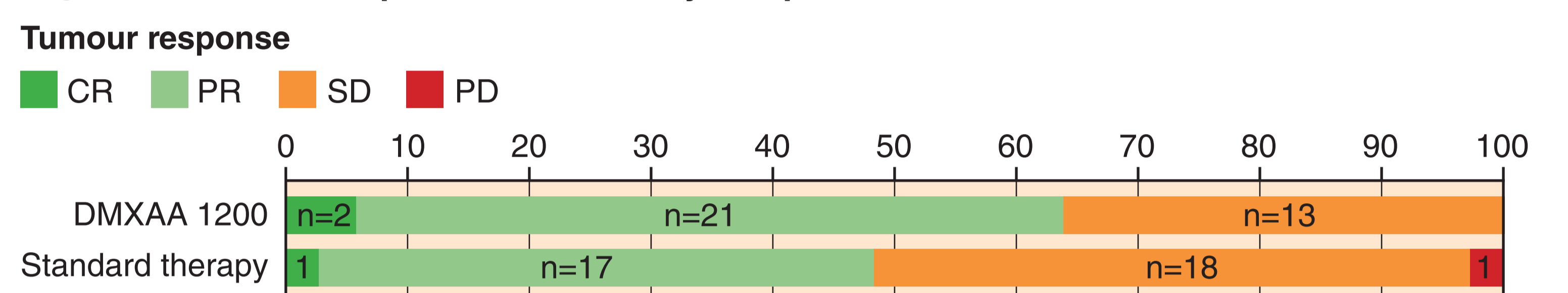
MedDRA system organ class	DMXAA 1200 n=37	Standard therapy n=38
Blood and lymphatic system	4	0
Gastrointestinal	6	3
General disorders and administration site conditions	3	0
Immune system	2	2
Infections and infestations	0	2
Injury, poisoning and procedural complications	2	0
Metabolism and nutrition	3	0
Nervous system disorders	1	0
Renal and urinary	0	1
Respiratory, thoracic and mediastinal	1	0
Vascular	1	0

### Efficacy

#### Tumour response (Figure 1)

- Response rate according to independently-assessed RECIST outcomes was 63.9% in the DMXAA arm compared with 48.6% in the standard arm

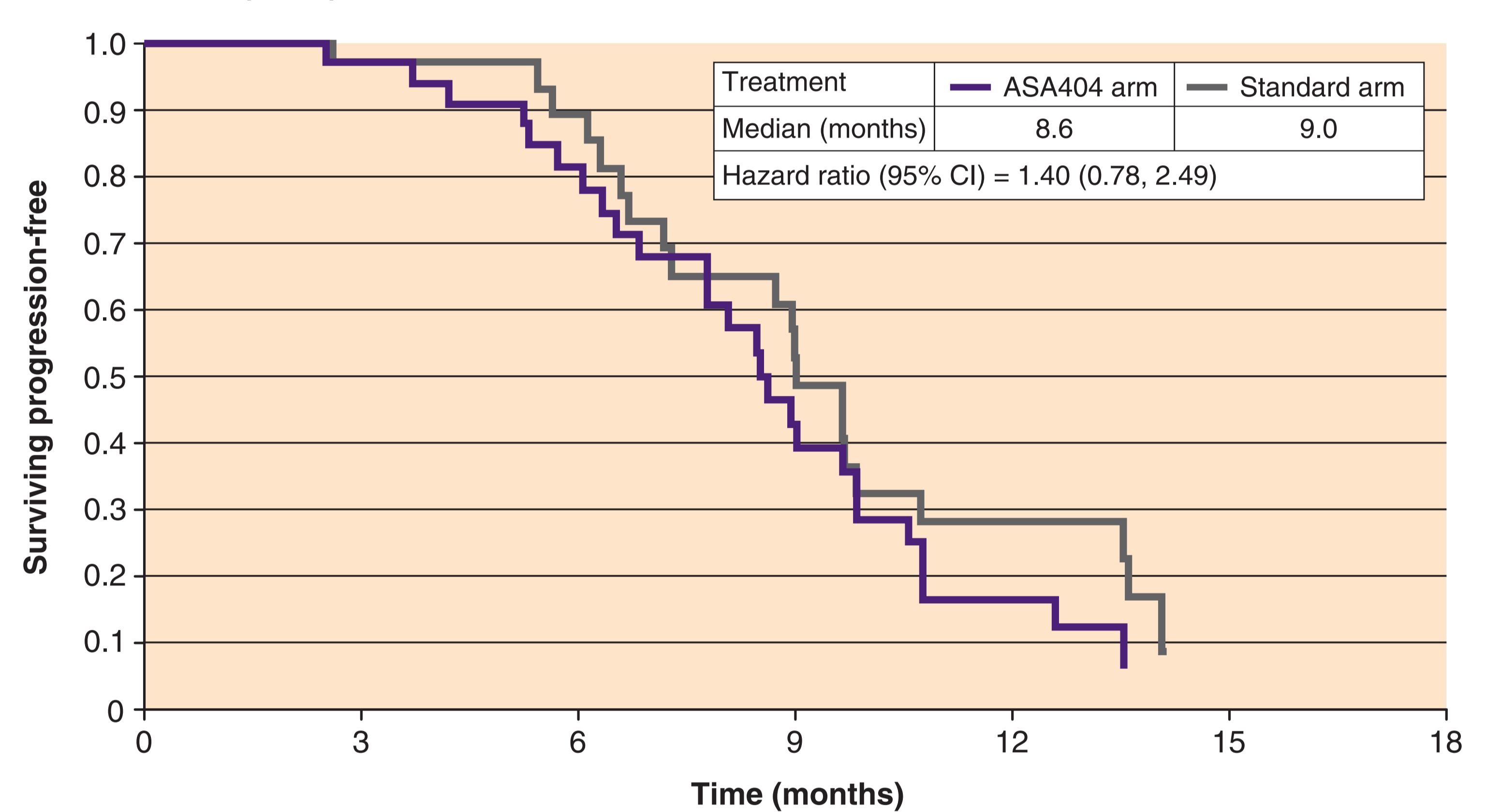
Figure 1: RECIST response outcomes by independent assessment



#### Time to tumour progression (Figure 2)

- Median TTP by independent assessment was 8.6 months in the DMXAA arm and 9.0 months in the standard arm (9.0 months in both arms by investigator assessment)

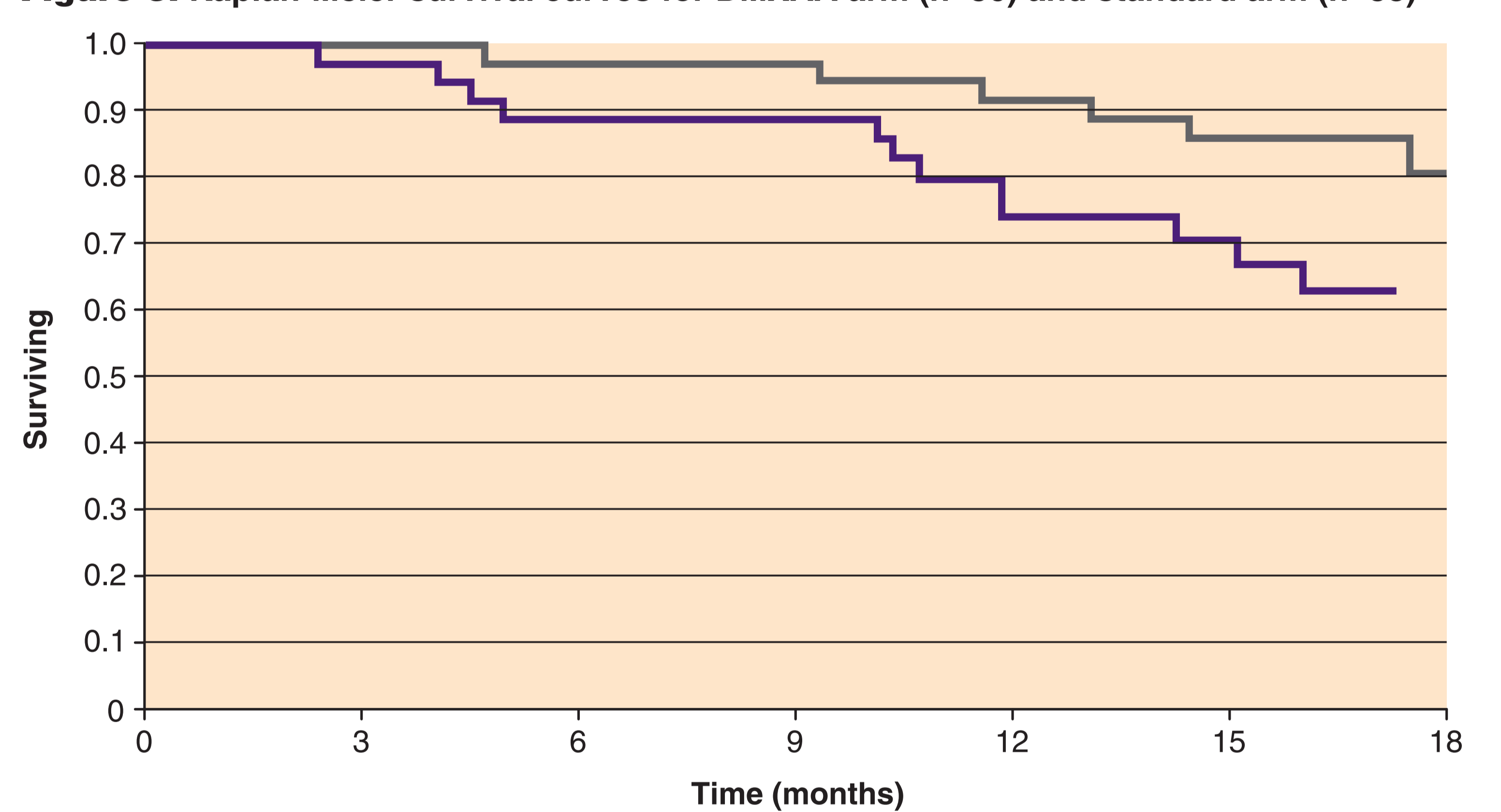
Figure 2: Kaplan-Meier time to tumour progression curves for DMXAA arm (n=37) and standard arm (n=37)



#### Survival (Figure 3)

- 1-year survival rates were 74.1% for the DMXAA arm and 91.8% for the standard arm

Figure 3: Kaplan-Meier survival curves for DMXAA arm (n=36) and standard arm (n=38)



## Conclusions

- Safety findings support those from other trials in prostate and lung cancers, which suggest that the combination of DMXAA with taxane or taxane plus platinum regimens is generally well tolerated
- Although response rates were higher with a DMXAA-chemotherapy combination than with chemotherapy alone, no advantage was observed in median time to tumour progression, and early survival data do not suggest that an improvement is likely with DMXAA
- Based on these data, ovarian cancer will not be a priority indication for future development of DMXAA

## References

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