Novel Cytotoxic Agents

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Emory University
Winship Cancer Institute
Disclosures

• Scientific Advisory Board (Ad hoc)
  – AVEO, Agennix, Boehringer Ingelheim, Genentech, Pfizer, Lilly, Teva.
Outline

• Tubulin binding agents
  – Nab- Paclitaxel
  – GRN1005
  – Eribulin

• Liposomal Irinotecan
Nab-Paclitaxel
Enhanced Penetration & Retention of albumin complexes

Receptor-mediated Transcytosis of albumin complexes across endothelial barrier to interstitium (gp60/caveolin-1 pathway)

High tumor uptake (SPARC binding of albumin complexes)
# Nab-Paclitaxel Studies in NSCLC

## Single Agent Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Phase</th>
<th>N</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green et al. (2006)</td>
<td>II</td>
<td>43</td>
<td>nab-P 260 mg/m² q3w</td>
</tr>
<tr>
<td>Rizvi et al. (2008)</td>
<td>I/II</td>
<td>40</td>
<td>nab-P 100 / 125 / 140 mg/m² days 1,8,15 q4w</td>
</tr>
</tbody>
</table>

## Combination Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Phase</th>
<th>N</th>
<th>Regimen(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allerton et al. (2006)</td>
<td>II</td>
<td>50</td>
<td>nab-P 100 mg/m² days 1,8,15 followed by carboplatin AUC 6 day 1 (30-min infusions on a 28-day cycle)</td>
</tr>
<tr>
<td>Reynolds et al. (2009)</td>
<td>II</td>
<td>50</td>
<td>nab-P 300 mg/m² + carboplatin + bevacizumab q3w</td>
</tr>
<tr>
<td>Socinski et al. (2010)</td>
<td>II</td>
<td>175</td>
<td>nab-P q3w + carboplatin (4 dose cohorts)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nab-P weekly + carboplatin (3 dose cohorts)</td>
</tr>
<tr>
<td>Socinski et al. (2010)</td>
<td>III</td>
<td>1050</td>
<td>nab-P 100 mg/m² qw (no premedication) + carboplatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Paclitaxel 200 mg/m² q3w (+ premedication) + carboplatin</td>
</tr>
</tbody>
</table>
Phase III Advanced NSCLC Trial of nab-Paclitaxel

Stratification factors:
- Stage (IIIb vs IV)
- Histology (squamous vs nonsquamous vs other histology)
- Age (<70 vs ≥70)
- Gender
- Geographic region

## Results: Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>nab-P/C (n = 521)</th>
<th>P/C (n = 531)</th>
<th>All Patients (N = 1052)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (range) years</strong></td>
<td>60 (28, 81)</td>
<td>60 (24, 84)</td>
<td>60 (24, 84)</td>
</tr>
<tr>
<td>&lt;70 years, n (%)</td>
<td>448 (86)</td>
<td>449 (85)</td>
<td>897 (85)</td>
</tr>
<tr>
<td>≥70 years, n (%)</td>
<td>73 (14)</td>
<td>82 (15)</td>
<td>155 (15)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>129 (25)</td>
<td>134 (25)</td>
<td>263 (25)</td>
</tr>
<tr>
<td><strong>ECOG, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>133 (26)</td>
<td>113 (21)</td>
<td>246 (23)</td>
</tr>
<tr>
<td>1</td>
<td>385 (74)</td>
<td>416 (78)</td>
<td>801 (76)</td>
</tr>
<tr>
<td><strong>Histology of Primary Diagnosis, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>254 (49)</td>
<td>264 (50)</td>
<td>518 (49)</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>228 (44)</td>
<td>221 (42)</td>
<td>449 (43)</td>
</tr>
<tr>
<td>Large Cell Carcinoma</td>
<td>9 (2)</td>
<td>13 (2)</td>
<td>22 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>29 (6)</td>
<td>33 (6)</td>
<td>62 (6)</td>
</tr>
<tr>
<td><strong>Stage at Current Diagnosis, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>99 (19)</td>
<td>107 (20)</td>
<td>206 (20)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>421 (81)</td>
<td>424 (80)</td>
<td>845 (80)</td>
</tr>
<tr>
<td><strong>Prior Chemotherapy, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 (2)</td>
<td>8 (2)</td>
<td>20 (2)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking Status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never Smoked</td>
<td>138 (27)</td>
<td>144 (28)</td>
<td>282 (27)</td>
</tr>
<tr>
<td>Smoked and Quit</td>
<td>165 (32)</td>
<td>146 (28)</td>
<td>311 (30)</td>
</tr>
<tr>
<td>Smoked and Still Smokes</td>
<td>210 (41)</td>
<td>231 (44)</td>
<td>441 (43)</td>
</tr>
</tbody>
</table>

*Data was missing for 1 pt at the time of this analysis*
Primary Endpoint Results (ITT Population)
Objective Response Rates – All Histologies

Response Ratio = 1.31
(1.082 – 1.593)
$P = 0.005$

Response Ratio = 1.26
(1.060 – 1.496)
$P = 0.008$

Percent Responses

<table>
<thead>
<tr>
<th>Type of Assessment</th>
<th>nab-P/C (n = 521)</th>
<th>P/C (n = 531)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent Radiologic Review</td>
<td>33%</td>
<td>25%</td>
</tr>
<tr>
<td>Investigator Assessment</td>
<td>37%</td>
<td>30%</td>
</tr>
</tbody>
</table>
Objective Response Rates by Squamous Histology* (N=449)

Response Ratio = 1.67
(1.26 – 2.21)
P = 0.001

Response Ratio = 1.29
(0.99 – 1.69)
P = 0.060

*Not a pre-specified endpoint
Objective Response Rates by Nonsquamous Histology* (N=602)

Response Ratio = 1.03  
(0.79 – 1.36)  
$P = 0.808$

Response Ratio = 1.23  
(0.98 – 1.54)  
$P = 0.069$

*Not a pre-specified endpoint
PFS – ITT Population

<table>
<thead>
<tr>
<th></th>
<th>Ab-P/ Carbo</th>
<th>Paclitaxel/ Carbo</th>
<th>HR</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/Events</td>
<td>521/297</td>
<td>531/312</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS (mo)*</td>
<td>6.3</td>
<td>5.8</td>
<td>0.902</td>
<td>0.214</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.6-7.0</td>
<td>5.6-6.7</td>
<td>0.767-1.060</td>
<td></td>
</tr>
</tbody>
</table>

* PFS based on Independent assessment

Ab-P/carboplatin (N=521)

Paclitaxel/carboplatin (N=531)

Pt at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
<th>30</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ab-P</td>
<td>521</td>
<td>330</td>
<td>167</td>
<td>86</td>
<td>38</td>
<td>23</td>
<td>10</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P</td>
<td>531</td>
<td>321</td>
<td>162</td>
<td>75</td>
<td>48</td>
<td>19</td>
<td>10</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Overall Survival – ITT Population

Probability of Survival

Months

Pt at risk

Ab-P/Pac

Ab-P/carboplatin (N=521)

Paclitaxel/carboplatin (N=531)

N/Events

521/360

531/384

Median OS (mos)

12.1

11.2

0.922

0.271

95% CI

10.8-12.9

10.3-12.6

0.797-1.066

HR

P-Value

0.00

0.25

0.50

0.75

1.00

0.00

0.25

0.50

0.75

1.00

0.00

0.25

0.50

0.75

1.00

Pt at risk

Ab-P

521

469

381

313

246

200

163

98

23

0

0

0

Pac

531

470

389

308

243

191

148

89

24

5

1

0
Exploratory Overall Survival Analysis in Selected Strata

**Squamous Histology**

HR = 0.890
95% CI [0.719, 1.101]
P-value = 0.284*

**≥70 years of age**

HR = 0.583
95% CI [0.388, 0.875]
P-value = 0.009*

*Subgroup analyses exploratory in nature
Safety

<table>
<thead>
<tr>
<th>Adverse Events, %</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>P-values for grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nab-P/C (n = 514)</td>
<td>P/C (n = 524)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>33</td>
<td>12</td>
<td>33</td>
<td>23</td>
<td>0.009*</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>4</td>
<td>6</td>
<td>2</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Anemia</td>
<td>22</td>
<td>5</td>
<td>6</td>
<td>&lt;1</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>1</td>
<td>&lt;1</td>
<td>NS</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>&lt;1</td>
<td>6</td>
<td>&lt;1</td>
<td>NS</td>
</tr>
<tr>
<td>Sensory Neuropathy</td>
<td>3</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2</td>
<td>0</td>
<td>&lt;1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>0</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>NS</td>
</tr>
<tr>
<td>Myalgia</td>
<td>&lt;1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0.011*</td>
</tr>
</tbody>
</table>

*Favors nab-P/C; †Favors P/C

No hypersensitivity reaction occurred in the nab-P/C arm without prophylactic premedication, while 3 occurred in the P/C arm (grade 1, 2, and 3, respectively).
GRN1005
GRN1005 is a peptide-drug conjugate (PDC) comprised of three molecules of paclitaxel linked (via a succinyl linker) to a proprietary peptide (AngioPep-2) that targets the low-density lipoprotein receptor-related protein 1 (LRP-1), one of the most highly expressed receptors on the surface of the blood-brain barrier.
GRN1005 Mechanism of Action: Brain and Tumor via LRP-1
(low-density lipoprotein receptor-related protein 1)

- Binding of GRN1005 to LRP-1 results in receptor-mediated transcytosis across the BBB, leading to high concentrations of paclitaxel in the brain compared to unconjugated paclitaxel.

- LRP-1 is upregulated in various cancer cells, including malignant glioma and metastatic brain cancers.
GRN1005 : Summary of Phase 1 Data

Number of patients
- 119 in two P1 studies: Solid Tumor Metastases (n = 56)
  Primary Brain Tumors (n = 63)

Efficacy
- Single agent responses observed in brain metastasis patients, including prior taxane failures.
- Extra-cranial disease often responded with reduced size of brain metastases.
- Single agent responses were also observed in GBM patients.

Safety
- Neutropenia was the main dose-limiting toxicity.

PK
- Plasma tₑ/₂ ~ 4 hrs
- GRN1005 plasma concentrations (Cmax and AUC) are significantly higher than naked paclitaxel.
- GRN1005 drug concentrations were detected in primary brain tumor samples within a few hours of dosing.

Source: Targeted Therapies Meeting, Santa Monica, 2012
Intra-cranial disease decreases observed in the Brain

Figure 3. Percent Change from Baseline to Best Response (1-D) by Primary Tumor Type

Each bar in Figure 3 represents one patient, depicting the best percentage change from baseline. Independent radiologist assessments were used whenever available.

SCLC = Small cell lung cancer; NSCLC = non-small cell lung cancer; * = prior taxane failure
## GRN1005: Phase 2 NSCLC with Brain Mets

### Objective
- To investigate whether GRN1005 improves the overall ORR of NSCLC patients with brain metastasis

### Primary Endpoint
- Overall ORR (intra-cranial and extra-cranial disease) by IRF according to modified RECIST v1.1

### Population
- NSCLC pts with brain metastasis progressed post WBRT or no WBRT, prior taxanes allowed, neurologically stable but steroids and anticonv allowed
- At least one $\geq 1.0$ cm measurable lesion - either intra-cranially or extra-cranially
- Tumor tissue for biomarker program assessment required

### Key Secondary Endpoints
- Duration of Overall PFS by IRF
- Duration of Intra-cranial PFS by IRF
- Duration of Extra-cranial PFS by IRF
- 6-month OS
- Duration of Overall ORR by IRF
- Safety & tolerability

### Timeline
- To initiate Q4 2011
- PI: Dr Wen

### Sites
- Karmanos, DFCI, CU, Moffit, UCSD, Ingalls Memorial, TN Oncology

### Dosing and Administration
- **Metastatic NSCLC with Brain Metastasis**
  - With or Without Whole Brain Radiation Therapy
  - N=50

- **GRN1005**
  - 650 mg/m² IV q3wks
  - N=50* (≥ 25 patients with prior WBRT)
Eribulin
Eribulin: A Unique Microtubule Dynamics Inhibitor

1. Eribulin inhibits microtubule growth

2. Eribulin has no measurable effect on microtubule shortening

3. Eribulin leads to nonproductive tubulin aggregates

Vincas: block polymerization, (promote depolymerization)

Taxanes & Epothilones: (stabilize microtubules, inhibit depolymerization)

Phase III Trial of Eribulin vs TPC* (EMBRACE) in heavily pre-treated Breast Cancer

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**Independent review**

<table>
<thead>
<tr>
<th>Tumour response</th>
<th>Eribulin (754)</th>
<th>TPC (n=354)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>3 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>54 (12%)</td>
<td>10 (5%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>208 (44%)</td>
<td>96 (45%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>190 (41%)</td>
<td>105 (49%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>12 (3%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Objective response rate†</td>
<td>57 (12%; 9.4-15.5)</td>
<td>10 (5%; 2-3.8)</td>
</tr>
<tr>
<td>Clinical benefit rate§</td>
<td>106 (23%; 18.9-26.7)</td>
<td>36 (17%; 12.1-22.5)</td>
</tr>
</tbody>
</table>

**Investigator review**

<table>
<thead>
<tr>
<th>Tumour response</th>
<th>Eribulin (95% CI)</th>
<th>TPC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>3 (3.3-3.9)</td>
<td>2.2 (2.1-3.4)</td>
</tr>
<tr>
<td>Partial response</td>
<td>0.87 (0.71-1.05)</td>
<td>0.037</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3.6 (3.3-3.7)</td>
<td>2.2 (2.0-2.6)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0.76 (0.64-0.90)</td>
<td>0.002</td>
</tr>
<tr>
<td>Not evaluable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Objective response rate†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical benefit rate§</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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*TPC: Therapy of Physician Choice

First-in-Human Phase I Pharmacokinetic and Target Validation Study of the novel anti-tubulin agent E7389: A California Cancer Consortium trial

- Inter-and intra-patient dose escalation
- 0.125 to 1.4 mg/M2 d 1, 8, 15 q 28 days
- 38 evaluable patients

E7389 plasma conc. (nM)

Figure 1a

2/24/04

4/15/04

Apical

Mid-point

from Synold et al: Submitted, CA62505
A Phase II Study of Halichondrin B Analog Eribulin Mesylate (E7389) in Patients with Advanced Non-small Cell Lung Cancer Previously Treated with a Taxane

A California Cancer Consortium Trial

Barbara J. Gitlitz, MD,* Denice D. Tsao-Wei, MS,* Susan Groshen, PhD,* Angela Davies, MD,† Marianna Koczywas, MD,‡ Chandra P. Belani, MD,§ Athanassios Argiris, MD,‖ Suresh Ramalingam, MD,¶ Everett E. Vokes, MD,# Martin Edelman, MD,** Philip Hoffman, MD,# Marc S. Ballas, MD,†† Stephen V. Liu, MD,* and David R. Gandara, MD†

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Taxane-Sensitive</th>
<th>Taxane-Resistant</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>45</td>
<td></td>
<td>21</td>
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<tr>
<td>Best response</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PR</td>
<td>3</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>27</td>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>PD</td>
<td>12</td>
<td>27</td>
<td>13</td>
</tr>
<tr>
<td>N/A</td>
<td>3</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Overall survival, mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>12.6 (9.9–17.5)</td>
<td>8.9 (5.0–15.4)</td>
<td>11.6 (8.2–13.7)</td>
</tr>
<tr>
<td>Progression free survival, mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>2.9 (2.5–4.8)</td>
<td>1.2 (1.1–2.9)</td>
<td>2.7 (1.3–3.9)</td>
</tr>
</tbody>
</table>
A Phase II Study of Eribulin Mesylate (E7389) in Patients With Advanced, Previously Treated Non–Small-Cell Lung Cancer

Alexander I. Spira,1 Nicholas O. Iannotti,2 Michael A. Savin,3 Marcus Neubauer,4 Nashat Y. Gabrail,5 Ronald H. Yanagihara,6 Edith A. Zang,7 Patricia E. Cole,7 Dale Shuster,7 Asha Das7

- Prior platin-treated NSCLC (N=103)
  - Taxane naïve (n=83)
  - Taxane pre-treated (n=20)

- Eribulin: 1.4mg/m2 d1,8,15 q28 days
  - Or d1, 8 q 21 days

- Response rate = 9.7%
- Disease control rate = 55%
- Median PFS: 3.4 mos
- Median OS = 9.4 months

Eribulin Combination Trials in NSCLC

- Eribulin + Carboplatin (1st line Phase Ib): Completed
- Eribulin + Erlotinib (Phase II): Completed
- Eribulin + Pemetrexed (relapse; Phase Ib/II): Ongoing
- Eribulin + Gemcitabine vs. Cisplatin + Gemcitabine (Phase III): Planned
PEP02/MM-398 (Liposome Irinotecan)

• Irinotecan is encapsulated in PEG-liposomes (PEP02/MM-398)
• Improved PK profile over free irinotecan in preclinical and clinical studies
• Enhanced permeability retention (EPR) effect - with the diameters adjusted at about 100 nm penetrating easily around tumor tissues
• Macrophages in tumors aid in converting CPT-11 to SN-38 to reach hypoxic tumor microenvironment
Pre-clinical evidence that MM-398 has improved circulation & tumor accumulation

**CPT-11**
- Sustained plasma levels

**SN-38**
- Moderately sustained plasma levels

**Sustained intra-tumor levels**

**Enhanced intra-tumor activation to SN38**

HT29 CRC xenograft model - MM-398 40mg/kg
PEP02/MM-398 Rodent Studies in Lung Cancer

Human Lung SCC H157 Xenograft in Nude Mice and Rats

Human SCLC H841 Xenograft in Nude Mice and Rats
# MM-398: Ph 1 Monotherapy Study

## Phase 1 Safety Study of the Drug MM-398 in Patients With Advanced Refractory Solid Tumors

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Patients with advanced refractory solid tumors</th>
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</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>To assess the safety of an MM-398 every 3-week regimen and identify the maximum tolerated dose</td>
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<tr>
<td>Number of Patients</td>
<td>11 patients (ITT population)</td>
</tr>
<tr>
<td>Trial Design</td>
<td>Open label, single arm standard 3+3 dose escalation study conducted in Taiwan</td>
</tr>
</tbody>
</table>

- MTD established at 120mg/m²

## Response

<table>
<thead>
<tr>
<th>Response</th>
<th>MM-398</th>
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</thead>
<tbody>
<tr>
<td>CR + PR</td>
<td>20% (2/11)</td>
</tr>
<tr>
<td>DCR (CR+PR+SD)</td>
<td>45.5% (5/11)</td>
</tr>
</tbody>
</table>
MM-398 is under investigation in multiple tumor types

Ongoing trials

◆ Phase 3: Gemcitabine-refractory pancreatic cancer (NAPOLI-1), monotherapy

◆ Phase 2: Colorectal cancer, MM-398 + 5Fu

◆ Phase 1: Glioma