Development of EC 1456 and Related Targeted Small Molecule Drug Conjugates

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VP Research
Exploiting the Folate Receptor (FR)

Delivery of macromolecules into living cells: A method that exploits folate receptor endocytosis

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High Affinity FR Ligand

- Proteins (RIPS)
- Liposomes
- Small Molecules < 3000 Da
- Plasmids Antisense siRNA

- Therapeutics
- Imaging Agents
- Optical
- Radiochemical Chelates
SMDCs reaching the FR target

View of localized region in peritoneal cavity of an ovarian cancer patient as seen with the naked eye (left) or with the aid of a tumor-targeted fluorescence dye (right).
Imaging NSCLC
EC20 positive pleural disease

- Non-invasive
- Real time
- Functional

Etarfolatide
($^{99m}$Tc-EC20)

Normal FR$^+$
- Lung
- Kidney (PT)
$^{99m}$Tc-Etarfolatide Imaging
Omental disease
EC 20 SPECT/CT imaging can be impressive
*Identifies lesions not obvious by CT

EC 1456 #100103S16: endometrial on 16 July 2015
BW Cohort #6 (3.5 mg/m²)
Targeted SMDC Therapy

Small Molecule Drug Conjugates
Our SMDC approach is modular in design.

- **Ligand** (Module 1):
  - High affinity
  - Small size
- **Hydrophilic Spacer** (Module 2):
  - Separates the ligand from the drug payload
  - Provides water solubility
- **Releasable Linker** (Module 3):
  - Stable in blood
  - Cleaves in the endosome
  - Self-immolative
- **Drug** (Module 4):
  - Highly potent
  - Critical mechanism
  - Derivatizable

- **Releasable Linker** (Module 3)
- **Drug** (Module 4)
Folate-SMDCs enter cells via the FR

1. Folate-conjugate binds the folate receptor
2. Upon binding to the folate receptor (Kd=10^{-10} M), the conjugate is internalized via endocytosis
3. The drug is cleaved inside endosome
4. Drug escapes endosome and exerts activity on cell
5. Folate receptor recycles back to cell surface

The reduced folate carrier binds folates with a low affinity (Kd=10^{-5} M). Folate conjugates will not enter cell through the reduced folate carrier.

most antifolates enter cells this way
Better solid tumor penetration with smaller conjugates

- **Tumor Uptake 1st 65 min (red)**
- **Cellular Level**

**Large Molecule**

**Small Molecule (1 min p.i.)**
Vintafolide (EC145; Vinfinıt®)
A folate-vinca alkaloid SMDC
Vintafolide is curative, specific and well-tolerated in vivo; the untargeted DAVLBH drug is not.

*Vintafolide and DAVLBH tested at 1 µmol/kg, TIW 2 wk
- regimen is MTD for DAVLBH and 1/5th MTD for Vintafolide
Clinical Utility

$^{99m}\text{Tc-etafolatide}$ predicts what tissues (lesions) will accumulate vintafolide
$^{99m}$Tc-Etafolatide accumulates in FR-positive, not FR-negative lesions

- **FR+** Treat with FR-targeted SMDC
- **FR-** Do not treat with FR-targeted SMDC
Companion imaging agent SMDC

**Folcepri® Whole Body Scan**

**FR negative ovarian patient**

**FR positive ovarian patient**

**Pre-specified Subgroups**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>FR Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>FR(100%)</td>
<td>All target lesions positive</td>
</tr>
<tr>
<td>FR(20%-80%)</td>
<td>At least one positive, but not all target lesions</td>
</tr>
<tr>
<td>FR(0%)</td>
<td>No target lesions positive</td>
</tr>
</tbody>
</table>

FR = Folate receptor
Single agent vintafolide phase 2 studies

**OS**

- FR(100%) Median 14.6 months
- FR(10-90%) Median 5.8 months
- FR(0%) Median 2.7 months

**OvCa**

**NSCLC**

**PFS**

- FR(100%)
- FR(10-90%)

**OS**

- FR(100%)
- FR(10-90%)
Randomized studies

**PRECEDENT (Phase 2)**

- PROC Patients
  - N = 149
  - Randomization: 2:1
  - Vintafolide + PLD
    - Vintafolide = 2.5mg TIW wks 1, 3
    - PLD = 50 mg/m² (IBW) every 28 days
  - PLD only
    - PLD = 50 mg/m² (IBW) every 28 days

**PROCCEED (Phase 3)**

- PROC Patients
  - N = 350 FR 100%
  - Randomization: 1:1
  - Vintafolide + PLD
    - Vintafolide = 2.5mg TIW wks 1, 3
    - PLD = 50 mg/m² (IBW) every 28 days
  - Placebo + PLD
    - Placebo TIW wks 1, 3
    - PLD = 50 mg/m² (IBW) every 28 days
PROC EED Phase 3 EC145 ovarian cancer efficacy consistent with Phase 2

- EC145 combination arms performed similarly between trials
- Ph3 PLD control performed better than Ph2 control

![Graph showing months from randomization versus probability of PFS for different treatment arms: Ph2 PLD Control, Ph2 EC145 + PLD, Ph3 PLD Control, Ph3 EC145 + PLD].
Median PFS of PLD in PROCEED trial was unusually high at 5.9 months.
NSCLC (adenocarcinoma) is a promising FR indication

**Preclinical Efficacy**

- **KB Control**
- **EC145 1 μmol/kg, TIW x 2 wk**: 1/5 cures
- **Docetaxel 10 mg/kg TIW x 2 wk (MTD)**: 0/5 cures
- **EC145 + Docetaxel**: 5/5 cures

**Distribution of NSCLC FR-alpha Positive Staining Intensity**

Source: Endocyte tissue sample analysis
TARGET EC145 trial PFS & OS improvement more pronounced in pre-defined adeno sub-group

<table>
<thead>
<tr>
<th>Adenocarcinoma</th>
<th>EC145+ DTX N=43</th>
<th>DTX N=49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months, 95% CI)</td>
<td>4.2 (2.6; 5.4)</td>
<td>3.0 (1.6; 4.2)</td>
</tr>
<tr>
<td>PFS HR (vs. DTX; 95% CI)*</td>
<td>0.73</td>
<td>0.0899 (0.46; 1.16)</td>
</tr>
<tr>
<td>1-sided p-value</td>
<td>0.08595 (0.44; 1.16)</td>
<td></td>
</tr>
<tr>
<td>Median OS (months, 95% CI)</td>
<td>12.5 (8.2; 16.8)</td>
<td>6.6 (4.8; 12.7)</td>
</tr>
<tr>
<td>OS HR (vs. DTX; 95% CI)*</td>
<td>0.72</td>
<td>0.0855 (0.44; 1.16)</td>
</tr>
<tr>
<td>1-sided p-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response rate</td>
<td>9 (20.9%)</td>
<td>7 (14.3%)</td>
</tr>
</tbody>
</table>

EC145 = BIW, 2 wk dosing may not be ideal

* Unstratified log-rank
TARGET trial summary

- Primary endpoint met (all patients): PFS HR=0.75, p=0.0696
- Vintafolide + docetaxel showed clinically meaningful improvement across all efficacy endpoints
- NSCLC (adenocarcinoma) is a promising indication for folate targeted therapy
  - OS improvement is especially meaningful because the primary endpoint of Phase 3 trial would be OS:
    - OS in adeno HR=0.72, p=0.0855
- Safety profile was manageable and expected
  - Increased incidence of hematologic and peripheral neuro toxicities
- Currently evaluating development alternatives
Beyond Vintafolide

EC 1456: Folate-tubulysin
Opening the door to super-potent drugs

SMDC technology allows us to treat using a new class of super-potent drugs.
Why tubulysin?
Benefits of EC 1456 (tubulysin) over EC 145 (vinca alkaloid)

Advantages

• **More potent than vinca alkaloids**
  - 20-50 times more potent than vinca alkaloids
  - Binds near the vinca domain of tubulin
  - Vinca alkaloids are non-competitive

• **Active against low FR-expressing cells**

• **Poor substrate for drug efflux pumps (pgp)**

• **Overcomes drug resistance**
  - Active against EC 145-resistant tumors
  - Active against Taxol-resistant tumors
EC 1456

Targeting Ligand (folic acid)

Reducible, self-immolative linker

Tubulysin Warhead

Hydrophilic Spacer
1. Water solubility
2. Separate drug from ligand
3. Decrease liver clearance

EC1456
C_{110}H_{160}N_{23}O_{45}S_{3}
Exact Mass: 2624.05
Mol. Wt.: 2625.81
Tubulysin SMDCs are more potent than EC145, and they’re active against low FR-expressing models.

### Activity of EC1456 in Various FR + and FR - Cell Lines

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Origin</th>
<th>FR Status</th>
<th>EC1456 Activity* (IC50)</th>
<th>Comptable up to 100 nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>KB</td>
<td>Human cervical carcinoma</td>
<td>+++</td>
<td>2.3 nM</td>
<td>Yes</td>
</tr>
<tr>
<td>NCI/ADR-RES-Cl2</td>
<td>Human ovarian carcinoma</td>
<td>++</td>
<td>1.4 nM</td>
<td>Yes</td>
</tr>
<tr>
<td>IGROV1</td>
<td>Human ovarian adenocarcinoma</td>
<td>+</td>
<td>0.72 nM</td>
<td>Yes</td>
</tr>
<tr>
<td>MDA-MB-231</td>
<td>Human breast adenocarcinoma (triple negative)</td>
<td>+</td>
<td>0.47 nM</td>
<td>Yes</td>
</tr>
<tr>
<td>A549</td>
<td>Human lung carcinoma</td>
<td>-</td>
<td>Inactive</td>
<td></td>
</tr>
<tr>
<td>H23</td>
<td>Human lung adenocarcinoma</td>
<td>-</td>
<td>Inactive</td>
<td></td>
</tr>
<tr>
<td>HepG2</td>
<td>Human hepatocellular carcinoma</td>
<td>-</td>
<td>Inactive</td>
<td></td>
</tr>
<tr>
<td>AN3CA</td>
<td>Human endometrial adenocarcinoma</td>
<td>-</td>
<td>Inactive</td>
<td></td>
</tr>
<tr>
<td>LNCaP</td>
<td>Human prostate adenocarcinoma</td>
<td>-</td>
<td>~ 850 nM</td>
<td></td>
</tr>
</tbody>
</table>

* EC1456 activity was evaluated from 0.1-100 nM

**Human lung model only responds to folate-tubulysin, not folate-vinca alkaloid**

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**A549LVFR27 Model**

- EC145
- Tubulysin SMDC
- Vintafolide
- Folate-Tub IC50 = 0.4 nM
Enabling power of folate targeting

Untargeted Tubulysin

Folate-Tubulysin


EC1456 Activity
(2μmol/kg, TIW, 2 wk)
EC 1456 consistently yields greater anti-tumor effect than EC 145 (vintafolide)

Outperforms in all models tested

Effective against resistant models

EC 145 = vintafolide = Vynfinit®
EC1456 is highly active against human NSCLC and OVCA PDX models.

LU2505 NSCLC PDX
(Adenocarcinoma; treatment naive)

- Docetaxel (DTX) 15 mg/kg, SIW {2,2,2} n=7
- EC1456 4 μmol/kg SIW x 2 {0,0,7} n=7
- LU2505 Control {0,0,0} n=7

ST024 Ovarian PDX
(serous carcinoma; treatment naive)

- Paclitaxel 15 mg/kg, SIW x 2 {0,0,0} n=7
- EC1456 4 μmol/kg SIW x 2 (2,0,5) n=7
- EC1456 + Paclitaxel {0,0,7} n=7

Key = {PR, CR, Cures}
EC1456 combines synergistically with approved drugs

Docetaxel Combination

Bevacizumab Combination

Halaven Combination

Carboplatin Combination

- Untreated
- EC1456
- SOC agent at MTD
- EC1456 + SOC
EC1456 plus anti-PD-1 mAb was curative against s.c. M109 tumors

Mice were re-challenged with 3x10^6 M109 cells on Day 84 and resisted new tumor growth → Memory
EC1456 (folate-tubulysin) Phase 1

Phase 1 Design
- Solid tumor Dose Escalation (3 patients per cohort)
- Two 3 week schedules being evaluated:
  - Once per week dose
  - Twice per week dose
  - More frequent daily induction to be added
- All patients imaged with Folcepri® (EC 20) prior to enrollment, but none excluded based on scan
- Expand at MTD in target indications

2015 ECCO ESMO Update
- 26/31 pts evaluable for response
- 11/26 pts had progressive disease (PD) as best study response
- 15/26 pts had stable disease (SD) as best study response

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Treatment</th>
<th>Duration (wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial Mesothelioma</td>
<td>0.5 (BIW)</td>
<td>78</td>
</tr>
<tr>
<td>GE junction</td>
<td>0.5 (BIW)</td>
<td>59</td>
</tr>
<tr>
<td>SC LC</td>
<td>2.0 (BIW)</td>
<td>28</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>1.5 (QW)</td>
<td>46</td>
</tr>
<tr>
<td>NSCLC</td>
<td>2.5 (QW)</td>
<td>37</td>
</tr>
</tbody>
</table>

Development Opportunities

Currently Dose Levels
QW: 10 mg/m²
BIW: 6 mg/m²
Average plasma concentration-time data for EC1456 patients

**EC1456**

- EC145 IC₅₀ = 17 mg/mL
- EC145 IC₅₀ = 2 mg/mL

**EC0347** (released tub-BH)

- Red: EC1456 0.5 mg/m²
- Green: EC1456 0.5 mg/m²
- Blue: EC1456 1.0 mg/m²
- Green: EC1456 1.5 mg/m²
- Blue: EC1456 2.0 mg/m²
- Green: EC1456 2.5 mg/m²
- Blue: EC1456 3.5 mg/m²
- Red: EC1456 4.0 mg/m²
- Green: EC1456 4.5 mg/m²
- Blue: EC1456 6.0 mg/m²
- Black: EC145 2.5 mg (n = 10)
EC 1456 development plan

**Dose escalation**

- **All Comers**
  - **Weekly**
  - **Bi-weekly**

**NSCLC Single Agent Efficacy**

- **Weekly** (n=15)
- **Bi-weekly** (n=15)
- **Daily Induction** (n=15)

**Other Indications & Combinations**

- **FR Positive**
  - **Weekly** (n=25)
  - **Bi-weekly** (n=25)
  - **Induction** (n=25)

**Optimal dose/schedule:**
- Ovarian, TNB, endometrial
- Carbo, Taxol, Docetaxel, PD1i
Constant pressure on tumor yields best response

Best response in the preclinical setting is seen with more frequent dosing

**Response Key:** {PR, CR, Cure}, n=5

- **4 μmol/kg total exposure**
  - Cervical cancer untreated controls
  - EC1456 2 μmol/kg SIW x 2wk (1,0,0)
  - EC1456 1 μmol/kg BIW x 2wk (3,0,0)
  - EC1456 0.67 μmol/kg TIW x 2wks (3,1,0)
  - EC1456 0.4 μmol/kg qd5 x 2wk (0,2,3)

- **12 μmol/kg total exposure**
  - Cervical cancer untreated controls
  - 4 μmol/kg SIW x 3 wk (2,2,1)
  - 2 μmol/kg TIW x 2 wk (0,1,4)
  - 1.2 μmol/kg qd5 x 2wk (0,0,5)

qd5 > TIW > BIW

More frequent dosing not helpful
More frequent dosing optimal
More frequent dosing not possible (toxically), but will infrequent dosing yield cures?
Advancements in SPECT/CT technology leads to more precise patient selection.

**Advanced SPECT/CT**
- In-line SPECT and CT
- Increased resolution
- Attenuation correction

**Results in:**
- Recognition of partial positivity within tumor
- Anatomical colocation
- Quantification

**Benefits:**
- More complete understanding of drug uptake
- Improved selection of FR100%
- High reader agreement

![Fused In line SPECT/CT](image)
Sample positive EC 20 with SPECT/CT

left: mesothelioma

top: ovarian
DNA-Reactive Payloads
Clinical strategy for DNA-reactive SMDC

- Select receptor-positive patient using companion imaging agent
- Treat with SMDC-1 (MTI mechanism)
- If progression, re-scan patient to confirm receptor expression
- Treat patient with SMDC-2 (DNA-reactive mechanism)
Patient convenience with new MOA
Folate-DNA crosslinker is more potent than Folate-Tubulysin when dosed weekly x 2

Program status: SMDC screening, linker optimization, tox
Different Cancer Targets

PSMA
Ligand development approach

*Source of competitive advantage

- Super computer enables review of millions of potential ligands
- Optimal ligand selected for binding affinity and specificity

PSMA crystal structure used in design of a prostate cancer targeting ligand

Cut away view of DUPA-99mTc imaging agent bound to PSMA
Change the ligand
PSMA: Imaging with $^{99m}$Tc-EC0652; therapy with EC1169

BioD of $^{99m}$Tc-EC0652 in PSMA$^+$ Tumor Bearing $nu/nu$ Mice

EC1169 is highly active against PSMA$^+$ cancer

EC1169 is well tolerated
EC 0652 identifies PSMA positive mets
Clinical Status

- Phase 1 enrolling
- Two dosing schedules (1X and 3X per week; 2 wk on, 1 week off)
- Prostate cancer patients (recurrent, metastatic, castration-resistant)
SMDC Attributes

- **Modular design**
  - Small targeting ligand, hydrophilic spacer, self-immolative liker, potent warhead
  - Multiple targets: FR, PSMA, CCK2R, NK1, SST2R, HER2, CXCR4

- **High tumor penetration**
  - Small size (<2.5 kDa)

- **Enabling, versatile technology**
  - e.g. tubulysin

- **Well-tolerated**
  - Curative activity without toxicity

- **Synergistic activity with most standard of care drugs**
  - Platinums, taxanes, bevacizumab, topotecan, Doxil, eribulin, PD1i

- **Companion imaging**
<table>
<thead>
<tr>
<th>Highlights</th>
<th>Information</th>
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<tbody>
<tr>
<td><strong>Folate receptor targeting validated</strong></td>
<td>• Positive EC145 Ph 2 results in NSCLC and Ovarian</td>
</tr>
<tr>
<td><strong>Enhanced next generation</strong></td>
<td>• More potent warhead (tubulysin)</td>
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<td></td>
<td>• Enhanced linker/spacer improves safety/dosing</td>
</tr>
<tr>
<td></td>
<td>• New cameras allow for more precise patient selection</td>
</tr>
<tr>
<td><strong>Robust EC1456 development plan</strong></td>
<td>• Up to 3 schedules tested in FR100 NSCLC patients</td>
</tr>
<tr>
<td></td>
<td>• Additional indications &amp; combinations follow</td>
</tr>
<tr>
<td><strong>EC1169 – A differentiated opportunity</strong></td>
<td>• PSMA receptor target</td>
</tr>
<tr>
<td></td>
<td>• Unmet need following hormone therapies</td>
</tr>
<tr>
<td><strong>Sufficient resources for development</strong></td>
<td>• Guidance for current cash ~$170m; current spend &lt;$40m/yr</td>
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<td></td>
<td>• Pipeline drugs with new targets, warheads, indications</td>
</tr>
<tr>
<td><strong>Key milestones in 2016</strong></td>
<td>• Max dose for both EC1456 and EC 1169</td>
</tr>
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<td></td>
<td>• Efficacy and safety data for both agents in selected patients</td>
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</tbody>
</table>
SMDC approach yields multiple new drug candidates

<table>
<thead>
<tr>
<th>SMDC (Target-Warhead)</th>
<th>Potential Indication</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC 145 Vynfinit® (Folate-DAVLBH)</td>
<td>NSCLC</td>
<td>New Payload</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EC 1456 (Folate-Tubulysin)</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td>New Payload</td>
<td></td>
</tr>
<tr>
<td>EC 1169 (PSMA-Tubulysin)</td>
<td>Prostate</td>
<td></td>
<td></td>
<td>New Target</td>
<td></td>
</tr>
<tr>
<td>EC 1788 (Folate-DNA alkylator)</td>
<td>Solid tumors</td>
<td></td>
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<td>New Payload</td>
<td></td>
</tr>
<tr>
<td>EC 2319 (Folate-Aminopterin)</td>
<td>Inflammation</td>
<td></td>
<td></td>
<td>New Disease</td>
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</tr>
<tr>
<td>EC 0371 (Folate-mTor inhibitor)</td>
<td>PKD²</td>
<td></td>
<td></td>
<td>New Disease</td>
<td></td>
</tr>
<tr>
<td>EC 20 Folcepri® (Folate-Tc99m)</td>
<td>FR-Imaging</td>
<td></td>
<td></td>
<td>Companion Imaging Agent</td>
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<tr>
<td>EC 0652 (PSMA-Tc99m)</td>
<td>PSMA-Imaging</td>
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1) The safety and efficacy of these agents have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

2) Polycystic kidney disease