Phase 2 Study of Aldoxorubicin Versus Topetecan for Relapsed/Refractory Small Cell Lung Cancer.

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Abstract

BACKGROUND: Aldoxorubicin is a novel prodrug that binds to albumin in the circulation. Doxorubicin is cleaved in low pH environments, allowing administration of 3½-4-fold higher doses than standard doxorubicin and 10-fold greater cumulative doses. Patients with metastatic small cell lung cancer (SCLC) who have failed prior chemotherapies have a poor prognosis with response rates (ORR) of 5-20%, progression-free survival (PFS) of 2-4 months and overall survival of 6-10 months. Topotecan is the standard therapy for these patients.

TRIAL DESIGN: Open label study, 132 patients, (1:1 randomization) to receive either aldoxorubicin (230 mg/m²), IV infusion, Day 1, every 3 weeks) or topotecan (either 2.3 mg/m²/day oral or 1.5 mg/m²/day IV, Days 1-5, every 3 weeks.

Key inclusions: confirmed SCLC, relapsed or refractory to ≥1 prior chemo, ECOG 0-2, measurable tumor (RECIST 1.1). Key exclusions: >375 mg/m² prior doxorubicin, prior topotecan, active CNS mets, lab abnormalities (ANC <1500/m³, platelets <100,000/mm³, Hgb <9 gm/dL, LFTs >3 or 5x ULN, albumin <2 gm/dL), serious myocardial dysfunction.

Key stratifications: relapse <90 days versus >90 days; ECOG 0-1 versus 2.

Primary endpoint: PFS (analysis after 110 events); assume PFS for topotecan=3.5 months, aldoxorubicin=5.5 months. Secondary endpoints: ORR, OS, disease control rate, adverse events, tolerability, lab abnormalities.

Study sites: Up to 35 sites in the US and Europe.

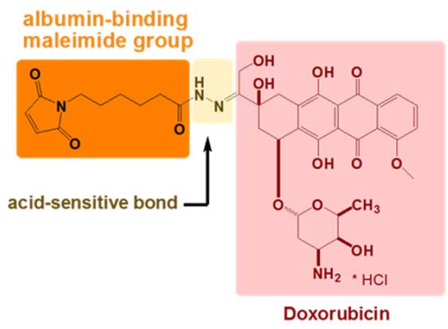
Background

- Small cell lung cancer (SCLC) comprises about 15% of all lung cancers, with an estimated 34,000 new cases in the US in 2012.[1]
- SCLC is a member of the neuroendocrine family of malignancies and almost all cases are associated with cigarette smoking.
- The tumor has an extremely rapid doubling time and is usually metastatic upon discovery, with only around 1 of 3 presenting with limited disease that is confined only to the chest.
- All patients with SCLC require chemotherapy. Etoposide + cisplatin is the most commonly used regimen as first line treatment, although carboplatin may be substituted for cisplatin with no change in efficacy.[2-5]
- For extensive-stage disease, response rates are as high as 65-75%, with 20% CRs. However, PFS is only 5.5-6 months, with OS reaching 9-10 months.[2-5]
- Topotecan plus platinum has more recently been substituted for etoposide-platinum, with a slight improvement in OS of around 1 month.[2-5]
- Topotecan is the only FDA-approved chemotherapy for treating patients refractory or relapsed after responding to initial chemotherapy. Patients who relapse in less than 90 days have response rates below 10% with progression after only 2-3 months. Patients who relapse beyond 90 days exhibit response rates of approximately 25% and progress at 3-4 months.[6]

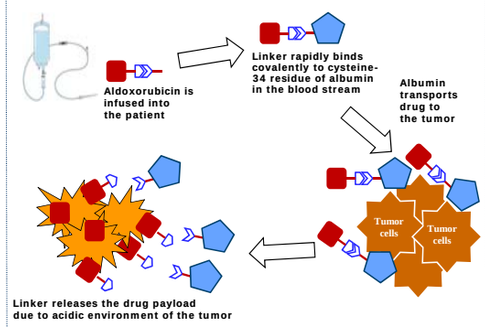
Aldoxorubicin

- Aldoxorubicin is a prodrug of the anticancer agent doxorubicin which is derivatized at its C-13 keto-position with a thiol-binding spacer molecule (6-maleimidocaproic acid hydrazide).[7]
- Aldoxorubicin is quantitatively and selectively bound to the cysteine-34 position of endogenous albumin within a few minutes. It has a half-life of ~ 20 hrs, a low Vd and clearance, and <2% of free doxorubicin is detected in the circulation over 72 hrs.
- Aldoxorubicin is significantly less cardiotoxic in a chronic rat model when compared to doxorubicin at an equitoxic dose.[9]

Structure of Aldoxorubicin



Proposed Mechanism of Action



Objectives

Primary

- Efficacy of aldoxorubicin compared to topotecan in subjects with extensive-stage SCLC who have relapsed or were refractory to prior chemotherapy, as measured by PFS.

Secondary

- OS, disease control rate, and tumor response.
- Safety, cardiac function.

Endpoints

Primary

- PFS

Secondary

- OS
- ORR (RECIST 1.1), disease control rate (ORR + SD at 4 months)
- Investigator-reported quality of life (ECOG PS).
- Treatment-related toxicities

Study Design

- Approximately 132 subjects randomized 1:1 to receive either aldoxorubicin or topotecan.
- Aldoxorubicin at a dosage of 230 mg/m² (doxorubicin equivalents of 170 mg/m²) will be administered as a 30 minute IVI every 21 days vs. topotecan administered IV at doses of 1.5 mg/m²/day for 5 consecutive days, every 21 days, or 4 mg/m² administered as a 30 min IVI on Days 1, 8 and 15 every 28 days.
- Treatment will continue until tumor progression is observed, subject withdraws, or unacceptable toxicity occurs.
- Safety assessments.
- Cardiac function (ECHO) for subjects receiving aldoxorubicin.
- Tumor response: screening and every 6 weeks from Cycle 1-Day 1 through week 33, and then every 12 weeks until disease progression using the RECIST 1.1 criteria.
- PFS determined by both Blinded Independent Radiology Review (primary) and investigator assessment (secondary).
- Subjects stratified according to their initial ECOG PS (0-1 vs 2) and whether they had progressed in less than or greater than 90 days after their initial chemotherapy.

Sample Size

- Estimated median PFS for aldoxorubicin is 6.5 months and 3.5 months for topotecan.
- Based on the use of a two-sided log rank test at the α=0.05 level of significance (type 1 error = 5%), a total of 110 PFS events will be required for 90% power (type II error = 10%) to detect this difference.
- Assuming an 18 month accrual period and a 6 month follow-up period after enrollment of the last subject, approximately 132 subjects will be needed to achieve the total of 110 PFS events.

Key Eligibility Criteria

Inclusion

1. Age ≥18 years male or female.
2. Histological confirmation of SCLC.
3. Relapsed or refractory to no more than 1 course of a systemic therapy regimen and is incurable by either surgery or radiation.
4. ECOG PS 0-2.
5. Life expectancy >8 weeks.
6. Measurable tumor lesions according to RECIST 1.1 criteria.

Exclusion

1. Prior exposure to >375 mg/m² of doxorubicin or liposomal doxorubicin.
2. Prior treatment with topotecan.
3. Palliative surgery and/or radiation treatment < 21 days prior to date of randomization.
4. Exposure to any investigational agent within 30 days of date of randomization.
5. Exposure to any systemic chemotherapy within 21 days of date of randomization.
6. Active (symptomatic) CNS metastasis.
7. Laboratory values: Screening serum creatinine >1.5×ULN, ALT >3×ULN or >5×ULN if liver metastases are present, total bilirubin >2×ULN, ANC <1,500/mm³, platelet concentration <100,000/mm³, hemoglobin <9 g/dL, albumin <2 gm/dL.
8. Serious myocardial dysfunction defined by ECHO as absolute LVEF below the institution's lower limit of predicted normal.

Global Trial Sites

Country	Estimated Number of Sites
United States	20
Hungary	7
Spain	11
Italy	6

Possible Adverse Events

Pooled data on subjects receiving 230mg/m² dose of aldoxorubicin (170mg/m² doxorubicin equivalents)

	Total of 16 subjects treated at 230 mg/m²			
	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	1 (6%)	2 (13%)	0	0
Thrombocytopenia	0	2 (13%)	1 (6%)	0
Anemia	0	2 (13%)	2 (13%)	0
Febrile neutropenia	0	0	0	0
Nausea/vomiting	8 (50%)	2 (13%)	0	0
Mucositis	5 (31%)	2 (13%)	0	0
Fatigue	4 (25%)	3 (19%)	1 (6%)	0
Alopecia	0	1 (6%)	0	0
Hypoalbuminemia	0	1 (6%)	0	0

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1. Please go to www.clinicaltrials.gov for a full description of the trial and clinical sites (NCT02200757).
2. If you are interested in participating in this trial, please contact Lisa Currie-Bennett (lisa.currie-bennett@psi-cro.com).

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Disclosures

Levitt & Wieland: *CytRx Corporation:* Employment, Equity Ownership.
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