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# Phase I/II trial of vorinostat (SAHA) and erlotinib for non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutations after erlotinib progression☆

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ABSTRACT

*Objectives:* Vorinostat or suberoylanilide hydroxamic acid (SAHA) is a novel histone deacetylase inhibitor with demonstrated antiproliferative effects due to drug-induced accumulation of acetylated proteins, including the heat shock protein 90. We prospectively studied the activity of vorinostat plus erlotinib in EGFR-mutated NSCLC patients with progression to tyrosine kinase inhibitors.
*Patients and methods:* We conducted this prospective, non-randomized, multicenter, phase I/II trial to evaluate the maximum tolerated dose, toxicity profile and efficacy of erlotinib and vorinostat. Patients with advanced NSCLC harboring EGFR mutations and progressive disease after a minimum of 12 weeks on erlotinib were included. The maximum tolerated dose of vorinostat plus erlotinib was used as recommended dose for the phase II (RDP2) to assess the efficacy of the combination. The primary end point was progression-free-survival rate at 12 weeks ($PFSR_{12w}$). Pre-treatment plasma samples were required to assess T790M resistant mutation.
*Results:* A total of 33 patients were enrolled in the phase I–II trial. The maximum tolerated dose was erlotinib 150 mg p.o., QD, and 400 mg p.o., QD, on days 1–7 and 15–21 in a 28-day cycle. Among the 25 patients treated at the RDP2, the most common toxicities included anemia, fatigue and diarrhea. No responses were observed. $PFSR_{12w}$ was 28% (IC95%: 18.0–37.2); median progression-free survival (PFS) was 8 weeks (IC 95%: 7.43–8.45) and overall survival (OS) 10.3 months (95% CI: 2.4–18.1).
*Conclusion:* Full dose of continuous erlotinib with vorinostat 400 mg p.o., QD on alternative weeks can be safely administered. Still, the combination has no meaningful activity in EGFR-mutated NSCLC patients after TKI progression.



## 1. Introduction

Driver mutations at the activation loop of the TK domain of EGFR are present in almost 17% of advanced NSCLC patients [1–3]. Data from prospective phase III trials have demonstrated superiority of TKIs over standard chemotherapy in this molecular selected NSCLC population [4–10]. Unfortunately, the overwhelming majority of responders will inevitably develop acquired resistance [11].

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**Table 1**
Number of patients with related adverse events (AEs) during phase I portion of the trial (first cycle).

| | Dose level 1 ($n=3$) | | Dose level 2 ($n=3$) | | Dose level 3 ($n=8$) | |
|---|---|---|---|---|---|---|
| Adverse event CTCAE v.3.0 | Grade 1–2 | Grade 3–4 | Grade 1–2 | Grade 3–4 | Grade 1–2 | Grade 3–4 |
| *Hematological* | | | | | | |
| Anemia | – | – | – | – | 3 | – |
| Neutropenia | – | – | – | – | 1 | – |
| Lymphopenia | – | – | – | – | 1 | – |
| *Gastrointestinal* | | | | | | |
| Diarrhea | 2 | – | 2 | – | 5 | 1[a] |
| Constipation | – | – | – | – | 1 | – |
| Dysgeusia | – | – | – | – | 1 | – |
| Nausea | – | – | 2 | – | 1 | 1 |
| Vomiting | – | – | – | – | 3 | – |
| Xerostomia | 2 | – | 2 | – | 2 | – |
| Dyspepsia | 1 | – | – | – | – | – |
| Mucositis | – | – | – | – | – | 1 |
| Thirstiness | – | – | 1 | – | – | – |
| Dehydration | – | – | – | – | 1 | – |
| Anorexia | – | – | 2 | – | 4 | – |
| Epigastralgia | – | – | – | – | 2 | – |
| *Skin* | | | | | | |
| Cheilitis | – | – | 1 | – | – | – |
| Hand erythema | 1 | – | – | – | – | – |
| Rash | 1 | – | 1 | 1 | 4 | – |
| Pruritus/itching | – | – | – | – | 1 | – |
| Dry skin | – | – | – | – | 1 | – |
| Paronychia | 1 | – | – | – | – | – |
| *Metabolic/laboratory* | | | | | | |
| SGOT (AST) | 1 | – | – | – | – | – |
| SGPT (ALT) | – | – | 1 | – | – | – |
| Hyperbilirubinemia | 1 | – | – | – | 2 | – |
| Hyperglycemia | – | – | 1 | – | – | – |
| Hyperkalemia | – | – | – | – | 1 | – |
| Creatinine | – | – | 1 | – | 2 | – |
| *Neurology/endocrine/constitutional* | | | | | | |
| Fatigue | 2 | – | 1 | – | 5 | 1[b] |
| Fever | – | – | – | – | 1 | – |
| Somnolence | – | – | 1 | – | – | – |

Abbreviations: CTCAE, common terminology criteria for adverse events; SGOT (AST), serum glutamic oxaloacetic transaminase; SGPT (ALT), serum glutamic pyruvic transaminase; GGT, γ-glutamyl transpeptidase.
[a] Dose limiting toxicity.
[b] Patient replaced before completing first cycle due to non-treatment compliance.

To date, two major mechanisms of acquired resistance that impair the drug's inhibitory action have been identified *in vivo*: a secondary mutation at exon 20 (T790M), which accounts for ∼50% of resistant tumors [12–14], and amplification of the c-Met oncogene (∼10–20%) [15,16]. Several strategies directed against these mechanisms of acquired resistance have been tested so far [17–21]; even so, the standard treatment of advanced EGFR mutated patients after TKI remains to be established.

One potential strategy for overcoming resistance is to target EGFR for degradation. One of the most relevant proteins involved in this process is the heat shock protein (Hsp) 90, a well-known client of several oncogenes [22,23]. It is known that EGFR relies on Hsp90 chaperone function for conformational maturation and stability, and the active form of EGFR is more dependent on this chaperone function than its wild-type counterpart [24]. Moreover, Hsp90 maintains the active confirmation of EGFR mutants, preventing ligand-induced down-regulation [25]. Novel Hsp90 inhibitors (IPI-504, AUY922) have shown promising results in EGFR-resistant advanced NSCLC patients [26].

Histone deacetylase inhibitors (HDACI) are compounds that can induce acetylation of Hsp90, disrupting its chaperone function and resulting in tumor cell death [22]. Importantly, treatment of EGFR-dependent human lung cancer cell lines with a HDACI induces apoptosis through Hsp90 acetylation and combination with a TKI results in a synergistic tumor cell death [27]. HDAC inhibition can also induce E-cadherin expression by acetylating the histones recruited by the zinc finger transcriptional repressor (ZEB1) [28] and clinical evidence points to the importance of this epithelial marker as a potential predictor of response to EGFR TKIs [29]. Based on this preclinical evidence, the use of an HDAC inhibitor has been postulated as a reasonable alternative to overcome resistance to TKIs in EGFR-active NSCLC patients.

Vorinostat (Zolinza®; Merck & Co., Inc., Whitehouse Station, NJ, USA), the drug formulation of Suberoylanilide hydroxamic acid or SAHA, is an oral, HDAI with demonstrated antiproliferative effects due to drug-induced accumulation of acetylated proteins [30]. Vorinostat is currently used as monotherapy for primary cutaneous T-cell lymphoma [31], and it has also been tested in combination with chemotherapy without major concerns [32,33].

We conducted this phase I/II trial to demonstrate if the addition of vorinostat to erlotinib could re-sensitize this molecularly selected subset of advanced NSCLC patients with active EGFR and TKI resistance.

## 2. Patients and methods

### 2.1. Study design and eligibility criteria

This is a phase I/II, non-randomized, open-label, multicenter and investigator-initiated study (ClinicalTrials.gov identifier: