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Original Paper

Inhibition of Erythrocyte Cell Membrane Scrambling Following Energy Depletion and Hyperosmotic Shock by Alectinib

Abdulla Al Mamun Bhuyan[a] Florian Lang[a,b]

[a]Department of Vegetative and Clinical Physiology, Eberhard-Karls-University of Tuebingen, Tuebingen,
[b]Department of Molecular Medicine II, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany

Key Words
Phosphatidylserine • Eryptosis • Alectinib • Glucose deprivation • Hyperosmolarity • Oxidative stress • Ionomycin • Calcium

Abstract
Background/Aims: The anaplastic lymphoma kinase (ALK) inhibitor alectinib is clinically used for the treatment of ALK positive non-small-cell lung cancer. At least in part the substance is effective by triggering suicidal death or apoptosis of tumor cells. Erythrocytes are lacking mitochondria and nuclei, key organelles of apoptosis but are, similar to apoptosis of nucleated cells, able to enter suicidal erythrocyte death or eryptosis. Stimulators of eryptosis include energy depletion, hyperosmotic shock, oxidative stress, and increase of cytosolic Ca^{2+} activity ($[Ca^{2+}]_i$). The present study explored, whether alectinib influences eryptosis. ***Methods:*** Flow cytometry was employed to quantify phosphatidylserine exposure at the cell surface from annexin-V-binding and cell volume from forward scatter. Measurements were made without or with energy depletion (glucose deprivation for 48 hours), hyperosmotic shock (+550mM sucrose for 6 hours), oxidative stress (50 min exposure to 0.3 mM tert-butylhydroperoxide), and Ca^{2+} loading (60 minutes treatment with 1 µM Ca^{2+} ionophore ionomycin). ***Results:*** A 48 hours exposure of human erythrocytes to alectinib (150-600 ng/ml) did not significantly modify the percentage of annexin-V-binding cells and forward scatter. Energy depletion, hyperosmotic shock, oxidative stress and Ca^{2+} loading were each followed by profound and significant increase of the percentage annexin-V-binding erythrocytes and a significant decrease of forward scatter. The effects of energy depletion and hyperosmotic shock, but not of oxidative stress or Ca^{2+} loading on annexin-V-binding were significantly blunted in the presence of alectinib (150-600 ng/ml). In none of the conditions was forward scatter significantly modified by alectinib. ***Conclusion:*** Alectinib inhibits cell membrane scrambling following energy depletion and hyperosmotic shock.

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Prof. Dr. Florian Lang
Department of Physiology,
University of Tuebingen, Wilhelmstr. 56, 72076 Tuebingen (Germany)
Tel. +49 7071 29-72194, Fax +49 7071 29-5618, E-Mail florian.lang@uni-tuebingen.de

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Introduction

The Anaplastic lymphoma kinase (ALK) inhibitor [1-3] Alectinib is used for the treatment of ALK positive non-small-cell lung cancer (NSCLC) [1-20]. Alectinib is at least in part effective by triggering suicidal death or apoptosis of tumor cells [21, 22].

Even though lacking mitochondria and nuclei, erythrocytes may similarly enter suicidal death or eryptosis, which is characterized by cell membrane scrambling with phosphatidylserine translocation to the cell surface [23-25]. Typically eryptosis is paralleled by cell shrinkage [26]. Eryptosis could be triggered by energy depletion, hyperosmotic shock, and oxidative stress [25]. Moreover, eryptosis is stimulated by a myriad of small chemicals and diverse clinical conditions [27-127]. The cellular machinery orchestrating eryptosis includes increase of cytosolic Ca^{2+} activity ($[Ca^{2+}]_i$) [25], ceramide [128], G-protein Galphai2 [89], and activation of diverse kinases including casein kinase 1α, Janus-activated kinase JAK3, protein kinase C, and p38 kinase [25]. Eryptosis is inhibited by several kinases including AMP activated kinase AMPK, cGMP-dependent protein kinase, PAK2 kinase, and mitogen and stress activated kinase MSK1/2 [129].

The present study was designed to test, whether alectinib is able to trigger eryptosis. Surprisingly, the substance turned out to inhibit eryptosis. Thus, the effect of alectinib on eryptosis following energy depletion, hyperosmotic shock, oxidative stress and cellular Ca^{2+} load was quantified. Accordingly, human erythrocytes from healthy volunteers were exposed to glucose deprivation, hypertonic extracellular osmolarity, the oxidant tert-butyl-hydroperoxide or the Ca^{2+} ionophore ionomycin, and phosphatidylserine surface abundance as well as cell volume determined by flow cytometry.

Materials and Methods

Erythrocytes, solutions and chemicals

Fresh Li-Heparin-anticoagulated blood samples were kindly provided by the blood bank of the University of Tübingen. The study is approved by the ethics committee of the University of Tübingen (184/2003 V). The blood was centrifuged at 120 g for 20 min at 21 °C and the platelets and leukocytes-containing supernatant was disposed. Erythrocytes were incubated *in vitro* at a hematocrit of 0.4% in Ringer solution containing (in mM) 125 NaCl, 5 KCl, 1 $MgSO_4$, 32 N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid (HEPES; pH 7.4), 5 glucose, 1 $CaCl_2$, at 37°C for 48 hours. Where indicated, erythrocytes were exposed for 48 hours to glucose containing or glucose depleted Ringer solution, for 6 hours to hyperosmotic extracellular fluid (550 mM sucrose added), for 50 minutes to the oxidant tert-butyl-hydroperoxide (0.3 mM, Sigma Aldrich, Hamburg, Germany), or for 60 minutes to Ca^{2+} ionophore ionomycin (1 µM, Merck Millipore, Darmstadt, Germany), each in the absence and presence of alectinib (150-600 ng/ml, MedChem Express, Princeton, USA).

Annexin-V-binding, forward scatter

After incubation under the respective experimental condition, a 150 µl cell suspension was washed in Ringer solution containing 5 mM $CaCl_2$ and then stained with Annexin-V-FITC (1:200 dilution; ImmunoTools, Friesoythe, Germany) in this solution at 37°C for 15 min under protection from light. The annexin-V-abundance at the erythrocyte surface was subsequently determined on a FACS Calibur (BD, Heidelberg, Germany). Annexin-V-binding was measured with an excitation wavelength of 488 nm and an emission wavelength of 530 nm. A marker (M1) was placed to set an arbitrary threshold between annexin-V-binding cells and control cells. The same threshold was used for untreated and alectinib treated erythrocytes. A dot plot of forward scatter (FSC) vs. side scatter (SSC) was set to linear scale for both parameters. The threshold of forward scatter was set at the default value of "52".

Statistics

Data are expressed as arithmetic means ± SEM. As indicated in the figure legends, statistical analysis was made using ANOVA with Tukey's test as post-test and *t* test as appropriate. n denotes the number of different erythrocyte specimens studied. Since different erythrocyte specimens used in distinct experiments are differently susceptible to triggers of eryptosis, the same erythrocyte specimens have been used for control and experimental conditions.

Results

The present study explored, whether alectinib influences eryptosis, the suicidal erythrocyte death. The two hallmarks of eryptosis, i.e. cell shrinkage and phospholipid scrambling of the cell membrane with phosphatidylserine translocation to the cell surface were determined by flow cytometry. Phosphatidylserine exposing erythrocytes were identified utilizing annexin-V-binding to phosphatidylserine, cell shrinkage was quantified utilizing forward scatter.

In a first series of experiments erythrocytes were incubated for 48 hours in the absence of glucose in order to induce energy depletion. As shown in Fig. 1, a 48 hours exposure to glucose depleted Ringer solution was followed by a marked increase of the percentage of annexin-V-binding erythrocytes. The addition of alectinib (150-600 ng/ml) significantly blunted the increase of the percentage of annexin-V-binding erythrocytes following energy depletion. However, even in the presence of alectinib, energy depletion significantly increased the percentage of phosphatidylserine exposing erythrocytes (Fig. 1).

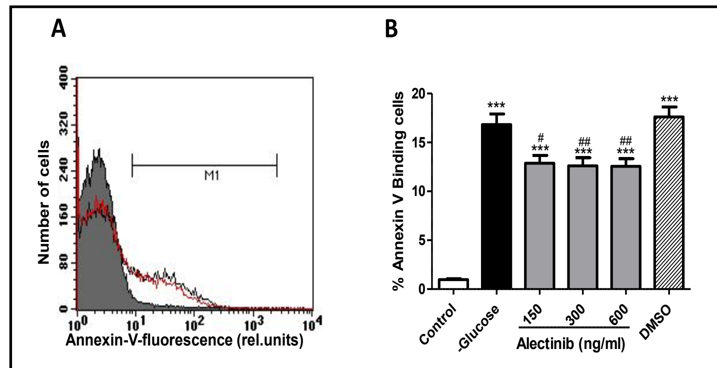

Fig. 1. Alectinib sensitivity of phosphatidylserine exposure following energy depletion A. Original histograms of annexin-V-binding of erythrocytes following exposure for 48 hours to glucose containing Ringer solution (grey area), Ringer solution without glucose (black line) and Ringer solution without glucose in the presence of alectinib (600 ng/ml) (red line). B. Arithmetic means ± SEM (n = 18) of the percentage annexin-V-binding erythrocytes after a 48 hours treatment with Ringer solution with (white bar, control) or without (black and grey bars) glucose in the absence (black bar) and presence of 150-600 ng/ml alectinib (grey bars) or of solvent alone (Striped bar). ***(p<0.001) indicates significant difference from the presence of glucose, #(p<0.05), ##(p<0.01) indicates significant difference from the absence of alectinib (ANOVA).

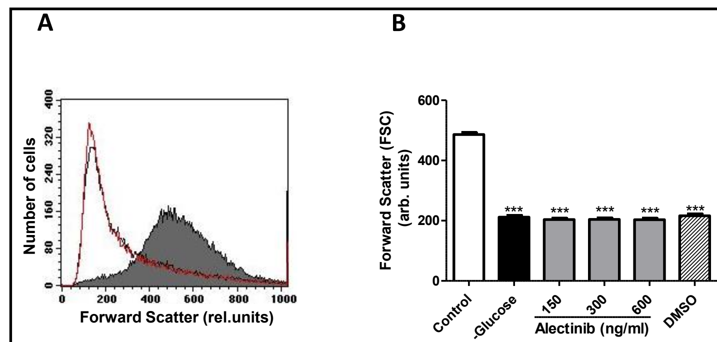

Fig. 2. Alectinib sensitivity of cell shrinkage following energy depletion. A. Original histograms of erythrocyte forward scatter following exposure for 48 hours to glucose containing Ringer solution (grey area), Ringer solution without glucose (black line) and Ringer solution without glucose in the presence of alectinib (600 ng/ml) (red line). B. Arithmetic means ± SEM (n = 15) of the erythrocyte forward scatter after a 48 hours treatment with Ringer solution with (white bar, control) or without (black and grey bars) glucose in the absence (black bar) and presence of 150-600 ng/ml alectinib (grey bars) or of solvent alone (Striped bar). ***(p<0.001) indicates significant difference from the presence of glucose.

Exposure of the erythrocytes to energy depletion was further followed by a significant decrease of forward scatter (Fig. 2). The effect on forward scatter was not significantly modified by alectinib (150-600 ng/ml).

In a second series of experiments erythrocytes were exposed for 6 hours to isotonic or hypertonic (+550 mM sucrose) extracellular fluid. As shown in Fig. 3, a 6 hours

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exposure to hyperosmotic shock was followed by a marked increase of the percentage of annexin-V-binding erythrocytes. The addition of alectinib (150-600 ng/ml) significantly blunted the increase of the percentage of annexin-V-binding erythrocytes following hyperosmotic shock. However, even in the presence of alectinib, hyperosmotic shock significantly increased the percentage of phosphatidylserine exposing erythrocytes (Fig. 3).

Exposure of the erythrocytes to hyperosmotic shock for 6 hours was further followed by a significant decrease of forward scatter (Fig. 4). The effect on forward scatter was not significantly modified by alectinib (150-600 ng/ml).

In order to induce oxidative stress, erythrocytes were exposed for 50 minutes to 0.3 mM tert-butyl-hydroperoxide. As illustrated in Fig. 5, oxidative stress was followed by a sharp increase of the percentage of annexin-V-binding erythrocytes. The effect was not appreciably modified by alectinib (Fig. 5).

Exposure of the erythrocytes for 50 minutes to 0.3 mM tert-butyl-hydroperoxide was further followed by a significant decrease of forward scatter (Fig. 6). The effect was again not significantly modified by alectinib (150-600 ng/ml).

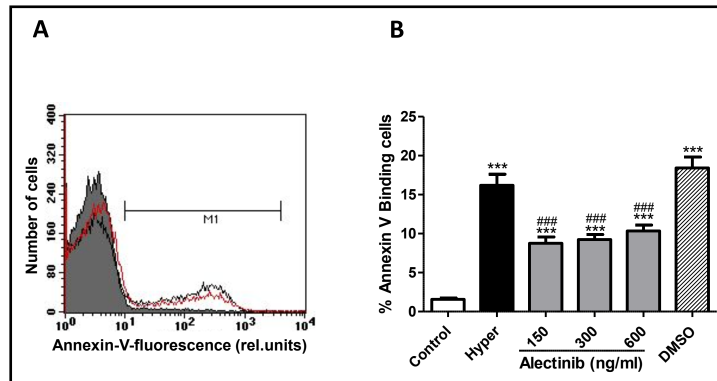

Fig. 3. Alectinib sensitivity of phosphatidylserine exposure following hyperosmotic shock. A. Original histograms of annexin-V-binding of erythrocytes following exposure for 6 hours to isosmotic Ringer solution (grey area), hyperosmotic Ringer (550 mM sucrose added) (black line) and hyperosmotic Ringer in the presence of alectinib (600 ng/ml) (red line). B. Arithmetic means ± SEM (n = 15) of the percentage annexin-V-binding erythrocytes after a 6 hours treatment with isotonic Ringer solution (white bar, control) or with hyperosmotic 550 mM sucrose added) Ringer (black and grey bars) in the absence (black bar) and presence of 150-600 ng/ml alectinib (light grey bars) or of solvent alone (Striped bar). ***(p<0.001) indicates significant difference from the presence of isotonic Ringer, ###(p<0.001) indicates significant difference from the absence of alectinib (ANOVA).

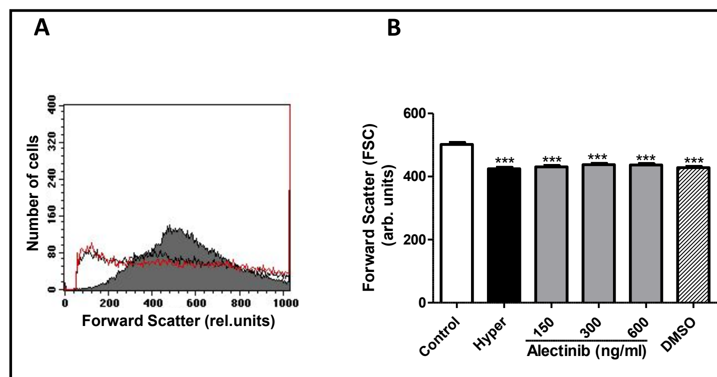

Fig. 4. Alectinib sensitivity of cell shrinkage following hyperosmotic shock. A. Original histograms of erythrocyte forward scatter following exposure for 6 hours to glucose containing isosmotic Ringer solution (grey area), hyperosmotic Ringer (550 mM sucrose added) (black line) and hyperosmotic Ringer in the presence of alectinib (600 ng/ml) (red line). B. Arithmetic means ± SEM (n = 15) of the erythrocyte forward scatter after a 6 hours treatment with isotonic Ringer solution (white bar, control) or with hyperosmotic (550 mM sucrose added) Ringer (black and grey bars) in the absence (black bar) and presence of 150-600 ng/ml alectinib (light grey bars) or of solvent alone (Striped bar). ***(p<0.001) indicates significant difference from the presence of isotonic Ringer.

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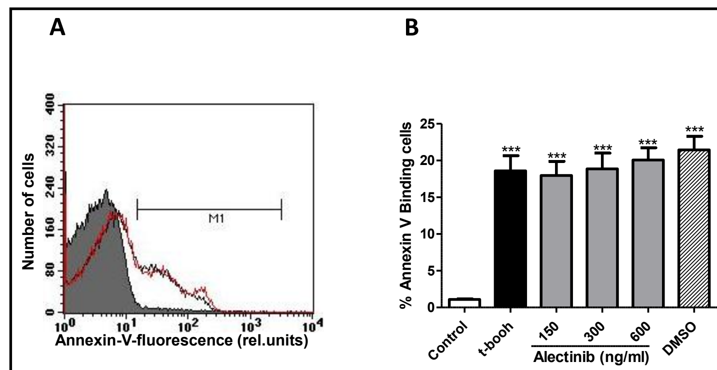

Fig. 5. Alectinib sensitivity of phosphatidylserine exposure following oxidative stress. A. Original histograms of annexin-V-binding of erythrocytes following exposure for 50 min to glucose containing Ringer solution without (grey area) or with 0.3 mM tert-butyl-hydroperoxide (t-BOOH) added (black and red lines) without (black line) and with (red line) presence of alectinib (600 ng/ml). B. Arithmetic means ± SEM (n = 5) of the percentage annexin-V-binding erythrocytes after 50 min treatment with Ringer solution without (white bar, control) or with (black and grey bars) 0.3 mM tert-butyl-hydroperoxide (t-BOOH) added in the absence (black bar) and presence of 150-600 ng/ml alectinib (light grey bars) or of solvent alone (Striped bar). ***(p<0.001) indicates significant difference from the abscence of 0.3 mM tert-butyl-hydroperoxide (t-BOOH) (ANOVA).

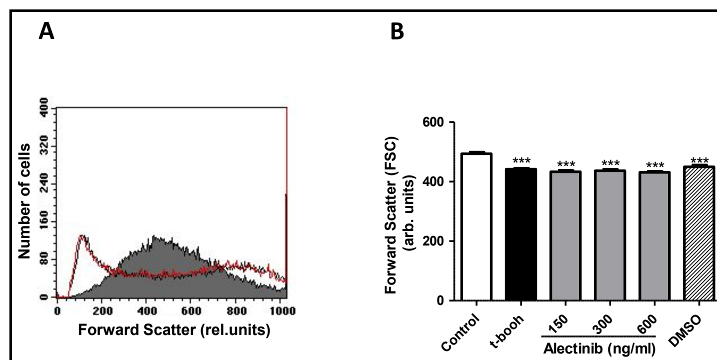

Fig. 6. Alectinib sensitivity of cell shrinkage following oxidative stress. A. Original histograms of erythrocyte forward scatter following exposure for 50 min to glucose containing Ringer solution without (grey area) or with 0.3 mM tert-butyl-hydroperoxide (t-BOOH) added (black and red lines) without (black line) and with (red line) presence of alectinib (600 ng/ml). B. Arithmetic means ± SEM (n = 5) of the erythrocyte forward scatter after a 50 min treatment with Ringer solution without (white bar, control) or with (black and grey bars) 0.3 mM tert-butyl-hydroperoxide (t-BOOH) added in the absence (black bar) and presence of 150-600 ng/ml alectinib (light grey bars) or of solvent alone (Striped bar). ***(p<0.001) indicates significant difference from the abscence of 0.3 mM tert-butyl-hydroperoxide (t-BOOH) (ANOVA).

Exposure of the erythrocytes for 60 minutes to 1 µM ionomycin was followed by a sharp increase of the percentage of annexin-V-binding erythrocytes (Fig. 7). The effect was not significantly modified by alectinib (150-600 ng/ml alectinib).

Exposure of the erythrocytes for 60 minutes to 1 µM ionomycin was further followed by a sharp decrease of forward scatter (Fig. 8), an effect again not significantly modified by the presence of alectinib (150-600 ng/ml).

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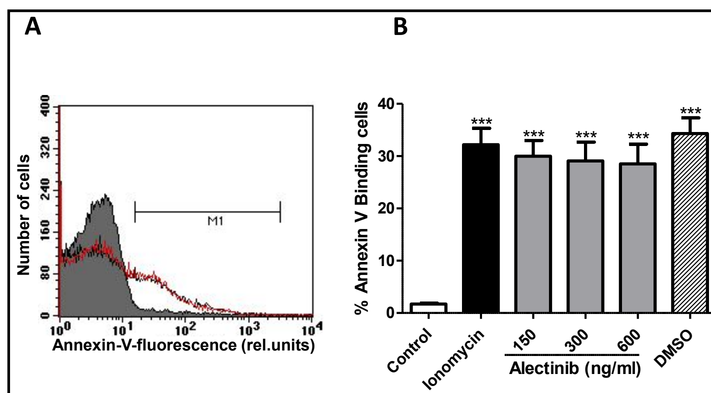

Fig. 7. Alectinib sensitivity of phosphatidylserine exposure following Ca^{2+} overload. A. Original histograms of annexin-V-binding of erythrocytes following exposure for 60 min to glucose containing Ringer solution without (grey area) or with 1.0 µM ionomycin added (black and red lines) without (black line) and with (red line) presence of alectinib (600 ng/ml). B. Arithmetic means ± SEM (n = 15) of the percentage annexin-V-binding erythrocytes after a 60 min treatment with Ringer solution without (white bar, control) or with (black and grey bars) 1.0 µM ionomycin added in the absence (black bar) and presence of 150-600 ng/ml alectinib (light grey bars) or of solvent alone (Striped bar). ***(p<0.001) indicates significant difference from the absence of Ionomycin (ANOVA).

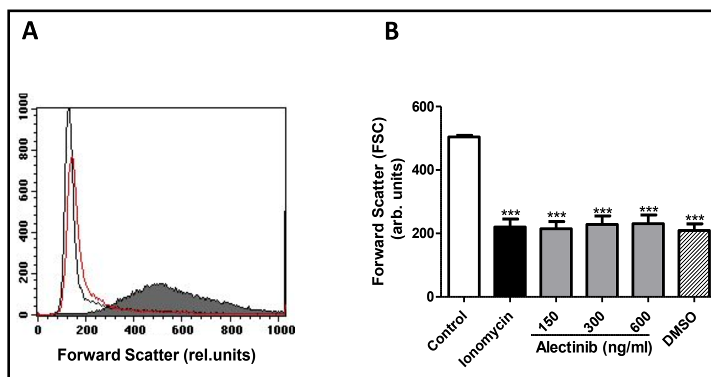

Fig. 8. Alectinib sensitivity of cell shrinkage following Ca^{2+} overload. A. Original histograms of erythrocyte forward scatter following exposure for 60 min to glucose containing Ringer solution without (grey area) or with 1.0 µM ionomycin added (black and red lines) without (black line) and with (red line) presence of alectinib (600 ng/ml). B. Arithmetic means ± SEM (n = 15) of the erythrocyte forward scatter after a 60 min treatment with Ringer solution without (white bar, control) or with (black and grey bars) 1.0 µM ionomycin added in the absence (black bar) and presence of 150-600 ng/ml alectinib (light grey bars) or of solvent alone (Striped bar). ***(p<0.001) indicates significant difference from the absence of Ionomycin, (ANOVA).

Discussion

The present observations disclose the unexpected inhibitory effect of alectinib on eryptosis, the suicidal erythrocyte death characterized by cell shrinkage and cell membrane scrambling with phosphatidylserine translocation to the erythrocyte surface [25].

Alectinib itself did not appreciably modify the percentage of phosphatidylserine exposing erythrocytes. Similar to earlier observations [25], cell membrane scrambling and cell shrinkage were observed following energy depletion, hyperosmotic shock, oxidative stress and Ca^{2+} loading. Alectinib did not significantly modify the effect of oxidative stress and Ca^{2+} loading on cell membrane scrambling, but significantly blunted the cell membrane scrambling following energy depletion and hyperosmotic shock.

Under none of the conditions, Alectinib significantly modified the forward scatter. Under most conditions leading to eryptosis, cell shrinkage is due to increase of cytosolic Ca^{2+} activity ($[Ca^{2+}]_i$) with subsequent activation of Ca^{2+} sensitive K^+ channels, K^+ exit, cell membrane hyperpolarization, Cl^- exit and thus cellular loss of KCl with water. Apparently, Alectinib fails to significantly interfere with those mechanisms.

Inhibition of eryptosis may be desirable in diverse clinical conditions associated with enhanced eryptosis including iron deficiency [25], dehydration [130], hyperphosphatemia [131], vitamin D excess [132], chronic kidney disease (CKD) [81, 133-137], hemolytic-uremic syndrome [138], diabetes [139], hepatic failure [111, 140], malignancy [25, 108, 141], sepsis [142], sickle-cell disease [25], beta-thalassemia [25], Hb-C and G6PD-deficiency [25], as well as Wilson´s disease [142]. The rapid clearance of the phosphatidylserine exposing erythrocytes from circulating blood [25] may lead to anemia as soon as the loss of erythrocytes outcasts the formation of new erythrocytes by erythropoiesis [25]. Phosphatidylserine exposing erythrocytes adhere to the vascular wall [143], stimulate blood clotting and trigger thrombosis [144-146]. Excessive eryptosis may thus interfere with microcirculation [128, 144, 147-150]. Inhibitors of eryptosis may counteract anemia and restore microcirculation in clinical conditions with enhanced eryptosis [25]. However, inhibition of eryptosis may prevent the clearance of defective erythrocytes from circulating blood leading to the risk that defective erythrocytes may undergo hemolysis [25] with release of hemoglobin which may pass the renal glomerular filter, precipitate in the acidic lumen of renal tubules, occlude nephrons and thus lead to renal failure [151]. Additional experimental effort is needed to decipher the benefits and risks of eryptosis prevention.

In conclusion, Alectinib interferes with cell membrane scrambling following energy depletion and hyperosmotic shock. The potential therapeutic implications of the present observations remain to be defined.

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Disclosure Statement

No conflict of interests exists.

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