**Combo Proffered Paper and Poster Discussion Session**

# Developmental Therapeutics

# 1270 - Phase I Study of Safety and Tolerability of Selinexor in Asian Patients with Advanced Solid Cancers: Updated Results

## Valerie Heong et al

Invited Discussant


**Christian Dittrich**

Ludwig Boltzmann Institute for Applied Cancer Research (LBI-ACR VIEnna)
Applied Cancer Research
Institution for Translational Research Vienna (ACR-ITR VIEnna)

3rd Medical Department – Centre for Oncology and Haematology
Kaiser Franz Josef-Spital, Vienna, Austria



SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

# Conflict of Interest Disclosure

I herewith declare that I have potential conflicts of interest with several pharmaceutical companies, the drugs of which will be mentioned during my presentation, predominantly in form of unrestricted research grants donated to the research institutes directed by me, but also as honoraria for consulting

# Selective Inhibition of Nuclear Export

- Nuclear-cytoplasmic shuttling is a control mechanism of normal cells to regulate the activity of a variety of molecules
- This transport of biological material is mediated by specialized carriers
- These nuclear transporters are abnormally (over-) expressed in cancer cells
- This dysregulation is involved in tumor progression, drug resistance, or poor cancer prognosis
- Nuclear-cytoplasmic export is mainly regulated by the nuclear export protein, exportin 1 (XPO1), in humans

# Selective Inhibition of Nuclear Export

- XPO (CRM1) is responsible for the nuclear export of many tumor suppressor proteins and the regulation of cell growth (e.g. p27, p53, Rb, BRCA1)
- Inhibition of XPO1 leads to accumulation of these suppressor proteins in the nucleus
- Inhibition of XPO restores their suppressor function
- The first CRM1 inhibitor tested in patients, leptomycin B, failed due to toxicity (nausea/vomiting, anorexia, malaise) and lack of activity
- The next generation small molecule selective inhibitor of nuclear export (SINE), selinexor (KPT-330), is now under extensive clinical evaluation (phase I-III)

# Phase I-Experience of the XPO1 Inhibitor Selinexor

| American/European Patients<br>Sørensen et al<br>(ASCO 2014) | | Asian Patients<br>Tan et al<br>(ASCO 2015 / ESMO Asia 2015) |
|---|---|---|
| S1 10 doses q 28 days<br>S2 8 doses (BIW) q 28 days | Schedules | S1 BIW q 28 days<br>S2 OW q 28 days<br>S3 BIW for 2 weeks q 21 days |
| S1 40 mg/m²<br>S2 35 mg/m² (BIW) – 65 mg/m² ongoing | Dose Escalation Steps | S1 40 mg/m²<br>S2 50 / 60 / 70 mg/m²<br>S3 40 / 50 mg/m² |
| 3+3 | Design | 3+3 |

# Phase I-Experience of the XPO1 Inhibitor Selinexor

| American/European Patients<br>Sørensen et al<br>(ASCO 2014) | | Asian Patients<br><br>Tan et al<br>(ASCO 2015 / ESMO Asia 2015) |
|---|---|---|
| S1 2 fatigue, dehydration<br>S2 1 nausea at 35 mg/m² | DLT | S1 None<br>S2 None<br>S3 None |
| S1 40 mg/m²<br>S2 not reached yet | MTD | S1 not formally reached but schedule / dosage intolerable<br>S2 not formally reached<br>S3 not formally reached |
| Cycle 1 only:<br>hyponatremia 9%, fatigue 6%, thrombocytopenia 5%, nausea 3%, vomiting 6%, anemia 3% | TEAE<br>≥ G3 | S1<br>hyponatremia 83%, fatigue 33%, diarrhoea 17%, dehydration 17%, thrombocytopenia 17%, anemia 17%<br>S2<br>50 mg/m²: none<br>60 mg/m²: hyponatremia 33%, nausea 33%, vomiting 33%, anemia 33%<br>70 mg/m²: fatigue 17%, neutropenia 17%, thrombocytopenia 17%, anemia 8%, vomiting 8%<br>S3<br>40 mg/m²: hyponatremia 67%, fatigue 33%<br>50 mg/m²: hyponatremia 31%, dehydration 15%, fatigue 15%, anemia 15%, nausea 8%, anorexia 8% |

# Phase I-Experience of the XPO1 Inhibitor Selinexor

| American/European Patients<br>Sørensen et al<br>(ASCO 2014) | | Asian Patients<br>Tan et al<br>(ASCO 2015 / ESMO Asia 2015) |
|---|---|---|
| 3 PR (CRC, melanoma, ovary)<br>39 SD (12 ≥ 6 months) | Activity | 2 PR (DLBCL)<br>8 SD (CRC, pancreas, SCC tongue, NSCLC, ovary, HCC) |
| linear | PK | linear |
| 50 mg/m² BIW | RP2D | S2 70 mg/m² OW<br>S3 50 mg/m² BIW |

# Presented Further Studies of Selinexor (Selection)

| | | | |
|---|---|---|---|
| Phase I<br>Guiterrez et al<br>ASCO 2014 | NHLs<br>(FL, MCL, DLBCL, T-FL, Richter‘s syndrome) | ORs in all entities | Reduction of XPO1 →<br>XPO1 mRNA increase |
| Phase I expansion cohort<br>Mau-Sørensen et al<br>ASCO-GI 2014 | Colon cancer | 1 PR<br>6 SD | Reduction of XPO1 →<br>XPO1 mRNA increase |
| Phase I expansion cohort<br>Martignetti et al<br>ASCO 2014 | Ovarian cancer<br>Pt-resistant/refractory | 1 PR<br>2 SD | |
| Phase Ib expansion cohort<br>Gounder et al<br>ASCO 2015 | Sarcomas | SDs | Reduction of XPO1 →<br>XPO1 mRNA increase |
| Phase II<br>Vergote et al<br>ASCO 2015 | Gynecologic cancers<br>(Ovarian, endometrial, cervical cancer) | ORR<br>OC 9% / EC 18% / CC 7%<br>DCR<br>OC 36% / EC 64% / CC 28% | |
| Phase II<br>Lassen et al<br>ASCO 2015 | Glioblastoma multiforme | PRs | Intratumoral drug concentration > IC 50 |

# Summary

- Despite the fact that MTD was formally hardly reached, both groups of investigators (American/European-Asian) were indicating RP2D
- Asian colleagues intend to optimize their RP2D
- The RP2D indicated will lead to different dose intensities that are lower for Asians
- Toxicities, especially their qualities, are rather consistent over all studies and between the different regions of the world
- Nevertheless, reporting periods are not always indicated in detail; direct comparison will dependent on full publication

# Summary

- Overall, drug activity in form of objective response has been documented in a large variety of tumors with different levels of pretreatment
- With the determination of XPO1 mRNA and its increase in case of successful inhibition of XPO1, a potential biomarker seems to be identified and should be developed further as such
- Developmental differences seem to be greater than those between Asian and American/European patients and their therapeutic reaction to the compound (class of compounds?)
- The development is very rational and justifies high expectations

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# Developmental Therapeutics

## 1280 - Phase I Study of S-trans, trans-Farnesylthiosalicylic Acid (Salirasib), a Novel Oral RAS Inhibitor, in Japanese Patients with Advanced Solid Tumors

## Toshio Shimizu et al

Invited Discussant


**Christian Dittrich**

Ludwig Boltzmann Institute for Applied Cancer Research (LBI-ACR VIEnna)
Applied Cancer Research
Institution for Translational Research Vienna (ACR-ITR VIEnna)

3rd Medical Department – Centre for Oncology and Haematology
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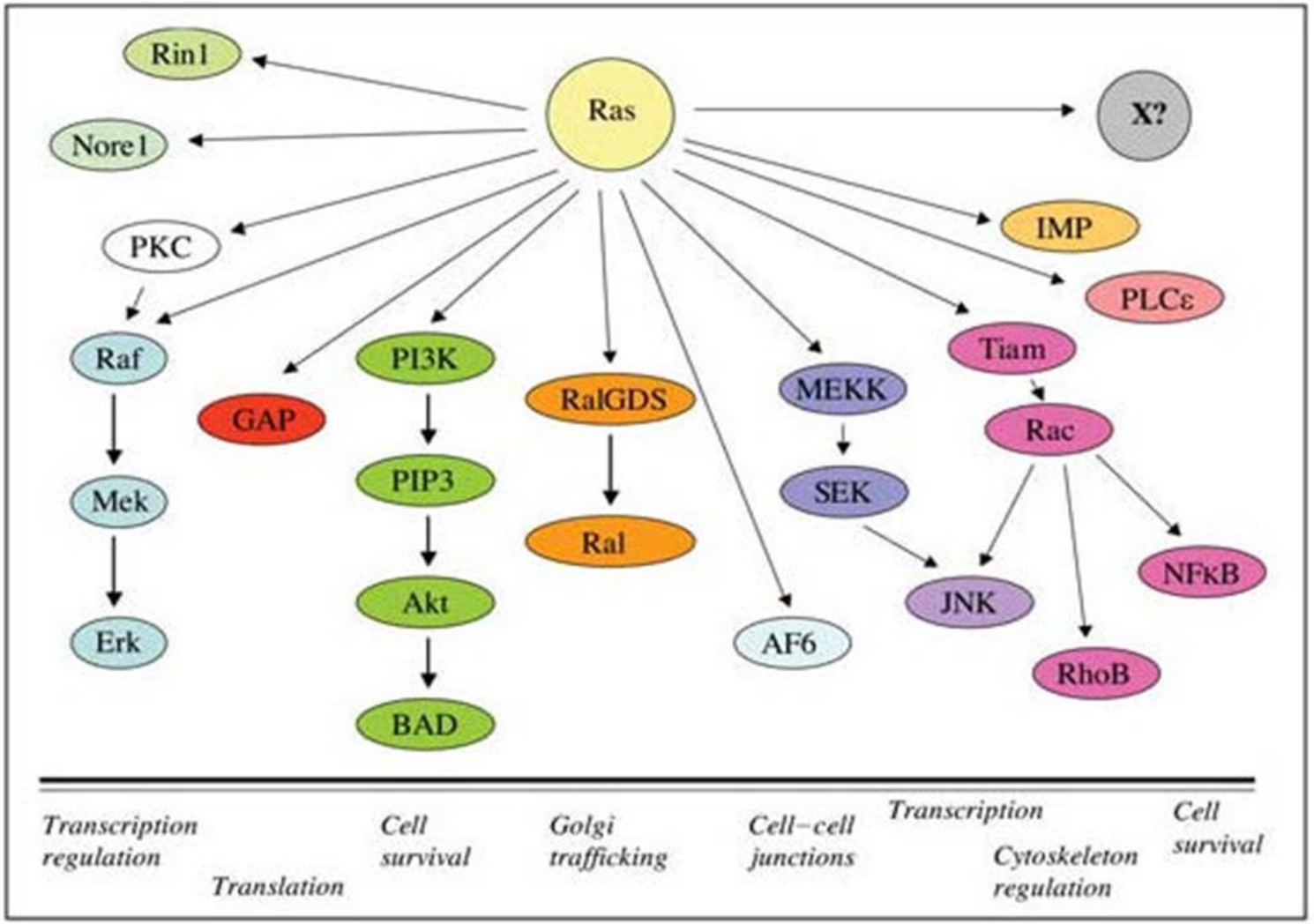
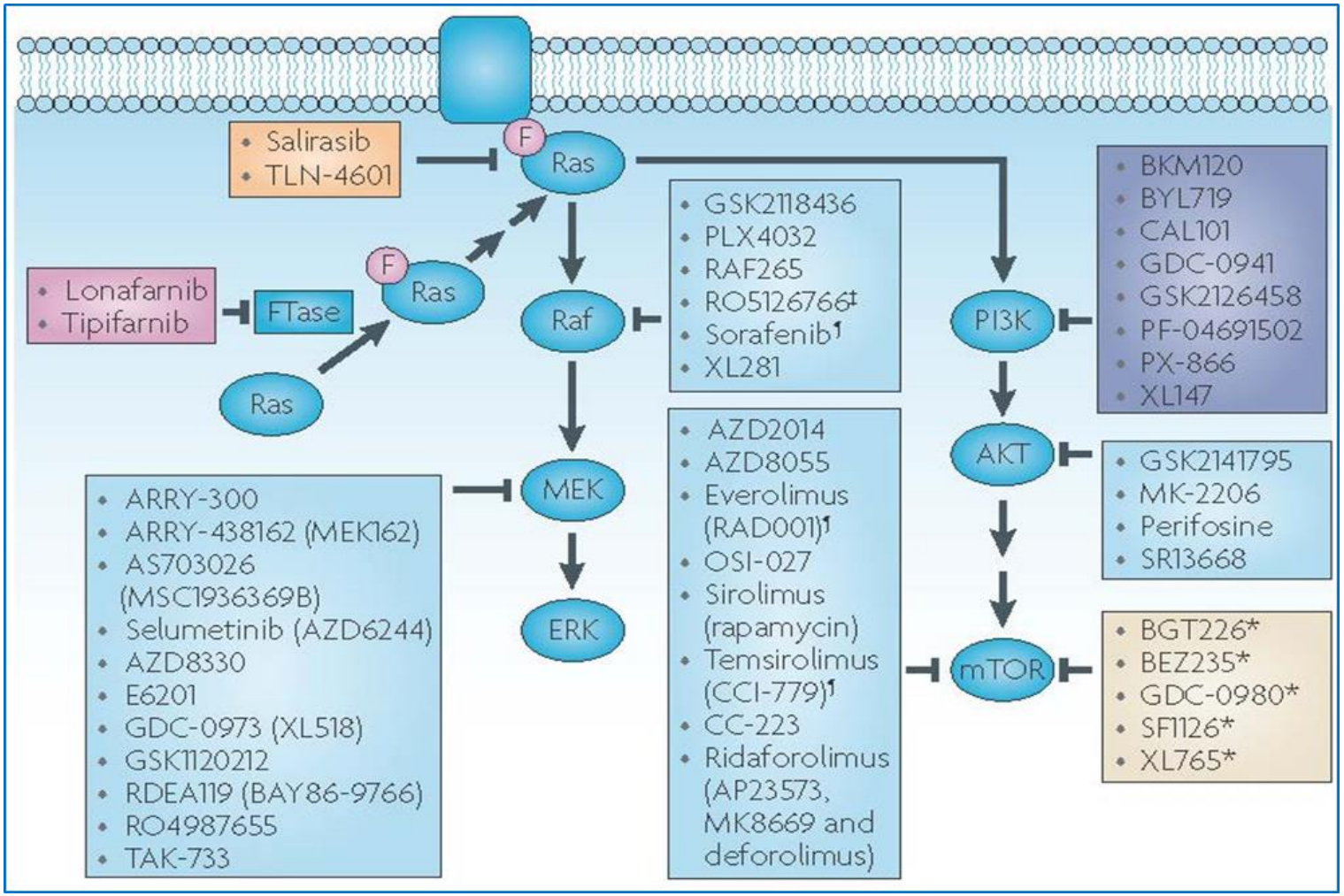
# Ras-Mediated Signal Transduction Pathways



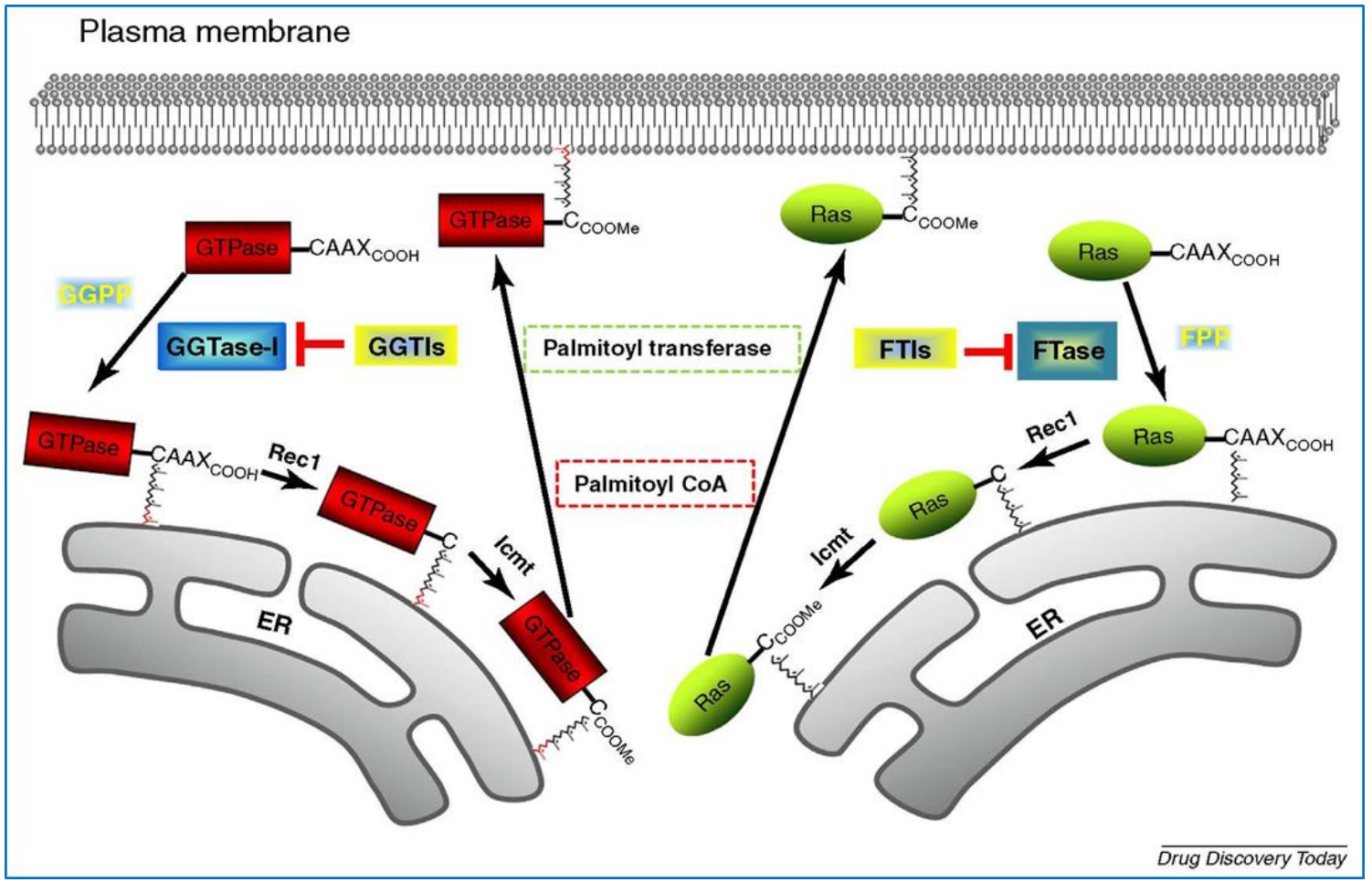

Appels et al; The Oncologist 10:565-578,2005

# Candidate anti-Ras Inhibitors




Vigil et al; Nature Reviews Cancer 10:842-857,2010

# Signaling Transduction Pathways of Farnesyltransferase (FTase) and Geranylgeranyltransferase (GGTase-I)




Shen et al; Drug Discovery Today 20:267-276,2015

# Potential Surrogate Markers for FTI / GGTI Activity

- Ras (prenylated and unprenylated)
- Ras mutation
- FTase
- HDJ-2 / DNA-J (substrate of FTase)
- Prelamin A (protein involved in the regulation of nuclear structure)
- Ras-GTP
- PxF (protein of 33 kDa at the outer side of peroxisomes)
- RhoB (member of the RhoGTPase family; acts as tumor suppression protein)
- Centromeric proteins CENP-E and -F
- Rheb (ras homologue enriched in brain)

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- Rap1A



Appels et al; The Oncologist 10:565-578,2005

# Phase II-Studies with the Farnesyltransferase Inhibitor R115777 (Tipifarnib) in the Treatment of Malignancies with Different Preponderance of *ras* Mutations

| Tumor type | Patients number | OR (%) | SD (%) | Inhibition of FT Surrogate Marker | Author |
|---|---|---|---|---|---|
| Pancreas (first-line)<br>(first-line) | 20<br>53 | 0<br>NE | 1 (5)<br>NE | Chaperone protein HDJ-2 in PBMCs | Cohen (2003)<br>McDonald (2005) |
| Colorectal (pretreated) | 55 | 1 PR (2)<br>3 uPR (6) | - | - | Whitehead (2006) |
| NSCLC (first-line) | 44 | 0 | 7 (16) | Prelamin A in buccal mucosa; Chaperone protein HDJ-2 in PBMCs | Adjei (2003) |
| SCLC (pretreated) | 22 | 0 | 1 (5) | - | Heymach (2004) |
| Urinary Tract TCC (first-line and pretreated) | 34 | 2 (6) | 13 (38) | - | Rosenberg (2005) |

# Phase II-Studies with the Farnesyltransferase Inhibitor R115777 (Tipifarnib) in the Treatment of Malignancies with Different Preponderance of *ras* Mutations

| Tumor type | Patients number | OR (%) | SD (%) | Inhibition of FT Surrogate Marker | Author |
|---|---|---|---|---|---|
| Breast (pretreated) | 41 continuous<br>35 intermittent | 4 PR (10)<br>5 PR (14) | 6 (15)<br>3 ( 9) | Ras mutation | Johnston (2003) |
| Multiple Myeloma (relapsed) | 36 | 0 | (64) | Chaperone protein HDJ-2 in PBMCs and BMCs | Alsina (2004) |
| AML poor risk (untreated) | 158 | 22 CR (14)<br>15 PR ( 9) | - | Chaperone protein HDJ-2 in BMCs | Lancet (2007) |
| MDS (untreated) | 27 | 2 CR (7)<br>1 PR (4) | - | (Codons 12/13/61 of Nras and Kras) | Kurzrock (2004) |

# Phase III Trial of Gemcitabine plus Tipifarnib Compared with Gemcitabine plus Placebo in Advanced Pancreatic Cancer

| Efficacy | Tipifarnib + Gemcitabine (n = 341) | Placebo + Gemcitabine (n = 347) | *P* |
|---|---|---|---|
| Overall survival | | | |
| Median, days | 193 | 182 | .75 |
| 95% CI | 176 to 218 | 155 to 206 | |
| 6-month survival, % | 53 | 49 | |
| 1-year survival, % | 27 | 24 | |
| Progression-free survival | | | |
| Median, days | 112 | 109 | .72 |
| 95% CI | 105 to 119 | 101 to 118 | |
| Best response reconciled, % | | | |
| CR or PR | 6 | 8 | |
| Stable disease | 53 | 52 | |
| Progression | 28 | 30 | |
| Not assessable | 13 | 10 | |
| Time to PS deterioration, days | 142 | 125 | .50 |
| 95% CI | 121 to 176 | 107 to 144 | |

Van Cutsem et al; J Clin Oncol 22:1430-1438,2004

# Mode of Action of S-trans,trans-Farnesylthiosalicylic Acid (FTS)

- Ras proteins regulate cell growth, differentiation, and apoptosis
- Their activities depend on their anchorage to the inner surface of the plasma membrane
- FTS disrupts the interactions of ras and the membrane anchorage domains
- FTS is not a farnesyltransferase inhibitor (FTI)
- FTS leads to inhibition of MAPK activity
- Only farnesylated ras isoforms are substrates
- FTS can target Kras which is insensitive to inhibition by FTIs



Elad et al; Biochim Biophys Acta 1452:228-242,1999

# Phase I First-In Human Study of S-trans, trans-Farnesylthiosalicylic Acid (Salirasib) in Patients with Solid Tumors

| Tsimberidou et al ASCO 2008 | | Shimizu et al ESMO Asia 2015 |
|---|---|---|
| 21 days q 28 days | Schedule | 21 days q 28 days |
| 100, 200, 400, 800 mg BID | DE steps | 100, 200, 400, 600, 800, 1000 mg BID |
| 3+3 | Design | 3+3 |
| (prolonged diarrhoea G1-2) | DLT | (diarrhoea G3) |
| No | MTD | No |
| Abdominal pain, nausea/vomiting, fatigue | TEAE | Abdominal pain, nausea/vomiting, loss of appetite |
| 29% SD $\geq$ 4 months | Activity | 24% SD / 19% SD > 6 months |
| Linear | PK | Non-Linear |
| 800 mg BID | RP2D | 800 mg BID |

# Summary

- No MTD was reached
- Although there was no formal rationale to stop dose escalation, the determination of 800 mg as RP2D seems justified based on the Japanese investigators' experience and that derived from the US phase I study (Tsimberidou et al, ASCO 2008)
- Clinical response in form of SD seems not to be dose related
- Extent of prior therapies of individual patients may provide the explanation for the length of SD
- Comparability to US phase I data is given with the exemption of the non-linear PK in the Japanese population

# Summary

- Overall, a 20% SD rate was reached in an unselected patient population
- No attempt of a rational development based on a biomarker or a biomarker panel was done
- Further development (combined or sequential or multimodality approach) is only justified in patient cohorts in whom functioning of the expected mechanism of action can be demonstrated