New Agents on the Horizon in Pancreatic Cancer

Malcolm J. Moore

Princess Margaret Cancer Centre

University of Toronto

"On the horizon": *Imminent or just becoming apparent*

New Agents on the Horizon in Pancreatic Cancer

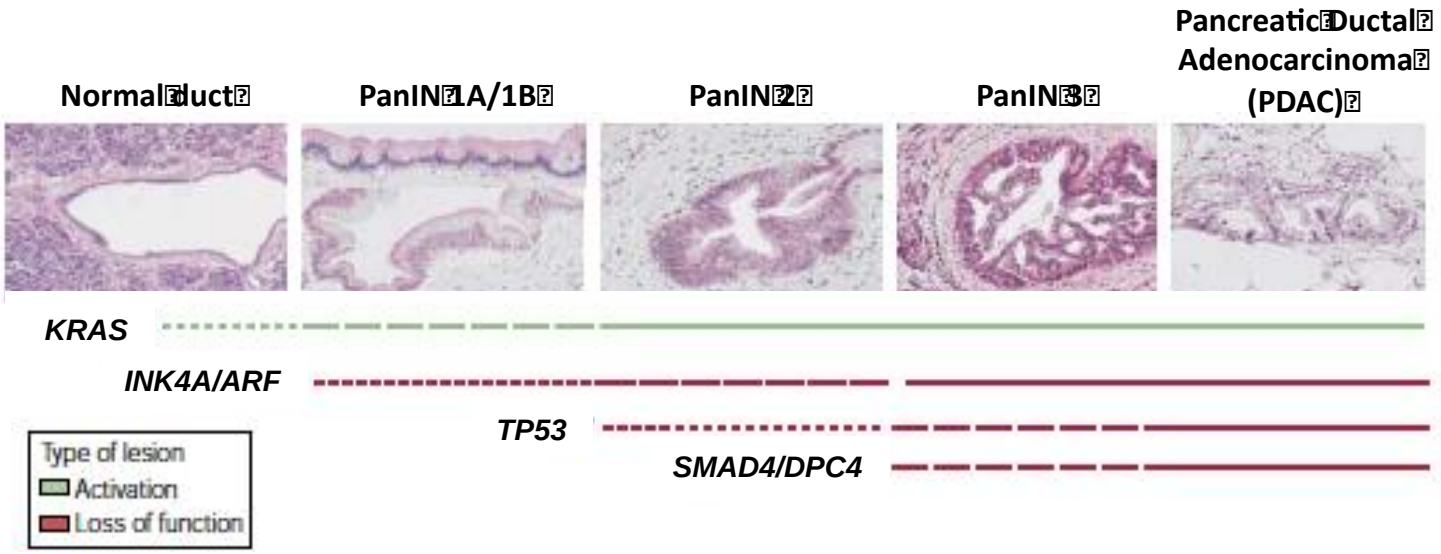
- What would be the characteristics of a good new agent in pancreatic cancer?
- Review a some agents and targets under development that have potential.
  - MM-398, JAK/STAT inhibition
  - PARP Inhibitors
  - Hypoxia - TH 302
  - Immunotherapy
  - MEK1/2 inhibitors
  - Notch Pathway inhibition.

Genetic progression of pancreatic ductal adenocarcinoma

Recurrent Mutations in Pancreatic Cancer

Australian Pancreatic Cancer Genome Initiative (Biankin, Nature 2012)

KRAS	
P53	
CDKN2A	
SMAD4/TGFBR2	
MLL3	Histone Methylation
ARID1A/ARID2	Nucleosome Remodelling
EPC1	Histone acetylation
ATM	
ROBO/SLIT	Axon Guidance



Cellular/Signalling Pathway Alterations

Pathway	% tumors with ≥1 genetic alteration	Pathway	% tumors with ≥1 genetic alteration
Apoptosis	100	JNK signalling	96
DNA damage control	83	KRAS signalling	100
Regulation of G_1/S phase transition	100	Regulation of invasion	92
Hedgehog signalling	100	Small GTPase-dep signalling	79
Homophilic cell adhesion	79	TGF-β	100
Integrin signalling	67	Wnt/Notch	100

Genetic alterations associated with 12 cellular signalling pathways can contribute to the development of pancreatic cancer

… *Pancreatic Cancer is a genetically complex disease*

Jones S, et al. *Science*. 2008;321:1801-1806.

Randomised phase III trials in pancreatic cancer (PC) (median overall survival in months)

	Gem	Gem + X	p value
Gem ± marimastat (Bramhall, BJC 2002)	5.5	5.5	NS
Gem ± 5-FU bolus (Berlin, JCO 2002)	5.4	6.7	NS
Gem ± tipifarnib (Van Cutsem, JCO 2004)	6.0	6.4	NS
Gem ± exatecan (Abou-Alfa, JCO 2006)	6.2	6.7	NS
Gem ± CPT-11 (Rocha-Lima, JCO 2006)	6.6	6.3	NS
Gem ± pemetrexed (Oettle, Ann Oncol 2006)	6.3	6.2	NS
Gem ± bevacizumab (Kindler, ASCO 2007)	6.1	5.8	NS
Gem ± cetuximab (Philip, ASCO 2007)		5.9	6.4 NS
Gem ± capecitabine (Herrmann, JCO 2007)	7.3	8.4	NS
Gem ± 5-FU/LV (Riess, JCO 2005)	6.2	5.9	NS
Gem ± capecitabine** (Cunningham, ECCO 2005)	6.0	7.4	NS
Gem ± cisplatin (Heinemann, JCO 2006)	6.0	7.5	NS
Gem ± oxaliplatin (Louvet, JCO 2005)		7.1	9.0 NS
Gem ± oxaliplatin (Poplin, ASCO 2006)	4.9	5.9	NS
Gem ± cisplatin (Colucci, ASCO 2009)		8.3	7.2 NS

… ***PC has had too many negative Phase III studies***

Positive randomised phase III trials in pancreatic cancer

	Gem	Gem + X	p
Gem ± erlotinib (Moore, 2007)	*5.9*	*6.4*	*0.02*
Gem ± nab-paclitaxel (vonHoff, 2014)	*6.6*	*8.7*	*0.0001*

	Gem	FOLFNX	p
Gem vs FOLFIRINOX (Conroy 2011)	*6.8*	*11.1*	*0.0001*

…Both Gem+ nab-paclitaxel and FOLFIRINOX had strong signals from earlier phase 2 studies.

Characteristics of a New Agent for Pancreatic Cancer

…In the short term, given the unmet need.

Any agent that controls the disease and improves survival.

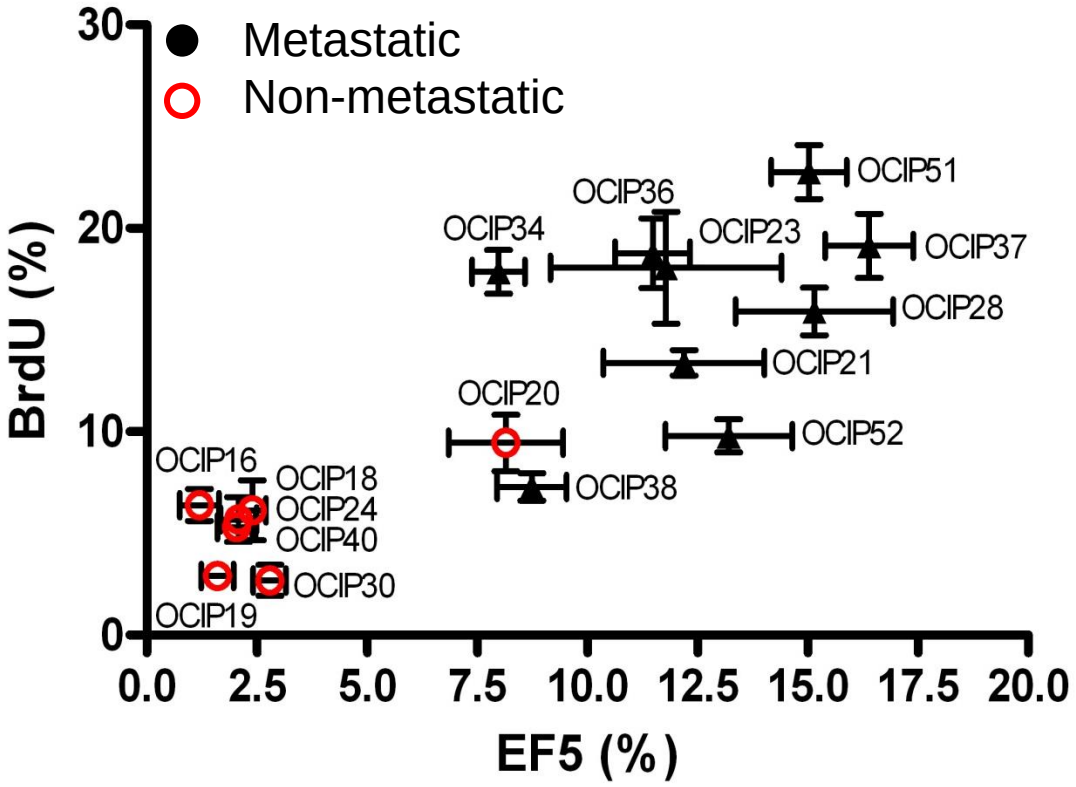
…In the longer term if we are to make meaningful impact

- Good science.
- Biomarker driven.
- Strong signal in Phase 2.

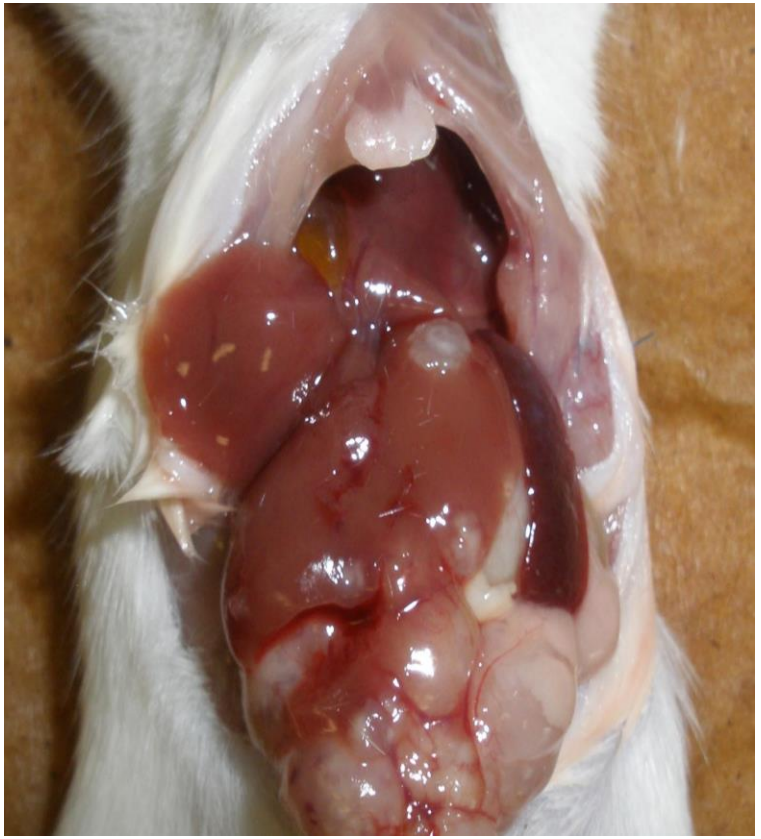
Agents/Targets for Pancreatic Cancer that haven't worked

- VEGF inhibitors – Bevacizumab, Axitinib, VEGF- trap …
- Metformin. (*Wilmink, ASCO 2014)*
- EGFR inhibitors – Cetuximab, Erlotinib?
- Oxaliplatin in second line therapy. (*Gill, ASCO 2014)*
- Insulin like Growth Factor Receptor targeting.
- Stromal Disruption – MMPI, Hedgehog
- HEENT1 expression and gemcitabine.

Hypoxia strongly correlated with rapid proliferation and spontaneous metastasis formation

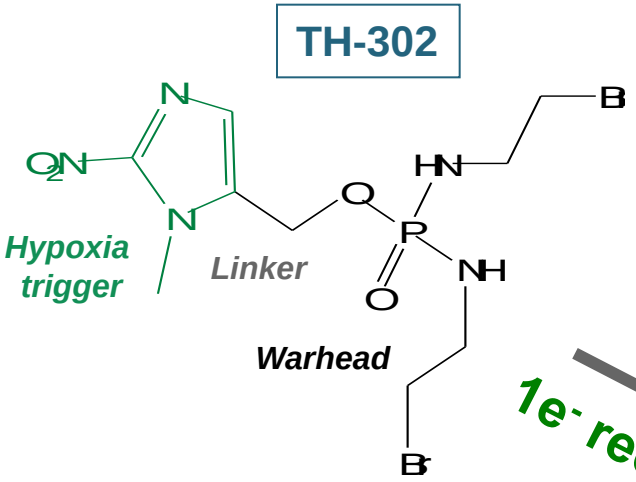


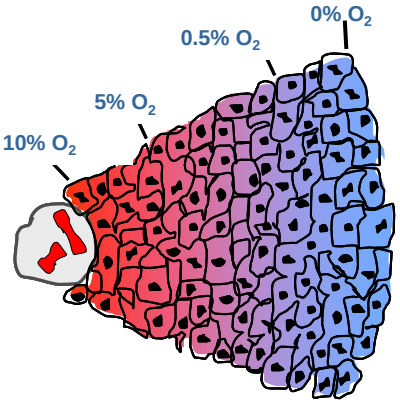
[Hypoxia]



Hypoxia Activated Pro-Drug (HAP) - TH-302

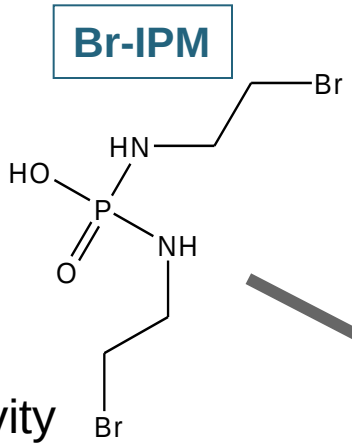
A tumor-selective hypoxia-activated cytotoxic prodrug

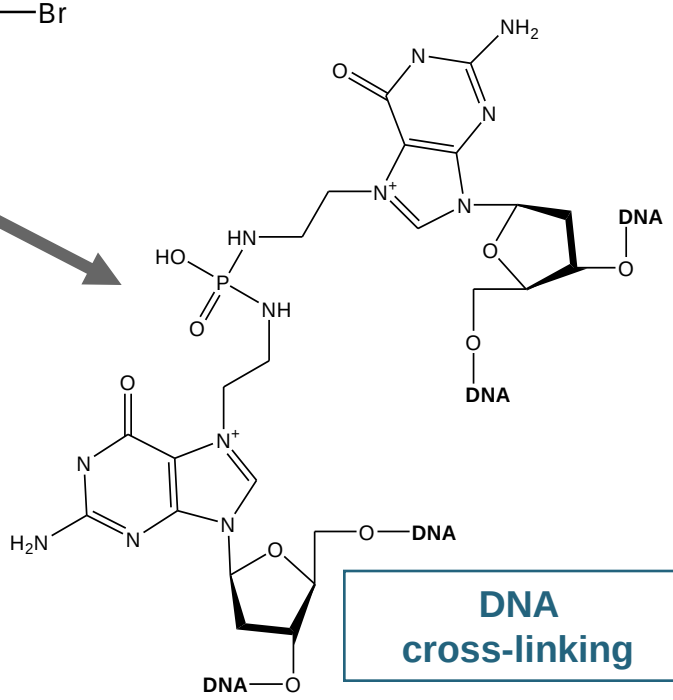




Absence of O_2

1e⁻ reductases





- Cytotoxic under hypoxic conditions
- Broad spectrum *in vitro* and *in vivo* activity both as monotherapy and in combination
- Favorable PK, metabolic and toxicology profile

Duan et al. J Med Chem 2008; 51:2412-20

Study TH-CR-404

Randomized Phase 2 Study Design (June 2010- June 2011; 45 sites)

Advanced Pancreatic Cancer

(N=214)
June 2010-June 2011
45 sites

Randomize 1:1:1

Gemcitabine + TH-302 (240 mg/m²)

Gemcitabine + TH-302 (340 mg/m²)

Gemcitabine

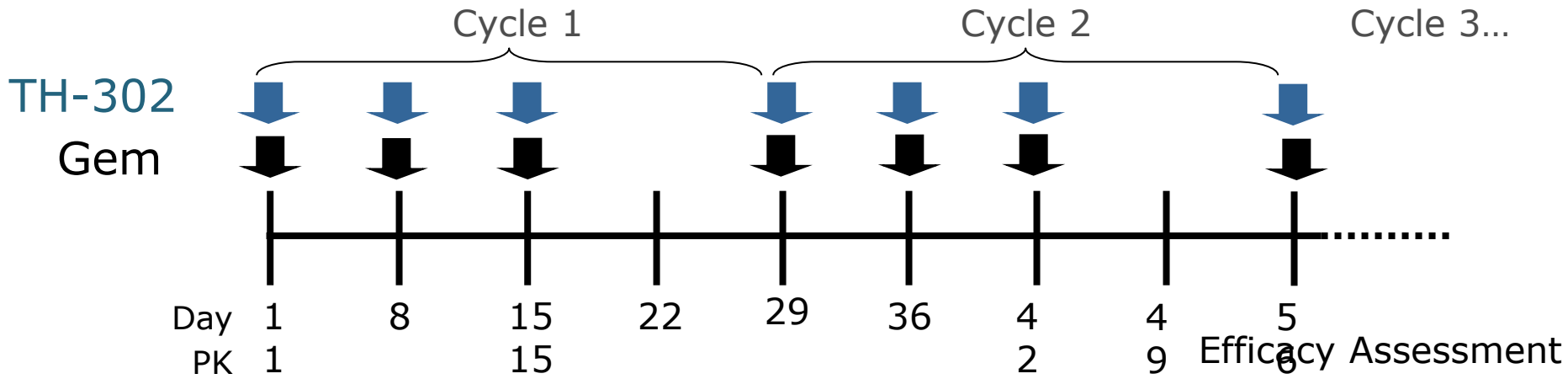
↓

Crossover (randomized to one of Gemcitabine plus TH-302 dose groups)

↓

Gemcitabine + TH-302 (240 or 340 mg/m²)

Stratification: Stage (Unresectable Locally Advanced Vs. Distant Metastases)



Study TH-CR-404

Summary

- TH-302 adds to the efficacy of gemcitabine in first-line pancreatic cancer with statistically significant improvements
  - Median PFS increased from **3.6** to **5.6 months** (p=0.005)
  - Response rate increased from **12%** to **22%** (p=0.066)
  - Mean CA19-9 decreased from **-523** to **-4669** (p=0.038)
- Dose response with greatest efficacy at TH-302 dose of 340 mg/m^2
  - Median PFS of **6.0 months** (p=0.008)
  - Response rate of **27%** (p=0.025)
  - Greater CA19-9 declines (p=0.008)
- Phase 3 study underway. Attempt to evaluate hypoxia within the study.

PARP Inhibitors

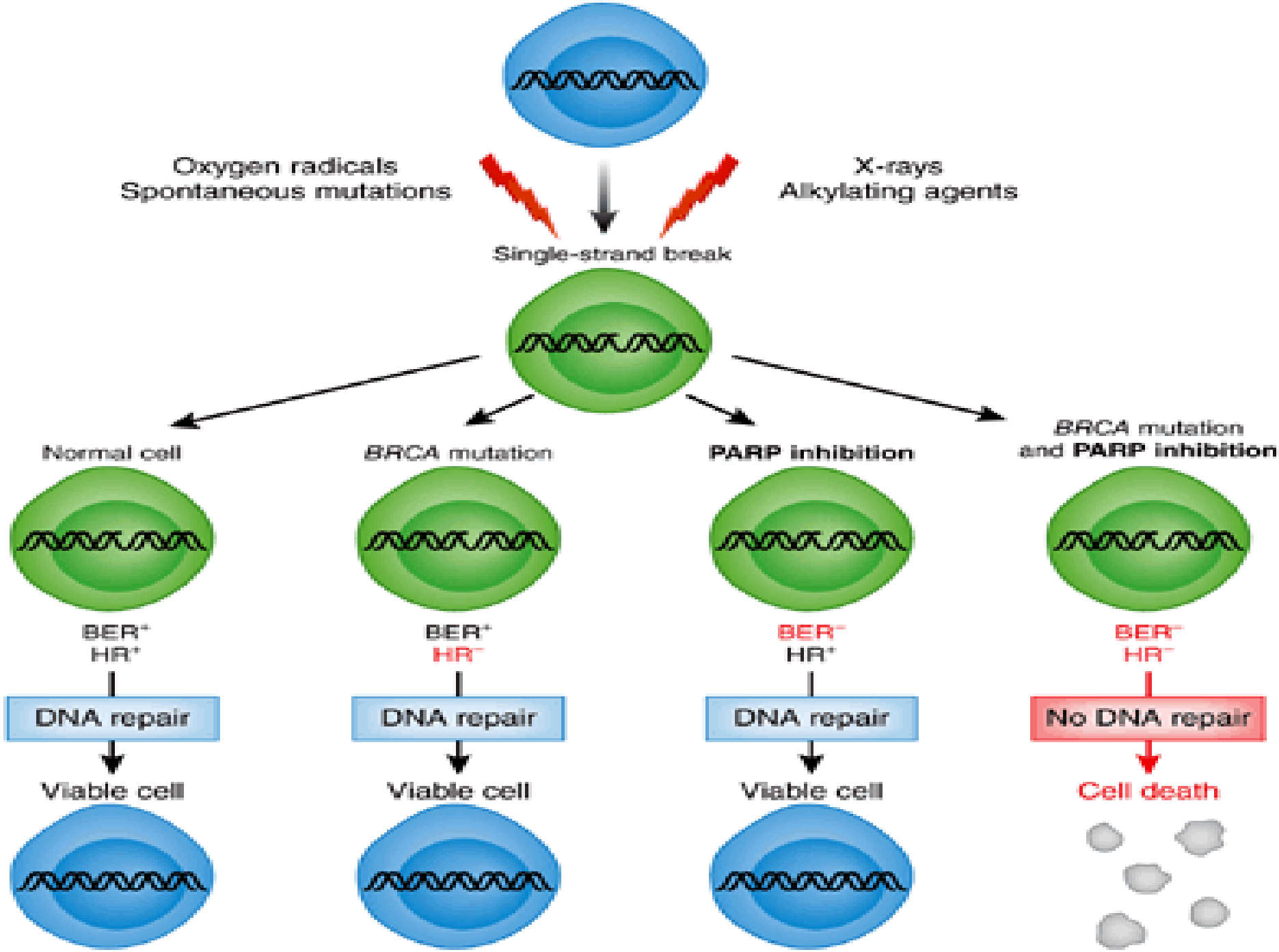
Science:

- 5 to 10% of pancreas cases harbor BRCA1/2 mutations.

- Loss of BRCA1/2 protein have Homologous Repair Deficiency - reduced ability to repair double stranded (ds) DNA breaks.

- Inhibition of Poly ADP ribose polymerase (PARP) prevents single strand DNA repair and leads to dsDNA breaks during cell division. More active when DNA repair ability is also impaired.

- PARP inhibitors may have activity beyond BRCA mutants, in other tumors with DNA repair defects (BRCAness)


Oxygen radicals
Spontaneous mutations
X-rays
Alkylating agents
Single-strand break
Normal cell
BRCA mutation
PARP inhibition
BRCA mutation
and PARP inhibition
BER+
HR+
BER+
HR−
BER−
HR+
BER−
HR−
DNA repair
DNA repair
DNA repair
No DNA repair
Viable cell
Viable cell
Viable cell
Cell death

PARP Inhibitors and BRCA

Clinical Evidence:

- Anecdotal reports of exceptional responses to platinating agents +/- PARPi in advanced pancreatic cancer.

- Studies are underway and some activity seen.

    - e.g.: 5PR and 4 SD in 9 BRCA+ patients in a study of Gem + Cisplatin + Veliparib (*O'Reilly, ASCO 2014)*

- Larger comparative studies being undertaken.

Biomarkers/Patient Selection

- Able to select patients based on germline mutations, BRCAness

Immunotherapy

- Undergoing a renaissance. Activity in melanoma and other refractory tumors.

- Microenvironment in pancreatic cancer is considered immunosuppressive.

- Strategies being tested include

  - Vaccines.

    – GVAX (irradiated pancreatic cell lines) _/-CRS207 (live-attenuated Listeria which stimulates immunity *(Le, ASCO GI 2014).* Larger Phase 2b underway.

  - Activation of T-cells via CD 40 pathway

  - Targeting PD-1/PDL-1 and CTLA-4

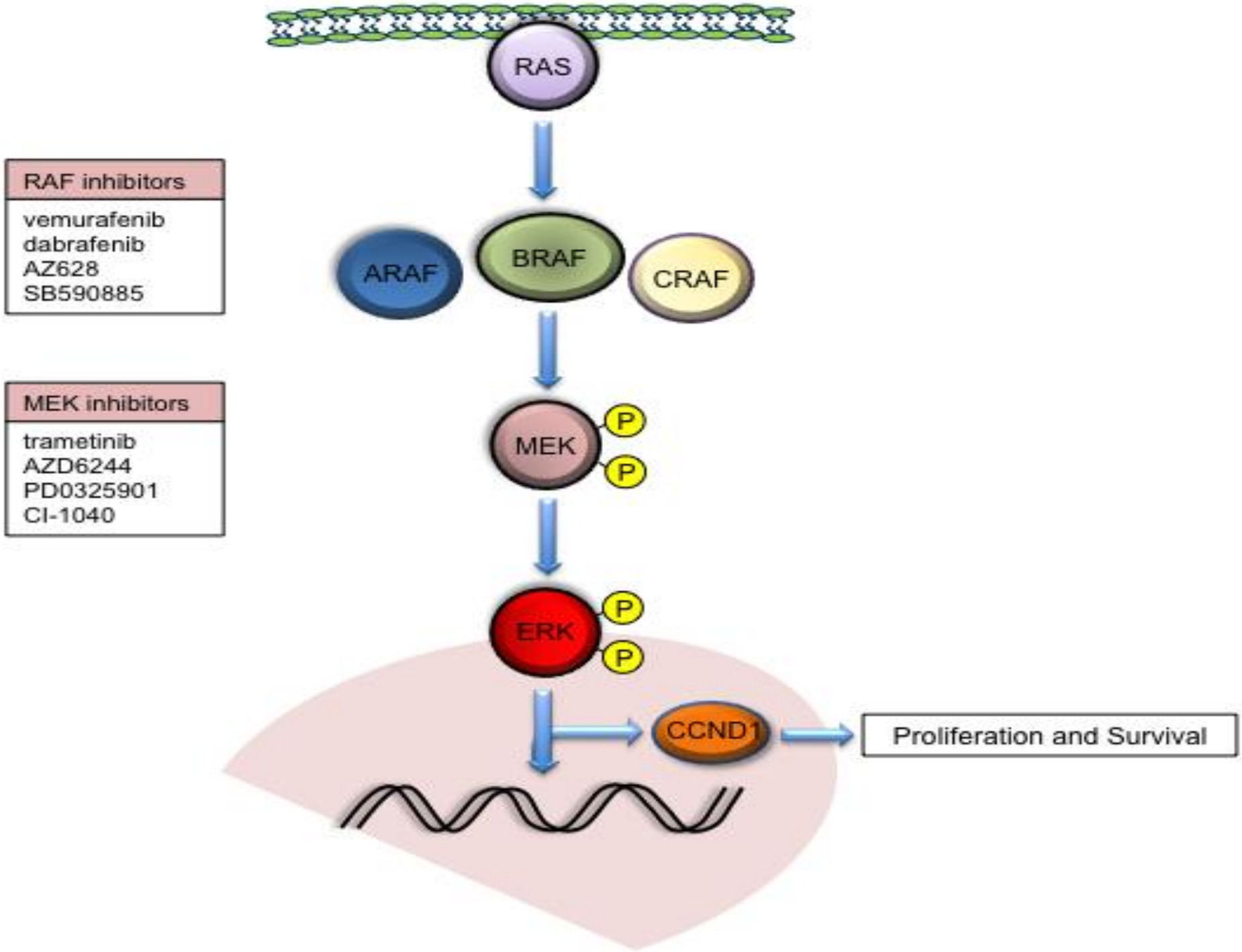
MEK1/2 Inhibitor

Science:

- MEK1/2 activate ERK and are part of MAP Kinase signaling pathway which is frequently activated in presence of K-ras mutations.

- Inhibition of MEK1/2 leads to reduced cell proliferation and apoptosis.

- Preclinical evidence of activity as single agent or in combination with gemcitabine in pancreatic cell lines.


RAF inhibitors
vemurafenib
dabrafenib
AZ628
SB590885
MEK inhibitors
trametinib
AZD6244
PD0325901
CI-1040
RAS
ARAF
BRAF
CRAF
MEK
P
P
ERK
P
P
CCND1
Proliferation and Survival

MEK1/2 Inhibitor

Clinical Evidence *(Van Laethem ASCO 2014)*:

- 60 patients: first line metastatic or locally advanced
- Refametinib oral MEK1/2 inhibitor with gemcitabine.
- RR 35%; PFS 6.2 months; OS 8.9 months.
- previous randomized phase II of gemcitabine +/- another MEK inhibitior trametinib showed no effect *(Infante, EJC 2014)*

Biomarkers/Patient Selection

- In this study trend to better outcome in the Kras wild-type.

Inhibitors of Notch Signaling Pathway

Science:

- Notch signaling pathway important for cell/cell communication and embryonic differentiation (pancreas)

- Aberrant Notch signaling can occur during the initiation and progression of pancreatic and other cancers.

- Gamma secretase inhibitors reduce aberrant Notch signaling by interacting with Notch receptor.

- Some preclinical activity of Gamma secretase inhibitors in pancreatic cell lines.

Inhibitors of Notch Signaling Pathway

Clinical Evidence:

- Still in early phase1/2 studies

Biomarkers/Patient Selection

- Not clear at this point.

Summary

- There are a number of novel agents in later phases of testing in pancreatic cancer.
- Approaches being explored include
  - Targeting Hypoxia.
  - DNA repair inhibition
  - MAP Kinase pathways
  - Embryonic signaling pathways.
  - Immunotherapeutic Approaches.
- The best is yet to come!