Combination of Molecularly Targeted Agents (MTAs)

- Clinical Perspectives

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Cancer targets and available agents – opportunities for combination studies (a partial list)

- Approved agents
  - Estrogen /androgen receptors
  - BCR-ABL (Imatinib, dasatinib, nilotinib)
  - C-KIT (Imatinib)
  - EGFR (Gefitinib, Erlotinib, Cetuximab, Panitumumab)
  - HER2 amplification (lapatinib, Trastuzumab)
  - PDGF mutation – Imatinib
  - mTOR (temsirolimus, everolimus)
  - VEGF (Bevacizumab, sunitinib, sorafenib, pazopanib)
  - Proteosome (Bortezomib)
  - HDAC (vorinostat)
  - Methylation (azacytidine)
  - CTLA-4 (ipilimumab)
- Validated targets with Investigational agents
  - PARP – BRCA deficient tumors
  - Hedgehog (PATCH mutation) - basal cell ca
  - JAK2 - myelofibrosis
  - EML4-ALK- crizotinib
  - BRAFV600E – melanoma
  - MEK
- Emerging targets/agents
  - AKT
  - TOR1/2
  - P13K
  - C-MET/HGF
  - IGF-1R
  - BCL-2 family
  - TRAIL
  - STAT
  - SRC
  - CK2, Ron, Axl
  - "Stem cell" targets
  - ....

Challenges in combining two or more NMEs:
IP, Regulatory, and Scientific

Outline of discussion – Scientific issues

- **General consideration**
  - Identifying and prioritizing combinations for clinical testing
- **Clinical experience**
  - Toxicity and efficacy
- **Challenges and critical gaps**

Which combination? - rationale and hypothesis

- **Derived from high throughput screening:**
  - **Genomic tools**: e.g. siRNA library + agent of interest
  - **Unbiased binary drug combination screen:** e.g. "COMBO-Plate"; CombinatoRx
- **Mechanism based experiments:**
  - **Maximize inhibition of a critical target**
    - *e. g, VEGFR + VEGF; Her2 TKIs and Abs*
  - **Maximize inhibition of a pathway (linearly):**
    - *e.g. Her2 + mTOR*
  - **Block parallel pathways/cellular process**
    - e.g. **antiangiogenic + antitumor;*
  - **Overcome resistance/escape mechanisms:**
    - *e.g. IGF-1R + mTOR; BRAFV600-MEK; MEK- AKT/PI3K; AKT –RTK*
    - *HDACi + Proteosome inhibitor*
    - *Many others…*

Prioritization for clinical evaluation amongst many possible combinations

Factors to consider (no set of criteria will fit all):

- **Most essential: credentials of the individual agents**
  - Adequate PK and safety of each agent
  - Evidence of clinical activity, and/or target engagement in patients
- **Level of clinical validation of the individual targets**
  - Biological activity in the indication to be treated
- **Strength of preclinical POP for the combination** (*esp. important if only one or neither agent was clinically active)*
  - Tested at clinically relevant doses/exposures?
  - Degree of therapeutic enhancement? (growth inhibition → cell kill)
  - Consistent results in multiple models?
    - Or molecular contexts of synergism identified?

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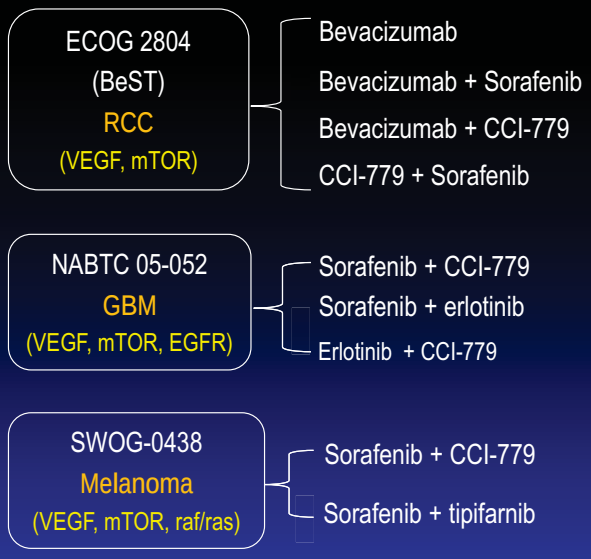
Examples of NME combination trials in the pilot project 2003 (VEGF, EGFR, mTOR)



- Investigational agents supplied by respective CRADA partners
- Phase I , followed by Randomized phase II design
- Mandatory baseline tissue collection and central banking
- Central depository of imaging data (DCE-MRI)

Trials based on best available knowledge and strong rationale

However,

- ***Limited knowledge about the optimal dose/schedule***
- ***No patient selection markers***

To date, hundreds of target agent combination trials have been conducted, for various targets, and agents ….

- Agents w/o selection markers
  - EGFR (in EGFR WT)
  - mTOR
  - VEGF
  - Proteosome (Bortezomib)
  - HDAC (vorinostat)
  - CTLA4
  - PARP
  - IGF-1R
  - BCL-2 family
  - SRC
  - SHH (in paracrine mechanisms)
  - NOTCH
- Agents with candidates of selection markers
  - AKT
  - P13K
  - C-MET/HGF
  - MEK
  - C-MET
  - ….
- Agents with known predictive markers
  - HER2 (amplification)
  - BRAFV600E
  - EGFR (mutation)….
  - BCR-ABL; PDGFRA (mutation)

http:Clinicaltrials.gov

Sponsored by industry, academia or NCI

Recent combination studies (a select list)

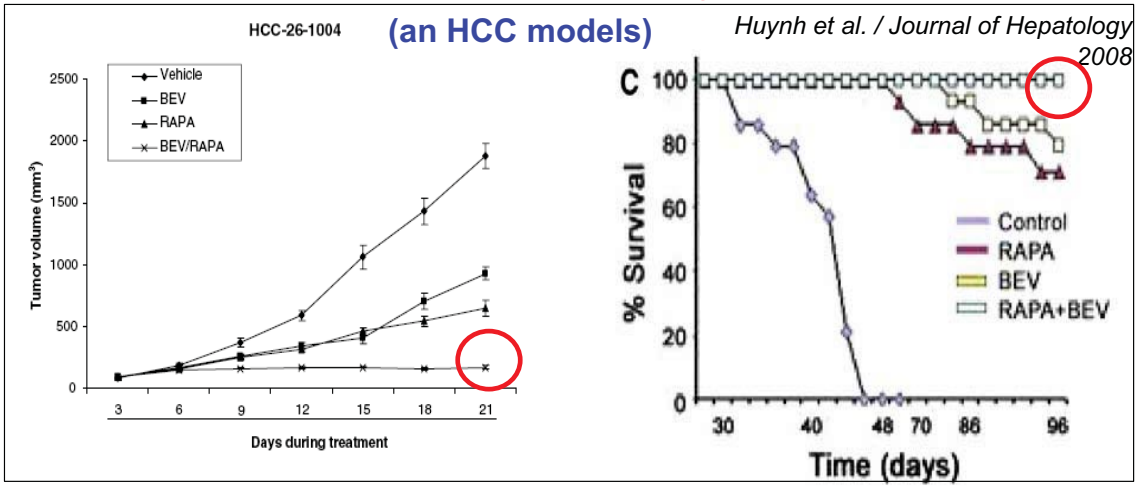
- IGF-1R + MEK
- IGF-1R + mTOR
- MEK + mTOR
- MEK + AKT
- EGFR/HER2 + mTOR
- HER2 + AKT

Clinical experience

- **Tolerability and efficacy**
- **Challenges**

Example 1 – VEGF + mTOR

- **Preclinical data supports the hypothesis**



***Similar results in ovarian, RCC and pancreatic ca models**

- **Clinical agents available and individually active**

mTOR inhibitors	VEGF/VEGFR inhibitors
•Temsirolimus; Everolimus ; Deforolimus	•Bevacizumab; Sorafenib; Sunitinib; ….. others
Active in:	***Active in:***
•RCC; Endometrial ca; Neuroendocrine ca •…..Lymphoma	•RCC; Endometrial ca; Neuroendocrine ca • ….HCC, Ovarian ca

Tolerability

VEGFR TKI + mTOR i	MTD
Sunitinib + Temsirolimus	Not tolerable despite dose reduction
Sorafenib + Temsirolimus	50% dose↓ (sorafenib)
Sorafenib + Everolimus	75% dose↓ (everolimus)

DLT:
- G3 hand and foot syndrome
- G3 cytopenia
- G3 renal dysfunction
- G3 rash
- G3 typhitis

Enhancement in efficacy?

Sorafenib + CCI-779 (Phase II)

- **GMB** – **not active** - RR: 0%; 6m PFS: 0%
- **Melanoma** – **not active** - RR: 0%; 6m PFS: 0%

- **RCC** – pending (BeST trial)

Example 1 – VEGF + mTOR

Bevacizumab + CCI-779

Phase I — **MTD = Full doses of both agents**
(Merchan et al, ASCO 2007)

Phase 2 — ***Prolonged therapy not well tolerated***
– ↑G3-4 toxicities (proteinuria; fistula, etc)

Enhanced Activity? (**TORAVA trial,** Escudier et al, ASCO 2010

	Temsirolimus/ Bevacizumab (n = 88)	Sunitinib (n = 42)	Bevacizumab/ Interferon (n = 40)
ORR	**28%**	**24%**	**36%**
mPFS	**8.2 m**	**8.2m**	**16.8m**
Median Rx duration	4.7 m		
Off-Rx w/o PD	50.0%	11.9%	30.0%

- ↑ ORR over historical single agent data; however, no clinical benefit over SOC
- Inadequate duration of therapy? Inappropriate discontinuation rules?

BeST trial (CTEP) and Phase 3 trial results pending

MTD of MTA combinations

		MTD (cycle 1-2)
VEGFR + mTOR i	Bevacizumab + CCI-779	Full dose
	Sunitinib + CCI-779	Not tolerable
	Sorafenib + CCI-779	Dose reduction ↓ (sorafenib)
EGFR + mTOR	Erlotinib + CCI-779	Dose reduction ↓
IGF-1R + mTOR	IMC-A12 + CCI-779	Dose reduction ↓ / Full dose
VEGF + VEGFR	Bevacizumab + Sorafenib	Dose reduction ↓↓ (> 50%↓)
	Bevacizumab + Sutent	Not tolerable
EGFR + MEK	Erlotinib + AZD 6244	Dose reduction ↓
MEK + AKT	AZD 6244 + MK2066	Dose reduction ↓↓
EGFR + c-MET	Erlotinib + MetMab	Full dose
EGFR + VEGF	Erlotinib + Bevacizumab	Full dose
	Erlotinib + Sorafenib	Full dose

- Agents with higher specificity more "combinable"
- Combinations targeting the same pathways or "nodal signals" less tolerable
- MTD based on cycle 1-2 did not always predict feasibility of longer therapy

MTA combinations with promising activity

Maximizing inhibition of the same target		
HER2 Ab + TKI	**Trastuzumab + lapatinib**	Breast ca → *phase 3 (PFS)*
VEGF + VEGFR	**Bevacizumab+ sorafenib**	RCC, Ovarian ca (phase I)
EGFR Ab + TKI	**Gefitinib + cetuximab**	NSCLC (pilot phase II)
Inhibition of parallel pathways		
VEGF + EGFR	**BV + Erlotinib**	NSCLC → *in phase 3 (PFS)*
		HCC
EGFR + c-MET	**Erlotinib + MetMab**	NSCLC (c-MET IHC+)
Other		
IGF-1R + mTOR	**IMC-A12 + Temsirolimus**	Ewing sarcoma (phase I)
PI3K + MEK	**GDC + GDC**	Phase I
BRAF + MEK	**GSK + GSK**	Melanoma

**Many still awaiting confirmatory trials*

- **Agents with clinical activities individually more likely to show additive efficacy when combined**

Combinations of MTAs that "failed" in clinical trials

Targets	Combinations	Indications
VEGR + EGFR	**BV + Chemo + panitumumab**	**Colon* → *worse PFS and OS***
	BV + Erlotinib	**Pancreatic, RCC, breast**
	Erlotinib + sorafenib	**GBM**
VEGF + PDGFR	**BV + Imatinib**	**RCC**
mTOR + Estrogen	**CCI-779 + aromatase i**	**Breast***
mTOR + ImmunoRx	**CCI-779 + INFα**	**RCC***
mTOR + EGFR	**CCI-779 + Erlotinib**	**GBM**
mTOR + VEGF	**CCI-779 + sorafenib**	GBM, Melanoma

*** Combinations failed, even though individual agents were active in the same clinical setting**

What went wrong?

- Wrong hypothesis? Incomplete understanding of the biology
- Inadequate dose or duration of therapy?
- Wrong patient population or lack of patient selection?

The dose and schedule question

If reduction of drug exposure is necessary for a combination**.....**

- **What would be the optimal dose ratio?**

  ½ dose of A + ½ dose of B
  ¼ dose of A + Full dose of B
  Full dose of A + ¼ dose of B

- **Is intermittent exposure sufficient or better?**

Need to known …

- Preclinical –
  - Optimal schedule/doses
  - PD/PK required for synergism; surrogate marker of cytotoxicity
- Clinical –
  - PD/PK at the chosen and deliverable doses
  - May need to test more than one dose/schedule (with clinical and PD endpoints)

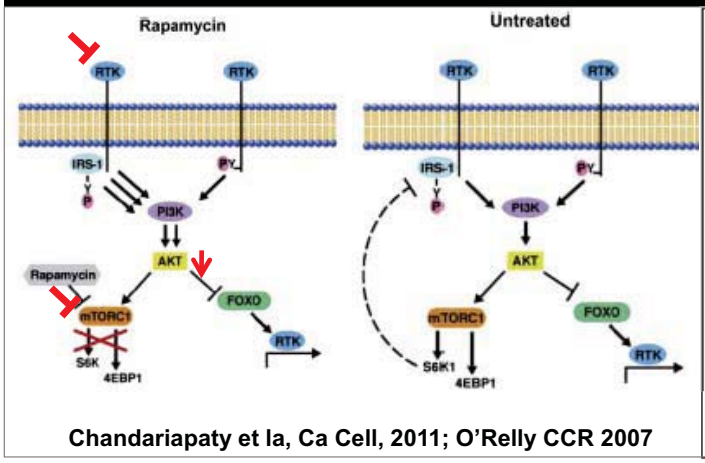
Patient selection issues

- A given combination can be synergistic or antagonist in different molecular contexts. Patient selection is key to …
  - Improving trial efficacy
  - Avoiding unnecessary drug exposure or negative outcomes

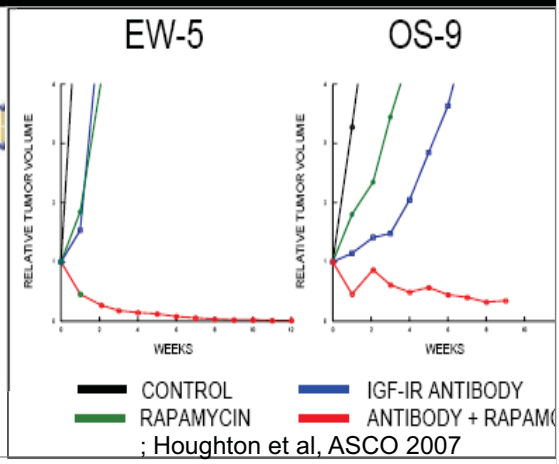
- **If a combination requires significant dose reduction, therapeutic window may still (only) exist in <u>selected</u> patients …**
  - **If the tumor is exquisitely sensitive to the agent**
    - * e.g. EGFR TKIs in EGFR mutant NSCLC ***(MTD may not be necessary)***
  - **If *the* molecular context is associated with synergism**
    - True synergism may confer better efficacy despite dose reduction

…. how to find these pts?

Issues with tumor biology
-- Experience of IGF-1R and mTOR combination



Chandariapaty et la, Ca Cell, 2011; O'Relly CCR 2007



; Houghton et al, ASCO 2007

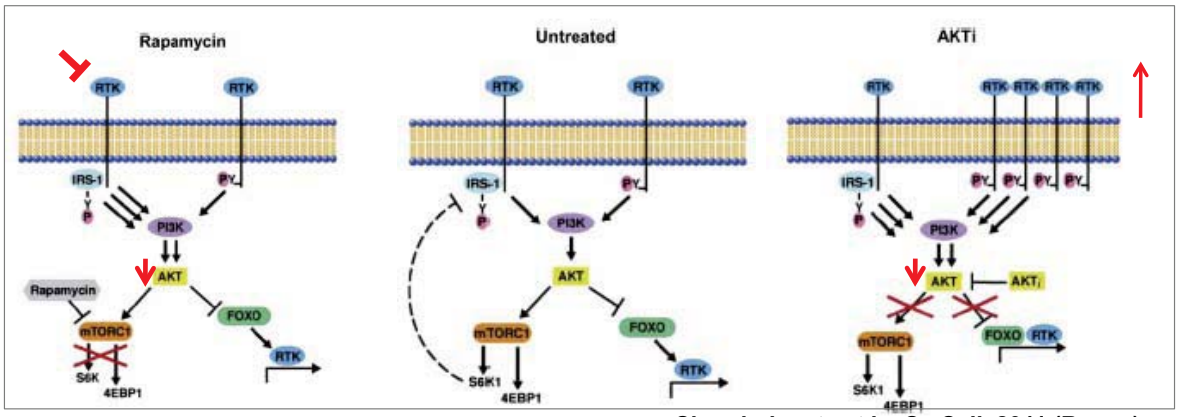
Phase 1 trial IMC-A12 + Temsirolimus (Naing, .. LoRusso, ASCO 2011)

- **Expansion cohort for EWS (n=17)**
  - **ORR: 2/17 (12%)**
    - **1CR (16m+) in pt with prior IGF-1R mab failure**
  - **PFS : 5/17 (29%) at 5 months**

IMC-A12 alone

- ORR: 1/18 (6%)
- PFS 2/18 (11%) at 2.8m

There are more escape mechanism!



Chandariapaty et la, Ca Cell, 2011 (Rosen)

- AKT inhibition can induce activation of an array of RTKs
  - **HER3, InR, EGFR, FGFR, EGFR, ……**
- **Which RTK is responsible for escape depends on different cell lines and underlying molecular makeup**

- Further studies may identify which RTK should be inhibited in which patients
- **However, other escape pathways may emerge!**

Optimizing the patient outcome – therapeutic goals and strategies

- **Search for combinations that are truly synthetically lethal to tumor cells:**
  - Intensive, short course (sustained response or cure)
- **If tumor control requires continuous therapy, consider**
  - "lighter" dose or regimen that can be tolerated up to tumor progression
  - Sequential rather than concurrent use of active components
- **Incorporate agents that act beyond the tumor molecular complexity**
  - Active immunotherapy (vaccine, anti-CTLA4, PD-1 …)
  - Other modalities

What have we learned about combinations among MTAs

- **Adverse effects on normal tissues may limit the spectrum and degree/duration of combined target inhibitions**
- **Efficacy results have been variable, with (modest) successes and notable failures –** preclinical data not easy to translate
- ***Identifying the optimal dose/schedule and the right patients may improve the therapeutic index and outcome***

Filling the Gaps

- Systematic preclinical studies across diverse molecular backgrounds
  - Identify molecular contexts predictive of synergism or antagonism
- In-depth studies on individual agents and their combinations
  - Define molecular effects on targets; surrogate markers of biological activity
- Models for toxicity studies
  - Predict risk, explore mechanism and mitigation strategy
- Systematic effort in biomarkers infrastructure
  - Marker discovery, assay development; assay performance
- Resource and tools to facilitate biomarker incorporation in clinical trials

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