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Opportunities and Challenges of Model-based Meta-analysis in Oncology

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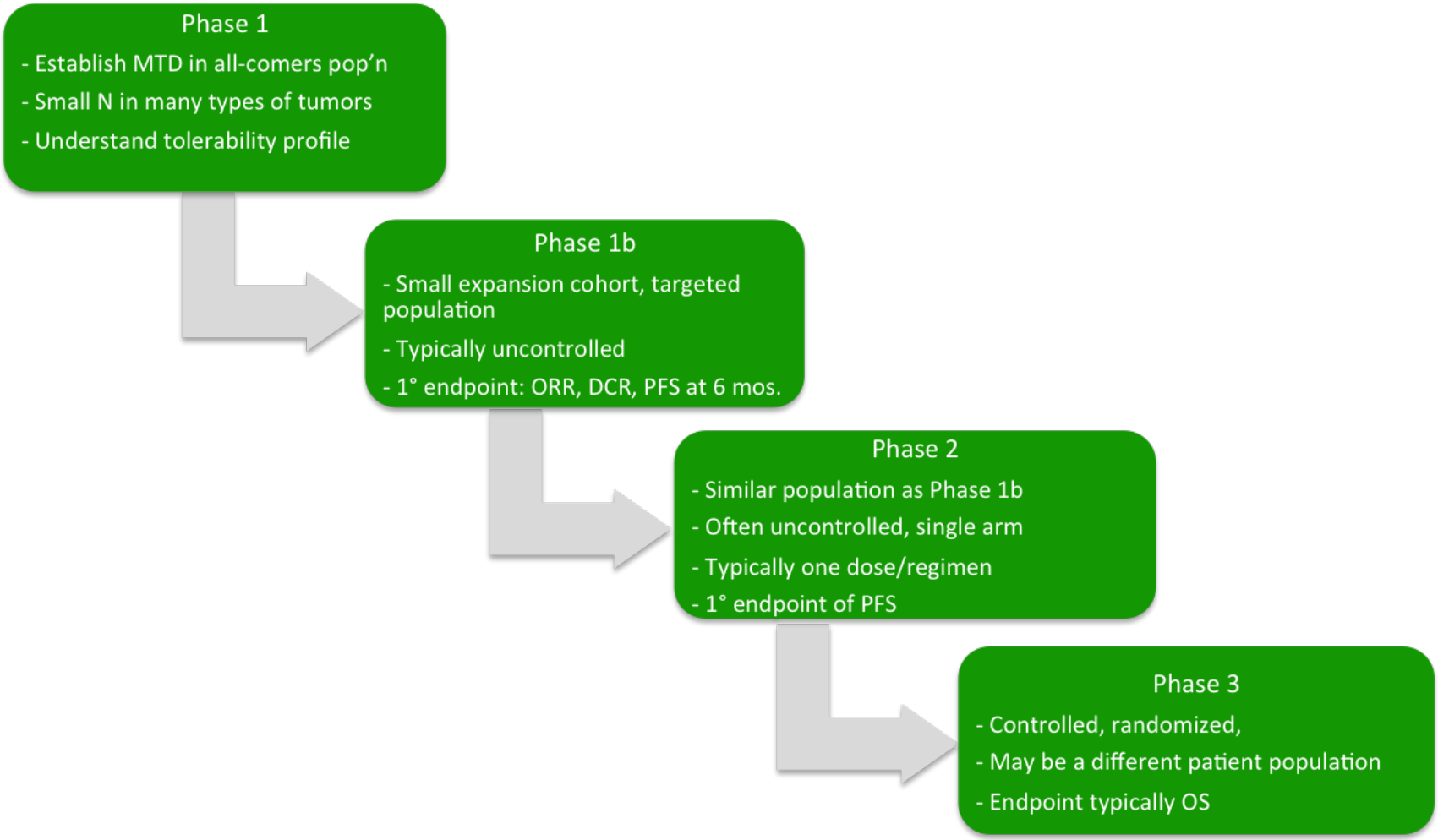
Drug development in oncology is slow and expensive



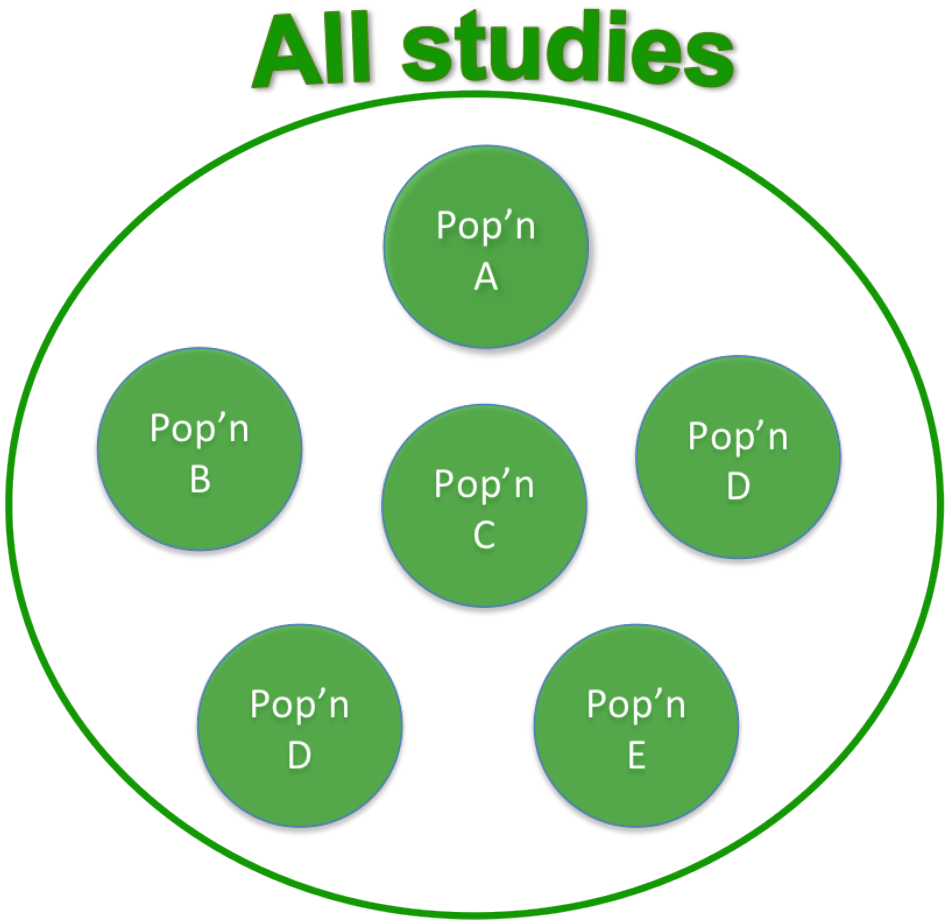
Need to use all information at-hand to inform decisions at each stage of development

- Put results of single-arm studies in context with expected comparator in Phase 2
  - For design of Phase 2 study and benchmark for go/no-go decision
- Put results of controlled (or uncontrolled) Phase 2 study in context
  - Connect Phase 2 to Phase 3 endpoints
  - Design of Phase 3 study
  - Benchmark for go/no-go decision
- Put results of Phase 3 study in context
  - Possibly for comparative efficacy discussion with regulators
  - Possibly for reimbursement discussions with payors

. . . Why is (MB)MA not used more often in oncology?

- Complex diseases
  - Typically have only one study per treatment comparison in a patient population
- Complexities of patient populations:
  - Unselected vs. selected populations
  - Line of treatment: neo-adjuvant, adjuvant, first-line, second-line, later lines
- Complex study designs
  - Single arm / uncontrolled studies
  - Cross-over after progression
- Complex dosing/regimens
  - Typically not enough data to model dose/exposure response
  - Different doses used in different populations/regimens
- Longitudinal data is typically only from survival curves

Splitting vs. Lumping



Challenge 0

Finding a balance between the two extremes of splitting and lumping.

Macedo *et al. BMC Cancer* 2012, **12**:89
http://www.biomedcentral.com/1471-2407/12/89

RESEARCH ARTICLE Open Access

Addition of bevacizumab to first-line chemotherapy in advanced colorectal cancer: a systematic review and meta-analysis, with emphasis on chemotherapy subgroups

Ligia Traldi Macedo, Andre Bacellar da Costa Lima and Andre Deeke Sasse*

Patients:	Advanced CRC
Interventions:	First-line treatment with Bev+chemo
Comparators:	6 chemo regimens
Outcomes:	OS, PFS

- 6 studies published 2002-2011

Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis

Vassilis Golfinopoulos, Georgia Salanti, Nicholas Pavlidis, John P A Ioannidis

Lancet Oncol 2007; 8: 898–911

Patients: Advanced CRC

Interventions: First-or second-line systematic treatment regimens

Comparators: Categorized by use of or no use of FU-based regimens, irinotecan, oxaliplatin, bev, and cetuximab

Outcomes: OS, PFS

- 242 trials published 1967-2007
- "...doses and schedules of the same regimen often differed between trials."

Complexities in the analysis

Challenge 1

Methodological challenges

- How to analyze data from K-M curves and appropriately account for censoring
- Connecting different clinical outcomes
  - E.g., objective response rates, progression-free survival, and overall survival
  - Predictive vs. prognostic effects
- Pooling across drugs with similar mechanism of action and/or diseases
  - Some efforts to combine within classes of drugs ([2],[4])

Complexities of study designs

Challenge 2

What to do with those pesky uncontrolled studies?

- Don't include them in your set of studies . . .
  - Prognostic factors can have a large effect on outcome
  - Differences between studies in prognostic factors can be the primary driver of differences
  - Without a control arm in the study, there is no way to separate effects of drug from covariates
- . . . unless you have adequately modeled the effects of prognostic covariates

Complexities of dosing

Bevicizumab regimens in Macedo 2012 meta-analysis

Study	Bevacizumab	FU	Capecitabine	Irinotecan	Oxaliplatin	Max Dur. Chemo
Kabb '03	5 mg/kg Q2W	500 mg/m^2 (b) Q1W/6W				48 weeks
	10 mg/kg Q2W	500 mg/m^2 (b) Q1W/6W				48 weeks
Kabb '05	5 mg/kg Q2W	500 mg/m^2 (b) Q1W/6W				96 weeks
Tebbutt '10	7.5 mg/kg Q3W		1.25 g/m^2 BID 2W/3W (*)			None
Stathopoulos '10	7.5 mg/kg Q3W	500 mg/m^2 (inf) Q3W		135 mg/m^2		24 weeks
Saltz '08	7.5 mg/kg Q3W		1 g/m^2 BID 2W/3W		130 mg/m^2 Q3W	48 weeks
	5 mg/kg Q2W	400 mg/m^2 (b) + 600 mg/m^2 (inf) for 2 days Q2W			85 mg/m^2 Q2W	48 weeks
Hurwitz '04 IFL	5 mg/kg Q2W	500 mg/m^2 (b) Q1W/4W		125 mg/m^2 Q1W/4W		96 weeks

Complexities of dosing

Challenge 3

Modeling dose response and effects of regimen

- Using different background chemotherapy regimens
- Duration of chemotherapy treatment
- Delivery method of drug (e.g., bolus vs. infused FU)
- Rarely get more than one dose/regimen of a drug in a study

- Potentially biased estimates if prognostic factors are associated with doses used across studies

Complexities of patient populations

Challenge 4

Personalized medicine

With targeted agents and populations, we want to put the drug effects in the correct context.

- Selected populations: e.g., genetic markers or treatment failures
- We are interested in effects in the selected population not a general population
- Data are only infrequently reported in a way that this can be determined
  - Either not reported at all
  - Or not reported by subsets

When might this be a challenge?

- Targeted treatments are a growing portion of oncology R & D portfolios
- ALK mutations in non-small cell lung cancer
  - Crizotinib is a targeted therapy against ALK mutations
  - A Phase 1b study shows very promising benefit in a single, arm study
  - But is an ALK mutation a predictive marker for effect of crizotinib or prognostic marker or both?
- KRAS in colorectal cancer
  - Cetuximab is an EGFR inhibitor and has been shown to be more effective in KRAS w.t.
  - Several studies conducted in unselected populations . . .
  - Average effect on PFS estimated in Golfinopoulous [2]

Complexities of the culture

Challenge 5

The perception that 'oncology is different'

Oncologists and oncology statisticians seem to be more resistant to meta-analysis than in other disease areas

- Changing treatment practice over time, so can't use older studies
  - Patients who enroll in second-line studies now are different than in older studies
- Impossible to account for different background treatment regimens
- Aggregate data alone is not adequate - you need IPD [1]
- MA cannot adjust for patient level prognostic factors or perform subgroup analyses [5]

Final challenge

Challenge 6

To not give up

MBMA can contribute to oncology drug development

- But it needs to be done thoughtfully
- Openly stating the assumptions when addressing challenges
  - Dosing complexities
  - Getting the right patient population
  - Modeling differences between patient populations
  - Methodological issues
- While acknowledging that there are limitations to what MA (including MBMA) can achieve
  - Correlations between prognostic/predictive factors and treatments/studies
- Need to have creative ways for convincing clinical teams of the value.

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