MONASH University

Medicine, Nursing and Health Sciences

Challenges in the systemic treatment of GU malignancy

Ian Davis

Professor of Medicine, Monash University and Eastern Health

Medical oncologist, Eastern Health

Chair, ANZUP Cancer Trials Group

Melbourne, Australia

ANZUP™ Cancer Trials Group Limited

easternhealth GREAT HEALTH AND WELLBEING

Disclosures

- Member and/or chair of industry advisory boards:
  - Astellas, Bayer, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Medivation, Novartis, Pfizer, Sanofi
- All payments and honoraria are invoiced by and paid to ANZUP Cancer Trials Group
- Unremunerated director and Chair of ANZUP Cancer Trials Group
- Unremunerated director, Clinical Oncology Society of Australia

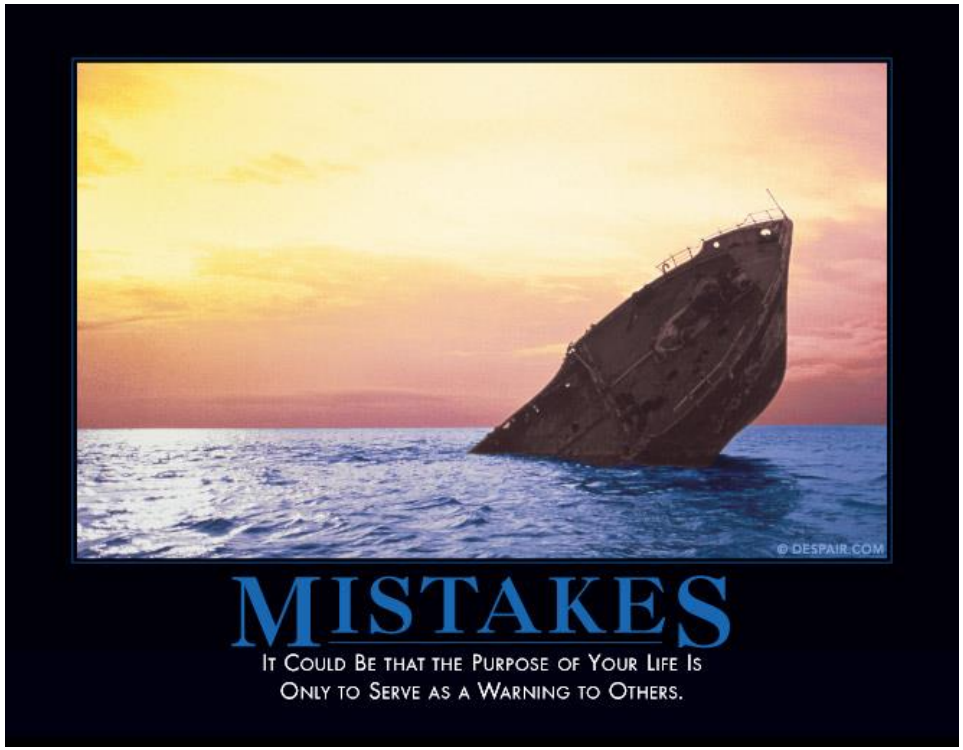
“Three Key Objectives”

- You will think about things other than genes, unpronounceable drugs, hazard ratios and p values
- You will challenge your assumptions about the way you take up and use evidence, and how you practice
- You will look critically at how you practise in the Real World

- “This would be a great time in the world for some man to come along that knew something” – Will Rogers

Challenges

- Until recently…
  - Effective therapy for germ cell cancers only
  - No other effective therapies or responsive GU cancers
- Today:
  - Six life-prolonging therapies for metastatic CRPC
  - Marked improvement in outcomes in RCC, with recent survival advantages
  - Treatments for urothelial cancers now tolerable
  - Impact of effective immunotherapies yet to be evaluated
- Are we now somewhat “spoiled for choice?”



www.despair.com

ASCO
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

ASCO Educational Book contained no genitourinary cancer section in 2002

The next set of challenges: 2016 and beyond

- Access
  - Funding for treatments
  - Infrastructure
- Expertise
  - Novel mechanisms and toxicities
- Optimal use of medications
  - Patient selection
  - Companion diagnostics
- Sequencing
  - Which treatment, when, how long?
- Evidence
  - Extrapolation beyond the data
  - Off-trial treatments affecting endpoints
  - Rare subtypes of common cancers
- Resistance
  - Understanding mechanisms of primary and acquired resistance
  - Preventing emerging resistance
- Practice patterns
  - Multidisciplinary involvement
  - Referral patterns
  - Changes in practice
- Technology “creep”
  - Equipment, imaging
- Drug development challenges
  - Industry trials, investigator-initiated trials, collaborative groups
- How to show improvement when we are already doing well

Access

- Access
  - Inequity of services and spending within and between regions
  - Funding for treatments (and diagnostics) is often not available
  - Access to diagnostics and therapeutics may be poor, even if funded
  - Manpower and infrastructure may be lacking
  - Geography may be challenging

Annals of Oncology 26: 1547–1573, 2015
doi:10.1093/annonc/mdv249
Published online 30 May 2015

A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

N. I. Cherny[1*], R. Sullivan[2], U. Dafni[3], J. M. Kerst[4], A. Sobrero[5], C. Zielinski[6], E. G. E. de Vries[7] & M. J. Piccart[8,9]

[1]Cancer Pain and Palliative Medicine Service, Department of Medical Oncology, Shaare Zedek Medical Center, Jerusalem, Israel; [2]Kings Health Partners Integrated Cancer Centre, King's College London, Institute of Cancer Policy, London, UK; [3]University of Athens and Frontiers of Science Foundation-Hellas, Athens, Greece; [4]Department of Medical Oncology, Antoni van Leeuwenhoek Hospital; [5]Department of Medical Oncology, IRCCS San Martino IST, Genova, Italy; [6]Division of Oncology, Medical University Vienna, Vienna, Austria; [7]Department of Medical Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [8]Jules Bordet Institute, UniversitéLibre de Bruxelles, Brussels, Belgium; [9]Netherlands Cancer Institute, Amsterdam, The Netherlands

The helpfulness of guidelines…

Table 7.3: EAU 2015 evidence-based recommendations for systemic therapy in patients with mRCC

RCC type	MSKCC risk group [323]	First-line	LE^	Second-line*	LE^	Third-line*	LE^	Later lines	LE
Clear cell*	Favourable, Intermediate and poor	sunitinib pazopanib bevacizumab + IFN Favourable-intermediate only)	1b 1b 1b	after VEGFR: axitinib sorafenib# everolimus after cytokines: sorafenib# axitinib pazopanib	 2a 2a 2a 1b 2a 2a	after VEGFR: everolimus after mTOR: sorafenib	 2a 1b	any targeted agent	4
Clear cell*	poor¶	Temsirolimus	1b	any targeted agent	4				
Non-clear-cell §	any	sunitinib everolimus temsirolimus	2a 2b 2b	any targeted agent	4				

IFN-α = interferon alpha; LE = level of evidence; MSKCC = Memorial Sloan-Kettering Cancer
mTOR = mammalian target of rapamycin inhibitor; RCC = renal cell carcinoma; TKI= tyrosine

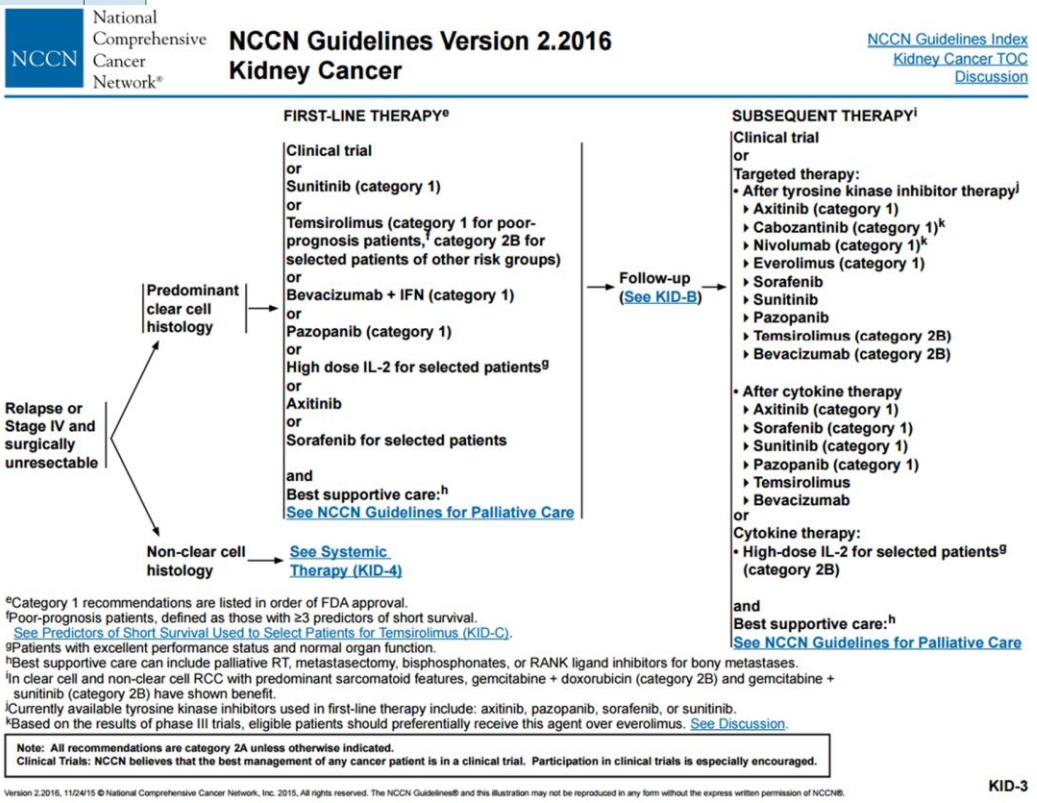
* Doses: IFN-α - 9 MU three times per week subcutaneously, bevacizumab 10 mg/kg biweekly intravenou
mg daily orally for 4 weeks, followed by 2 weeks of rest (37.5 mg continuous dosing did not show signif
temsirolimus 25 mg weekly intravenously; pazopanib 800 mg daily orally. Axitinib 5 mg twice daily, to be
mg twice daily, unless greater than grade 2 toxicity, blood pressure higher than 150/90 mmHg, or the pa
antihypertensive medication. Everolimus, 10 mg daily orally.

§ No standard treatment available. Patients should be treated in the framework of clinical trials or a decisi
consultation with the patient to perform treatment in line with ccRCC.

¶ Poor risk criteria in the NCT00065468 trial consisted of MSKCC [323] risk plus metastases in multiple o

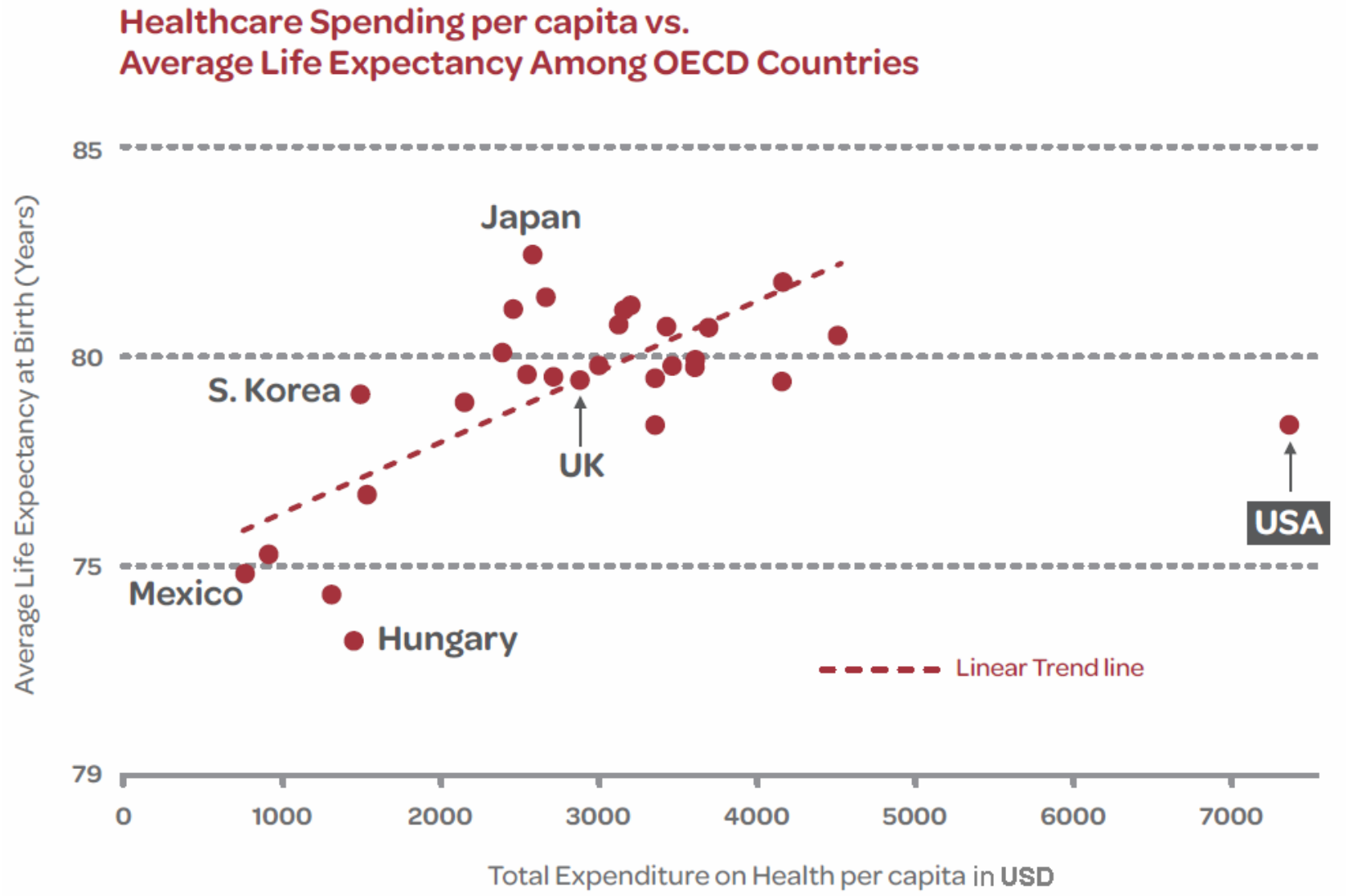
Sorafenib was inferior to axitinib in a RCT in terms of PFS but not OS [351].

^ Level of evidence was downgraded in instances when data were obtained from subgroup analysis with



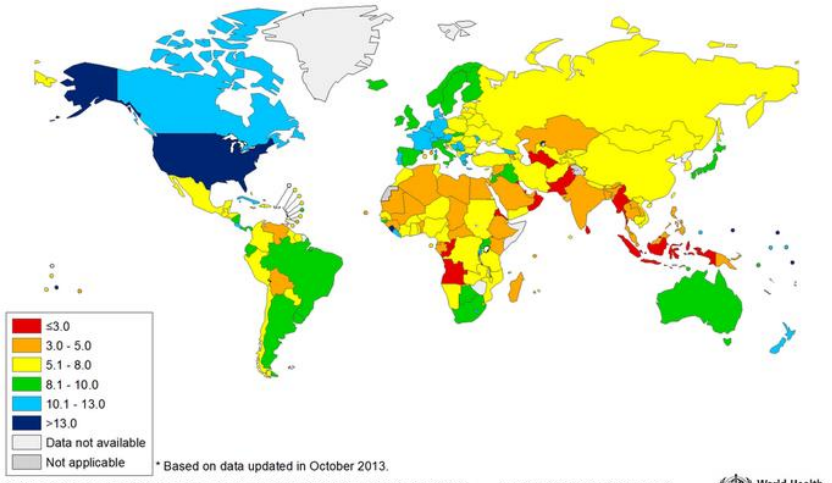
MONASH University

Ljungberg B et al. http://uroweb.org/wp-content/uploads/10-Renal-Cell-Carcinoma_LR1.pdf
http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

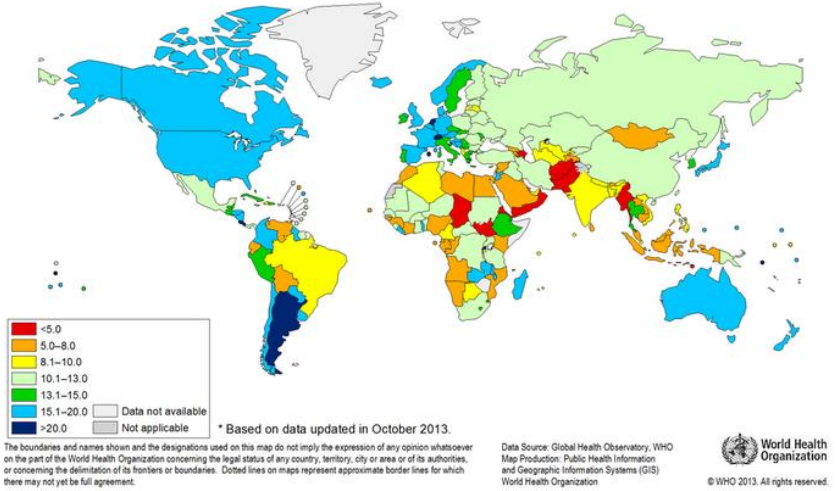


www.forbes.com/sites/danmunro/2012/01/19/u-s-healthcare-hits-3-trillion/

Total expenditure on health as a percentage of the gross domestic product, 2011 *



General government expenditure on health as a percentage of total government expenditure (in US$), 2011 *



www.who.int/health-accounts/expenditures_maps/en/

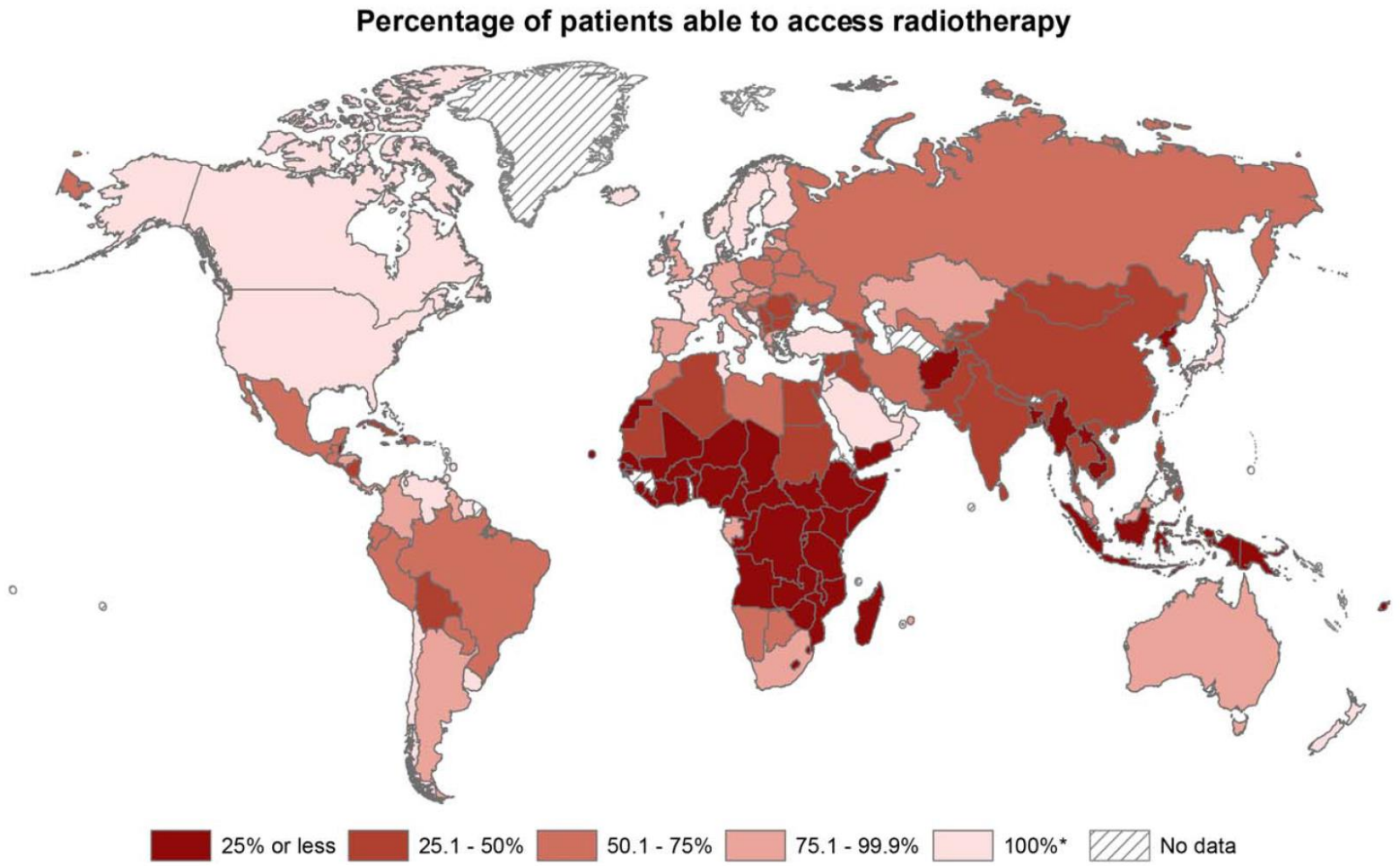
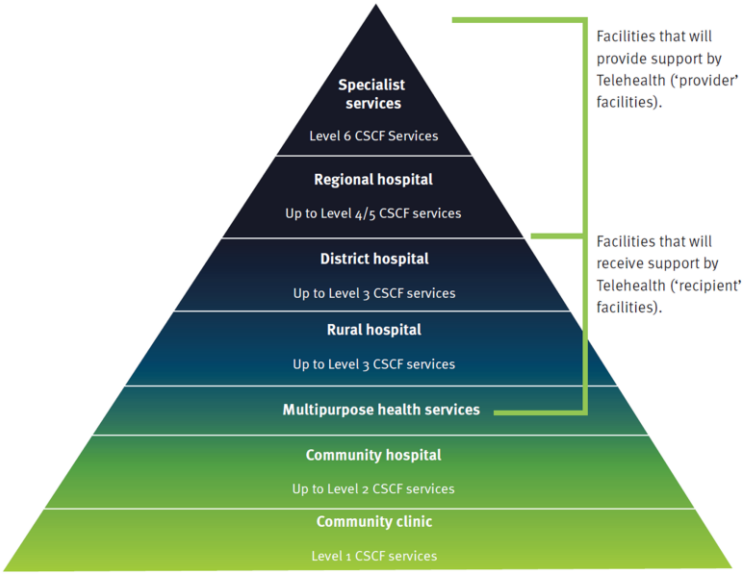


FIGURE 3. Estimated Percentage of Patients Able to Access Radiotherapy, 2013.
*Countries with 100% of patients able to access radiotherapy may also include countries where radiotherapy supply is greater than demand, although disparities in access may still exist within these countries.
Source: The Cancer Atlas, second edition, as obtained from the International Atomic Energy Agency.

Torre LA et al. CA Cancer J Clin 65: 87-108, 2015

Queensland teleoncology / teletrials model

Figure 1 Health service network



Queensland remote chemotherapy supervision (QReCS) model

CSCF = Clinical Services Capability Framework (Cancer Services)[2]

The minimum workforce required to support the QReCS model is shown in the table below.

	Medical	Nurse	Pharmacy	Allied health	Administration
Provider	Medical oncologist Haematologist	Chemotherapy administration proficient nurse	Cancer pharmacist with two years' cancer care experience	Allied health professional experienced in management of cancer patients	Administration officer for Telehealth coordination
Recipient	Identified medical officers	Chemotherapy administration supervised or capable nurse	Hospital or outreach pharmacist	Access to allied health professional	Administration officer for Telehealth coordination

A/Prof Sabe Sabesan

www.health.qld.gov.au/circs/Docs/QReCS%20Guide.pdf

Expertise

- New treatments involve novel mechanisms of action, toxicities, supportive care, evaluation of outcomes
- Example: effective immunotherapy (CTLA4 / PD1 targeted treatment)
  - Evaluation of response and progression
    - Immune-related response criteria
  - Recognition of unusual toxicities
    - Eg hypophysitis: often masked by disease-related symptoms
  - Supportive care
    - Immunosuppression; anti-TNF treatments; parenteral nutrition
- Example: VEGFR-targeted TKIs
  - RECIST can be misleading
  - Importance of previously “unimportant” toxicities
  - Need to involve other disciplines

Optimal use of medications

- Greatest benefit will be obtained by:
  - Treating those most likely to respond
  - Not treating those who are not likely to respond
  - Treating for the correct period of time
- Clinical factors – examples:
  - Angiomyolipoma / tuberous sclerosis: everolimus?
  - Positive family history / young prostate cancer: PARP inhibitor?
  - (RCC prognostic categories)
- Predictive biomarkers:
  - Commonly used in other types of cancer:
    - eg c-kit, BRAF V600E, EGFR, ALK, RAS, Her2/neu
  - None yet validated for any GU cancer
    - ARv7 or other AR variants? PD-L1? DNA repair genes?
- Requirements for companion diagnostics: cost, regulatory issues
- Drug development challenges when targeting rare populations

Sequencing

- The goal is the best outcome for this patient across the entire course of the illness
  - Which treatment? When? How long?
- Clinical trials address one intervention
  - Was “this patient” represented by the trial population?
  - Results need interpretation in the light of other treatments received
  - Common error: individual treatments will be just as effective when given in any order
    - Assumes each treatment is biologically independent
- Examples:
  - Prostate cancer: role and timing of docetaxel
    - Enzalutamide or abiraterone pre / post chemo
  - Renal cell carcinoma: which post-first-line therapy, and when?
    - AXIS trial and effects of prior therapy

Sequencing in renal cell carcinoma

All patients:
Median PFS
6.7 vs 4.7 mo

Prior cytokine:
Median PFS
12.1 vs 6.5 mo

Prior sunitinib:
Median PFS
4.8 vs 3.4 mo

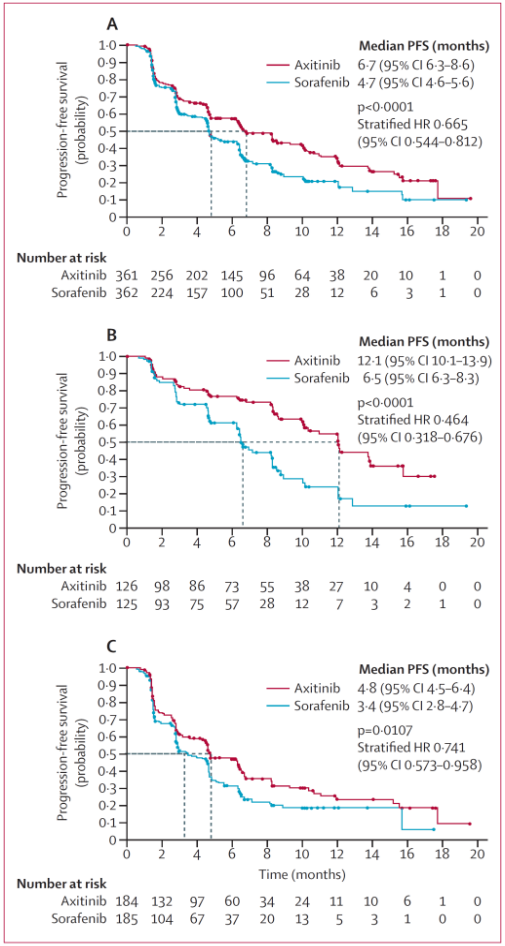


Figure 2: **Kaplan-Meier estimated median PFS in patients who received axitinib or sorafenib as second-line therapy for metastatic renal cell cancer**
HR=hazard ratio. PFS=progression-free survival. (A) all patients, (B) patients previously treated with cytokine-based regimen, and (C) patients previously treated with sunitinib-based regimen (full analysis set, by independent review committee assessments). p values based on one-sided, stratified log-rank test.

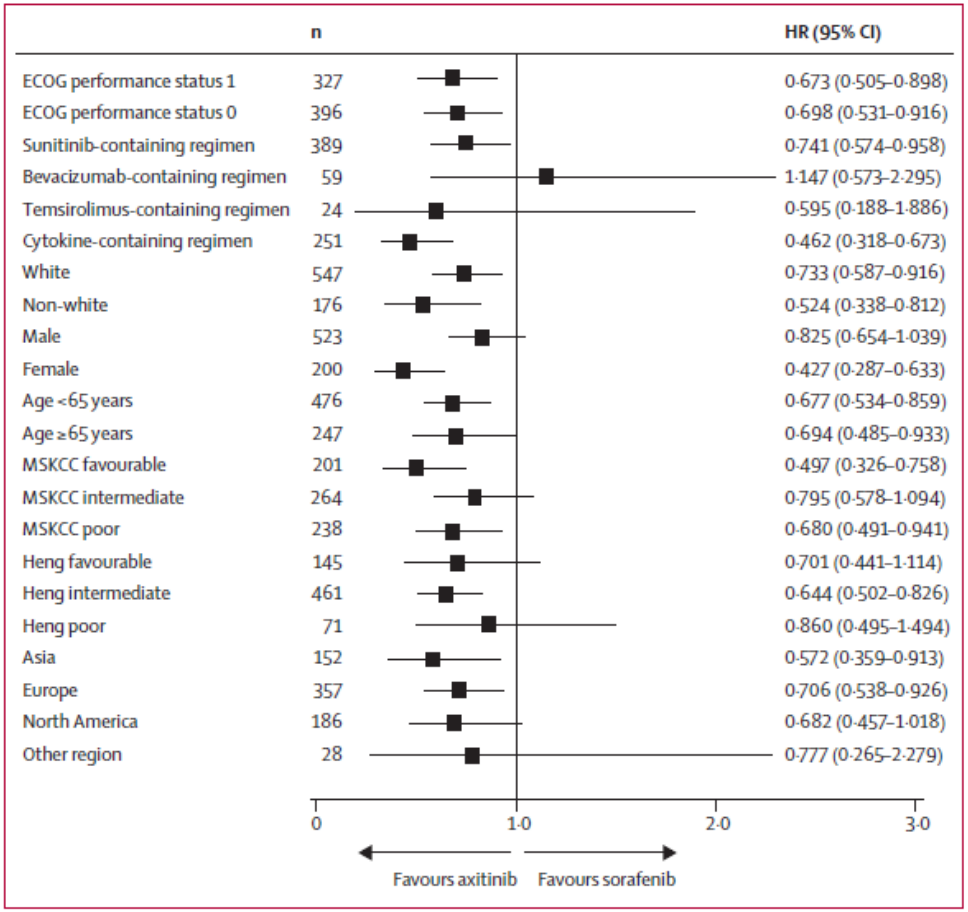


Figure 3: **Cox proportional-hazards analysis of progression-free survival by various patient's baseline and prognostic factors**
ECOG=Eastern Cooperative Oncology Group. MSKCC=Memorial Sloan-Kettering Cancer Center.

Rini BI et al. Lancet 378: 1931-1939, 2011

Evidence

- “No plan survives first contact with the enemy”

- We must be aware of when we work beyond the evidence
  - Different patient populations
  - Different clinical scenarios
  - Rare patient populations

- Everyday examples:
  - Choice of chemotherapy regimen for perioperative bladder cancer
  - Arbitrary capping of BSA for chemotherapy dosing
  - Treating poor performance status patients
  - Drug substitution
  - Altering regimens for convenience

RCC in the “real world”

PFS from first line

PFS from second line

OS from first line

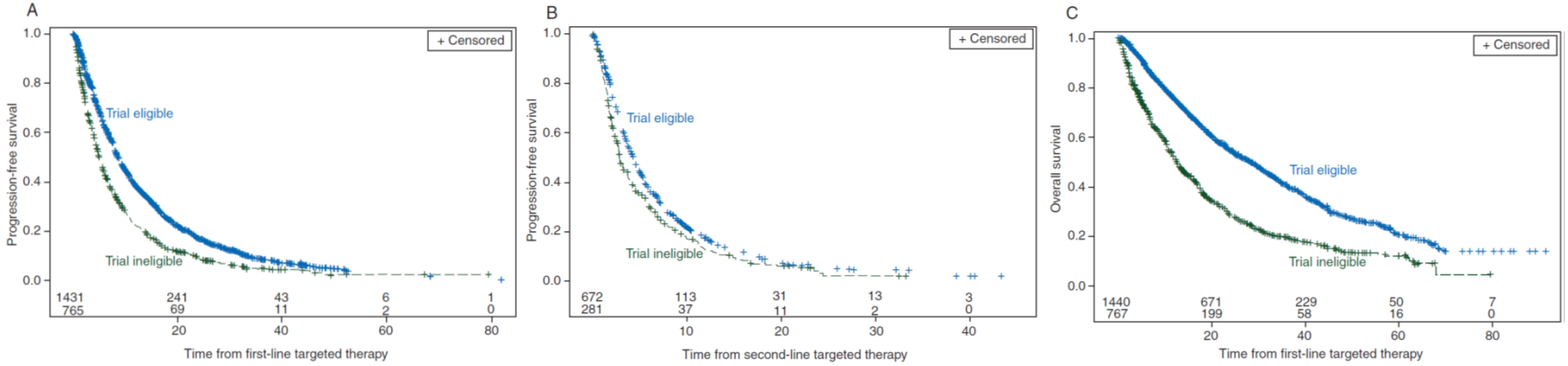


Figure 2. (A) Median PFS from first-line targeted therapy was 5.0 versus 8.6 months ($P < 0.0001$) in the trial ineligible versus trial eligible patients. (B) Median PFS from second-line targeted therapy was 2.8 versus 4.3 months ($P = 0.0039$) in the trial ineligible versus trial eligible patients. (C) Median overall survival from first-line targeted therapy was 12.5 versus 28.4 months ($P < 0.0001$) in the trial ineligible versus trial eligible patients.

Heng DYC et al. Ann Oncol 25: 149-154, 2014

Resistance

- Primary resistance:
  - Need to identify futile treatment early
  - Allows early swap to another (more effective?) treatment
- Acquired resistance:
  - What is clinically meaningful treatment failure?
  - PCWG3: “no longer clinically benefitting”
    - Rising PSA?
    - Bone flare?
    - Clinical symptoms?
    - Radiological progression?
      - How much / what / where?
      - 1cm → 2cm in lung? Liver? Brain?
    - Note: regulatory and reimbursement indications
      - e.g. Australian PBS indication for sunitinib for ongoing therapy: “Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST)”
- Can we predict or prevent resistance?

Practice patterns

- Urologists are a distinct surgical subset:
  - Have managed metastatic disease for years
  - Gatekeepers of referral patterns – more than most surgical subspecialties
  - Depending on region:
    - Coordinate and/or administer systemic therapies
    - May have good specialist nursing support
- New systemic therapies for prostate / RCC:
  - Oral treatments need no complex infrastructure to give
  - Often have familiar mechanisms of action and toxicities
- Practice patterns
  - Multidisciplinary involvement
  - Referral patterns
  - Changes in practice eg high risk localized prostate cancer

Technology creep

- Robotic-assisted surgery
  - Marked changes in practice patterns
  - Cost and resource implications
- Other novel therapies
  - Stereotactic body radiotherapy
  - Other ablative techniques
- Novel imaging modalities
  - PSMA PET
    - Rapid uptake by Australian clinicians and patients
    - Which patients will benefit?
  - “Will Rogers” phenomenon

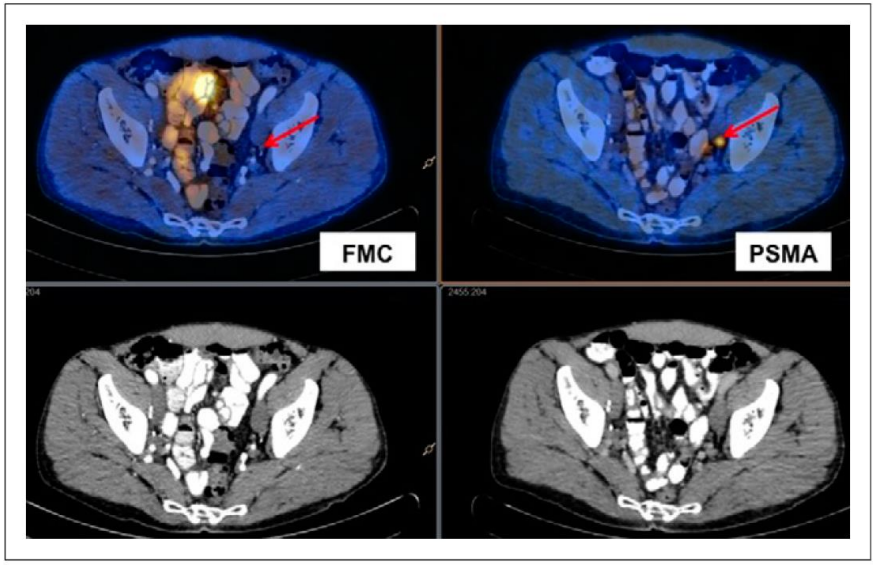
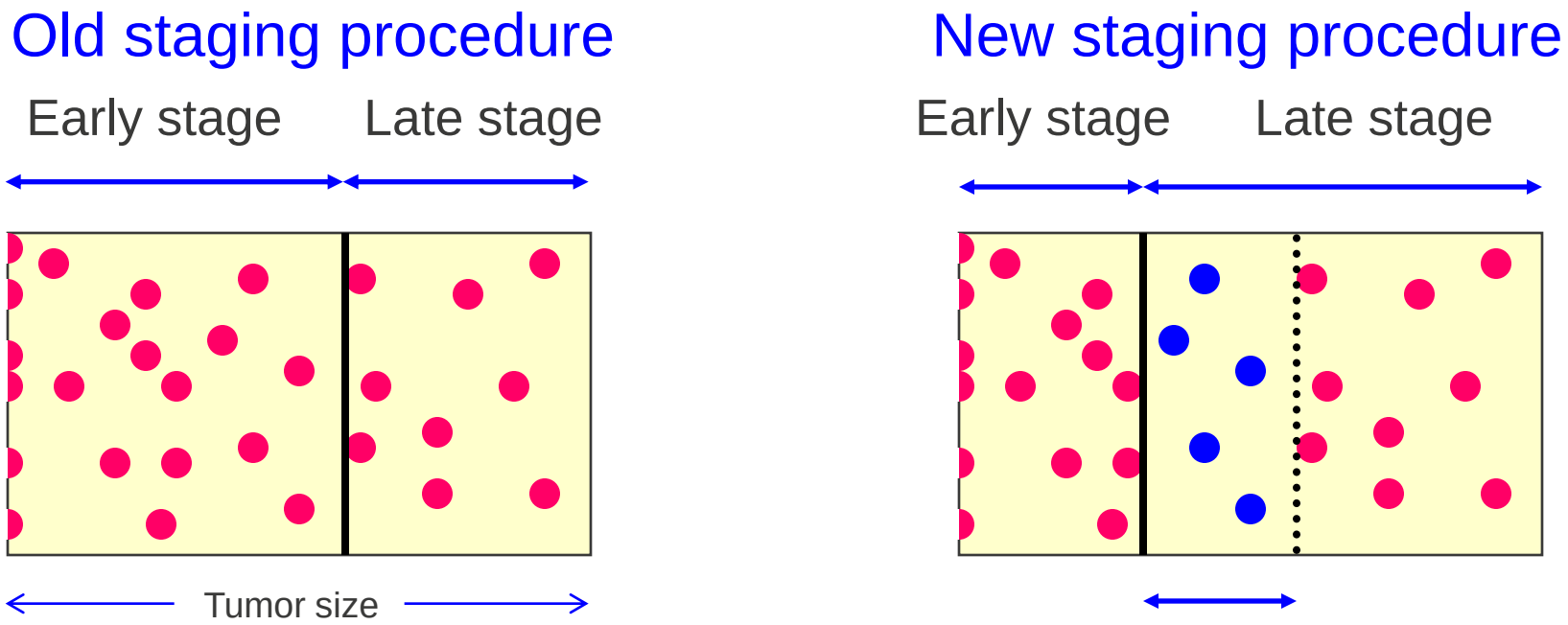


FIGURE 5. A 62-y-old man with Gleason 7 prostate cancer treated with radical prostatectomy and salvage radiation who presented with rising PSA level (0.4) and PSA doubling time of 8 mo. ^{18}F-fluoromethylcholine (FMC) PET/CT findings were negative, whereas ^{68}Ga-PSMA PET/CT scan demonstrated single positive left obturator lymph node (maximum standardized uptake value, 3.7). Subsequent biopsy confirmed prostate cancer recurrence.

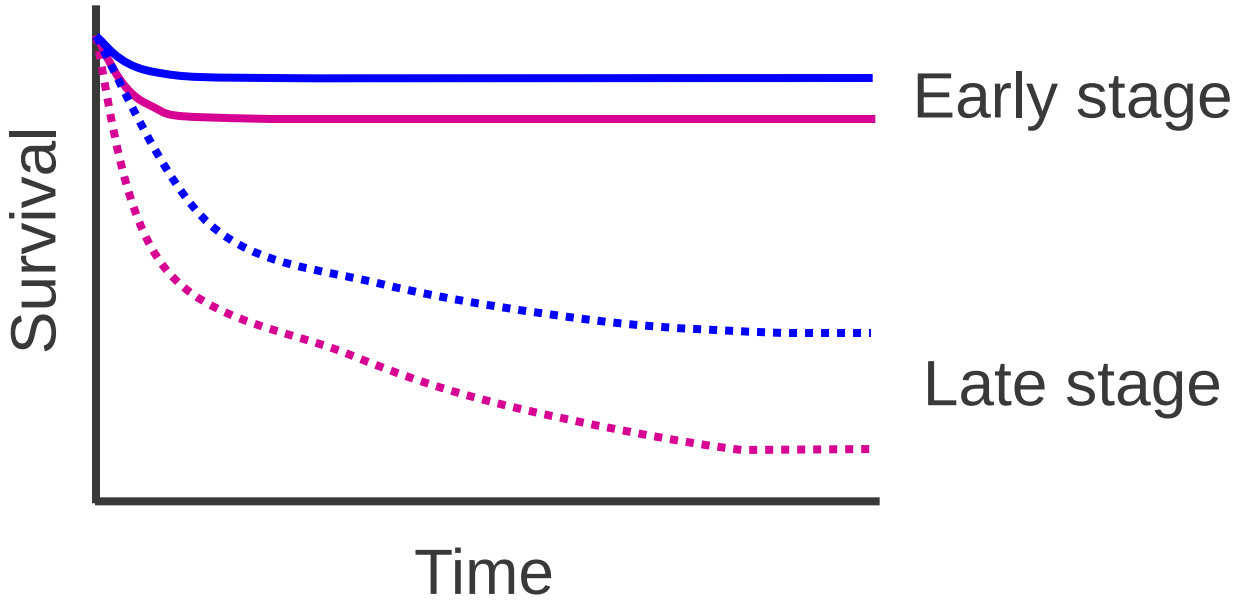
Morigi JJ et al. J Nucl Med 56: 1185-1190, 2015

Stage migration: the “Will Rogers” phenomenon



- Were in early stage but were truly late stage
- Lower burden of disease than other late stage patients
- Previously worsened prognosis for early stage group
- Now improving prognosis for late stage group

Effects of stage migration



Results:

- Breakthrough in cancer treatment!!" – *New York Times, New England Journal of Medicine*
- Grants
- Glory
- Guilt

Drug development

- Industry drug development:
  - Expensive and carries shareholder risk
- Increasing tendency to target subpopulations
- Some lack of willingness to take additional risk in drug development
  - Investigator-initiated trials
  - Combinations with other agents (companies)
  - Sequencing
- Importance of collaborative groups

Improving on success

- New treatments
- Better toxicity
- Lower costs
- Ease of use
- Challenge: Low risk testicular cancer - almost always curable
  - Is it statistically / logistically possible now to demonstrate further improvement?
- Related issues:
  - Supportive care
  - Decision support
  - Subgroups – rare cancers, uncommon situations

One more challenge… smugness!

- Just when you thought you understood things…

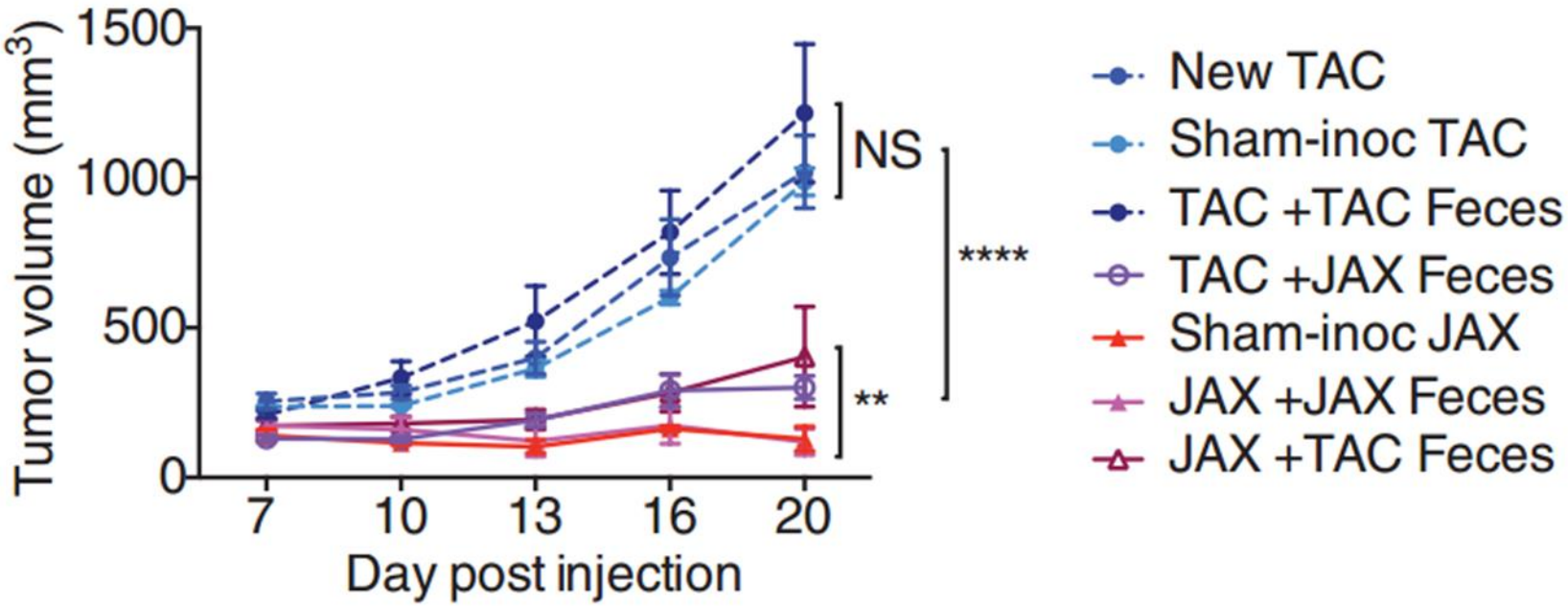
CANCER IMMUNOTHERAPY

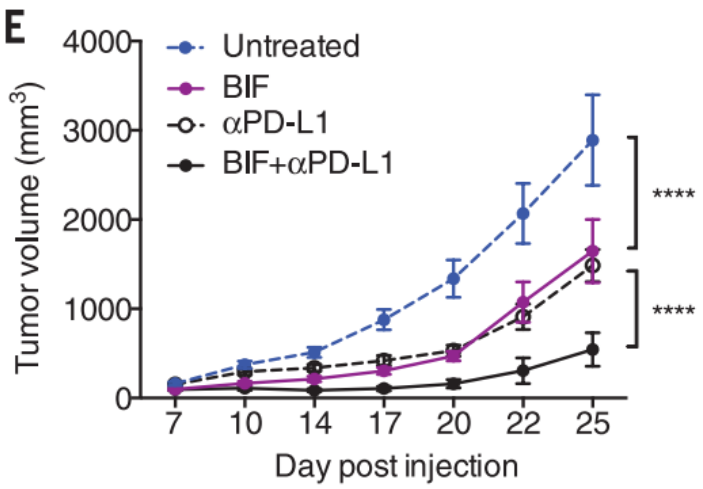
Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti–PD-L1 efficacy

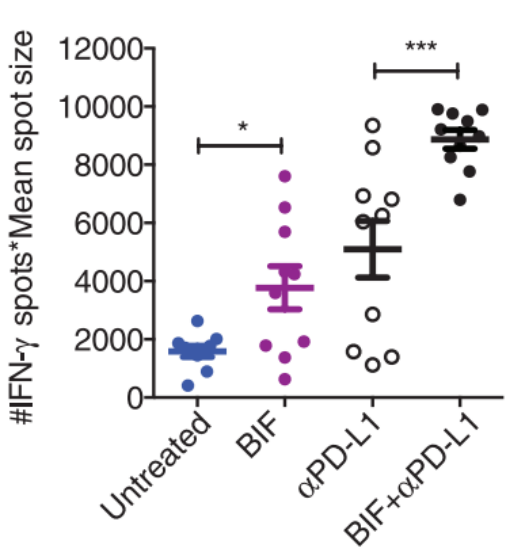
Ayelet Sivan,[1*] Leticia Corrales,[1*] Nathaniel Hubert,[2] Jason B. Williams,[1] Keston Aquino-Michaels,[3] Zachary M. Earley,[2] Franco W. Benyamin,[1] Yuk Man Lei,[2] Bana Jabri,[2] Maria-Luisa Alegre,[2] Eugene B. Chang,[2] Thomas F. Gajewski[1,2†]

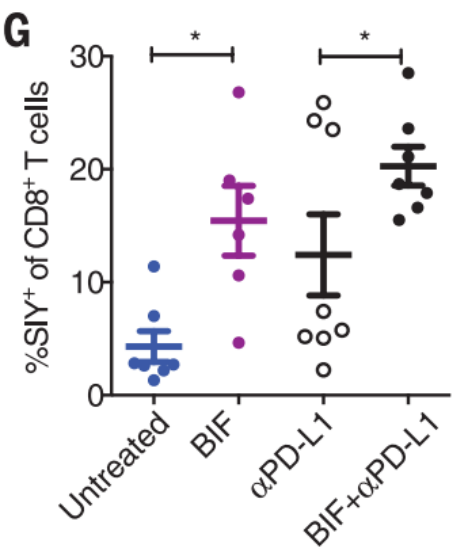
- B16.SIY melanoma model in JAX and TAC C57BL/6 mice
  - TAC mice grew tumors, JAX did not
  - Different patterns of tumor growth disappeared when mice were housed together
- Found to be due to faecal microbiome: Bifidobacterium

Sivan A et al. Science 350: 1084-1089, 2015 (27 Nov 2015)









Sivan A et al. Science 350: 1084-1089, 2015 (27 Nov 2015)

Conclusions

- GU cancers now have effective systemic therapies
  - Are they accessible?
  - Do we know how best to use them?
- Substantial room exists for further improvement
  - There are still surprises to be uncovered
- Non-clinical factors are the biggest impediment to effective use
  - Access
  - Expertise
  - Patterns of practice
  - Unintended consequences
- What we must do:
  - Understand the evidence
  - Understand the clinical and social contexts
  - Push for better and more equitable resourcing and use of resources
  - Ensure the important trials are done, and done well

Discussion questions

- Are the published trials relevant to your patient populations?
- Are new treatments or new technologies taken up too quickly?
- What do you do when you must treat outside the evidence?
- How do you deal with lack of access?
  - Drugs not approved
  - Funding not available
- Who manages systemic therapies in your hospital / region?
  - Is a multidisciplinary approach valuable?
- Does the sequence of therapy really matter?