Cost-effectiveness of 2nd line chemotherapies for ovarian cancer

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The NICE process

- Systematic review of existing clinical effectiveness and cost-effectiveness evidence
- Includes an estimate of cost-effectiveness of technology considered
  - NICE have specified Reference Case
    - Probabilistic
    - Use generic preference-based measure of quality of life
    - Costs from the perspective of the NHS

Overview

- Probabilistic decision analytic model from UK perspective
  - Life time costs and quality-adjusted life-years (QALYs)
- Assesses topotecan, paclitaxel and pegylated liposomal doxorubicin hydrochloride (PLDH)
  - Other comparators include platinum (carboplatin and cisplatin), paclitaxel+platinum, cyclophosphamide+doxorubicin+cisplatin (CAP)

Patient groups

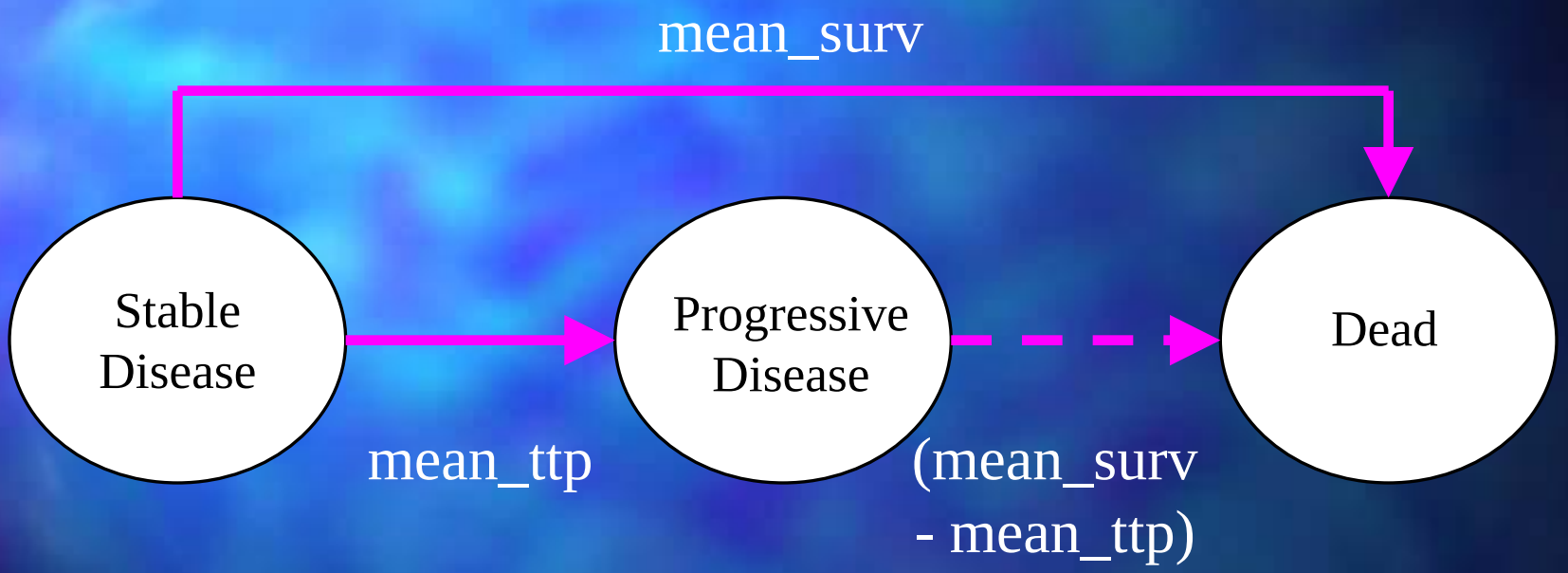
- Response to 1st line platinum therapy predictive of response to subsequent therapy
- Consider 2 separate cohorts
  - Relapse greater than 6 months following 1st line therapy: PLATINUM SENSITIVE
  - Relapse within 6 months or failure to respond:

    PLATINUM RESISTANT/REFRACTORY

Model structure

- Objective: estimate lifetime costs and QALYs
- Calculate survival as sum of 2 distinct periods
  - Progression-free period
  - Period from progression to death
- Quality adjust each period to calculate QALYs
- Costs: only 2nd-line treatment, admin and adverse events

Diagram of model structure



Key:
mean_surv = mean (overall) survival time
mean_ttp = mean time to progression

Comparisons in RCTs

Trial	Treatments compared					
	Paclitaxel	Topotecan	PLDH	Paclitaxel combination	Platinum	CAP
Overall patient population (platinum resistant/refractory and platinum sensitive)						
039	✓	✓				
30-49		✓	✓			
30-57	✓		✓			
Platinum sensitive patients						
ICON4				✓	✓	
Cantu	✓					✓

Main challenges

1. No direct trial comparison of all relevant therapies
2. Incorporating ICON4
3. No data on absolute hazards or mean survival
4. Lack of quality of life (QoL) data
   - In particular no utility data for toxicity events reported in trials

1. Approach to lack of direct comparison

- Bayesian mixed treatment comparison (MTC) to calculate relative effects
  - Synthesise (log) hazard ratios θ

    $Log(HR_{Pac\_Top}) \sim N(\theta_{Pac\_Top}, \tau^2_{Pac\_Top})$
- Extends standard meta-analysis to include principle of transitivity
  - Assume $\theta_{Pac\_PLDH} = \theta_{Pac\_Top} + \theta_{Top\_PLDH}$

2. Incorporating ICON4

- Problem
  - No common comparator with other trials
  - Only trial data for 2 relevant comparators in platinum sensitive
- Solution
  - Use exponential approximation to calculate absolute hazard
  - Calculate relative effect versus topotecan by taking ratio of absolute hazards
- LIMITATION – breaks randomisation

3. Baseline in the model

- Selected topotecan to provide baseline
  - Most comprehensive available data
  - No trials included 'best supportive care'
- Calculate absolute hazard λ from median survival using exponential approximation

$\lambda = -LN(0.5)/t$; *t = median survival (weeks)*

$Var(\lambda) = \lambda^2/r$; *r = # events*

mean survival (weeks) = $1/\lambda$

4. Quality of Life

- No utility data available for toxicity events reported in trials
  - As treatment is palliative, QoL important
- Available data:
  - Utility stable advanced ovarian cancer 0.63
  - Utility decrement of move from stable to progressive advanced breast cancer
    - Apply relative decrement to 0.63 as proxy
- **Important area for future research**

Populating the model

- Used direct output from evidence synthesis model in WinBUGS for treatment effects including adverse events
- Characterised other inputs using appropriate distributions to incorporate uncertainty

Results – Platinum resistant/refractory

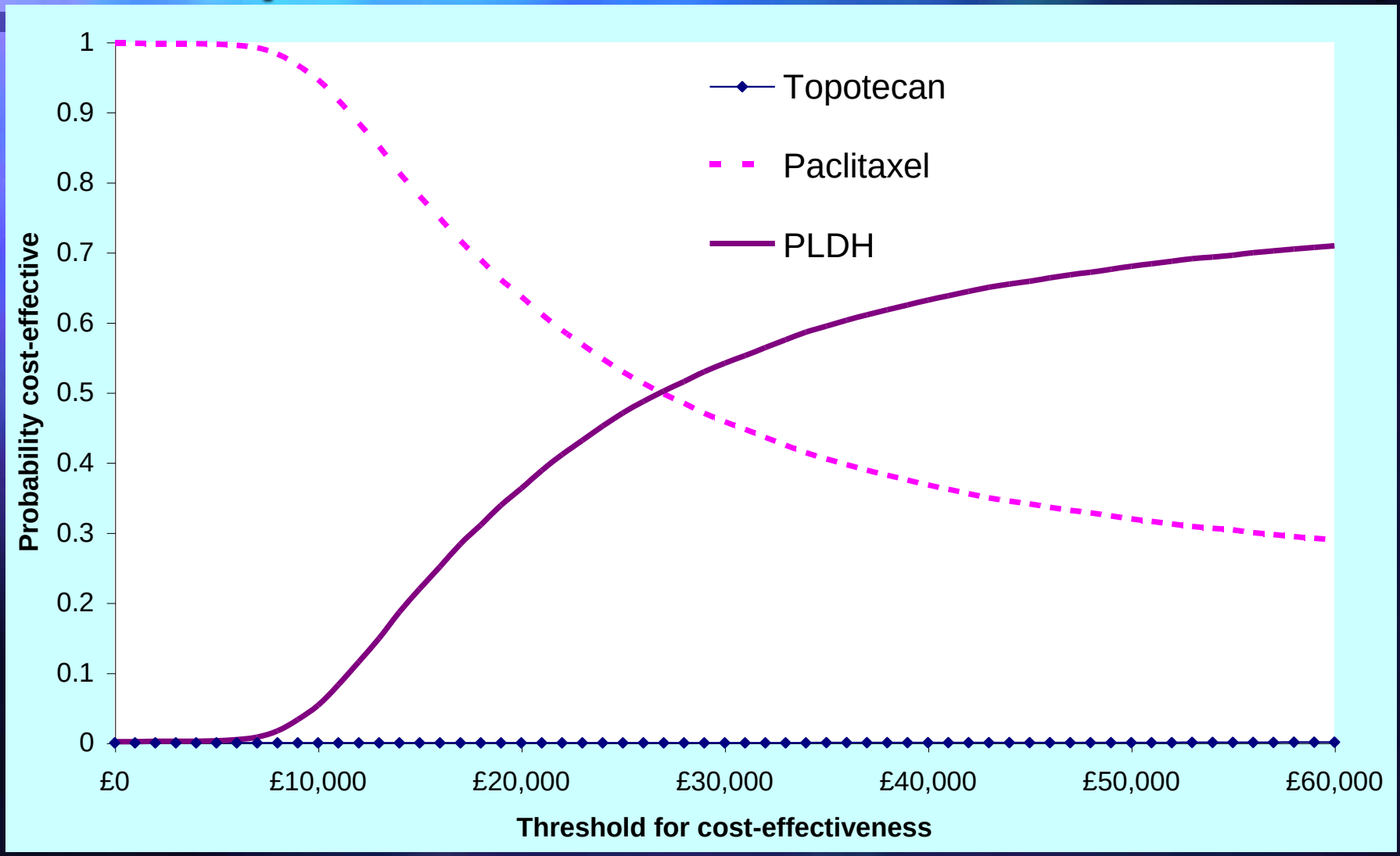
Treatment	PFS (wks)	OS (wks)	Quality-adjusted survival (wks)	Cost	ICER
Topotecan	19.8	61.2	25.1	£11,394	D
Paclitaxel	16.2	65.5	25.3	£6,354	-
PLDH	22.2	79.8	28.5	£7,713	£21,778

PFS = progression-free survival; OS = overall survival; wks = weeks; ICER = incremental cost-effectiveness ratio; D = dominated

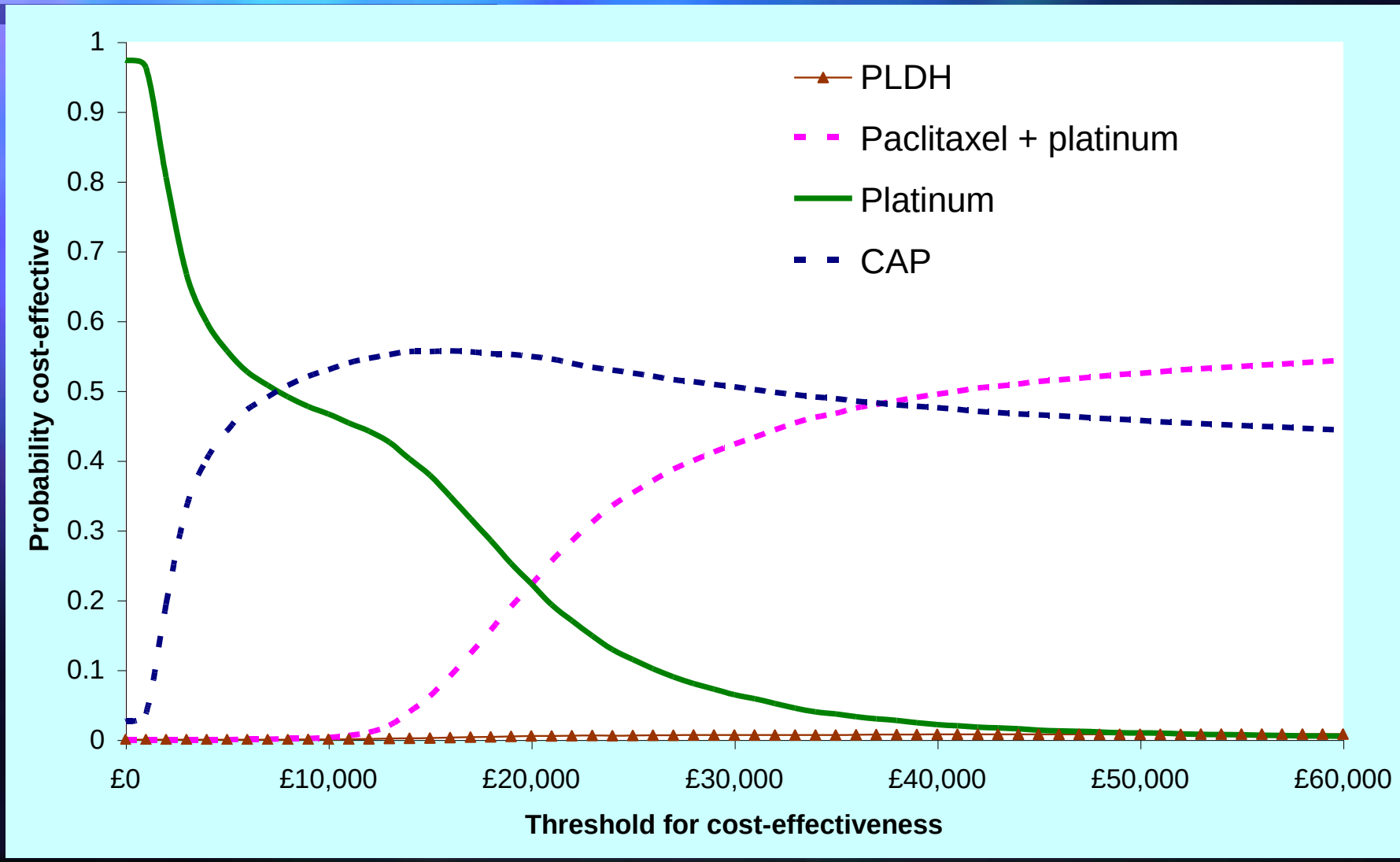
Results – Platinum sensitive

Treatment	PFS (wks)	OS (wks)	Quality-adjusted survival (wks)	Cost	ICER
Topotecan	33.1	101.4	41.7	£11,276	D
Paclitaxel	28.0	116.3	44.6	£6,274	D
PLDH	43.0	138.1	56.1	£7,662	D
Paclitaxel + Pt	82.3	179.5	81.5	£8,841	£34,542
Platinum (Pt)	63.1	148.9	66.0	£2,876	-
CAP	47.9	192.2	74.2	£3,988	£7,001

CEAC platinum resistant/refractory



CEAC for platinum sensitive



Choice of comparators

- Broke randomisation to include ICON4
  - If ICON4 excluded, CAP appears cost-effective in platinum sensitive
- CAP no longer used in practice
- Lack of available data may mean side effects not fully reflected in model
  - If CAP excluded, ICER for paclitaxel combination versus platinum £19,926
- If exclude CAP and ICON4, PLDH appears cost-effective for platinum sensitive

Final thoughts

- MTC approach
  - allows incorporation of trials otherwise discarded
  - still faced with choice of which trials to include
  - works best with complete network
- Implications for future work
  - Extend search strategy/systematic review to pick up all relevant trials and ↑ likelihood of complete network