Regulatory Background

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Outline

- FDA requirements for new drug approval
- Regular and accelerated approval
- Drug approval endpoints
- Past FDA approvals in ovarian cancer

Requirements for Drug Approval

- Safety (FD&C Act of 1938)
- Efficacy demonstrated in adequate and well controlled studies (1962 amendment)
- The methods of assessment of subjects' response are well-defined and reliable
  - 21 CFR 314.126(b)(6)

Approval Pathways and Efficacy Requirements

Regular approval

- Clinical Benefit
  - Prolongation of life
  - Better life: Improvement in tumor-related symptoms
- Established surrogate for clinical benefit

Accelerated approval

- Surrogate reasonably likely to predict clinical benefit

Accelerated Approval

- Serious or life-threatening disease
- Drug must provide benefit over *available therapy*
- Surrogate endpoint *reasonably likely* to predict clinical benefit
- Subsequent confirmation of clinical benefit is required (Post-Marketing Commitment)

Drug Approval Endpoints

Definition of Endpoints

- Clinical endpoint is a measurement or sign that directly measures how a patient feels, functions or survives.

- Surrogate endpoint is a measurement or sign that is used as a substitute for a clinical endpoint. It is assumed that it is a reliable predictor of the primary endpoint of interest.

Surrogate Endpoints in Oncology

Established surrogate (Regular Approval)

- Durable CR in acute leukemias
- PFS in adjuvant breast cancer

Surrogates that are "*reasonably likely* to predict clinical benefit" (Accelerated Approval)

- Durable tumor response in solid tumors

Endpoints for Oncology Drug Approval

- 1970 – mid 80s: tumor response rate alone
- Mid-1980s: improvement in survival or patients symptoms required for approval
- 1990s: other endpoints that potentially demonstrated clinical benefit were examined (e.g., DFS in adjuvant setting, durable CRs)

Drug Approval Endpoints

- Survival
- Progression Free Survival
- Response rate
- Measures of how patients feel or function
  - Observed
  - Patient-reported

Survival

- Pro
  - 100% accurate for the event and date
  - Not subject to investigator bias
- Cons
  - Requires larger sample size, longer follow-up
  - Cross-over and secondary Rx may obscure result

Progression Free Survival

- Pros
  - Shorter follow up time, faster results
  - Result is not obscured by secondary therapy
- Cons
  - Potential for bias
  - Result is sensitive to timing of the assessment
  - Usually assessed every 2 – 4 months

Response Rate

- Treatment is “entirely” responsible for tumor reduction
- Must consider duration of response
- Reliably assessed in single arm trials

Patient Reported Outcome

Pro

Patient's perspective on treatment

Cons

- Blinding is essential, but difficult to do
- Adequate development and validation is critical
- Inconclusive findings with small score changes
- Inconclusive findings with missing data
- Statistical analysis must plan for multiple comparisons

Past FDA Approvals in Ovarian Cancer

Ovarian Cancer Approvals

DRUG	YEAR	ENDPOINT
1st Line		
Cisplatin	1978	RR
Carboplatin	1991	Survival
Paclitaxel/Cisplatin	1998	Survival
2nd Line, Refractory		
Cisplatin	1978	RR
Carboplatin	1989	RR
Altretamine	1990	RR
Paclitaxel	1992	RR
Topotecan	1996	TTP, survival, RR
Liposomal Doxorubicin	1999/2005	RR/OS

Cisplatin for 1st and 2nd line (1978)

- Phase 2, randomized, N= 52
  - Cisplatin vs. cisplatin/adriamycin vs. thiotepa alone or plus methotrexate
  - RR 42% vs. 67% vs. 36%
- Phase 2, randomized, N= 52
  - Cisplatin alone vs. cisplatin/hydration/mannitol
  - RR 42% vs. 63%

Carboplatin/Cyclophosphamide 1st line (1991)

Study	Arms + cyclophosp	N	OS (m)	
1	Cisplatin	223	24.7	**HR 0.98** 95 % CI 0.78, 1.23
	Carboplatin	224	27.5	
2	Cisplatin	171	19.7	**HR 1.01** 95% CI 0.78, 1.30
	Carboplatin	171	21.5	

Paclitaxel/Cisplatin 1st line (1998)

Study	Arms	N	OS (m)	
1	Paclitaxel/Cisplatin	196	35.5	***p* 0.0002** **HR 0.64** 95 % CI 0.50 -0.81
	Cisplatin/Cycloph.	214	24.2	
2	Paclitaxel/Cisplatin	342	35.6	***p* 0.0016** **HR 0.73** 95% CI 0.60 – 0.89
	Cisplatin/Cycloph.	338	25.9	

Altretamine 2nd line (1990)

- Received regular approval based on:
  - Two single arm studies
  - Results: RR 20% (13/51) and 14% (3/21) Duration of response 2-36 months.

Paclitaxel for 2nd line (1992)

- Phase 3, bi-factorial design, compared
  - 2 different doses (135 or 175 mg/m^2)
  - 2 schedules (3- or 24- hrs infusion)

- Results: N=407
  - RR 16.2%, 95% CI 12.8 - 20.2%
  - Duration of response: 8.3 m (3.2 – 21.6)

Topotecan 2nd line (1996)

- Randomized study of topotecan vs. paclitaxel

	Topotecan N = 112	**Paclitaxel** N =114
RR	21%	14%
Duration of response (wks)	25.9	21.6
TTP (wks)	18.9	14.7
	HR 0.76, p =0.07	
OS (wks)	63.0	53.0
	HR 0.97 p= 0.87	

- Single arm
  N =111, RR 14%, median duration 22 wks

Liposomal Doxorubicin for 2nd line

- Accelerated approval in 1999
  - 3 single arm studies
  - RR 13.8 % (20/145), duration of response 39.4 wks
- Regular approval in 2005
  - Randomized study Doxil® vs. Topotecan (239/235)
  - Result: OS 14.4 m vs. 13.7 m (p 0.05, HR 0.82)
    TTP 4.1 m vs. 4.2 m (p 0.617, HR 0.95)
    RR 19.7% vs. 17.0%
    Duration of response: median 6.9 m vs. 5.9 months

Basis of Approval

1st line therapy

- RR (1978)
- Survival

2nd /3rd line therapy

- Response rate
- TTP, OS, RR
- RR, OS

White Oak, FDA