

# ASSG study concepts in osteosarcoma



# ASSG strategy

- Early phase/translational studies
- Collaboration
- Adolescent and Young Adult cancer priority

# Research activity in osteosarcoma

- Pooled analyses of osteosarcoma clinical trials looking at gender and age and outcomes
- AYAPK study
- Translational studies
  - Wnt pathway
  - Hh pathway

# Pooled analyses in osteosarcoma

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# Rationale

- Outcomes for adolescents and young adults said to be worse than for children with a range of cancers (ALL, Ewing sarcoma, osteosarcoma)
- Possible pharmacologic basis, linked to gender

# Pooled analyses in osteosarcoma

**Table 2.** Patient Characteristics (N = 2407)

Characteristics	n
Age	
Median Age	17
Range	(2 -43)
Pubertal Status	
Total number of pre pubertal males/ females	284/240
Total number of pubertal patients males/ females	625/289
Total number of post pubertal patients males/ females	530/336
Sex	
Male	1439
Female	964
Mets at diagnosis	
Non Metastatic	2322
Metastatic	85
Localization	
Axial	13
Extremities	2095

# Pooled analyses in osteosarcoma

**Table 1.** Summary of Trials included in Pooled Analysis

Group	Trial	Eligibility	Surgery	Treatment	Accrual Period	Age Range	No. of Patients
ISG	COSS-IOR	< 40, non metastatic, OS of extremity	neoadjuvant	IFO/HDMTX/DDP/ADR	1991-1992	(3-37)	61
	IOR-OS1	< 50, non metastatic, OS of extremity	neoadjuvant	MTX/DDP	1983-1987	(5-43)	127
	IOR-OS2	< 40, non metastatic, OS of extremity	neoadjuvant	HDMTX/DDP/ADR	1986-1989	(3-39)	164
	IOR-OS3	< 40, non metastatic, OS of extremity	neoadjuvant	HDMTX/DDP/ADR	1990-1991	(4-42)	95
	IOR-OS4	< 40, non metastatic, OS of extremity	neoadjuvant		1993-1996	(3-43)	133
	ISG-SSG1	< 40, non metastatic, OS of extremity	neoadjuvant	HDIFO/HDMTX/DDP/ADR	1997-2005	(4-40)	154
	Pilot-ISG	< 40, non metastatic, OS of extremity	neoadjuvant	HDIFO/HDMTX/DDP/ADR	1995-1997	(4-35)	68
MRC	BO02	< 40, non metastatic, OS of extremity	adjuvant	ADR/DDP vs ADR/DDP/HDMTX	1992	(4-41)	179
	BO03	< 40, non metastatic, OS of extremity	adjuvant	ADR/DDP vs MTX/vincristine/ADR	1997	(3-39)	391
	BO06	< 40, non metastatic, OS of extremity	neoadjuvant	ADR/DDP vs ADR/DDP/G-CSF	2007	(4-41)	497
SSG	SSG II	< 40, non metastatic	neoadjuvant	HDMTX	1982-1989	(6-36)	103
	SSG VIII	< 40, non metastatic	neoadjuvant	HDMTX/DDP/ADM	1990-1997	(7-39)	129
	SSG XIV	< 40, non metastatic, OS of extremity	neoadjuvant	IFO/MTX/DDP/ADR	2001-2005	(7-39)	66
BOTG	OST-III	< 25, non metastatic and metastatic, OS of extremity	neoadjuvant	EPI/CARBO/IFO/ vs EPI/CARBO/IFO/HDMTX	1991-1995	(6-22)	79
	OST-IV	< 25, non metastatic and metastatic, OS of extremity	neoadjuvant	DDP/CARBO/ADR/IFO	1996-1999	(6-25)	72
	OST-2000		neoadjuvant	DDP/ADR/HDIFO	2000-2005	(6-29)	92
<b>Total</b>							<b>2407</b>

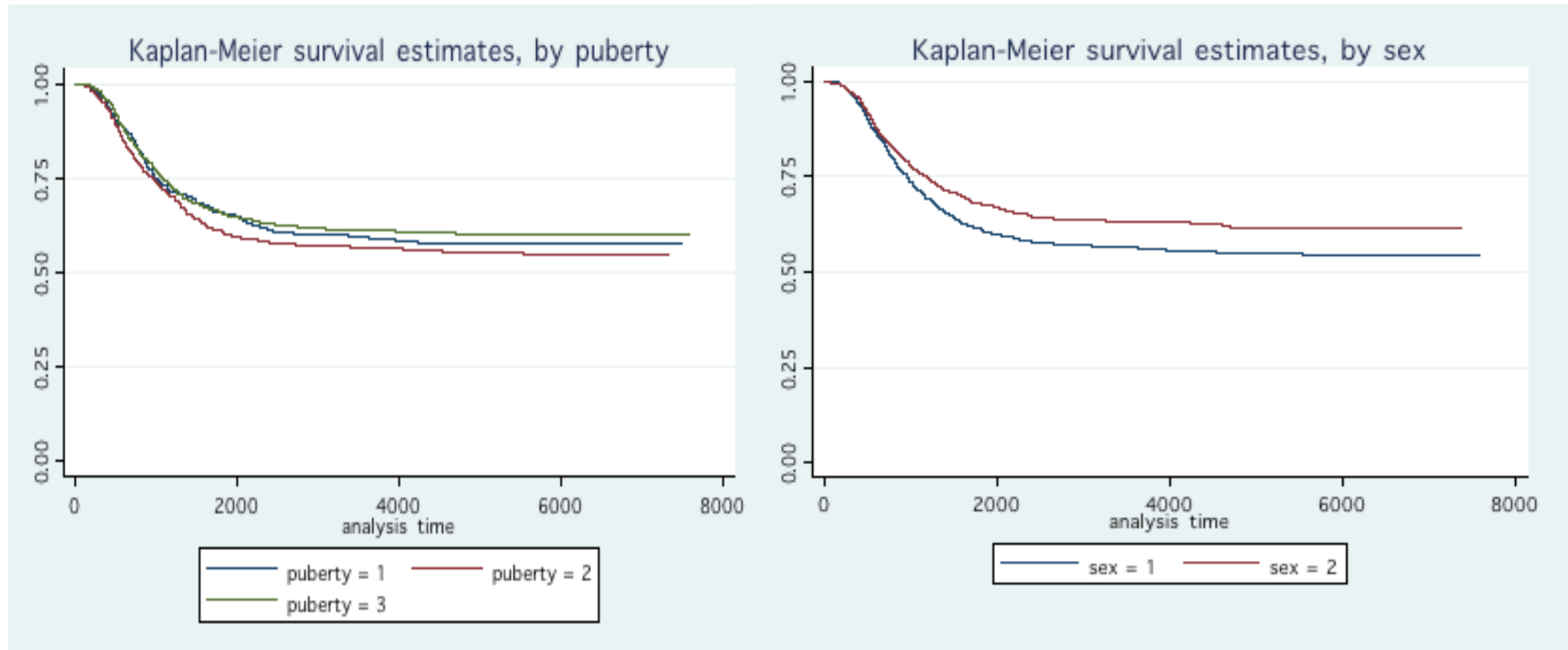
Abbreviations: ADR, doxorubicin; DDP, cisplatin; HDMTX, high dose methotrexate; G-CSF, granulocyte colony-stimulating factor; HDIFO, high dose ifosamide; EPI, epirubicin. CARBO, carboplatin; MTX, methotrexate; OS, osteosarcoma

# Preliminary analyses

	Child	Adolescent	Adult
Number	524	1013	867
M/F	284/240	625/388	530/337
Volume (mm <sup>3</sup> )	165±11	235±11	246±19
Metastases	18 (3.4%)	42 (4.1%)	25 (2.9%)
% intralesional margins	31/244 (13%)	8/455 (2%)	4/381 (1%)
>90% necrosis	243/441 (55%)	417/813 (51%)	299/680 (44%)
G3/4 Thrombocytopenia	170/294 (58%)	273/577 (47%)	236/536 (44%)
G3/4 Mucositis	55/237 (23%)	111/485 (23%)	80/434 (18%)
G3/4 Febrile neutropenia	155/210 (74%)	232/369 (63%)	178/323 (55%)
Treatment-related deaths	10 (1.9%)	15 (1.5%)	14 (1.6%)
Other causes of death	1 (0.2%)	6 (0.5%)	11 (1.3%)

# Preliminary analyses

DFS

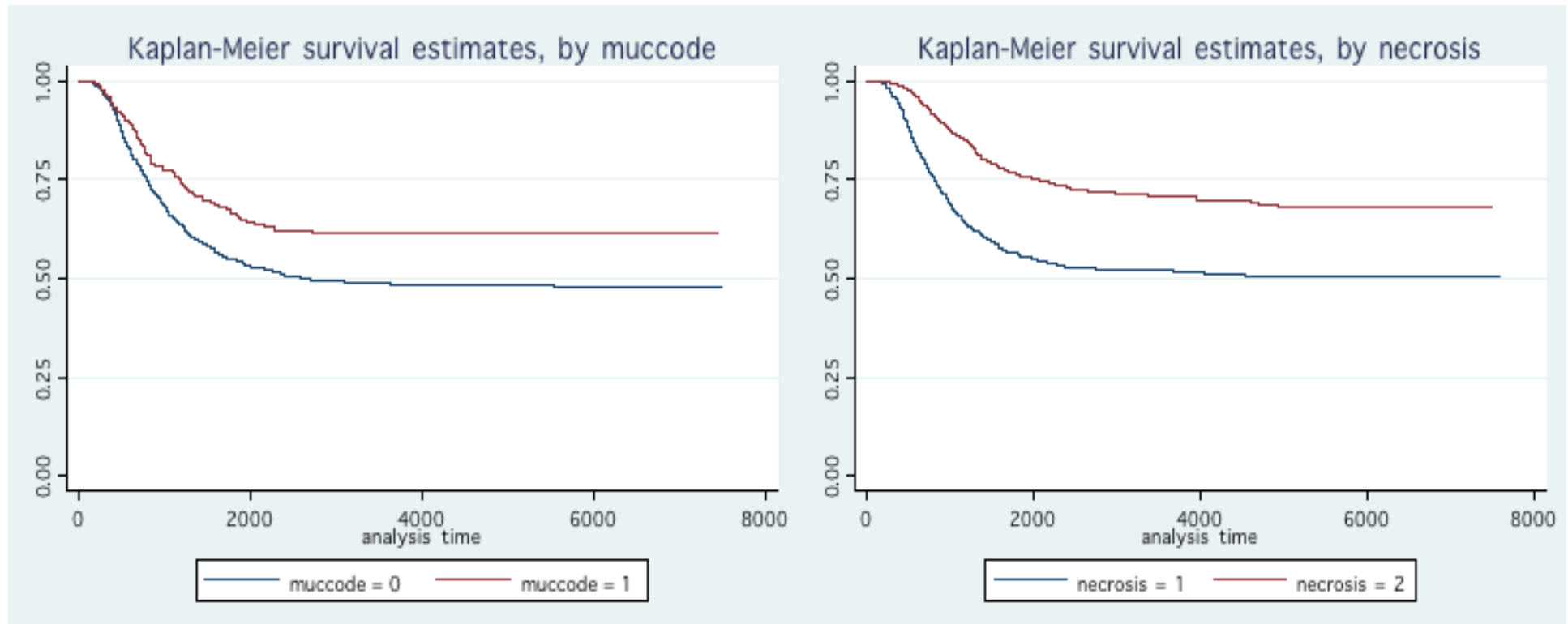


HR 0.81 (0.71-0.93)  $P=0.003$

# Preliminary analyses

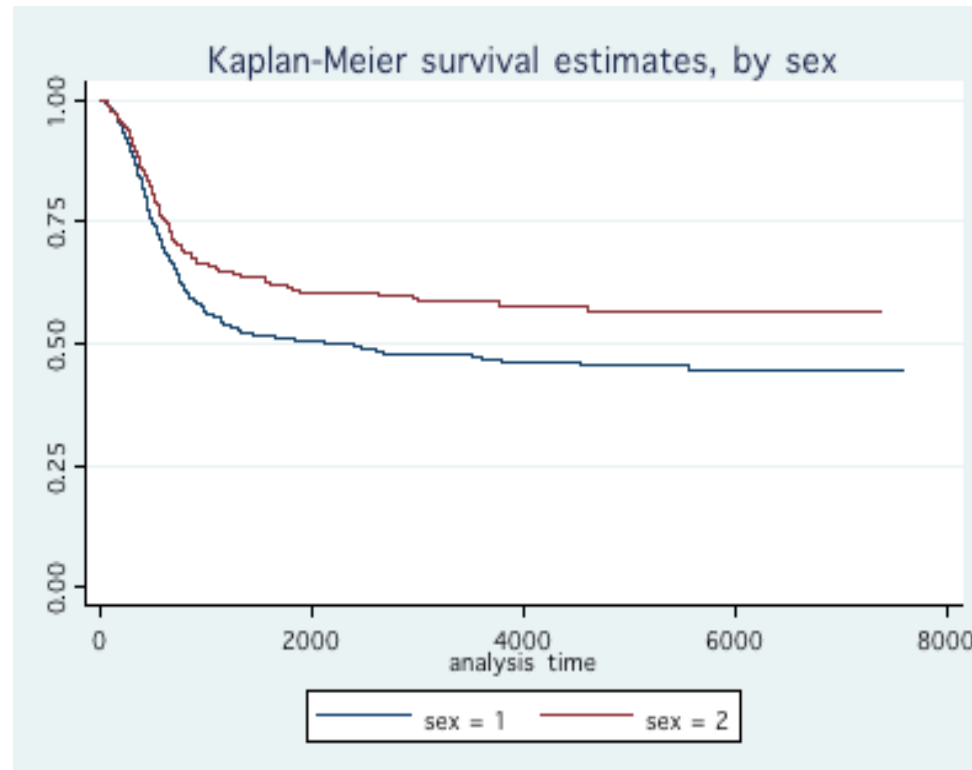
	Adult	
	Male	Female
Volume (mm <sup>3</sup> )	279±32	203±7
Metastasis	15/530 (2.8%)	10/340 (2.9%)
Treatment-related deaths/all deaths	6/221 (2.7%)	8/111 (7.2%)
G3/4 Febrile neutropenia	106/202 (53%)	72/121 (60%)
G3/4 Thrombocytopenia	140/347 (40%)	96/189 (51%)
G3/4 Mucositis	48/246 (17%)	32/148 (22%)
>90% necrosis at resection	167/412 (41%)	132/267 (49%)
5Y DFS	62±2 (58-66)	71±3 (66-76)
10Y DFS	58±2 (53-62)	68±3 (62-73)

# Preliminary analyses



HR 0.68  $P=0.002$

# Preliminary analyses



Adults

HR 0.72  $P=0.009$

# Conclusions I

- Good evidence from various cancer types that pharmacology changes with age and gender
- Pharmacodynamic metrics attenuate with age, and male gender
- Additional prognostic factors related to longitudinal skeletal growth probably operate

# Conclusions II

- Need to incorporate PK/PD measures in any prospective 'standard' chemotherapy trials
- Increase participation rates for AYA and stratify?
- Response-adapted therapy?
- Applies to Ewing sarcoma in particular, but also osteosarcoma (and other chemosensitive AYA diseases)

# Concepts in AYA pharmacology

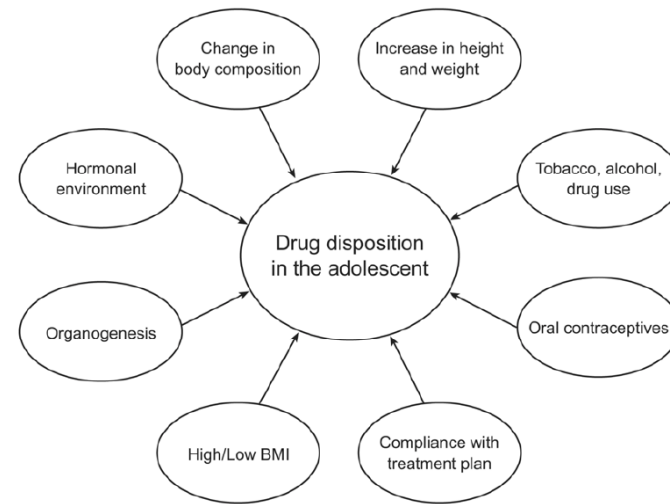
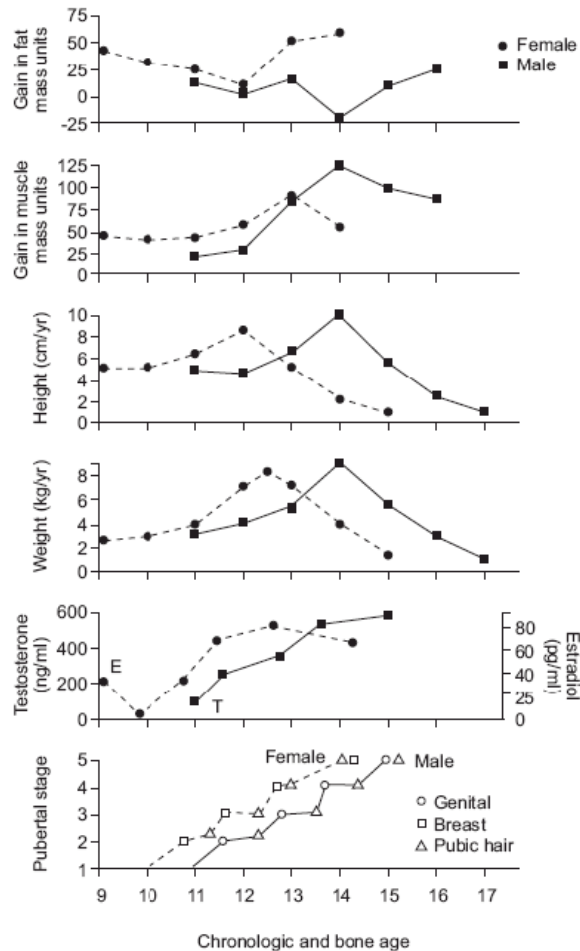


Table 1. Summary of the pharmacology studies published in adolescents.

Drug	Number of patients	Age range	Gender (M/F)	Summary of findings
Temozolomide <sup>67</sup>	39	0.7 – 21.9	20/19	- No difference in Cl between adolescents (>10 years) and younger children.
Dexamethasone <sup>68</sup>	214	1.0 – 18.8	115/99	- Age (< or > 10 yrs) a significant predictor of Cl in children with low albumin. Lower apparent oral Cl in adolescents consistent with increased toxicity.
Topotecan <sup>69</sup>	162	0.04 – 22	110/52	- No differences in systemic Cl between adolescents and younger children.
Vincristine <sup>70,71</sup>	54	0.2 – 18	N/A	- Cl normalized to BW differed significantly between adolescents and children <10 years.
	98	1.3 – 17.3	N/A	- No relationship between age and pharmacokinetics.
Imatinib <sup>72</sup>	26	7.0 – 24	17/9	- Median Cl greater in children >12 years but no statistically significant correlation with age observed.
	15	6.0 – 22	N/A	
Etoposide <sup>76-79,94</sup>	29	1.58 – 23.9	N/A	- No correlation between age and etoposide Cl after adjusting for body size.
	16	0.3 – 22	N/A	- AUC normalized to BW correlated to age.
	31	0.8 – 23.7	N/A	- No correlation between Cl normalized for BSA and age but significant inverse relationship between Cl normalized for BW and age.
	18	1.1 – 17	10/8	- Inverse relationship between Cl and age.
	109	0.4 – 18.7	N/A	- Age negatively correlated with Cl normalized for BSA.
Methotrexate <sup>81-83</sup>	134	0.33 – 18.5	76/58	- Age negatively correlated with plasma concentration.
	122	0.25 – 15	N/A	- Cl faster in children <10 years than in adolescents.
	49	0.5 – 17	N/A	- Cl in children <10 years 2-fold greater than in those > 10 years.
Actinomycin D <sup>80</sup>	31	1.0 – 20	18/13	- Higher AUC in younger children (<40kg) than in adolescents.
Busulfan <sup>59,93</sup>	27	1.3 - 50	10/17	- Shorter elimination half-life and higher clearance values in children <5 years versus children aged 5-16 years.
	25	0.5 – 54	15/10	- Significant increase in busulfan apparent oral clearance expressed relative to body surface area in children 0.5 – 4 years versus older children (≥ 12 yrs).

# AYA-PK

- 140-210 patients with Hodgkin lymphoma, osteosarcoma and Ewing sarcoma
- Pharmacokinetic & pharmacodynamic analyses of doxorubicin handling in children and adults
- Linked to outcomes (responses, relapse)
- Detailed biometric data
- 5 Australian sites and UCHL

# In development

- Hh antagonists
- Phase 2 in metastatic paediatric sarcomas
  - Good basic data to support role for Hh in RMS, Ewing sarcoma, osteosarcoma
  - Novartis compound (LDE225)
  - 30 patient signal seeking study in advanced disease
  - Linked to extensive biologic substudies